Pancreatic Adenocarcinoma

Number of Positive Nodes Allows to Distinguish Several N Categories

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Objective: To determine the prognostic value of PLN and LNR based on a large series with standardized lymphadenectomy and pathological workup.

Background: Lymph node (LN) involvement is a major prognostic factor in pancreatic adenocarcinoma. However, the distinction N0/N1 is not sufficient to accurately predict prognosis. To improve prognostic accuracy in N1 tumors, different LN parameters have been tested. Previous studies were based on series with variable numbers of examined lymph nodes (ELN) and came to inconsistent conclusions as to the value of the number of positive lymph nodes (PLN) and the lymph node ratio (LNR).

Methods: 811 patients who underwent pancreatoduodenectomy for pancreatic adenocarcinoma between October 2001 and June 2012 were identified from a prospective database. Clinicopathological parameters included LN status (N0/N1), ELN, PLN, and LNR. Univariate and multivariate survival analyses were performed.

Results: The median number of ELN was 24 (interquartile range: 18–32). By univariate analysis, both PLN and LNR were significantly associated with survival in N1 tumors. However, by multivariate analysis, only the number of PLN was confirmed as independent predictor of survival. Median survival in patients with only 1 PLN was 31.1 months and comparable to the survival in N0 (33.2 months). With increasing numbers of PLN median survival significantly decreased (2–3 PLN: 26.1 months, 4–7 PLN: 21.9 months, ≥8 PLN: 18.3 months, $P < 0.0001$).

Conclusions: This study demonstrates that, based on high numbers of ELN, PLN is superior to LNR in predicting survival and allows to distinguish several N-categories that improve prognostic accuracy in LN-positive resectable pancreatic adenocarcinoma.

Keywords: lymph node involvement, lymph node ratio, number of positive nodes, pancreatic cancer, pancreatoduodenectomy, staging, survival

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Pancreatic adenocarcinoma is the fourth leading cause of cancer-related death in the Western world.[1] Complete resection in combination with systemic (usually adjuvant) chemotherapy offers the only chance of a potential cure. However, even after resection and adjuvant chemotherapy, the prognosis is limited with a median survival of 25 to 30 months and a 5-year survival rate of around 20%.[1,2] In large retrospective studies, several important prognostic parameters have been identified.[3] Lymph node (LN) involvement has consistently been characterized as one of the strongest predictors of survival after resection of pancreatic adenocarcinoma. However, in contrast to most other gastrointestinal cancers such as colon or gastric cancer, there are not sufficient data to allow for the distinction of several LN-positive categories (eg, N1, N2, N3). Therefore, the current TNM staging system for pancreatic adenocarcinoma only distinguishes N0: "no involvement of regional LN" and N1: "regional LN involved."[4,5] Consequently, TNM-based clinical American Joint Committee on Cancer (AJCC) staging is inaccurate and summarizes patients with different prognoses into the same stage groups.[3,4] Several large population-wide studies based on the Surveillance, Epidemiology, and End Results Registry (SEER) data set, as well as single institutional studies, have investigated the required number of examined lymph nodes (ELN) for correct staging of N0[6,7] or the prognostic value of the number of positive lymph nodes (PLN) and the lymph node ratio (LNR: PLN divided by ELN).[8–23] These studies report different numbers varying between 10 and 16, to be adequate and come to differing conclusions about the prognostic values of PLN and LNR. By simple mathematics, both PLN and LNR are highly dependent on the number of ELN, which is influenced by individual differences in the actual number of LN, the extent of lymphadenectomy, and the pathological workup of the resected specimen.

The SEER-based studies rely on very heterogeneous data with nonstandardized lymphadenectomy and pathologic workup, resulting in low numbers of ELN (median: 7). Many single-institutional studies are based on data collected over several decades including cases with low numbers of ELN from earlier years.

We aimed to determine the prognostic value of PLN and LNR based on a single high-volume center series with standardized lymphadenectomy and pathological workup.

PATIENTS AND METHODS

This study was approved by the local ethics committee and is based on a prospective database with 2289 consecutive pancreatic resections performed for pancreatic carcinoma at our institution between October 2001 and June 2012. Because LN parameters may depend on the type of resection, we decided to include only patients who underwent partial pancreatoduodenectomy in the current analysis, and to exclude patients with left resection, total pancreatectomy, and other resections. A total of 1008 consecutive patients who underwent a partial pancreatoduodenectomy for pancreatic adenocarcinoma were identified. As overall survival was the main outcome determinant, patients belonging to distinct subgroups with exceptionally favorable (pTis, n = 26) or poor outcomes (pM1, n = 61; R2-resections, n = 44) were excluded. Patients with hospital mortality (n = 33, 3.68% of the remaining 897 patients, 30-day mortality: n = 24, 2.68%), patients with missing values regarding LN numbers (n = 3), and patients lost to follow up (n = 30, 3.48%) were also excluded. This resulted in a cohort of 811 patients for the final analysis.

