Lymph node metastases in resected pancreatic ductal adenocarcinoma: predictors of disease recurrence and survival

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Background: Few studies have simultaneously assessed the prognostic value of the multiple classification systems for lymph node (LN) metastases in resected pancreatic ductal adenocarcinoma (PDAC).

Methods: In 600 patients with resected PDAC, we examined the association of LN parameters (AJCC 7th and 8th editions, LN ratio (LNR), and log odds of metastatic LN (LODDS)) with pattern of recurrence and patient survival using logistic regression and Cox proportional hazards regression, respectively. Regression models adjusted for age, sex, margin status, tumour grade, and perioperative therapy.

Results: Lymph node metastases classified by AJCC 7th and 8th editions, LNR, and LODDS were associated with worse disease free-survival (DFS) and overall survival (OS) (all $P_{trend} < 0.01$). American Joint Committee on Cancer 8th edition effectively predicted DFS and OS, while minimising model complexity. Lymph node metastases had weaker prognostic value in patients with positive margins and distal resections (both $P_{interaction} < 0.03$). Lymph node metastases by AJCC 7th and 8th editions did not predict the likelihood of local disease as the first site of recurrence.

Conclusions: American Joint Committee on Cancer 8th edition LN classification is an effective and practical tool to predict outcomes in patients with resected PDAC. However, the prognostic value of LN metastases is attenuated in patients with positive resection margins and distal pancreatectomies.

Pancreatic cancer is the third leading cause of cancer death in the United States (Siegel *et al*, 2016). Regional lymph node (LN) involvement is an important predictor of survival in patients undergoing resection for pancreatic cancer (Lim *et al*, 2003; Richter *et al*, 2003; Schwarz and Smith, 2006; Winter *et al*, 2006). The current standard for pancreatic cancer staging is the American Joint Committee on Cancer (AJCC) 7th edition system that classifies nodal involvement as pN0 if no regional LN metastases are present or pN1 when regional LN metastases are identified (Edge *et al*, 2010).

Recent studies have suggested that the number of metastatic LN provide additional prognostic information (Murakami *et al*, 2007; Basturk *et al*, 2015; Malleo *et al*, 2015; Strobel *et al*, 2015). Therefore, the upcoming 8th edition of the AJCC system will stratify LN-positive patients into pN1 (metastases in 1–3 regional LN) and pN2 (metastases in $\geqslant$4 regional LN) (Allen *et al*, 2017). Several studies in pancreatic cancer and other malignancies have suggested that prognosis is associated with the relationship of metastatic-to-examined LN, as assessed by the LN ratio (LNR) and log of the odds of metastatic LN (LODDS) (Slidell *et al*, 2008; Valsangkar *et al*, 2013; La Torre *et al*, 2014; Riediger *et al*, 2016). Simultaneous investigations of these different LN parameters in relation to patient outcomes are lacking, particularly in large, multi-institutional patient cohorts. How these LN parameters predict patterns of disease recurrence (e.g., local *vs* distant recurrence) is not well understood, yet has important implications for perioperative treatment programmes. Recent clinical practice guidelines from the American Society of Clinical Oncology (ASCO) recommend the use of adjuvant radiation in patients with LN metastases at resection (Khorana *et al*, 2016). In contrast, current National Comprehensive Cancer Network guidelines for treatment of pancreatic cancer do not take LN status into consideration when recommending for or against radiation treatment in the adjuvant setting (National Comprehensive Cancer Network). Moreover, the number of examined LN and presence of lymphovascular invasion have been reported as prognostic factors particularly in patients with LN-negative disease (Hellan *et al*, 2008; Takahashi *et al*, 2012; Valsangkar *et al*, 2013), raising the question of whether these factors influence outcomes differently in patients with LN-negative and -positive tumours.

The primary aim of the current study was to evaluate the ability of different LN classification systems to predict disease recurrence and survival in a large series of patients with resected pancreatic ductal adenocarcinomas (PDAC) from multiple US centres. As a secondary goal, we also sought to determine whether LN involvement predicts pattern of disease recurrence following resection.

MATERIALS AND METHODS

Study population. The initial patient population consisted of 600 patients who underwent surgical resection for PDAC at academic and community hospitals in the United States. Surgery was performed at Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC, Boston, MA, USA; $n = 274$) between October 2002 and June 2015, at 35 academic and community hospitals between September 2000 and June 2015 referred to the DFCI/BWCC for a second opinion ($n = 87$; list of hospitals in Supplementary Table 1), at the University of Rochester Medical Center (URMC, Rochester, NY, USA; $n = 90$) between 1 March 2006 and 1 November 2013, and at Stanford Cancer Institute (SCI, Stanford, CA, USA; $n = 149$) between September 1995 and May 2013. Institutional Review Board (IRB) approval was granted at DF/BWCC, URMC, and SCI. Patients who received care at DF/BWCC signed informed consent for participation in this study. For those receiving treatment at

URMC and SCI, informed consent was waived as patients were identified retrospectively on Institutional Review Board exempt protocols.

