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Prognostic value of examined lymph node count in patients with lymph node negative pancreatic head carcinoma: A single-center experience

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Ethics Committee Approval
The study was approved by Local Ethical Committee of Ondokuz Mayıs University School of Medicine (2012/799).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: One of the important prognostic factors for pancreatic cancer is the count of examined lymph nodes (ELN). The ratio of metastatic to ELNs reflects survival and is required for accurate staging. The survival effect of the count of ELNs in patients with an absence of metastatic lymph nodes is unclear. However, the single-center survival outcomes related to higher ELN count based on only lymph node negative-patients are limited to a few studies with controversial results. We aimed to present the single-center experience in survival outcomes based on ELN count in patients with lymph node-negative pancreatic head cancer after pancreaticoduodenectomy.

Methods: The data of 129 patients who underwent pancreaticoduodenectomy for pancreatic cancer from October 2011-December 2021 were analyzed. Among them, those who had metastatic lymph nodes, those who died from non-PC causes, died in the first 90 days postoperatively, or had missing follow-up data were excluded. Finally, 37 patients with negative lymph nodes who satisfied our criteria were included. The cut-off value for the examined lymph node count was 15, according to the minimum LN count recommended by the International Study Group of Pancreatic Surgery and the European Society for Medical Oncology for accurate staging. Thus, node-negative patients were divided into ELN <15 and ≥15 groups. The effect of <15 and ≥15 ELN count, tumor T stage, tumor grade, presence or absence of lymphovascular invasion and perineural invasion, and the resection margin status on cancer-specific survival were evaluated by univariate and multivariate survival analyses.

Results: The median age was 63 years (interquartile range (IQR) 55.50-75.0), and 17 (45.9%) were female. The median count of examined lymph nodes was 15. The median follow-up time was 36.5 months (IQR 21.4-56.2). The 1- 3- 5- years of cancer-specific survivals were 86.2%, 61.5%, 49.6%, respectively. Seventeen patients died due to pancreatic carcinoma during the follow-up period, and 12 out of 17 patients were in the <15 group. In multivariate analyses, the examined lymph node count <15 was a negative independent risk factor for cancer-specific survival (HR: 0.293; 95% CI, 0.096-0.897; *P*=0.032). The other negative independent risk factor was a positive resection margin (HR: 5.777; 95% CI, 1.436-23.245; *P*=0.014).

Conclusion: Patients with node-negative pancreatic head cancer with <15 ELN count, and positive resection margin have shorter survival, suggesting missed metastatic lymph nodes due to assessment of too few lymph nodes. At least a 15 ELN count is required to stratify the survival more accurately in these cohorts.