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Surgical Approach, Pathologic Workup, and Multimodal Treatment

At our center, we follow a standardized surgical approach. In patients with suspected malignancy and a resectable mass in the pancreatic head, a standard lymphadenectomy is performed that includes peripancreatic LN and a complete clearance of LN in the hepatoduodenal ligament along the portal vein and hepatic artery to the right side of the celiac trunk, as well as on the right side of the upper aspect of the superior mesenteric artery and vein. Interaortocaval LN are only resected if suspicious. Cases with positive interaortocaval LN are considered pM1 and were excluded from the main analysis. Except for interaortocaval LN, the LN locations were not routinely marked and information about the location of positive regional LN was not available retrospectively for this study.

In a standardized pathologic workup, all resected LN were completely embedded as previously described.[24,25] Labeling of the LN was performed according to the International Union Against Cancer TNM LN grouping.[5] Determination of the R status was based on a refined pathological workup and stricter definition of R1 (distance of the tumor from the resection margin of $\leq$1 mm) resulting in R1 status in up to 70% of resections for pancreatic cancer as previously demonstrated.[24,25]

We aim for resection and adjuvant chemotherapy in all patients with resectable pancreatic adenocarcinoma. The study includes 80 (9.7%) patients with primarily irresectable tumors who received neoadjuvant chemoradiation or chemotherapy. Adjuvant/postoperative therapy was given in 83.8% of patients (Table 1).

Data Acquisition

Clinicopathological data were recorded prospectively in our database and included patient age at diagnosis; sex; American Society of Anesthesiologists (ASA) score; tumor type; tumor site; tumor diameter; TNM stages; tumor grade; type of surgery; neoadjuvant therapy; type of operation; and overall, surgical, and nonsurgical morbidity. LN variables recorded were number of ELN, number of PLN, and LNR calculated by dividing PLN by ELN.

Follow-up

All patients were followed until their latest oncologic follow-up examination or until death. Follow-up data were acquired in our outpatient care unit, by external oncologic follow-up examinations, or by an additional telephonic interview of patients, relatives, or general practitioners in spring 2013 and included the follow-up status and the administration of adjuvant therapy. In the case of death, the date of death was recorded. Median follow-up of 291 patients alive at last contact was 29.7 months (interquartile range: 19.1–47.4 months). Detailed data on follow-up of dead patients and survivors in different groups of LN involvement are provided in Supplemental Table 1, available at http://links.lww.com/SLA/A582.

Statistical Analysis

SAS software (Release 9.1; SAS Institute, Inc, Cary, NC) was used. The quantitative parameters of age, tumor diameter, ELN, PLN, and LNR are expressed as medians with their interquartile range. The nonparametric Mann-Whitney *U* test was used to compare these quantitative parameters between N0 and N1 tumors. Categorical parameters are presented as frequencies and compared between N0 and N1 tumors using the χ^2 test, if appropriate, or the Fisher exact test. The Spearman correlation coefficient, *r*, with its corresponding *P* value was used to examine the relationship of ELN and PLN. In all graphs, overall survival is defined as the time from the date of the operation to either death from any cause or last follow-up. The survival rates were estimated using the Kaplan-Meier method. Patients alive at the last follow-up were censored and marked in the figures (|). 5-year survival rates and the median survival times are presented. The log-rank test was used to compare survival curves of subgroups. Univariate and multivariate proportional hazard regression (Cox model) analyses of the prognostic value of the parameters ELN, PLN, and LNR were performed with regard to the parameters grading, neoadjuvant therapy, adjuvant therapy, and R status. These analyses were performed separately for N0 and N1 stages. Two-sided *P* values were computed, and a difference was considered statistically significant at $P \leq 0.05$.

RESULTS

Patient and tumor characteristics are shown in Table 1 for all patients and separately for patients staged N0 or N1. Overall, LN-negative tumors were significantly smaller in diameter and T stage and were more frequent in female patients and in patients who had received neoadjuvant therapy. R0 resection was achieved more frequently in N0 tumors. In N0 cases, the median number of ELN was significantly lower than in N1 tumors (20 vs 25 ELN).

Overall and surgical morbidity, including minor complication such as wound infections and Grade-A Delayed Gastric Emptying, was 51.1% and 30.7%, respectively.

Median survival in 166 patients staged N0 was 33.2 months versus 23.6 months in 645 patients with N1 tumors ($P = 0.0006$). Five-year survival was 31.7% in N0 versus 17.4% in N1 tumors. Thus, as known from the literature, LN status clearly represents an important prognostic parameter and distinguishes 2 subgroups with different prognoses. Therefore, the survival analyses of LN parameters are performed separately for N0 and N1 tumors in the following. In contrast to most previous studies that included N0 as the reference category, the univariate and multivariate survival analyses of LNR and PLN presented here are calculated within the N1 subgroup.

N0 Tumors

The only LN variable to be independently associated with survival in N0 tumors by multivariate analysis was a number of ELN less than or equal to 10 (Table 2). In patients with 10 or less ELN, median survival was 25.7 months and the 5-year survival rate was 17.9%, compared with 34.5 months median survival and a 5-year survival rate of 34.4% in patients with more than 10 ELN ($P = 0.0634$ by univariate analysis). If more than 10 LN were examined, a further increase in the number of ELN was not associated with a further gain in survival (data not shown). Tumor differentiation and neoadjuvant therapy were independently associated with survival. In contrast, adjuvant therapy was not significantly associated with survival in N0 tumors. Perioperative morbidity was not associated with survival ($P = 0.5501$).