Assessment of LN parameters. The AJCC (7th edition) system classifies LN involvement as pN0 (no regional LN metastases), pN1 (regional LN metastases), or pNx (regional LN cannot be assessed) (Edge *et al*, 2010). The upcoming AJCC (8th edition) system classifies LN involvement as pN0 (no regional LN metastases), pN1 (metastases in 1–3 regional LN), pN2 (metastases in $\geqslant$4 regional LN), or pNx (regional LN cannot be assessed) (Allen *et al*, 2017). lymph node ratio was calculated as (no. of positive LN/ no. of examined LN) and classified into four categories: 0, 0.01–0.20, 0.21–0.40, and >0.40 (Malleo *et al*, 2015; Strobel *et al*, 2015). Log odds of metastatic LN was calculated as ((no. of positive LN + 0.5)/ (no. of negative LN + 0.5)), where 0.5 is added in the numerator and denominator to avoid null and undefined values, and then transformed to natural logarithmic scale (La Torre *et al*, 2014; Riediger *et al*, 2016). We explored the number of examined LN and LVI in secondary analyses.

Assessment of covariates. We collected data from medical records, operative notes, and pathology reports. We assessed sex, age, type of pancreatectomy, perioperative systemic and radiation treatment, tumour location, AJCC (7th and 8th editions) pT stage, tumour grade, resection margin status, LVI, and perineural invasion. Resection margins were classified as R0 (no tumour cells within 1 mm of any pathologic margin), R1 (microscopic foci of tumour cells within 1 mm of a pathologic margin), R2 (gross residual disease), or Rx (margins not evaluable). For patients referred to DF/BWCC after undergoing surgery at another institution, slides were rereviewed by DF/BWCC gastrointestinal pathologists. The above covariates were considered for multi-variable-adjusted model building as detailed below.

Outcome measures. Disease-free survival (DFS) was defined as time between date of surgery and date of disease recurrence. For patients who received neoadjuvant therapy, follow-up started on the date preoperative treatment was initiated. Patients who were alive and free of disease at the end of follow-up and those who died without definitive evidence of recurrence were censored for DFS analysis on the date of last clinical contact. Overall survival (OS) was defined as time between date of surgery (or date of start of neoadjuvant treatment) and date of death from any cause. Pattern of first recurrence was classified as 'local only' (recurrence in/or adjacent to the pancreatic remnant, retroperitoneum and periad-venvitial tissues near the resected pancreas), 'distant only' (recurrence only outside areas defined by local recurrence), or 'synchronous local and distant' (evidence of local and distant disease). Follow-up continued through 28 June 2016 for DF/BWCC patients, 17 March 2016 for URMC, and 11 March 2016 for SCI.

Case selection. Supplementary Figure 1 illustrates the derivation of the patient populations for outcome and recurrence analyses. We excluded patients found to have metastatic spread at the time of resection ($n = 10$), pNx status ($n = 3$), and patients who died within 30 days after surgery or during initial hospitalisation ($n = 13$).

Statistical analysis. Associations between LN parameters, DFS, and OS were evaluated using multivariable-adjusted Cox proportional hazards regression models calculating hazard ratios (HRs) and 95% confidence intervals (CIs). To build the multivariable-adjusted model, we used a training set consisting of subjects who received treatment at DF/BWCC ($n = 361$). We identified covariates for inclusion in the final model by performing stepwise selection with Cox proportional hazards regression using 'entry' and 'keep' thresholds of $P \leqslant 0.2$ and $P \leqslant 0.1$, respectively. With

these parameters, we fitted a model that included six covariates: age at the time of surgery, sex, tumour grade (well/moderately differentiated, poorly differentiated/undifferentiated, unknown), perioperative systemic chemotherapy (yes, no), perioperative radiation treatment (yes, no), and resection margin status (R0, R1, R2, Rx). Proportionality of hazards assumption was satisfied by evaluating a time-dependent variable of the cross-product of the exposure of interest and time.

Using the above model, we compared the LN classification parameters by measuring model discrimination and calibration in the validation set, which consisted of subjects who received care at the URMC and SCI ($n = 239$). We evaluated model discrimination for each LN parameter using the overall C index – an extension of the area under a receiver-operator curve to survival analysis – and calculated its 95% CI (Pencina and D'Agostino, 2004). Model calibration for each LN parameter was assessed using the Greenwood–Nam–D'Agostino goodness-of-fit test, where $P < 0.05$ indicates model miscalibration (Demler et al, 2015).

As neoadjuvant treatment may affect LN status and the number of examined LN, we conducted sensitivity analyses restricted to patients who did not receive neoadjuvant therapy in the training set. We also performed stratified analyses by resection margin status (R0 or R1) and type of pancreatectomy (pancreaticoduodenectomy or distal resection). Interaction was assessed by including the cross-product term of the exposure and stratification variable in the regression model. Given that sample sizes were reduced in stratified analyses and similar associations were identified in the training and validation sets, these analyses were conducted in the entire study population (i.e., training and validation sets combined) and were further adjusted for the institution where patients received care (DF/BWCC, URMC, or SCI). Survival was also shown and assessed using Kaplan–Meier curves and log-rank tests in the entire study population.

