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Prognostic impact of lymph node status in patients after total pancreatectomy for pancreatic ductal adenocarcinoma

A strobe-compliant study

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Abstract

The optimal number of examined lymph nodes (ELN) for staging and impact of nodal status on survival following total pancreatectomy (TP) for pancreatic ductal adenocarcinoma (PDAC) is unclear. The aim of this study was to evaluate the prognostic impact of different lymph node status after TP for PDAC.

The Surveillance, Epidemiology, and End Results (SEER) database was used to identify patients who underwent TP for PDAC from 2004 to 2015. We calculated overall survival (OS) of these patients using Kaplan–Meier analysis and Cox proportional hazards model.

Overall, 1291 patients were included in the study, with 869 node-positive patients (49.5%). A cut-off points analysis revealed that 19, 19, and 13 lymph nodes best discriminated OS for all patients, node-negative patients, and node-positive patients, respectively. Higher number of ELN than the corresponding cut-off points was an independent predictor for better prognosis [all patients: hazard ratios (HR) 0.786, $P = .002$; node-negative patients: HR 0.714, $P = .043$; node-positive patients: HR 0.678, $P < .001$]. For node-positive patients, 1 to 3 positive lymph nodes (PLN) correlated independently with better survival compared with those with 4 or more PLN (HR 1.433, $P = .002$). Moreover, when analyzed in node-positive patients with less than 13 ELN, neither the number of PLN nor lymph node ratio (LNR) was associated with survival. However, when limited node-positive patients with at least 13 ELN, univariate analyses showed that both the number of PLN and LNR were associated with survival, whereas multivariate analyses demonstrated that only number of PLN was consistently associated with survival (HR 1.556, $P = .004$).

Evaluation at least 19 lymph nodes should be considered as quality metric of surgery in patients who underwent TP for PDAC. For node-negative patients, a minimal number of 19 lymph nodes is adequate to avoid stage migration. For node-positive patients, PLN is superior to LNR in predicting survival after TP, predominantly for those with high number of ELN.

Abbreviations: AJCC = American Joint Committee on Cancer, CI = confidence intervals, DP = distal pancreatectomy, ELN = examined lymph nodes, HR = hazard ratios, IQR = interquartile range, LNR = lymph node ratio, OR = odds ratios, OS = overall survival, PD = pancreaticoduodenectomy, PDAC = pancreatic ductal adenocarcinoma, PLN = positive lymph nodes, SEER = Surveillance, Epidemiology, and End Results, TP = total pancreatectomy.

Keywords: examined lymph nodes, lymph node ratio, pancreatic ductal adenocarcinoma, positive lymph nodes, survival, total pancreatectomy

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related mortality for both men and women in the United States, with estimated 45,750 deaths in 2019.[1] Radical surgical resection with adjuvant therapy offers the only chance of potential cure. However, the 5 years overall survival (OS) rate is only 20.7% in pancreatic cancer patients with adjuvant gemcitabine treatment after complete tumor resection.[2] Some

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studies have shown that greater number of examined lymph nodes (ELN) was associated with better survival after surgery for pancreatic cancer, especially in node-negative patients.[3–5] This is probably due to inadequate number of ELN may result in missing metastatic nodes.[6,7] However, some other studies have demonstrated that the number of ELN was not associated with prognosis.[8–11] In addition to the number of ELN, previous studies have intensively focused on predictive value of 3 other kinds of nodal status on survival: N stage, number of positive lymph nodes (PLN), and lymph node ratio (LNR), which is the ratio of the number of PLN to ELN.[8–10,12,13] Furthermore, the number of ELN was positively correlated with proportion of patients with lymph node involvement and number of PLN.[14,15] In contrast, number of ELN was negatively correlated with LNR.[3,13] Therefore, the number of ELN is the basic lymph node parameter. The recommendations for the optimal number of ELN range from 11 to 23.[3,4,6,7,14–19]

However, previous studies on lymph node parameters have been limited to patients underwent pancreaticoduodenectomy (PD),[3,13,20–22] distal pancreatectomy (DP),[3,4,23,24] as well as combination of all the surgical procedures.[12,14,25–29] The optimal number of ELN for staging and impact of nodal status on survival following total pancreatectomy (TP) for PDAC are unclear. Due to different range of pancreatectomy and lymphadenectomy between different types of surgery,[17,30] the diversity of number of ELN may exist. Some population-based studies and single-institution series have demonstrated that TP patients had more lymph nodes harvested than partial pancreatectomy, such as PD and DP.[28,29,31,32] Thus, the consensus[17] that the minimum number of ELN for an accurate staging should be 15 may not suitable for patients who underwent TP for PDAC.

The aim of the present study was to investigate the Surveillance, Epidemiology, and End Results (SEER) database to:

1. evaluate the impact of the number of ELN on nodal status following TP for PDAC.
2. identify the optimal number of ELN to maximize survival and to decrease the probability of stage migration in patients who underwent TP for PDAC.
3. determine the impact of the number of ELN, the number of PLN, and LNR on survival in PDAC overall and within different N stages following TP.

2. Methods

2.1. Patients

The present study used data from the SEER database. The SEER program collects clinical information from 18 population-based cancer registries covering approximately 34.6% of the United States population.[33] The SEER database includes data about demographics, tumor characteristics, treatment methods as well as survival. The dataset for this study was released April 2018 according to November 2017 submission.

Patients who underwent TP (codes 40 and 60) for microscopically confirmed pancreatic duct adenocarcinoma (PDAC) from 1998 to 2015 were included in present study. PDAC were identified by the third edition of the International Classification of Diseases for Oncology (ICD-O-3) histology codes (8140 and 8500) and behavior code 3. Then, we used the following exclusion criteria:

1. age at diagnosis was less than 18 years;
2. number of ELN was 0 or unknown;

3. number of PLN was unknown;
4. had more than 1 kind of primary cancer and pancreatic cancer was not the first one;
5. tumor stage was unknown or had stage IV;
6. unknown tumor size and tumor size >20 cm;
7. had stage T4;
8. survival months was unknown;
9. discordant N stage and number of PLN.