N1 Tumors

The multivariate survival analysis in N1 tumors (Table 3) revealed that a number of ELN less than or equal to 10 was significantly associated with shorter survival times also in LN-positive tumors (ELN $\leq$ 10: 21.3 months median survival, 0% 5-year survival vs ELN > 10: 23.8 months median survival, 18.7% 5-year survival; $P = 0.0612$ by univariate analysis). Similar to N0 tumors, a further increase in the number of ELN was not associated with improved survival (data not shown). Tumor differentiation was again significantly associated with survival. In N1 tumors neoadjuvant therapy was significantly associated with shorter survival, whereas the administration of adjuvant therapy was significantly associated with longer

TABLE 1. Characteristics

Parameter	Total	N Negative	N Positive	*P*
Sex				0.0086
Male	455 (56.1%)	78 (47.0%)	377 (58.4%)	
Female	356 (43.9%)	88 (53.0%)	268 (41.5%)	
Age, y*	65.8 (58.5–71.7)	65.7 (56.4–72.8)	65.8 (58.7–71.5)	0.9242
ASA score				0.9790
ASA I	17 (2.2%)	3 (1.9%)	14 (2.3%)	
ASA II	426 (54.8%)	88 (54.3%)	338 (54.9%)	
ASA III	333 (42.8%)	71 (43.8%)	262 (42.5%)	
ASA IV	2 (0.3%)	0 (0%)	2 (0.3%)	
Missing	33	4	29	
Neoadjuvant therapy	80 (9.7%)	37 (22.3%)	43 (6.7%)	<0.0001
Adjuvant therapy	642 (83.8%)	118 (73.8%)	524 (86.5%)	0.0001
Type of surgery				0.2600
clPD	124 (15.3%)	26 (15.7%)	98 (15.2%)	
ppPD	661 (81.5%)	138 (83.1%)	523 (81.1%)	
prPD	26 (3.4%)	2 (1.2%)	24 (3.7%)	
Additional colon resection	37 (4.4%)	6 (3.6%)	31 (4.8%)	0.6768
Additional artery resection	13 (1.6%)	4 (2.4%)	9 (1.4%)	0.3158
Additional venous resection	197 (24.3%)	28 (16.9%)	169 (26.2%)	0.0124
Histology				<0.0001
Pancreatic ductal adenocarcinoma	764 (91.3%)	145 (87.3%)	619 (96.0%)	
Malignant IPMN	27 (3.3%)	17 (10.2%)	10 (1.6%)	
Undifferentiated pancreatic carcinoma	6 (0.7%)	2 (1.2%)	4 (0.6%)	
Adenosquamous carcinoma	14 (1.7%)	2 (1.2%)	12 (1.9%)	
Tumor diameter, cm*	3 (2.5–4.0)	2.5 (2.0–3.0)	3.2 (2.5–4.0)	<0.0001
T stage				<0.0001
T1	19 (2.3%)	18 (10.8%)	1 (0.2%)	
T2	11 (1.4%)	4 (2.4%)	7 (1.1%)	
T3	773 (95.3%)	143 (86.1%)	630 (97.7%)	
T4	8 (1.0%)	1 (0.6%)	7 (1.1%)	
Median no. ELN, n*	24 (18–32)	20 (14–28)	25 (19–33)	<0.0001
No. ELN, n				<0.0001
≤10	42 (5.2%)	21 (12.7%)	21 (3.3%)	
11–15	87 (10.7%)	28 (16.9%)	59 (9.1%)	
16–20	150 (18.5%)	36 (21.7%)	114 (21.4%)	
21–25	167 (20.6%)	29 (17.5%)	138 (8.2%)	
26–30	121 (14.9%)	19 (11.4%)	102 (15.8%)	
>30	244 (30.1%)	33 (19.9%)	211 (32.7%)	
No. PLN, n*	3 (1–7)	0 (0–0)	4 (2–8)	<0.0001
LNR*	0.13 (0.04–0.27)	0 (0–0)	0.17 (0.08–0.31)	<0.0001
Grading				0.0641
G1	26 (3.4%)	9 (6.4%)	17 (2.7%)	
G2	505 (65.2%)	92 (65.7%)	413 (65.1%)	
G3	243 (31.4%)	39 (27.9%)	204 (32.2%)	
Missing	37	26	11	
R classification				<0.0001
R0	341 (42.0%)	106 (63.9%)	235 (36.4%)	
R1	470 (58.0%)	60 (36.1%)	410 (63.6%)	

*Median and interquartile range.
cl indicates classical; pp, pylorus preserving; pr, pylorus resecting; G, tumor grading according to;[5] IPMN, intraductal papillary mucinous neoplasia; PD, pancreatoduodenectomy.

survival. Perioperative morbidity was not associated with survival ($P = 0.6131$).