Associations between LN parameters and pattern of first recurrence were analysed with logistic regression calculating odds ratios (ORs) and 95% CI in the entire study population. Logistic regression models included the same covariates as in the Cox models described above. We also performed stratified analyses by receipt of perioperative radiation treatment.

We conducted linear trend tests across categories of exposure variables by assigning each subject the median value for the exposure category and modelling it as a continuous variable in Cox or logistic regressions. As we evaluated four LN classification parameters in our main analyses, statistical significance was adjusted for multiple comparisons and set at $P < 0.013$. All hypothesis tests were two sided and analyses were performed using the SAS Software (version 9.4; SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics of the 600 patients in the initial study population are shown in Table 1. At the end of follow-up, 173 (30.4%) patients were alive and 108 (19.4%) were alive without recurrent disease. Median follow-up time among patients who were alive at the end of follow-up was 26.4 months. In our study population, median DFS and OS were 14.3 and 22.5 months, respectively, and 5-year DFS and OS were 14.1% and 15.4%, respectively, comparable to recent randomised trials of pancreatectomy followed by adjuvant therapy (Supplementary Table 2) (Oettle et al, 2007, 2013; Regine et al, 2008, 2011; Neoptolemos et al, 2010, 2017). As noted in other contemporary patient populations with resected PDAC (Oettle et al, 2007; Neoptolemos et al, 2010), nearly two in three patients had LN metastases.

We first examined the association of LN parameters with DFS and OS in the training set (Table 2) and found that higher categories of LN involvement were significantly associated with worse outcomes. We next evaluated the LN parameters' prognostic performance in the validation set, noting similar associations to those identified in the training set (Table 3). Lymph node involvement as classified by the 7th and 8th editions of the AJCC system was significantly associated with poor outcomes. Lymph node ratio and LODDS were associated with a stepwise increase in the hazards for recurrence ($P_{trend} = 0.004$ and 0.005, respectively). The overall C index was similar for the four LN parameters, indicating good discrimination without demonstrating superiority of one parameter over the others. Likewise, the Greenwood–Nam–D'Agostino goodness-of-fit test indicated adequate calibration for all LN parameters (all $P > 0.60$). Kaplan–Meier survival curves of DFS and OS for each LN parameter in the entire study population are presented in Figure 1 and Supplementary Figure 2. Associations were largely unchanged after excluding the 14% of patients who received neoadjuvant therapy from the training set (Supplementary Table 3).

A recent validation study of AJCC (8th edition) classification was restricted to patients with R0 resections (Allen et al, 2017). Therefore, we assessed whether the relationship of LN parameters with survival differed by resection margin status (Table 4). We found that associations of AJCC (7th edition) and AJCC (8th edition) pN status with DFS were seen primarily in patients who underwent R0 resections, with less prognostic ability in patients with R1 margins ($P_{interaction} < 0.02$).

Given that anatomical differences influence surgical LN dissection, we also evaluated whether the association between LN parameters and survival differed by resection type. Lymph node metastases classified by AJCC (7th edition) and AJCC (8th edition) were significantly associated with disease recurrence and mortality among patients who underwent pancreaticoduodenectomy, but not among patients who underwent distal resection (Table 4). Pancreaticoduodenectomy specimens had higher number of examined (median, 16 LN vs 12.5 LN, $P < 0.01$) and positive LN (median, 2 LN vs 0 LN, $P < 0.01$) compared with distal resections.

We next assessed the number of examined LN and presence of LVI as markers of disease recurrence and survival (Supplementary Table 4). Fewer than 12 LN examined was not associated with DFS or OS among LN-negative or -positive patients. In contrast, the presence of LVI revealed a trend towards poor DFS in patients with LN-negative (HR 1.50; 95% CI: 0.90–2.51) and LN-positive (HR 1.27; 95% CI: 0.96–1.67) disease ($P_{interaction} = 0.783$).

Recent ASCO clinical practice guidelines recommend consideration of adjuvant chemoradiation for patients with R1 resections and/or LN-positive tumours (Khorana et al, 2016). Since the primary aim of chemoradiation is achieving local control, we assessed whether LN involvement predicts local recurrence (Table 5). In our study population, AJCC (7th edition) and AJCC (8th edition) LN status did not predict local recurrence as first site of failure. Nevertheless, 41.8% of patients received perioperative radiotherapy that could influence their patterns of disease recurrence. Therefore, we conducted stratified analyses based on receipt of perioperative radiation (Supplementary Table 5). Although somewhat limited by sample size, LN metastases were not predictive for local disease as first site of recurrence even among patients who received no perioperative radiation.