This study did not require ethical approval, as the SEER data were analyzed anonymously and were publicly available.

2.2. Variables

In our study, the following variables were reviewed: age, gender, race, years of diagnosis, tumor location, tumor grade, tumor size, T stage, N stage, number of ELN, number of PLN, survival months, and vital status. Patients were staged according to the 7th edition of American Joint Committee on Cancer (AJCC) staging system. For the tumor grade status, we combined the "well differentiated" and "moderately differentiated" as "G1 +G2," and combined the "poorly differentiated" and "undifferentiated" as "G3+G4". For the T stage status, patients in the "T1 stage" and "T2 stage" were clustered as "T1+T2 (tumors limited to the pancreas)". LNR was calculated by dividing number of PLN by ELN, and was divided into 3 classes ($0 < LNR \leq 0.2$, $0.2 < LNR \leq 0.4$, $LNR > 0.4$) according to previous studies.[3,11] The primary outcome was OS, which was defined as interval from date of diagnosis to date of death (all causes) or last follow-up (cutoff date: December 31, 2015).

2.3. Statistical analysis

Standard statistical programs (SPSS for Windows, version 22.0; Chicago, Ill) was used to carry out all statistical analyses. Continuous data were expressed in the form of medians with interquartile range (IQR) and Mann–Whitney U tests was used to compared these data. Categorical data were compared using χ^2 test. The multivariate logistic regression was used to identify the relationship between number of ELN and nodal metastasis. The resulting odds ratios (OR) and 95% confidence intervals (CI) were presented. To determine the optimal cut-off points for number of ELN in discriminating survival, χ^2 scores were calculated using the log-rank test for thresholds ranging from 4 to 25. The maximum χ^2 score was considered as the optimal cut-off value.[16,34] The survival curves were estimated via the Kaplan–Meier method. The log-rank test helped to test the difference. The Cox proportional hazards model was applied to assess the prognostic factor associated with survival. Variables with a $P < .1$ in univariable analyses were considered for the multivariable model. The resulting hazard ratios (HR) and 95% CI were presented. Two-sided $P < .05$ was considered statistically significant.

3. Results

3.1. Clinicopathologic characteristics

A total of 1291 patients who underwent TP for PDAC from 2004 to 2015 were included in the study (Supplementary Fig. 1, http://links.lww.com/MD/D852). Of these, 422 patients were lymph node negative (N0 stage) and 869 patients had nodal metastases (N1 stage). The demographics and clinicopathologic characteristics of these patients are shown in Table 1. There was no

The demographics and clinicopathologic characteristics of patients underwent total pancreatectomy for pancreatic ductal adenocarcinoma.

	Total (n = 1291)	Node-negative (n = 422)	Node-positive (n = 869)	P
Age, yrs				.113
≤65	619 (47.9%)	189 (44.8%)	430 (49.5%)	
>65	672 (52.1%)	233 (55.2%)	439 (50.5%)	
Gender				.804
Male	658 (51.0%)	213 (50.5%)	445 (51.2%)	
Female	633 (49.0%)	209 (49.5%)	424 (48.8%)	
Race				.297
White	1035 (80.2%)	333 (78.9%)	702 (80.8%)	
Black	138 (10.7%)	53 (12.6%)	85 (9.8%)	
Other	118 (9.1%)	36 (8.5%)	82 (9.4%)	
Years of diagnosis				.634
2004–2009	566 (43.8%)	189 (44.8%)	377 (43.4%)	
2010–2015	725 (56.2%)	233 (55.2%)	492 (56.6%)	
Tumor location				<.001
Head	1014 (78.5%)	306 (72.5%)	708 (81.5%)	
Body/tail	126 (9.8%)	64 (15.2%)	62 (7.1%)	
Other	151 (11.7%)	52 (12.3%)	99 (11.4%)	
Grade				.008
G1+2	739 (61.0%)	254 (66.5%)	485 (58.5%)	
G3+4	472 (39.0%)	128 (33.5%)	344 (41.5%)	
Unknown	80	40	40	
Tumor size				<.001
≤2cm	217 (16.8%)	104 (24.6%)	113 (13.0%)	
>2cm	1074 (83.2%)	318 (75.4%)	756 (87.0%)	
T stage				<.001
T1/2	245 (19.0%)	139 (32.9%)	106 (12.2%)	
T3	1046 (81.0%)	283 (67.1%)	763 (87.8%)	
Number of ELN	15 (10–21)	12 (7–18)	16 (11–22)	<.001
Number of PLN	1 (1–4)	0 (0–0)	3 (1–5)	-
LNR	0.10 (0–0.26)	0 (0–0)	0.20 (0.10–0.35)	-

ELN = examined lymph nodes, LNR = lymph node ratio, PLN = positive lymph nodes.

significant difference in age, gender, race, and years of diagnosis between node-negative and node-positive patients. Node-positive patients were more likely to be pancreatic head cancer, higher tumor grade, more than 2 cm of tumor size, nonarterial tumor extension beyond the pancreas (stage T3). The median number of ELN was 15 (IQR, 10–21) in entire cohort, significantly lower in node-negative patients as compared with node-positive patients [12 (IQR, 7–18) vs 16 (IQR, 11–22); $P < .001$]. For node-positive patients, the median number of PLN was 3 (IQR, 1–5), the median LNR was 0.20 (IQR, 0.10–0.35).