By univariate analysis, both the number of PLN and the LNR were significantly associated with survival and allowed to distinguish subgroups with different survival times (Fig. 1. Note: N0 cases are included for comparison in the figures, but N0 was not used as reference category in the uni- and multivariate analyses). Importantly, by multivariate analysis, only the number of PLN, but not the LNR, was confirmed as an independent factor significantly associated with survival (Table 3). In LN-positive cases, patients with only 1 PLN had the longest median survival (31.1 months). With increasing numbers of PLN median survival significantly decreased (2–3 PLN: 26.1 months, 4–7 PLN: 21.9 months, ≥8 PLN: 18.3 months, $P < 0.0001$).

Distinction of Several Prognostic Categories of LN Involvement by PLN

To further assess the prognostic impact of PLN, and the possibility to distinguish several LN-positive categories according to the number of PLN as in many other malignancies, LN-positive cases were divided in 3 groups and their survival was compared to N0

TABLE 2. Multivariate Survival Analysis of 135 N0 Tumors (Missing Values N = 31)

Parameter	HR	95% CI	*P*
ELN ≤10 vs >10	1.99	1.05–3.79	0.0361
Neoadjuvant therapy, yes vs no	1.93	1.04–3.56	0.0361
G3 vs G1/2	1.67	1.03–2.71	0.0378
Not included:			
R1 vs R0			0.6140
ELN ≤20 vs >20			0.4145
Adjuvant chemotherapy, yes vs no			0.1637

CI indicates confidence interval; HR, hazards ratio.

TABLE 3. Multivariate Survival Analysis of 597 N1 Tumors (Missing Values N = 48)

Parameter	HR	95% CI	*P*
ELN ≤ 10 vs >10	1.80	1.09–2.97	0.0219
Neoadjuvant therapy, yes vs no	1.76	1.17–2.64	0.0065
Adjuvant chemotherapy, yes vs no	0.45	0.34–0.61	<0.0001
G3 vs G1/2	1.65	1.32–2.06	<0.0001
PLN 2/3 vs 1	1.40	1.00–1.96	0.0496
PLN 4–7 vs 1	1.75	1.26–2.44	0.0010
PLN ≥ 8 vs 1	2.26	1.61–3.16	<0.0001
Not included:			
R1 vs R0			0.7053
LNR >0.2–0.4			0.8675
LNR >0.4			0.8835
ELN ≤20 vs >20			0.5562

CI indicates confidence interval; HR, hazards ratio.

tumors (0 PLN) (Fig. 1a). In this analysis, survival in 1 PLN does not detectably differ from survival in the N0 group, whereas both median and 5-year survival in the other LN-positive groups significantly decrease with higher numbers of PLN. Survival in the subgroup with 8 or more PLN was almost as poor as that observed in M1 disease due to positive interaortocaval LN (n = 25 patients excluded from the main analysis; 13.6 months median survival; 9.9% 5-year survival). Thus, the number of PLN allows to clearly distinguish 3 categories of LN-positive groups with considerably different prognoses that almost span in the range between N0 and M1 (due to positive extraregional LN) but are currently all staged N1 according to the current TNM staging system and are classified as stage IIb in the clinical staging systems.[5]

Overall morbidity ranged between 46.5% (1 PLN) and 53.4% (≥8 PLN, $P = 0.6756$) and surgical morbidity ranged between 27.2% (1 PLN) and 28.6% (≥8 PLN, $P = 0.6809$) without significant differences between PLN groups. Perioperative morbidity was not associated with survival in the different PLN groups.

The administration of adjuvant chemotherapy appeared to be associated with improved survival in all PLN groups. Interestingly, this association was only significant in high PLN groups with the highest effect in PLN more than or equal to 8 (Table 4).

Accuracy of PLN and LNR Depends on the Number of ELN

The presented data are based on a high median number of ELN compared to most of the previous studies (Table 5). The adequate number of ELN for accurate staging using LN variables remains an important question.

In our series, the number of cases with low numbers of ELN does not allow to assess the adequate number of ELN to accurately stage N0 based on a survival analysis. To assess if the lack in a difference in survival between N0 and cases with only 1PLN was due to "understaging" in the N0 group, we performed separate analyses after exclusion of cases with less than 10 and less than 15 ELN, but still found no difference in survival between N0 and 1 PLN.

Furthermore, we analyzed the frequency of N0 cases and of cases with different numbers of PLN and different LNR in the context of the number of ELN (Fig. 2). On the basis of the assumption that the actual nodal involvement and the number of ELN are independent of one another, if lymphadenectomy and pathologic workup are standardized, the frequency distribution of PLN and LNR should theoretically remain stable with increasing numbers of ELN. In contrast, the comparison of frequencies of different categories of nodal involvement according to PLN (Fig. 2a) and LNR (Fig. 2b) reveals potential reasons for the superiority of PLN in higher numbers of ELN. In LN-positive cases, a regression analysis revealed that the number of PLN significantly correlates with the number of ELN ($r = 0.3616$, $P < 0.0001$), that is, if more LN are examined, more PLN are identified. Consequently, N0 and lower numbers of PLN are more frequently found in cases with lower numbers of ELN, especially if less than 20 LN are examined. With increasing numbers of ELN the portion of cases with higher numbers of PLN increases (Fig. 2a) whereas the portion of cases with higher LNR decreases (Fig. 2b), although more involved LN are identified. This inverse trend of PLN and LNR reflects an underestimation of the extent of nodal involvement by LNR in higher numbers of ELN and may explain why the number of PLN is the superior prognostic marker.