DISCUSSION

In the current study, we found that LN categorisation by AJCC (7th edition), AJCC (8th edition), LNR, and LODDS all predicted

Table 1. Baseline characteristics of 600 patients with resected pancreatic ductal adenocarcinoma

		DF/BWCC			
	Overall	Internal resection	Outside resection	URMC	SCI
Number of subjects	600	274	87	90	149
Men (N, %)	300 (50%)	113 (41%)	48 (55%)	51 (57%)	88 (59%)
Age, median (IQR)	67 (15)	67 (16)	63 (13)	67.5 (15)	69 (13)
Surgery type (N, %)					
Pancreaticoduodenectomy	441 (74%)	203 (74%)	62 (71%)	71 (79%)	105 (70%)
Distal pancreatectomy	147 (24%)	65 (24%)	24 (28%)	18 (20%)	40 (27%)
Total/other	12 (2%)	6 (2%)	1 (1%)	1 (1%)	4 (3%)
Tumour location (N, %)					
Head/uncinate	443 (74%)	203 (74%)	62 (71%)	69 (77%)	109 (73%)
Body	62 (10%)	31 (11%)	7 (8%)	8 (9%)	16 (11%)
Tail	81 (14%)	35 (13%)	17 (20%)	12 (13%)	17 (11%)
Overlapping sites	14 (2%)	5 (2%)	1 (1%)	1 (1%)	7 (5%)
pT stage (N, %)					
T1–T2	88 (15%)	28 (10%)	11 (13%)	8 (9%)	41 (28%)
T3–T4	507 (84%)	243 (89%)	76 (87%)	82 (91%)	106 (71%)
Tx	5 (1%)	3 (1%)	—	—	2 (1%)
pN stage (N, %)					
N0	203 (34%)	104 (38%)	29 (33%)	21 (23%)	49 (33%)
N1	394 (65%)	168 (61%)	58 (67%)	69 (77%)	99 (66%)
Nx	3 (1%)	2 (1%)	—	—	1 (1%)
No. of examined lymph nodes, median (IQR)	15 (13)	13 (11)	11.5 (9)	18 (12)	18 (14.5)
No. of positive lymph nodes, median (IQR)	1 (4)	1 (3)	1 (3)	2 (5)	2 (5)
Tumour differentiation (N, %)					
Well/moderately differentiated	344 (57%)	144 (52%)	56 (64%)	46 (51%)	98 (66%)
Poorly differentiated/undifferentiated	232 (39%)	114 (42%)	30 (35%)	41 (46%)	47 (31%)
Unknown	24 (4%)	16 (6%)	1 (1%)	3 (3%)	4 (3%)
Resection margin status (i, %)					
R0	308 (51%)	132 (48%)	45 (52%)	50 (56%)	81 (54%)
R1	277 (46%)	135 (49%)	40 (46%)	40 (44%)	62 (42%)
R2	11 (2%)	7 (3%)	—	—	4 (3%)
Rx (not evaluable)	4 (1%)	–	2 (2%)	—	2 (1%)
Lymphovascular invasion (N, %)					
Negative	271 (45%)	126 (46%)	42 (48%)	31 (35%)	72 (48%)
Positive	282 (47%)	134 (49%)	39 (45%)	57 (63%)	52 (35%)
Unknown	47 (8%)	14 (5%)	6 (7%)	2 (2%)	25 (17%)
First site of recurrence (N, %)					
Local only	87 (14%)	44 (16%)	13 (15%)	5 (5%)	25 (17%)
Distant only	228 (38%)	103 (38%)	38 (44%)	32 (36%)	55 (37%)
Synchronous local and distant	77 (13%)	33 (12%)	18 (21%)	14 (16%)	12 (8%)
No known recurrence	172 (29%)	87 (32%)	15 (17%)	29 (32%)	41 (27%)
Unknown	36 (6%)	7 (2%)	3 (3%)	10 (11%)	16 (11%)
Neoadjuvant treatment (N, %)					
None	540 (90%)	234 (86%)	75 (87%)	88 (98%)	143 (96%)
Chemotherapy only	23 (4%)	17 (6%)	2 (2%)	—	4 (2%)
Radiation or chemoradiation only	14 (2%)	11 (4%)	2 (2%)	—	1 (1%)
Chemoradiation and chemotherapy	23 (4%)	12 (4%)	8 (9%)	2 (2%)	1 (1%)
Adjuvant treatment (N, %)					
None	159 (26%)	67 (25%)	20 (23%)	31 (34%)	41 (28%)
Chemotherapy only	187 (31%)	91 (33%)	26 (30%)	25 (28%)	45 (30%)
Radiation or chemoradiation only	34 (6%)	17 (6%)	8 (9%)	2 (2%)	7 (5%)
Chemoradiation and chemotherapy	180 (30%)	90 (33%)	32 (37%)	27 (30%)	31 (21%)
Other/unknown	40 (7%)	9 (3%)	1 (1%)	5 (6%)	25 (16%)

Abbreviations: DF/BWCC = Dana-Farber/Brigham and Women's Cancer Center; IQR = interquartile range; SCI = Stanford Cancer Institute; URMC = University of Rochester Medical Center.