3.2. Impact of the number of examined lymph nodes on nodal status

Patients were divided into 5 groups based on number of ELN. The proportion of patients with node-positive disease increased with an increasing of number of ELN ($P < .001$; Supplementary Fig. 2a, http://links.lww.com/MD/D853). Furthermore, node-positive patients were stratified according to the 8th edition of AJCC N staging system. A significant increase in the proportion of patients with more than or equal to 4 PLN was associated with an increasing of ELN ($P < .001$; Supplementary Fig. 2b, http://links.lww.com/MD/D853). With increasing of ELN, the proportion of patients with lower LNR ($0 < LNR \leq 0.2$) increased, and the proportion of patients with higher LNR ($LNR > 0.4$) decreased ($P < .001$; Supplementary Fig. 2c, http://links.lww.

com/MD/D853). After adjusting for potential confounders (tumor location, tumor grade, tumor size, and T stage) associated with nodal metastasis, the multivariable logistic regression showed that successive increasing number of ELN increased the likelihood of finding nodal metastases (OR, 1.056; 95% CI 1.039–1.073; $P < .001$; Supplementary Table 1, http://links.lww.com/MD/D857).

3.3. Impact of the number of examined lymph nodes on survival

All patients were stratified according to the number of ELN in increments of 5 and 3-year survival rates were calculated. Survival for each increment is listed for entire cohort and for each lymph node stage (Supplementary Table 2, http://links.lww.com/MD/D858). 3-year survival increased from 22.3% (1 to 5 lymph nodes examined) to 27.2% (>20 lymph nodes examined) in the entire cohort. An equal trend was observed for other subgroups, with range from 28.1% to 45.8% (N0 stage) and 13.6% to 22.5% (N1 stage). For N0 subgroup, the best survival results were observed in patients with more than 20 ELN. Although the best survival results were encountered with 16 to 20 ELN for entire patient cohort and for N1 subgroup, increasing number of ELN had the trend to be superior survival results. This trend for superior survival based on number of ELN is shown in Supplementary Fig. 3, http://links.lww.com/MD/D854.

Table 2

Univariate survival analyses comparing various lymph node cut-off points in all patients and by lymph node stages.

	Total (n=1291)		Node-negative (n=422)		Node-positive (n=869)	
	χ^2	P	χ^2	P	χ^2	P
≤4 vs ≥5	0.157	.692	2.515	.113	1.033	.309
≤5 vs ≥6	0.091	.763	3.619	.057	0.437	.509
≤6 vs ≥7	0.925	.336	0.193	.660	0.240	.624
≤7 vs ≥8	0.003	.953	0.850	.357	1.778	.182
≤8 vs ≥9	1.212	.271	3.704	.054	3.794	.051
≤9 vs ≥10	1.706	.192	3.588	.058	5.978	.014
≤10 vs ≥11	1.474	.225	3.169	.075	6.160	.013
≤11 vs ≥12	3.361	.067	3.881	.049	8.500	.004
≤12 vs ≥13	4.374	.036	3.614	.057	**13.280**	**<.001**
≤13 vs ≥14	6.459	.011	6.284	.012	11.504	.001
≤14 vs ≥15	3.553	.059	5.340	.021	5.667	.017
≤15 vs ≥16	5.241	.022	5.009	.025	8.754	.003
≤16 vs ≥17	3.179	.075	3.085	.079	7.436	.006
≤17 vs ≥18	4.706	.030	4.844	.028	6.504	.011
≤18 vs ≥19	**6.997**	**.008**	**8.644**	**.003**	5.774	.016
≤19 vs ≥20	4.077	.043	6.085	.014	3.524	.060
≤20 vs ≥21	2.970	.085	2.591	.107	5.793	.016
≤21 vs ≥22	2.051	.152	0.902	.342	6.260	.012
≤22 vs ≥23	2.901	.089	1.344	.246	6.574	.010
≤23 vs ≥24	2.356	.125	1.034	.309	5.734	.017
≤24 vs ≥25	1.989	.158	1.028	.311	4.884	.027

Bold values represent the lymph node cut-off point associated with the greatest survival difference.

3.4. Optimal number of examined lymph nodes

A cut-off points analyses was performed to determine the optimal number of ELN that generated the greatest survival difference. As shown in Table 2, for the entire cohort, the greatest survival difference was observed at the 19 lymph nodes cut-off point ($\chi^2 = 6.997$, $P = .008$). The optimal cut-off points were 13 in node-positive patients ($\chi^2 = 13.280$, $P < .001$) and 19 in node-negative patients ($\chi^2 = 8.644$, $P = .003$), respectively.

3.5. Survival analyses of all patients

The median follow-up period was 15 months (range, 0–143 months). The median OS time was 18 months in all patients. The 3- and 5-year OS rates were 26.2% and 16.2%. Kaplan–Meier

survival curve based on cut-off points of 19 ELN is depicted in Fig. 1a. Patients who had 1 to 18 ELN had a shorter median OS (18 months) compared to those who had ≥19 lymph nodes examined (21 months; $P = .008$). The 3- and 5-year OS rates were 24.7% and 14.7% for patients with 1 to 18 ELN, and ≥19 ELN were 29.5% and 19.9%, respectively.

In the univariate analyses, age older than 65 years (HR 1.227, 95% CI 1.080–1.393, $P = .002$; Table 3), higher tumor grade (G3+G4, HR 1.664, 95% CI 1.456–1.901, $P < .001$; reference: G1+G2; Table 3), more than 2 cm tumor size (HR 1.862, 95% CI 1.537–2.255, $P < .001$; Table 3), T3 stage (HR 1.444, 95% CI 1.223–1.706, $P < .001$; Table 3), more PLN (≥4 PLN, HR 2.042, 95% CI 1.723–2.420, $P < .001$; 1–3 PLN, HR 1.539, 95% CI 1.317–1.797, $P < .001$; reference: negative lymph
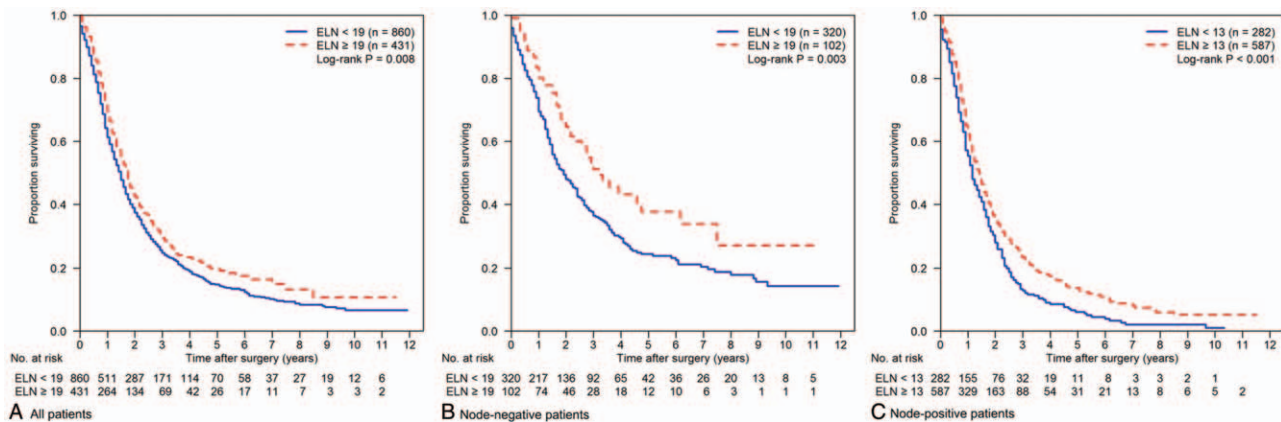