In the literature, there is conflicting data as to the prognostic values of the different LN variables. Table 5 gives an overview of the findings of previous publications and the present series in the context of the number of ELN. Studies with lower numbers of ELN tend to favor LNR as the best prognostic parameters. In the only 2 studies with more than 20 ELN (Murakami et al[17] and this study), PLN was superior to LNR and was confirmed as an independent factor associated with survival by multivariate analysis.

DISCUSSION

This study assesses the value of parameters of LN involvement for the prediction of survival in pancreatic ductal adenocarcinoma. It has become clear from many studies that the current TNM-based clinical AJCC staging system alone is not sufficient to predict survival in LN-positive resectable pancreatic cancer. We have previously shown that a scoring system based on independent positive and negative predictors is able to identify subgroups with significantly different survival times within the predominant AJCC IIA and IIB stage groups.[3] In this previous analysis, multiple factors described as predictors of survival in the literature were included and LNR was one of the independent predictors identified by multivariate analysis.[3] The number of PLN was not analyzed because data from the literature did not sufficiently support its prognostic value. In contrast to pancreatic cancer, there is compelling evidence for most other gastrointestinal cancers that the number of PLN is both an easily accessible and highly reliable predictor of survival and this is used to distinguish different categories of LN involvement with prognostic and therapeutic relevance in these cancers.[5] For pancreatic cancer such data were lacking until now. Of multiple studies analyzing the value of different LN parameters, Table 5 summarizes studies with more than 100 patients assessing LNR and/or PLN after resection of pancreatic adenocarcinoma. Most of these studies found LNR to be predictive. However, they included N0 cases as the reference category (total LNR), that

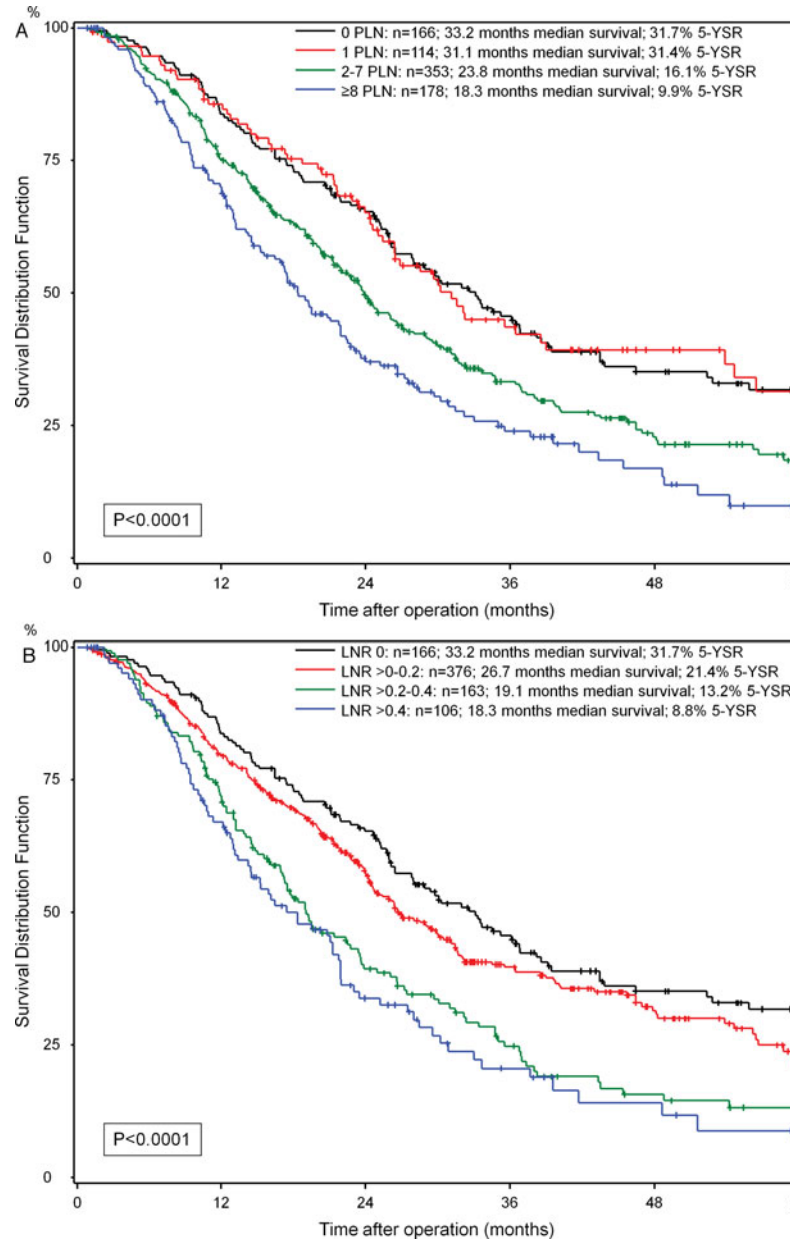

FIGURE 1. Overall survival of 811 patients with pancreatic adenocarcinoma after pancreatoduodenectomy. A, Survival distribution in N0 cases and in different LN-positive subgroups according to the number of PLN. Note that there is no survival difference between N0 and 1PLN, but a considerable survival difference among 1PLN, 2–7 PLN, and ≥8 PLN. B, Survival distribution in N0 cases and in different LN-positive subgroups according to the LNR. Although LNR is able to distinguish different subgroups of LN-positive cases, the discriminatory power is lower than by PLN. 5YSR indicates 5-year survival rate.