DFS and OS in patients undergoing resection for PDAC. The AJCC (8th edition) provided good model fit, while minimising model complexity compared with LNR and LODDS. The prognostic value of LN metastases was stronger in patients with R0 resections and those who underwent pancreaticoduodenectomy, with weaker prognostic ability in patients with microscopically positive or close margins (R1) or patients with distal resections. Lymph node metastases did not predict local disease recurrence as first site of failure, even among patients who received no perioperative radiation. The presence of LVI was marginally associated with adverse outcomes in patients with both LN-negative and -positive tumours, while the number of LN examined was not prognostic in either group. These findings are relevant to prognostication for patients, while suggesting that positive LN status may not be useful in selecting patients for adjuvant radiotherapy.

Table 2. DFS and OS by lymph node classification: training set

	Disease-free survival				Overall survival			
	Number of patients	Median DFS (months)	HR[a] (95% CI)	P_{trend}[a]	Number of patients	Median OS (months)	HR[a] (95% CI)	P_{trend}[a]
AJCC (7th edition)								
pN0	124	18.5	1.00 (reference)		128	33.9	1.00 (reference)	
pN1	214	12.9	1.46 (1.09–1.95)	0.010	220	20.1	1.43 (1.07–1.91)	0.016
AJCC (8th edition)								
pN0	124	18.5	1.00 (reference)		128	33.9	1.00 (reference)	
pN1	139	14.3	1.25 (0.91–1.72)		143	22.5	1.24 (0.91–1.70)	
pN2	75	9.6	2.01 (1.40–2.87)	<0.001	77	16.6	1.88 (1.33–2.68)	<0.001
LNR								
LRN = 0	124	18.5	1.00 (reference)		128	33.9	1.00 (reference)	
0 < LNR ≤ 0.2	111	13.4	1.24 (0.89–1.73)		115	21.1	1.31 (0.94–1.81)	
0.2 < LNR ≤ 0.4	58	10.9	1.61 (1.10–2.37)		60	16.7	1.50 (1.02–2.20)	
LNR > 0.4	45	10.7	2.04 (1.33–3.12)	<0.001	45	20.2	1.76 (1.15–2.69)	0.007
LODDS								
Quartile 1	83	18.5	1.00 (reference)		85	34.1	1.00 (reference)	
Quartile 2	88	17.3	1.02 (0.70–1.50)		91	31.4	0.96 (0.65–1.41)	
Quartile 3	80	11.0	1.60 (1.07–2.37)		84	18.5	1.55 (1.06–2.26)	
Quartile 4	87	10.7	1.82 (1.24–2.68)	<0.001	88	17.3	1.56 (1.05–2.30)	0.003

Abbreviations: AJCC = American Joint Committee on Cancer; CI = confidence intervals; DFS = disease-free survival; HR = hazard ratio; LODDS = log of the odds of metastatic lymph nodes; LNR = lymph node ratio; OS = overall survival.
[a]Adjusted for age, sex, tumour grade, perioperative systemic chemotherapy, perioperative radiation therapy, and resection margins.

Table 3. DFS and OS by lymph node classification: validation set

	Disease-free survival						Overall survival					
	Number of patients	Median DFS (months)	HR[a] (95% CI)	P_{trend}[a]	C index[b] (95% CI)	P_{GND}[c]	Number of patients	Median OS (months)	HR[a] (95% CI)	P_{trend}[a]	C index[b] (95% CI)	P_{GND}[c]
AJCC (7th edition)												
pN0	62	27.8	1.00 (reference)	<0.001	0.77 (0.61–0.91)	0.75	64	42.3	1.00 (reference)	<0.001	0.79 (0.63–0.91)	0.79
pN1	158	10.8	2.59 (1.68–4.00)				158	17.4	2.90 (1.87–4.48)			
AJCC (8th edition)												
pN0	62	27.8	1.00 (reference)	0.001	0.77 (0.61–0.91)	0.83	64	42.3	1.00 (reference)	<0.001	0.79 (0.63–0.91)	0.62
pN1	77	10.8	2.60 (1.63–4.14)				77	16.9	2.79 (1.75–4.46)			
pN2	81	11.0	2.58 (1.58–4.21)				81	17.4	3.03 (1.87–4.93)			
LNR												
LRN = 0	62	27.8	1.00 (reference)	0.004	0.77 (0.61–0.91)	0.94	64	42.3	1.00 (reference)	<0.001	0.78 (0.63–0.91)	0.68
0 < LNR ≤ 0.2	76	13.1	2.52 (1.59–4.00)				76	18.4	2.64 (1.64–4.24)			
0.2 < LNR ≤ 0.4	53	10.7	2.73 (1.56–4.78)				53	16.0	3.36 (2.01–5.63)			
LNR > 0.4	29	6.6	2.69 (1.45–5.01)				29	14.8	3.04 (1.68–5.53)			
LODDS												
Quartile 1	54	20.0	1.00 (reference)	0.005	0.78 (0.61–0.91)	0.98	54	49.8	1.00 (reference)	<0.001	0.79 (0.64–0.91)	0.74
Quartile 2	57	14.8	1.83 (1.10–3.04)				58	20.0	2.21 (1.27–3.85)			
Quartile 3	56	10.8	1.64 (0.96–2.81)				57	15.8	3.04 (1.78–5.19)			
Quartile 4	53	9.7	2.37 (1.36–4.12)				53	14.8	3.44 (1.96–6.05)			

Abbreviations: AJCC = American Joint Committee on Cancer; CI = confidence intervals; DFS = disease-free survival; HR = hazard ratio; LODDS = log of the odds of metastatic lymph nodes; LNR, lymph node ratio; OS = overall survival.
[a]Adjusted for age, sex, tumour grade, perioperative systemic chemotherapy, perioperative radiation therapy, and resection margins.
[b]Overall C index is a measure of model discrimination.
[c]P-value for the Greenwood–Nam–D'Agostino goodness-of-fit test is a measure of model calibration; $P < 0.05$ indicates miscalibration.