Figure 1. Kaplan–Meier survival analyses of overall survival according to cut-off points of examined lymph nodes (ELN). a: comparison of survival for 1 to 18 vs ≥19 ELN in all patients ($P = .008$). b: comparison of survival for 1 to 18 vs ≥19 ELN in node-negative patients ($P = .003$). c: comparison of survival for 1 to 12 vs ≥13 ELN in node-positive patients ($P < .001$).

Table 3

Univariate and multivariate analyses of overall survival in all patients.

All patients	Univariable			Mutivariable		
	HR	95% CI	P	HR	95% CI	P
Age, yrs						
≤65	1			1		
>65	1.227	1.080–1.393	.002	1.202	1.053–1.371	.006
Gender						
Male	1					
Female	0.985	0.867–1.118	.813			
Race						
White	1					
Black	0.850	0.687–1.052	.135			
Other	1.007	0.801–1.267	.950			
Years of diagnosis						
2004–2009	1			1		
2010–2015	0.891	0.782–1.016	.084	1.144	0.996–1.313	.056
Tumor location						
Head	1					
Body/tail	0.763	0.603–0.965	.024			
Other	1.009	0.829–1.229	.927			
Grade						
G1+2	1			1		
G3+4	1.664	1.456–1.901	<.001	1.518	1.327–1.738	<.001
Tumor size						
≤2 cm	1			1		
>2 cm	1.862	1.537–2.255	<.001	1.651	1.355–2.012	<.001
T stage						
T1/2	1			1		
T3	1.444	1.223–1.706	<.001	1.158	0.968–1.385	.110
Number of PLN						
0	1			1		
1–3	1.539	1.317–1.797	<.001	1.409	1.195–1.661	<.001
≥4	2.042	1.723–2.420	<.001	1.809	1.500–2.182	<.001
Number of ELN						
<19	1			1		
≥19	0.830	0.721–0.955	.009	0.786	0.677–0.913	.002

ELN = examined lymph nodes, PLN = positive lymph nodes.

nodes; Table 3) were predictors of poor OS. In contrast, more than or equal to 19 ELN (HR 0.830, 95%CI 0.721–0.955, P = .009; Table 3) was associated with better OS. In the multivariate analyses, most of these factors remained independent prognostic factors, with the exception of T stage (P = .110; Table 3). Additionally, more recent years of diagnosis had a trend to be an independent prognostic factor for OS (P = .056; Table 3).

3.6. Survival analyses of node-negative patients

In considering the node-negative patients, the median OS time was 27 months. The 3- and 5-year OS rates were 39.8% and 27.3%. Kaplan–Meier survival curves of node-negative patients based on lymph node cut point of 19 is shown in Fig. 1b. Only 24.2% of node-negative patients had ≥19 ELN. The median OS for patients who had 19 or more nodes examined was 39 months, whereas the median OS for those who had 1 to 18 nodes examined was 23 months. The difference in median OS between these 2 groups was 16 months (P = .003). The 3- and 5-year OS rates were 36.4% and 24.4% for patients with 1 to 18 ELN, and ≥19 ELN were 51.2% and 37.7%, respectively.

In the univariate analyses, age older than 65 years (HR 1.429, 95% CI 1.119–1.824, P = .004; Table 4), higher tumor grade (G3 +G4, HR 1.890, 95%CI 1.456–2.447, P < .001; reference: G1 +G2; Table 4), more than 2 cm tumor size (HR 2.053, 95%CI 1.510–2.791, P < .001; Table 4), T3 stage (HR 1.526, 95%CI 1.169–1.992, P = .002; Table 4) were predictors of poor OS. In contrast, more than or equal to 19 ELN (HR 0.629, 95%CI 0.459–0.862, P = .004; Table 4) was associated with better OS. In the multivariate analyses, after controlling for age, grade, tumor size, and T stage, examined 19 or more lymph nodes remained significantly associated with better OS (HR 0.714, 95%CI 0.515–0.990, P = .043; Table 4).

3.7. Survival analyses of node-positive patients

In patients with node-positive disease, the median OS time was 16 months. The 3- and 5-year OS rates were 19.5% and 10.7%. Kaplan–Meier survival curves of node-positive patients based on lymph node cut point of 13 is shown in Fig. 1c. The median OS for patients who examined 13 or more lymph nodes was better than those who examined 1 to 12 lymph nodes (18 vs 15 months, P < .001). The 3- and 5-year OS rates were 12.9% and 6.1% for

Univariate and multivariate analyses of overall survival in node-negative patients.