Keywords: Lymph node ratio, Regional lymphadenectomy, Whipple

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Introduction

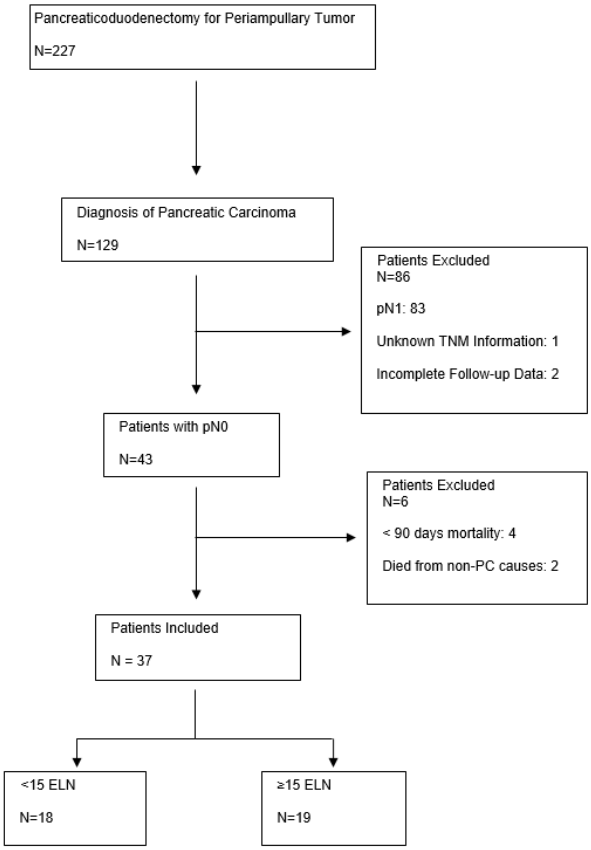
Pancreatic cancer (PC) has a poor prognosis, and it is the seventh worldwide in cancer-related deaths [1]. Although pancreatectomy is the only potentially curative treatment option for PC, overall survival is dismal [2]. Many factors, including curative resection, tumor size, lymph node (LN) status, location of positive LNs within the draining nodal basins, and locoregional invasion have prognostic significance after all types of pancreatic resections [3]. Of these, LN status is one of the most important factors, and LN metastasis is associated with worse survival and more frequent local recurrence. Accurate staging determined with LN status guides postoperative adjuvant treatment strategy [4]. In addition, the number of examined lymph nodes (ELNs) reflects survival; more ELN is associated with prolonged survival with or without the presence of metastatic lymph nodes [4-10]. Therefore, sufficient lymphadenectomy during surgery may improve pancreatic cancer survival without considering tumor localization. The objective of this study was to present the impact of ELN count on the survival of our patients who were LN negative (pN0) in the pathological examination after pancreaticoduodenectomy (PD) for PC.

Materials and methods

Patient selection and study variables

This study was approved by the research ethics committee of Ondokuz Mayıs University (2021/799). Informed consent was obtained from all patients. From October 2011-December 2021, the clinical data of 227 patients who underwent PD were prospectively recorded and retrospectively evaluated. Of these, 129 patients underwent PD for PC. We performed a standard Whipple procedure for all patients. During the surgery, regional lymphadenectomy was performed, as recommended by the International Study Group of Pancreatic Surgery (ISPGS) consensus report [10]. Pathological data were evaluated according to the 8th edition of the American Joint Committee on Cancer staging system [11]. A positive surgical margin (R1) was defined as tumor cells being closer than 1 mm to the surgical resection margin. Patients with one or more evaluated ELN in the pathology report were included in the study. Patients were excluded if they had metastatic LN, unknown TNM information, died from non-PC causes, died in postoperative first 90 days, or had incomplete follow-up data. Finally, 37 patients with pN0 satisfied our inclusion criteria. The data was evaluated in terms of age, gender, ELN count, tumor grade, lymphovascular-perineural invasion, surgical margin status, adjuvant treatment, and cancer-specific survival (CSS). The optimal cut-off value of ELN count was 15, based on the minimum LN count recommended by the International Study Group of Pancreatic Surgery (ISPGS) [10] and the European Society for Medical Oncology (ESMO) [12] for accurate staging. Then, the patients were evaluated in two groups: ELN <15 and ≥15 (Figure 1). CSS was identified as the time from the operation until death due to recurrent or metastatic disease. Patients still alive were censored. The last follow-up was on 30 November 2021.

Figure 1: ELN: Examined lymph node, PC: Pancreatic carcinoma



Statistical analysis

Survival curves were formed using the Kaplan-Meier method, and the log-rank test compared the differences between the curves. Cox proportional hazards regression models were both used to evaluate potential risk factors for survival outcomes and were used for multivariate analysis with the backward elimination method. Risk factors with a *P*-value <0.1 in univariate analysis were taken into account in the multivariate analysis. The hazard ratio (HR) and 95% confidence interval (CI) were calculated. All statistical tests were two-directional, and a *P*-value of <0.05 was considered significant. We evaluated the data using the IBM SPSS (version 26.0; IBM Corp., Armonk, New York, USA) statistical package program.