Recent studies have suggested that the number of positive LN may improve prognostication over the binary designation of negative vs positive LN involvement (Murakami et al, 2007; Basturk et al, 2015; Malleo et al, 2015; Strobel et al, 2015). Consequently, the new AJCC (8th edition) staging of pancreatic cancer will distinguish patients with 1–3 metastatic LN from those with ≥ 4 metastatic LN (Allen et al, 2017). In this study, we confirmed the additional prognostic benefit to this approach, with median OS times of 35.1, 20.6, and 16.8 months in the entire study population for patients with N0, N1, and N2 disease, respectively. Importantly for clinicians, the value of either AJCC nodal classification in predicting patient outcomes was stronger among patients with margin-negative resections and those with proximal tumours undergoing pancreaticoduodenectomy. The prognostic
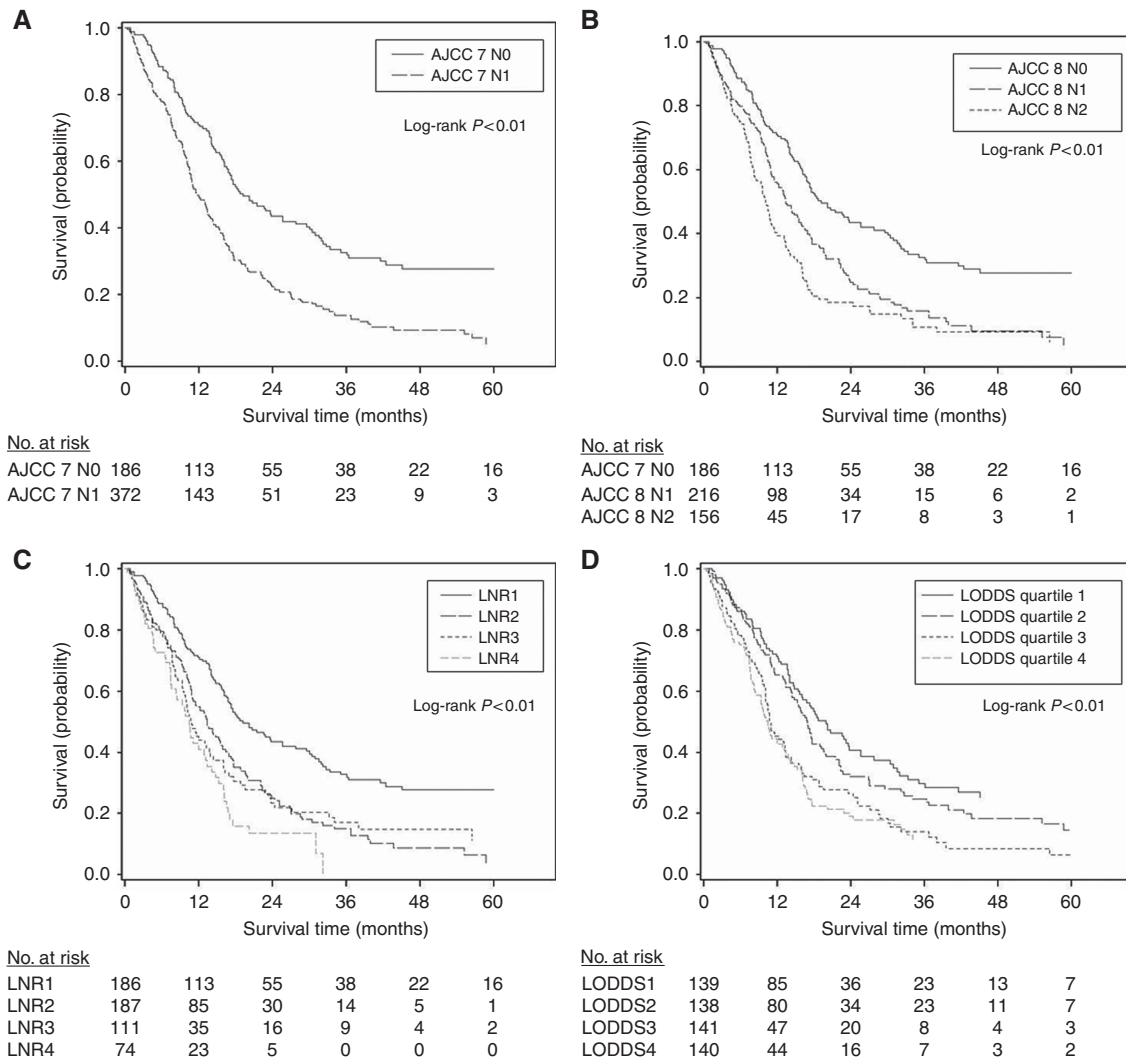
Figure 1. Kaplan–Meier curves for disease-free survival. (**A**) American Joint Committee on Cancer (AJCC) 7th edition. (**B**) American Joint Committee on Cancer 8th edition. (**C**) Lymph node ratio (LNR). LNR1: LNR = 0; LNR2: 0 < LNR ⩽ 0.2; LNR3: 0.2 < LNR ⩽ 0.4; LNR4: LNR > 0.4. (**D**) Quartiles of log(e) odds of metastatic lymph nodes (LODDS).