Node-negative patients

	Univariable			Mutivariable		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, yrs						
≤65	1			1		
>65	1.429	1.119–1.824	.004	1.468	1.134–1.899	.004
Gender						
Male	1					
Female	1.031	0.812–1.309	.801			
Race						
White	1					
Black	0.860	0.593–1.247	.425			
Other	1.292	0.846–1.972	.236			
Years of diagnosis						
2004–2009	1					
2010–2015	0.881	0.687–1.131	.320			
Tumor location						
Head	1					
Body/tail	0.628	0.428–0.921	.017			
Other	0.878	0.608–1.268	.488			
Grade						
G1+2	1			1		
G3+4	1.890	1.456–2.447	<.001	1.879	1.444–2.444	<.001
Tumor size						
≤2 cm	1			1		
>2 cm	2.053	1.510–2.791	<.001	1.774	1.286–2.449	<.001
T stage						
T1/2	1			1		
T3	1.526	1.169–1.992	.002	1.491	1.121–1.983	.006
Number of ELN						
<19	1			1		
≥19	0.629	0.459–0.862	.004	0.714	0.515–0.990	.043

ELN = examined lymph nodes.

patients with 1 to 12 ELN, and ≥13 ELN were 23.3% and 13.5%, respectively.

Figure 2 shows the survival curves of node-positive patients according to number of PLN and LNR class. Patients with 1 to 3 PLN had better median OS than those with ≥4 PLN (18 vs 13 months, *P* < 0.001; Fig. 2a). The 3- and 5-year OS rates were 22.5% and 12.3% for patients with 1 to 3 PLN, and ≥4 PLN were 15.0% and 8.4%, respectively. Patients with smaller LNR had significantly longer median OS (19 months for 0 < LNR ≤ 0.2 vs 15 months for 0.2 < LNR ≤ 0.4 vs 12 months for LNR>0.4, *P* < .001; Fig. 2b). The 3- and 5-year OS rates were 22.2% and 14.0% for patients with 0 < LNR ≤ 0.2, 19.2% and 8.3% for patients with 0.2 < LNR ≤ 0.4, 13.3% and 6.9% for patients with LNR>0.4, respectively. However, to further assess the patients with suboptimal lymph nodes examination, the patients was restricted to those with less than 13 ELN. There was no significant difference in OS between patients with 1 to 3 PLN and patients with 4 or more PLN (15 vs 11 months, *P* = .301; Supplementary Fig. 4a, http://links.lww.com/MD/D855). Similarly, there was no significant difference in OS between different LNR categories (14 months for 0 < LNR ≤ 0.2 vs 15 months for 0.2 < LNR ≤ 0.4 vs 13 months for LNR > 0.4, *P* = .268; Supplementary Fig. 4b, http://links.lww.com/MD/D855). In contrast, after limiting the evaluate to the patients with 13 or more ELN. The median OS of patients with 1 to 3 PLN was significantly better than those with 4 or more PLN (21 vs 13

months, *P* < .001; Supplementary Fig. 5a, http://links.lww.com/MD/D856). Patients with smaller LNR had significantly lower risk of death (median OS: 19 months for 0 < LNR ≤ 0.2 vs 15 months for 0.2 < LNR ≤ 0.4 vs 12 months for LNR > 0.4, *P* = .004; Supplementary Fig. 5b, http://links.lww.com/MD/D856).

In the univariate analyses, age older than 65 years (HR 1.213, 95% CI 1.044–1.409, *P* = .012; Table 5), higher tumor grade (G3+G4, HR 1.497, 95%CI 1.281–1.749, *P* < .001; reference: G1+G2; Table 5), more than 2 cm tumor size (HR 1.570, 95%CI 1.238–1.990, *P* < .001; Table 5), ≥4 PLN (HR 1.335, 95%CI 1.145–1.556, *P* < .001; Table 5), higher LNR (LNR > 0.4, HR 1.487, 95%CI 1.224–1.808, *P* < .001; reference: 0 < LNR ≤ 0.2; Table 5) were predictors of poor OS. However, the risk of death for patients with 0.2 < LNR ≤ 0.4 was similar to that for the patients with 0 < LNR ≤ 0.2 (HR 1.187, *P* = .055; Table 5). More than or equal to 13 ELN (HR 0.755, 95%CI 0.646–0.881, *P* < .001; Table 5) was associated with better OS. In the multivariate analyses, after controlling for age, years of diagnosis, grade, and tumor size, ≥4 PLN (HR 1.433, 95%CI 1.140–1.801, *P* = .002; Table 5) and ≥13 ELN (HR 0.678, 95% CI 0.564–0.816, *P* < .001; Table 5) were still independent prognostic factors for OS. In contrast, the LNR was not independently associated with OS. Furthermore, when high number of lymph nodes (≥13) were examined, increasing number of PLN remained independently associated with decreasing
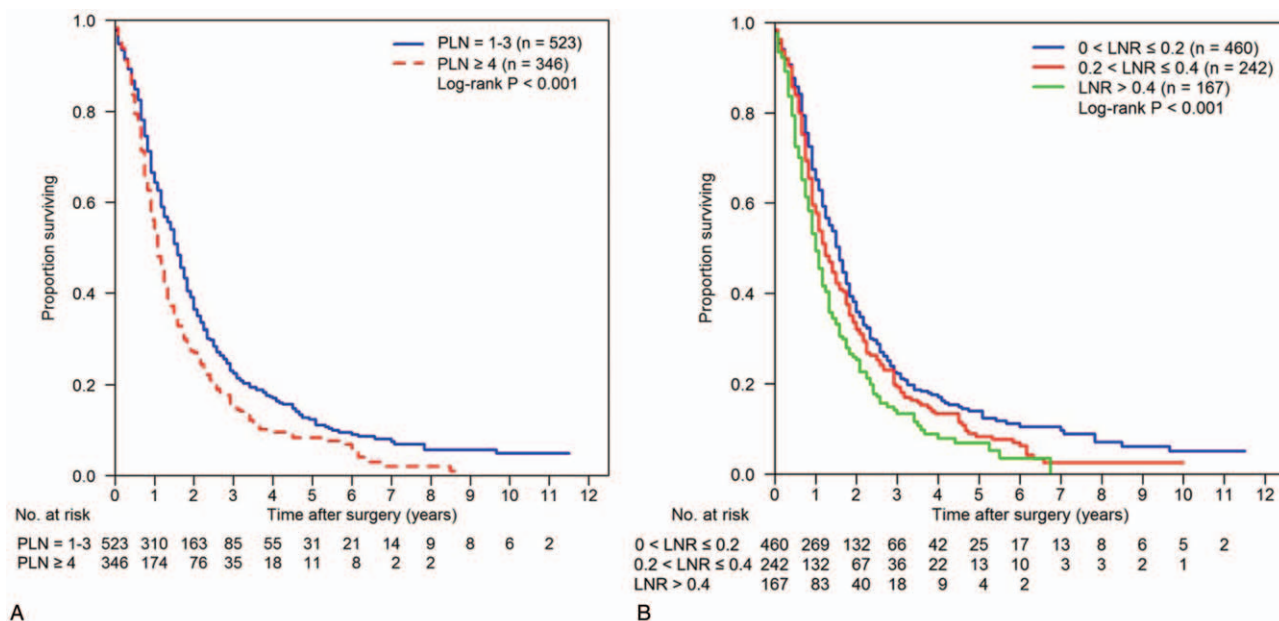
Figure 2. Kaplan–Meier survival analyses of overall survival according to number of positive lymph nodes (PLN) and lymph node ratio (LNR) class in node-positive patients. a: comparison of survival for 1 to 3 vs ≥4 PLN ($P < .001$). b: comparison of survival for different categories of LNR ($0 < $ LNR≤ 0.2 vs $0.2 < $ LNR≤ 0.4 vs LNR > 0.4; $P < .001$).