TABLE 4. Adjuvant Therapy and Survival in Different PLN Categories

	Adjuvant Chemotherapy			No Adjuvant Chemotherapy				
PLN	No.	Median Survival, mo	95% CI	No.	Median Survival, mo	95% CI	Survival Difference, mo	*P*
1	100	32.1	26.4–54.6	14	24.3	14.2–53.8	7.8	0.1628
2–3	141	28	23.6–40.1	20	17.9	10.3–36.5	10.1	0.2333
4–7	146	23.8	20.7–28.9	23	14.9	10.3–27.4	8.9	0.0261
8	136	21.9	18.3–26.6	25	8.3	4.8–12.4	13.6	<0.0001

CI indicates confidence interval.

TABLE 5. Studies Assessing the Prognostic Value of LNR and/or PLN (Inclusion Criteria: Pancreatic Adenocarcinoma, n > 100, Median Number of ELN Reported)

						Prognostic Value of Different LN Parameters					
Study	Setting Period	Included Cases	n	Median Survival, mo	ELN, Median	N Status	Total LNR	LNR-N1	Total PLN	PLN-N1	Cutoff Values/Best Parameters
Berger 2004	Single center 1987–2002	Adenocarcinoma Head (PD)	128	N0: 23 N1: NR	17	NR	++	NR	NR	NR	LNR: 0, 0–0.15, >0.15
Pawlik 2007	Single center 1995–2005	Adenocarcinoma Head (PD)	905	N0: 25.3 N1: 16.5	17	(+)	++	NR	NR	NR	LNR: 0, >0–0.2, >0.2–0.4, >0.4
House 2007	Single center 1995–2005	Adenocarcinoma Any location	696	N0: 27 N1: 16	17	++	(+)	(+)	(+)	(+)	LNR, PLN not included in multivariate analyses
Slidell 2008	SEER 1988–2003	Adenocarcinoma Any location	3868	N0: 18 N1: 12	7	++	++	ns	++	NR	LNR: 0, >0–0.2, >0.2–0.4, >0.4 Best LN parameter: LNR
Smith 2008	Single center 1997–2006	Adenocarcinoma Head (PD)	109	N0: 24.1 N1: 13.3	17	(+)	++	NR	NR	NR	LNR: cutoff values NR
Riediger 2009	Single center 1994–2006	Adenocarcinoma Any location	182	18 all	16	(+)	++	++	(+)	NR	LNR: <0.2, ≥0.2 and <0.3, ≥0.2 PLN: 0 or 1 vs. ≥2
Murakami 2010	Single center 1994–2009	Adenocarcinoma Any location	119	14.1 (all)	28	++	(+)	ns	++	(+)	LNR: <0.1, ≥0.1 and <0.2, ≥0.2 PLN: 0 or 1 vs. ≥2 Best LN parameter: PLN
Konstantinidis 2010	Single center 1993–2008	Adenocarcinoma Any location	517	N0: 30.8 N1: 16.4	13	(+)	++	NR	(+)	NR	LNR: <0.2, ≥0.2 PLN: 0, 1, 2, >2
Showalter 2011	Multicenter 1998–2002	Adenocarcinoma Any location	445	NR	9/11	++	++	NR	++	ns	LNR: 0 to ≤0.15, >0.15–≤0.33, >0.33 PLN: 0, 1–3, >3
Hartwig 2011	Single center 2001–2009	Adenocarcinoma Any location	1071	NR	22	(+)	++	NR	NR	NR	LNR: ≤0.2, >0.2
Robinson 2012	Single center 2002–2009	Adenocarcinoma Head (PD)	134	N0: 56% 5YSR N1:12.9% 5YSR	19	(+)	++	NR	NR	NR	LNR: ≤0.15, >0.15
Opfermann 2012	SEER 1998–2006	Adenocarcinoma Any location	3314	17 (all)	10	NR	++	NR	(+)	NR	LNR: >0–<0.2, 0.2–0.4, >0.4
Huebner 2012	Single center 1981–2007	Adenocarcinoma Any location	499	N0: 23.1 N1: 19.0	10	(+)	++	++	++	++	LNR: <0.17, ≥0.17 PLN: 0, ≤2, >2 Best LN parameter: LNR
Valsangkar 2013	1: SEER 1988–2009	Adenocarcinoma Any location	14907	N0: 22 N1: 14	8	(+)	++ if ≥ 13 ELN	NR	++	NR	LNR: 0, <0.2, 0.2–0.3, >0.3 PLN: 0, 1, 2, ≥3
	2: MGH 1988–2009		902	N0: 37 N1: 17	13	++	++ if ≥ 17 ELN	NR	++	NR	Best LN parameter: LNR
This study	Single center 2001–2012	Adenocarcinoma Head (PD)	811	N0: 30.1 N1: 23.4	24	(+)	(+)	(+)	(+)	++	LNR: >0–0.2, >0.2–0.4, >0,4 PLN: 1, 2–3, 4–7, ≥8 Best LN parameter: PLN

N status, nodal status; 5YSR, 5-year survival rate; (+), significant in univariate analysis; ++, significant in multivariate analysis; ns, not significant; NR, not reported; total LNR/PLN: reference category: N0, LNR/PLN-N1: within N1.