role of LN metastases in patients undergoing distal pancreatic resections for PDAC is not well characterised (Basturk *et al*, 2015; Malleo *et al*, 2015; Strobel *et al*, 2015). Our findings highlight the need to evaluate the prognostic role of LN involvement in surgical series with distal resections and margin-positive resections and should be interpreted cautiously, given the potential for diminished statistical power in stratified analyses.

We examined two other LN classification approaches, LNR and LODDS, which incorporate the total number of LN examined. Single-centre and population-based studies have found that LNR is a significant predictor of survival in resected PDAC (Slidell *et al*, 2008; Valsangkar *et al*, 2013). In our data, we saw little evidence for improved prognostication using LNR compared with AJCC (8th edition); this may partly be due to a relatively high number of LN harvested in our patient population. However, it has been unclear whether the prognostic value of LNR is due to accounting for misclassification, where fewer LN examined by the pathologist leads to lower likelihood of finding involved LN and an inappropriate pN stage, or better surgical technique, where more LN are harvested leading to fewer involved LN remaining in the patient.

The LODDS classification has also been recently evaluated in PDAC (National Comprehensive Cancer Network; Riediger *et al*, 2016). A proposed advantage of this parameter is that it assigns a

value to LN-negative patients based on the number of examined LN. Therefore, it is designed to risk stratify patients with both LN-negative and -positive tumours. In the current study, no advantage to this classification approach was evident when divided into four exposure groups by quartiles. Overall, our data suggest that the AJCC (8th edition) classification adds value to prognostication while only modestly increasing complexity for practicing clinicians.

We observed that the presence of LVI was associated with a trend towards poor recurrence and survival outcomes in both LN-negative and -positive cases. As LVI has been associated with higher risk of disease recurrence and mortality (Takahashi *et al*, 2012), these results suggest that LVI may be considered regardless of LN status.

Recent ASCO clinical practice guidelines for potentially curable pancreatic cancer recommended adjuvant chemoradiation for patients with R1 resections or LN-positive disease (Khorana *et al*, 2016). The primary aim of adjuvant radiation therapy is to prevent local recurrence around the pancreatic resection bed, ultimately aiming for reduced local symptoms and improved survival. However, studies have been inconclusive regarding the benefits of adjuvant radiation (Neoptolemos *et al*, 2004; Regine *et al*, 2011), leaving clinicians and patients with a difficult choice regarding inclusion of chemoradiation in adjuvant treatment programmes. In our patient population, we found no evidence

Table 4. Disease-free survival and overall survival by lymph node classification stratified by resection margin status and pancreatic resection type

	Disease-free survival						Overall survival					
	R0		R1		$P_{interaction}$		R0		R1		$P_{interaction}$	
	Number of patients	HR[a] (95% CI)	Number of patients	HR[a] (95% CI)			Number of patients	HR[a] (95% CI)	Number of patients	HR[a] (95% CI)		
AJCC (7th edition)												
pN0	121	1.00 (reference)	63	1.00 (reference)	0.016		121	1.00 (reference)	64	1.00 (reference)	0.248	
pN1	170	2.16 (1.55–3.01)	201	1.33 (0.94–1.88)			172	2.10 (1.51–2.92)	202	1.67 (1.15–2.43)		
AJCC (8th edition)												
pN0	121	1.00 (reference)	63	1.00 (reference)	0.005		121	1.00 (reference)	64	1.00 (reference)	0.233	
pN1	108	1.91 (1.33–2.74)	107	1.20 (0.82–1.74)			109	1.94 (1.35–2.77)	107	1.51 (1.01–2.25)		
pN2	62	2.75 (1.82–4.17)	94	1.59 (1.06–2.40)			63	2.44 (1.63–3.66)	95	1.95 (1.28–2.99)		