survival (HR 1.566, 95% CI 1.151–2.131, $P = .004$; Table 5). However, increasing LNR was still irrelevant to poor survival.

4. Discussion

Recently, due to improved surgical techniques and advances in perioperative care, TP can be performed with similar perioperative morbidity and mortality as that of partial pancreatectomy.[35–37] Also, the development of long-acting insulin and pancreatic enzymes provides options for overcoming severe glucose fluctuations and intestinal malabsorption following TP.[36] Thus, a renewed interest has been risen in TP for the treatment of large invasive PDAC at high-volume pancreatic centers over the past 2 decades.[38,39] However, no study to date has focused on optimal number of ELN for staging and impact of nodal status on survival following TP for PDAC. This is the first population-based study to address these issues.

The number of ELN after surgery of pancreatic cancer is influenced by age, gender, tumor grade, tumor size, type of surgery, as well as experience of surgeon, and pathologist.[21,29] The present study provides following evidences that number of ELN is associated with nodal status in PDAC patients who underwent TP. First of all, node-positive patients have greater number of ELN than node-negative patients. The number of ELN is independent predictive factor for probability of finding metastatic lymph node. Then, an increased number of ELN is associated with an increased proportion of node-positive patients. Moreover, for node-positive patients, an increased number of ELN is associated with an increased proportion of patients with higher number of PLN and lower LNR. A similar correlation has been found for pancreatic cancer after PD or DP.[3,13] These results demonstrated that greater number of ELN could enhance the reliability of nodal status.

Subsequently, we investigated the association between the number of ELN and survival after TP for PDAC, and found that

the trend towards superior survival in patients with increasing number of ELN. The result was supported by previous studies of gastric cancer,[34] lung cancer,[40] as well as PDAC after PD.[16,41]

Then, a further study was performed to identify the optimal number of ELN that maximizing survival difference. The optimal threshold was examined by evaluating log-rank χ^2 scores of Kaplan–Meier survival curves. Tomlinson et al[16] used this statistical method in 1150 node-negative patients underwent PD, showing that at least 15 lymph nodes should be examined to accurately stage node-negative PDAC after PD. Recently, by population-based study, Contreras et al[41] utilized same approach in 26,792 patients underwent PD for PDAC, showing that the optimal cut-off point of 10 defined adequate ELN. In present study, we first applied this statistical method to assess PDAC patients who underwent TP. Our data demonstrated that the optimal number of ELN were 19 in all patients, 19 in node-negative patients, and 13 in node-positive patients.

For all patients in this study, number of ELN was included into the multivariate survival analyses, given a $P < .1$ in univariable analyses. We found that it was an independent prognostic factor. Thus, it was further confirmed that at least 19 lymph nodes should be examined to get better survival in all patients who underwent TP, when the lymph node stage was unknown during operation. This is consistent with previous study by Strobel et al[13] of patients underwent PD for PDAC, in which patients with >10 ELN had better survival than patients with ≤10 ELN in all cohort. Similar, using the SEER database, Slidell et al[42] demonstrated that patients who had fewer than 12 lymph nodes examined had significantly worse survival compared with patients who had at least 12 nodes removed in all patients underwent resection for PDAC. The explanations for these findings are not clear, but may reflect the number of ELN was partly influenced by extent of nodal dissection,[43] which may have an effect on survival to some extent.[44] Conversely, Schwarz et al[18] evaluated data for patients underwent resection for

Table 5

Univariate and multivariate analyses of overall survival in node-positive patients.