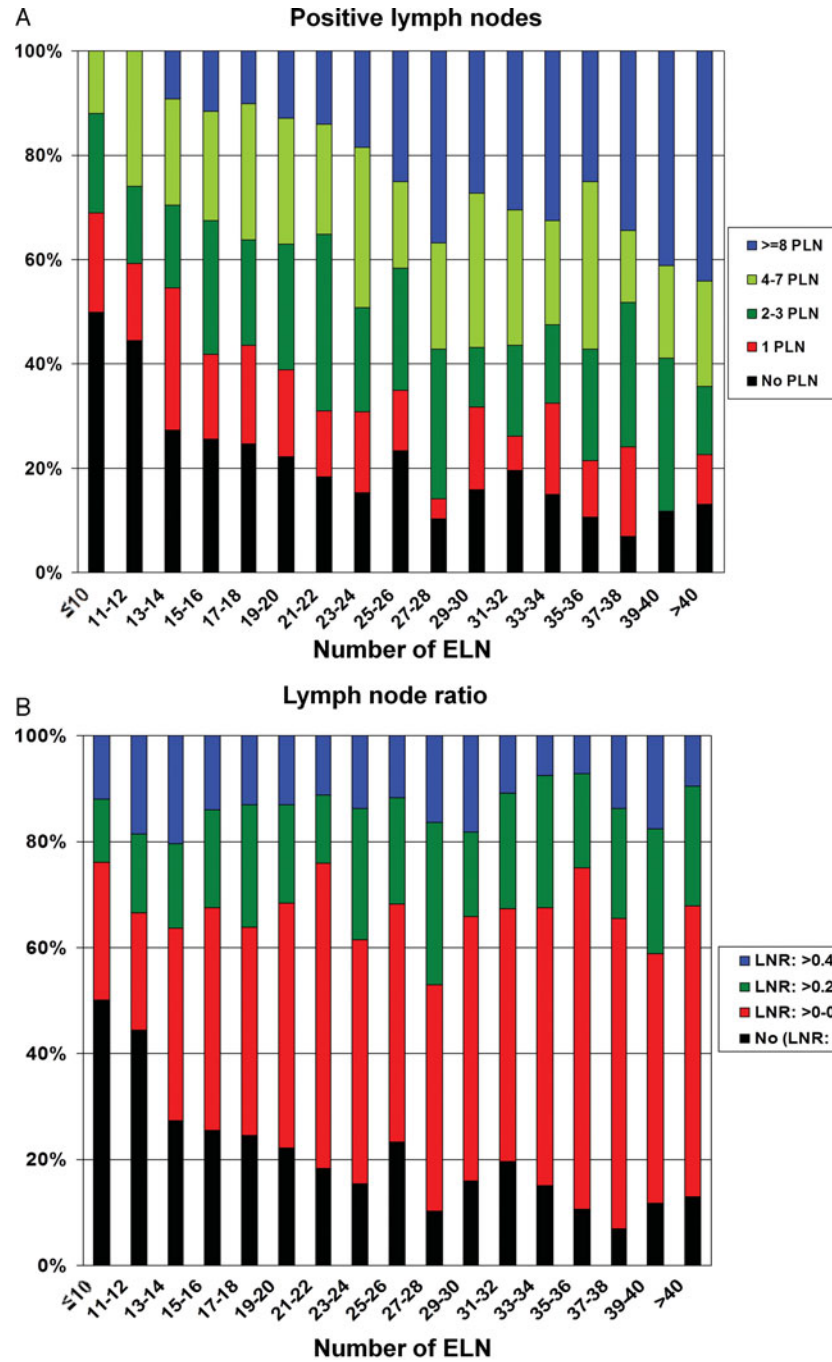

FIGURE 2. Influence of the number of ELN on PLN and LNR. Frequency distribution of subgroups with different extent of nodal involvement determined in the same data sets by PLN (A) and LNR (B) in the context of the number of ELN. With increasing number of ELN, the portion of cases with high numbers of PLN increases (A), while the portion of cases with high LNR decreases (B), resulting in a relative underestimation of the extent of nodal involvement by LNR in cases with high numbers of ELN.

is, the LNR was not assessed as a prognostic factor *within* the group of N1 tumors (LNR-N1), which is necessary to assess its value to distinguish prognostic subgroups of LN-positive tumors. LNR-N1 was described as an independent predictor in only 2 studies[15,20] and in these studies it was superior to the number of PLN. The number of PLN was found to be superior to LNR in only 1 previous study; however, PLN was only an independent predictor of survival if N0 cases were included (total PLN), but not within N1 (PLN-N1).[17] In this study, we for the first time demonstrate that (1) LNR-N1 is the superior LN variable to predict survival and (2) it is even able to distinguish several categories of LN involvement within LN-positive tumors (Fig. 1). On the basis of high numbers of ELN, only PLN but not LNR is confirmed as an independent predictor of survival by multivariate analysis within N1 cases (Table 3).