Results

The median age was 63 years (interquartile range (IQR) 55.50-75.0), and 17 (45.9%) were female. The median count of ELNs was 15 (IQR 11-26). The clinicopathological factors of the cohort were summarized in Table 1.

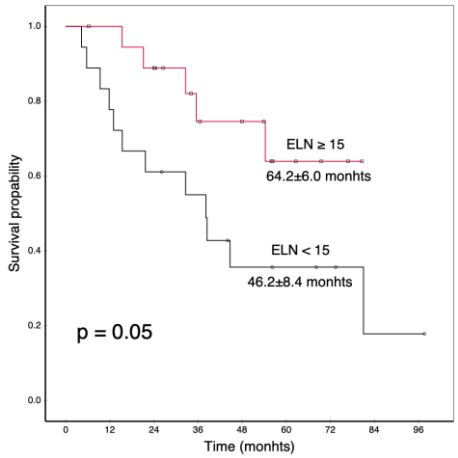
Table 1: Clinicopathological features of patients

Characteristics	Number of patients (n=37)	Percentage (%)
Age, ≥65	17	45.9
Gender, female	17	45.9
T stage		
I-II	23	62.2
III-IV	14	37.8
Grade		
Well/moderately differentiated	34	91.9
Poorly differentiated/undifferentiated	3	8.1
Lymphovascular invasion, yes	9	24.3
Perineural invasion, yes	18	48.6
Resection margin status, R1	4	10.8
ELN		
<15	18	48.6
≥15	19	51.4
Adjuvant chemotherapy, yes	29	78.4

ELN, examined lymph node; R1, positive resection margin

The median follow-up time was 36.5 months (IQR 21.4-56.2). The 1-3-5 years CSSs were 86.2%, 61.5%, 49.6%, respectively. The mean overall CSS survival was 57.8 (6.5) months, 46.2 (8.4) months for the <15 ELN group, and 64.2 (6.0) months for the ≥15 ELN group. Of the 37 patients with negative ELN, 17 died due to PC during the follow-up period, and 12 out of 17 patients were in the <15 ELN group. Patients with <15 ELN had shorter CSS than patients with ≥15 ELN (P=0.05) (Figure 2).

Figure 2: Kaplan Meier survival graph for Examined lymph node (ELN)



In multivariate analyses, ELN <15 (HR: 0.293; 95% CI: 0.096-0.897; P=0.032) and positive resection margin (HR: 5.777; 95% CI: 1.436-23.245; P=0.014) were negative independent risk factors for CSS (Table 2).

Table 2: Univariate and multivariate Cox proportional hazards regression analysis for CSS

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Gender,						
Female	Reference			—		
Male	0.888	0.332—2.374	0.813	—	—	—
Age,						
<65	Reference			—		
≥65	1.333	0.513—3.466	0.554	—	—	—
T stage,						
I—II	Reference			—		
III—IV	0.615	0.216—1.749	0.362	—	—	—
Grade						
Well/moderately differentiated	Reference			—		
Poorly differentiated/undifferentiated	2.105	0.477—9.292	0.326	—	—	—
LVI,						
No	Reference			Reference		
Yes	0.201	0.027—1.524	0.085	0.341	0.043—2.732	0.290
PNI,						
No	Reference			—		
Yes	2.122	0.803—5.613	0.121	—	—	—
Resection margin status						
R0	Reference			Reference		
R1	3.924	1.099—14.008	0.035	5.777	1.436—23.245	0.014
ELN,						
≥15	Reference			Reference		
<15	0.364	0.126—1.048	0.050	0.293	0.096—0.897	0.032
Adjuvant chemotherapy,						
Yes	Reference			—		
No	1.757	0.395—7.804	0.452	—	—	—

LVI: lymphovascular invasion, PNI: perineural invasion, ELN: examined lymph node, R1: positive resection margin, HR: hazard ratio, CI: confidence interval