| | Node-positive patients | | | | | | Node-positive patients with ≥13 ELN | | | | | |
| | Univariable | | | Mutivariable | | | Univariable | | | Mutivariable | | |
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age, yrs												
≤65	1			1			1					
>65	1.213	1.044–1.409	.012	1.155	0.989–1.349	.070	1.164	0.963–1.408	.117			
Gender												
Male	1						1					
Female	0.970	0.835–1.127	.690				0.961	0.795–1.162	.680			
Race												
White	1						1					
Black	0.908	0.700–1.178	.469				0.745	0.524–1.060	.102			
Other	0.878	0.669–1.154	.351				0.840	0.596–1.184	.320			
Years of diagnosis												
2004–2009	1			1			1			1		
2010–2015	0.878	0.753–1.024	.097	0.859	0.732–1.010	.065	0.848	0.697–1.031	.098	0.801	0.656–0.978	0.030
Tumor location												
Head	1						1					
Body/tail	1.128	0.837–1.519	.429				1.176	0.810–1.709	.394			
Other	1.147	0.908–1.448	.251				1.254	0.946–1.661	.115			
Grade												
G1+2	1			1			1			1		
G3+4	1.497	1.281–1.749	<.001	1.448	1.237–1.696	<.001	1.465	1.205–1.782	<.001	1.359	1.114–1.657	0.002
Tumor size												
≤2cm	1			1			1			1		
>2cm	1.570	1.238–1.990	<.001	1.616	1.259–2.074	<.001	1.964	1.397–2.761	<.001	1.761	1.222–2.536	0.002
T stage												
T1/2	1						1					
T3	1.096	0.882–1.362	.407				0.936	0.706–1.239	.643			
Number of PLN												
1–3	1			1			1			1		
≥4	1.335	1.145–1.556	<.001	1.433	1.140–1.801	.002	1.530	1.263–1.854	<.001	1.566	1.151–2.131	0.004
Number of ELN												
<13	1			1			-	-	-	-	-	-
≥13	0.755	0.646–0.881	<.001	0.678	0.564–0.816	<.001	-	-	-	-	-	-
LNR												
0<LNR≤0.2	1			1			1			1		
0.2<LNR≤0.4	1.187	0.996–1.413	.055	0.848	0.681–1.057	.142	1.250	1.005–1.555	.045	0.806	0.589–1.101	0.176
>0.4	1.487	1.224–1.808	<.001	0.937	0.706–1.243	.650	1.516	1.152–1.997	.003	0.890	0.605–1.310	0.555

ELN = examined lymph nodes, LNR = lymph node ratio, PLN = positive lymph nodes.

PDAC from the SEER database and concluded that the cut-off point of 25 ELN failed to show significant difference in survival for the entire cohort. This was possibly due to the sample size of subgroup for patients at least 25 ELN was small.

We also found that the number of PLN is another important independent prognostic factor in all patients. The mortality increased with the increase of the number of PLN. While previous study showed that PDAC patients with low number of PLN and negative LN had comparable survival.[6,10,13,26,45] In addition, Torre et al[46] performed separate analyses after dividing PDAC patients by cut-off point of 12 ELN. The prognostic influence of nodal metastasis did not reach significance for patients with less than 12 ELN. However, node-positive patients had worse OS compared to node-negative patients in subgroup of more than 12 ELN. It revealed that the lack in a difference in survival between patients with low number of PLN and negative LN might be due to misclassify node-positive patients as negative patients in these with inadequate number of ELN. On the contrary, the results from other studies are similar to those of our study. Tarantino et al,[12] by analyzing the SEER database, including 5036 patients who underwent resection for PDAC with at least 12 ELN, demonstrated that the survival of node-negative patients had better survival than patients with 1 or 2 positive LN and those with 3 or more positive LN. Additionally, Kang et al[47] reported that the presence of a single metastatic LN significantly worsened the prognosis of patients underwent resection for pancreatic head cancer, as compared to node-negative patients. The findings of previous reports and our study implied that presence of metastatic LN of such a lethal tumor as pancreatic cancer will strongly impact survival irrespective of its number.

Our studies demonstrated that patients with involved lymph nodes have different clinicopathologic characteristics compared with patients without any metastatic lymph nodes. Furthermore, nodal involvement is one of the important predictor of worse survival in patients with PDAC.[48,49] Thus, in the end, to deep analyze the clinical implications of optimal cut-off point for ELN and other LN parameters, we further performed the survival analyses in patients with node-negative and positive diseases, respectively.

In theory, for truly node-negative patients, greater number of ELN should not provide any survival benefit. However, in fact, several studies demonstrated that number of ELN was relevant to prognosis in node-negative patients.[4,13,16,18,41,42,50,51] Notably, the effect is more obvious in patients with node-negative disease vs positive disease.[18,42] The findings confirmed not only the existence of staged migration which is attributed to the understaging of patients with inadequate number of ELN, but also the understaging is frequent in node-negative disease. Therefore, in previous studies, the cut-off points of ELN for maximum survival difference in node-negative patients were considered as cutoff for correct staging.[4,16,42] Based on population-based and single-institutional studies, the optimal number of ELN was 11 for Ashfaq et al,[4] 15 for Tomlinson et al,[16] 12 for Slidell et al,[42] to accurately stage PDAC after surgery. However, these studies included patients underwent PD, DP, and all types of pancreatic resection. In this study, we found that the impact on survival of number of ELN in node-negative patients who underwent TP for PDAC. The effect was maximum when 19 or more LN were examined. In the multivariate analyses, patients with ≥19 ELN had 28.6% decrease in mortality compared to those with <19 ELN. Based on the analyses in node-negative disease, we suggested that a minimum of 19 lymph nodes should be examined to ensure correct staging in patients who underwent TP for PDAC. Although, more accurate staging is unlikely to have an impact on recommendation of adjuvant therapy for PDAC,[52] which is inconsistent with colon cancer.[53] However, more accurate staging may help in designing clinical trials evaluating the effect of adjuvant therapy and accurately estimate postoperative survival time.[12] Our study showed that only 24.2% of node-negative patients had ≥19 ELN, which suggested that the majority of patients who underwent TP for PDAC may not be accurately staged. The adequate number of ELN was considered as a quality measure in the treatment of PDAC.[12] As thus, both refined lymphadenectomy and careful pathological examination is important to increase the adequacy of lymph nodes. Fortunately, using SEER database, Marmor et al[29] demonstrated the number of ELN significantly increased in patients after pancreas cancer resection over time from a median of only 7 in 1990 to 15 in 2010. The observed improvement is likely due to an improved awareness of the need for adequate lymph nodes.