	Pancreaticoduodenectomy		Distal resection		$P_{interaction}$	Pancreaticoduodenectomy		Distal resection		$P_{interaction}$
	Number of patients	HR[b] (95% CI)	Number of patients	HR[b] (95% CI)		Number of patients	HR[b] (95% CI)	Number of patients	HR[b] (95% CI)	
AJCC (7th edition)										
pN0	115	1.00 (reference)	67	1.00 (reference)	0.179	117	1.00 (reference)	71	1.00 (reference)	0.022
pN1	300	2.13 (1.58–2.89)	64	1.51 (0.94–2.43)		305	2.13 (1.57–2.87)	65	1.23 (0.77–1.98)	
AJCC (8th edition)										
pN0	115	1.00 (reference)	67	1.00 (reference)	0.116	117	1.00 (reference)	71	1.00 (reference)	0.003
pN1	161	1.85 (1.34–2.56)	49	1.53 (0.94–2.49)		164	1.85 (1.34–2.56)	50	1.37 (0.82–2.28)	
pN2	139	2.63 (1.87–3.70)	15	1.42 (0.60–3.36)		141	2.56 (1.84–3.57)	15	0.89 (0.40–1.97)	

Abbreviations: AJCC = American Joint Committee on Cancer; CI = confidence intervals; HR = hazard ratio.
[a]HR adjusted for age, sex, tumour grade, perioperative systemic chemotherapy, perioperative radiation therapy, and institution.
[b]HR adjusted for age, sex, tumour grade, perioperative systemic chemotherapy, perioperative radiation therapy, resection margins, and institution.

Table 5. Odds ratios for local recurrence by AJCC (7th and 8th edition) lymph node classification

	Any local recurrence[a]		
	Number of cases	OR[b] (95% CI)	P_{trend}
AJCC (7th edition)			
pN0	110	1.00 (reference)	0.472
pN1	262	0.84 (0.52–1.36)	
AJCC (8th edition)			
pN0	110	1.00 (reference)	0.815
pN1	151	0.76 (0.45–1.29)	
pN2	110	0.99 (0.56–1.75)	

Abbreviations: AJCC = American Joint Committee on Cancer; OR = odds ratio.
[a]First site of recurrence as local only recurrence or synchronous local and distant recurrence.
[b]Odds ratio adjusted for age, sex, tumour grade, perioperative systemic chemotherapy, perioperative radiation therapy, resection margins, and institution.

that nodal metastases increased the risk for local disease as first site of recurrence. Although our sample sizes were reduced when stratified by treatment, this finding was consistent in patients who received perioperative radiation and those who did not. Therefore, data from our population would not support selecting patients for adjuvant chemoradiation based on nodal status, if the primary objective is to reduce local recurrence rates. The ongoing RTOG 0848 study will provide valuable information regarding the benefits of adjuvant chemoradiation.

The current study has several important strengths. Our patient population was derived from three US academic institutions in distinct geographic regions, as well as 35 other academic and community centres across the country. Patients were sequentially captured and selected based only on having undergone surgical resection. Thus, the study population represents a diversity of patient characteristics, surgical and pathological practices, and treatment approaches. Moreover, we had direct access to medical records and follow-up information, allowing for consistent and detailed data abstraction, including patterns of disease recurrence. These data also allowed for appropriate adjustment for confounding covariates in multivariate models and stratified analyses by other important characteristics, such as resection margin status. Last, we used training and validation sets to evaluate the performance of the different LN classification parameters and compared them with model discrimination and calibration metrics.

Study limitations also deserve mention. We included patients who received neoadjuvant therapy in our main analyses, and LN status may have been affected by preoperative treatment. However, sensitivity analyses confirmed highly similar results after excluding patients who received neoadjuvant therapy. The study period was not uniform across the contributing centres. However, adjuvant therapy programmes have not changed significantly during the follow-up time of the study, with most patients receiving adjuvant 5-fluorouracil or adjuvant gemcitabine. Notably, the ESPAC-3 study demonstrated that patient outcomes are nearly identical with 5-fluorouracil or gemcitabine delivered after surgical resection (Neoptolemos et al, 2010). We did not centrally rereview pathological specimens for resection margins and LVI, and therefore, our findings represent the information that is available for practicing clinicians in the real-world setting. Additional studies to compare LVI and resection margins across centres and pathologists would be of interest. Finally, follow-up of patients after surgical resection was performed as per standard institutional practice. If postoperative imaging was performed more frequently

for patients with LN-positive disease, then this could accentuate differences in DFS time between the LN-positive and -negative groups. Nevertheless, no standard follow-up programme has been defined to improve outcomes in patients with resected PDAC, and imaging intervals would not be expected to alter overall survival times, which were markedly different between the LN-positive and -negative groups.

In conclusion, we confirmed the prognostic importance of regional LN metastases after resection for PDAC in a large, multi-institutional database including patients from across the United States. In this patient population, the upcoming AJCC (8th edition) staging system is an effective and practical classification of regional LN involvement that incorporates the number of metastatic LN as a prognostic factor in the prediction of disease recurrence and survival. Nevertheless, its prognostic value may be weaker in patients with positive resection margins and in patients with distal resections. Notably, outcomes for patients with LN-positive disease were extremely poor. Novel approaches to treatment of this disease are greatly needed, including consideration to preoperative treatment, multiagent chemotherapy programmes, and therapeutic approaches based on an improved biologic understanding of this highly lethal malignancy (Perez *et al*, 2016; Ying *et al*, 2016; Neoptolemos *et al*, 2017).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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