The number of ELN seems to be the predominant reason for the differences between the present findings and previous studies: Valsangkar et al[23] demonstrated that the predictive values of both PLN and LNR depend on the number of ELN, but in PLN, the effect of low numbers of ELN is much more pronounced. In this study, the frequency distribution of LN variables in groups with different numbers of ELN (Fig. 2) reveals that, compared to PLN, the LNR underestimates the extent of nodal involvement in high numbers of

ELN. Thus, PLN becomes superior with higher numbers of ELN. This is mirrored in the overview of previous studies (Table 5): Only the studies with more than 20 ELN favor PLN over LNR, whereas in all other studies that analyze both parameters, LNR is superior to PLN. It has been suggested previously that, on the basis of survival data, 15 ELN are required to accurately stage N0 tumors.[7] It is not surprising that more ELN may be necessary to accurately distinguish different categories within N1 tumors or to distinguish N0 from cases with only 1 PLN. However, the number of ELN that is necessary to adequately predict prognosis by PLN remains to be determined. Recently, the International Study Group for Pancreatic Surgery issued a consensus statement on standard lymphadenectomy for pancreatic cancer (not yet published), which resembles the lymphadenectomy performed at our center. In our experience, one should regularly get more than 20 ELN if this standard lymphadenectomy is performed, and if the pathologists aim to identify all resected LN.

A further reason for differences between our results and previous studies may be differences in median overall survival as the main outcome determinant. Although survival prediction in SEER-based studies is compromised by poor survival results in comparison to the published single center series, there is also a trend toward better survival results in the single center series published since 2010 (Table 5).

Finally, the predictive value of LN variables may depend on the overall study collective. To generate a homogenous cohort as to ELN and survival, we focused on patients undergoing pancreatoduodenectomy for pancreatic adenocarcinoma and excluded other types of resections (which may differ in regard to ELN) and pTis-, R2-, and M1-cases from the main analysis. Previous studies assessing the predictive value of PLN included pancreatic adenocarcinoma of any location and, thus, left resections and total pancreatectomies (Table 5).

Our data reveal that in a series with a relatively high number of ELN (median: 24), PLN is superior to LNR in predicting survival in LN-positive tumors. In N1-staged tumors, median survival varied between 31.1 months, if only 1 LN was involved, and 18.3 months, if 8 or more LN were involved. Importantly, neither morbidity nor the administration of adjuvant therapy was associated with PLN numbers. Therefore, increased morbidity and subsequent failure to perform adjuvant chemotherapy were ruled out as possible confounders with respect to the survival differences observed between PLN groups. Clearly, PLN allows us to distinguish subgroups of LN-positive tumors with very different survival times. Comparison of these subgroups with N0 tumors and tumors staged M1 based on positive interaortocaval LN, reveals that expected survival of patients with 1 PLN (currently staged N1) is almost identical to patients with 0 PLN (staged N0) while survival in 8 or more PLN (currently also staged N1) more closely resembles survival in M1 disease due to positive interaortocaval LN. These observations point to the possibility of introducing different categories of nodal involvement (for instance N1, N2, N3) based on the number of PLN, provided that adequate numbers of LN are examined.

Limitations of this study in regard to the general applicability of its results are the single center setting and the inclusion of only pancreatoduodenectomies for the analysis. The presented results, therefore, have to be validated for tumors treated by left resection or total pancreatectomy, and our results should ideally be validated in a multicenter setting. Furthermore, we cannot address the impact of the exact locations of PLN on survival outcome due to the retrospective setting of our study. The frequency of LN involvement at different locations has been previously described; however, the impact on survival has not yet been established.[26] With the background of our data, it will be interesting to address this question in future studies.

CONCLUSIONS

We demonstrate that, based on a sufficient number of ELN obtained by standard lymphadenectomy and standard pathological workup, the number of PLN is superior to LNR in predicting survival after pancreatoduodenectomy for pancreatic adenocarcinoma. The number of PLN can be used to distinguish several subgroups of LN-positive tumors that are currently all staged N1 but have very different survival outcome. With respect to the clinical impact of these findings, the proposed PLN categories will certainly be useful for improved staging of LN-positive pancreatic cancers but will first have no direct impact on therapy decisions. However, differential stage-adapted adjuvant therapies can only be tested on the basis of such improved staging data for LN-positive tumors, because they are predominant in surgical series. The differences in survival of patients with and without adjuvant chemotherapy in the different PLN groups suggest that the benefit of adjuvant chemotherapy may not be equally distributed among resected patients but may be higher in patients with high numbers of PLN. Thus, these PLN categories are useful in future trials testing the benefit of different adjuvant regimens. After validation in independent cohorts, these PLN-based categories should be considered in future revisions of the pathologic and clinical staging systems for pancreatic adenocarcinoma.

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