Discussion

LN metastasis reflects cancer survival and guides treatment strategies after surgery [4, 6, 13, 14]. Sufficient lymphadenectomy provides accurate nodal staging and prevents stage migration [4, 8]. Higher lymph node ratio (i.e., the count of metastatic LN divided by the total count of ELN) indicates a poor prognosis for PC [4-9] as well as other gastrointestinal malignancies such as gastric [15] and colorectal [16] carcinoma. Patients with more ELNs also have a better prognosis with or without the presence of metastatic LNs [4-9]. Huebner et al. [4] found that patients with >11 ELNs had better overall survival than those with <11 (HR: 1.33, 95% CI: 1.1–1.7; P=0.001) after PD for pancreatic cancer in pN0 patients. Recently, ELN >11 [5], >12 [6], and >20 [17], respectively, were associated with better overall survival in pN0 patients after undergoing distal pancreatectomy for pancreatic body/tail cancer. Slidell et al. [7] reported the importance of more than 12 ELN in identifying stratified survival for all locations of PC patients. Tomlinson et al. [9] reported that patients who underwent PD with ≥15 ELN had better overall survival than those with <15 ELN in pN0 patients. Similarly, the current study demonstrated that ≥ 15 ELN was associated with improved survival. We think complete LN dissection and detailed pathological evaluation are required to improve CSS for PC.

We found that the count of ELN was an independent prognostic factor for CSS in our cohort. Increased ELN count was reflected in improved survival in pN0 PC patients. In this study, survival rates of 1, 3, 5 years, respectively, were better than in population-based studies [4-9]. This result may be related to the small number of patients, which was the main limitation of our study. Lidsky et al. [18] reported that high-volume medical centers have higher ELN counts and improved survival. Fortunately, the median count of ELN (15, IQR 11-26) in this cohort was similar to those presented in the critical studies [6, 7].

Some scenarios may explain how an increased ELN count is associated with improved survival in pN0 patients and include the quality of surgery and pathological evaluation. False-positive pN0 patients are less likely to be observed, targeted adjuvant treatment is distinguished with accurate staging [6]. Improved survival after more LN examination is due to the understaging of patients with insufficient lymph nodes evaluated [9]. The count of ELN after PD may correlate with the type of specimen, the extent of surgery, regional nodes present in a given individual, and the technique of the pathologist [9]. It may be advantageous for this study to consist of patients who underwent surgery in a single center with a single team and the same surgical technique.

Another important issue is the role of extended lymphadenectomy during PD. Extended lymphadenectomy is related to severe postoperative complications and prolonged hospital stay [2]. In addition, no survival difference between extended lymphadenectomy and regional lymphadenectomy was presented before [19, 20]. Also, ISPGS [10] and ESMO [12] consensus reports do not recommend extended lymphadenectomy. Considering these, we performed regional lymphadenectomy on all patients, and we achieved an acceptable count of ELN and survival results.

Another negative independent risk factor in this study was the R1 resection margin, observed in only 4 patients (HR: 5.777; 95% CI: 1.436-23.245). R1 resection is associated with reduced overall survival for PC [21]. However, R1 resection

margin rates vary distinctly in the literature [22, 23]. Standardized pathological resection margin evaluation is required to stratify survival accurately [21]. According to this study, R1 resection may be more critical for survival in the pN0 cohort.

Limitations

This study had several limitations. The main limitations were its retrospective nature and the small number of patients. Others were the fact that adjuvant protocols could not be included, that different pathologists evaluated the specimens, the lymph node stations were not analyzed in detail, and disease-free survival could not be assessed. However, regional lymphadenectomy was performed by a single center and the same team, in contrast to many extensive studies, wherein the strength of our study lies [6, 17].

Conclusion

Patients with node-negative pancreatic head cancer with <15 ELN count, and positive resection margin have shorter survival, suggesting missed metastatic lymph nodes due to assessment of too few lymph nodes. At least a 15 ELN count is required to stratify the survival more accurately in these cohorts. During pancreaticoduodenectomy, complete lymphadenectomy should be performed and yield a verified negative surgical margin.

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