For node-positive patients, we evaluated the prognostic value of ELN, PLN, and LNR on OS in patients following TP for PDAC. The number of ELN was a significant prognostic factor not only by univariate analyses but also by multivariate analyses. In particular, prognosis worsened in patients with less than 13 ELN. This finding was consistent with other studies for patients underwent resection (e.g., all types of procedures collectively) for pancreatic cancer.[14,18,29] By using SEER database, Schwarz et al[18] reported survival of node-positive patients was significantly different at lymph node count cutoff levels of 10 or 15, always in favor of the subgroups with more number of ELN. More recently, Marmor et al[29] also used data from SEER database, found that 15 or more lymph nodes was associated with significantly improved survival for node-positive patients. In addition, the survival benefit in node-positive pancreatic cancer with more than 20 retrieved lymph nodes was confirmed in multivariable analyses as well as after propensity score adjustment.[14] The mechanism explaining the survival benefit in node-positive patients with greater number of ELN is probably that greater number of ELN is a proxy for high quality of cancer care,

high-volume clinical settings, or more strict selection of patients with less comorbidity.[18,34] For example, by using National Cancer Database, Contreras et al[41] found that patients with pancreatic cancer following PD at an academic hospital had a greater number of ELN than those at non-academic hospital.

Recently, the 7th edition AJCC staging system changed the N staging of PDAC from 2 categories to 3 categories in the 8th edition. Based on the latest nodal stage, we divided node-positive patients in to 2 subgroups, namely 1 to 3 PLN as well as more than or 4 PLN.[54] We found that patients with 1 to 3 PLN had better OS than those with 4 or more PLN. Although using various cutoffs for PLN, several studies have found that increased number of PLN is associated with poor prognosis in PDAC patients presenting with metastatic lymph nodes.[3,7,10–13,55,56] Especially, 2 of these studies, whose class of PLN was as same as our study, only focused on patients underwent PD or DP.[3,55] Our finding demonstrated that the 8th edition AJCC N stage was also valid to predict the prognosis of patients who underwent TP. Furthermore, when they were stratified by the number of ELN, the number of PLN emerged as heterogeneous prognostic factor for patients who underwent TP. For patients with low number of ELN, PLN failed to show any significant differences in survival. The predictive value of PLN was significantly improved in the subgroup with high number of ELN. The survival heterogeneity in different lymph node subgroups confirmed the predictive value of PLN were dependent on the number of ELN. Results from the present study was supported by the previous findings by Valsangkar et al.[50] However, this study included node-negative patients as the reference category.

LNR was considered as a potent prognostic factor after resection of pancreatic cancer.[9,28,50,57–61] However, due to almost all of these studies included node-negative patients in analyses, the predictive value of LNR may be confused. Thus, the present study only investigated the relationship between LNR and survival in node-positive patients and demonstrated that LNR had limited ability to predict prognosis by univariate analyses, moreover, was not associated with prognosis by multivariate analyses. The result was similar to findings in previous reports. With a survival analyses of 240 patients underwent DP for PDAC, Malleo et al[3] reported that the relationship between LNR and survival was not significant in node-positive patients both by univariate and multivariate analyses, even if limiting the analyses to node-positive patients with at least 20 ELN. Kang et al[47] reported that in a series of 227 node-positive patients undergoing PD, LNR was not significantly associated with OS by univariate and multivariate analyses. In addition, a study of 811 PDAC patients after PD demonstrated that LNR was significantly associated with survival by univariate analyses in node-positive patients. However, in the multivariate analyses, LNR was no longer an independent prognostic factor for survival.[13] The findings of these studies and ours may be due to the exclusion of node-negative patients from the analyses. In the univariate analyses, our study demonstrated that LNR was not a significant predictor of OS in node-positive patients with less than 13 ELN, whereas the survival difference was significant in those with at least 13 ELN. This finding indicated that although LNR is more likely to avoid the phenomenon of stage migration, the adequate number of ELN is still required to accurately assess the prognosis.[9,46]

With regard to the number of PLN and LNR, there is an ongoing debate over which is superior prognostic indicators. Our study demonstrated that the number of PLN was an independent

predictor of survival in the multivariate analyses within node-positive patients, but LNR was not. This finding suggested that the number of PLN was superior to LNR for prediction of survival in node-positive patients who underwent TP for PDAC, which was consistent with other studies.[3,10,11,13] However, several studies indicated that LNR was a more powerful prognostic factor than the number of PLN.[9,46,62,63] The reasons for these controversial findings might be that

1. most of these studies[46,62,63] that favored the LNR included node-negative patients, which may introduce bias due to the better survival of these patients in comparison with those with nodal metastases;
2. the studies that favored PLN showed an inverse tendency between the number of PLN and LNR, reflecting an underestimation of the extent of nodal metastases by LNR when higher number of LN was examined.[3,11,13]

In our study, when we further investigate node-positive patients with at least 13 ELN by multivariate analyses, the HR of PLN was increased relative to all node-positive patients. This result suggested that the predictive power of PLN strengthened in patients who underwent TP with higher number of ELN.

Several limitations of the present study should be taken into account. Firstly, both the extent of lymph nodes dissection and the quality of the pathological examination of TP specimen were heterogeneous across SEER regions, leading to variation in the number of lymph nodes evaluated from institution to institution.[64] Secondly, the exact location of PLN is unavailable from SEER database, which is an important lymph node parameter for assessing survival. Thirdly, there is no information on factors that are associated with the number of PLN and LNR, such as neoadjuvant chemotherapy.[65] However, the SEER database is an excellent source to investigate outcomes following a relatively rare surgery, such as TP.

In conclusion, our study indicates that the number of ELN has an impact on nodal status and survival in TP for PDAC, and demonstrates that greater number of ELN could enhance the reliability of nodal status. Moreover, our study has some clinical practice implications. Firstly, at least 19 lymph nodes should be removed to get better survival, when making a plan for TP. The threshold should be considered as an indicator for quality of surgical procedure. Secondly, for node-negative patients, a minimal number of 19 lymph nodes are adequate to minimize the effect of stage migration. Finally, for node-positive patients, the predictive value of PLN and LNR is dependent on the number of ELN. The number of PLN is superior to LNR in predicting survival after TP for node-positive patients, predominantly for those with high number of ELN.

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