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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Defining the Role of Lymphadenectomy for Pancreatic Neuroendocrine Tumors: An Eight-Institution Study of 695 Patients from the US Neuroendocrine Tumor Study Group

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ABSTRACT

Background. Preoperative factors that reliably predict lymph node (LN) metastases in pancreatic neuroendocrine tumors (PanNETs) are unclear. The number of LNs needed to accurately stage PanNETs has not been defined.

Methods. Patients who underwent curative-intent resection of non-functional PanNETs at eight institutions from 2000 to 2016 were analyzed. Preoperative factors associated with LN metastases were identified. A procedure-specific target for LN retrieval to accurately stage patients was determined.

Results. Of 695 patients who underwent resection, 33% of tumors were proximal (head/uncinate) and 67% were distal (neck/body/tail). Twenty-six percent of patients ($n = 158$)

had LN-positive disease, which was associated with a worse 5-year recurrence-free survival (RFS; 60% vs. 86%; $p < 0.001$). The increasing number of positive LNs was not associated with worse RFS. Preoperative factors associated with positive LNs included tumor size ≥ 2 cm (odds ratio [OR] 6.6; $p < 0.001$), proximal location (OR 2.5; $p < 0.001$), moderate versus well-differentiation (OR 2.1; $p = 0.006$), and Ki-67 $\geq 3\%$ (OR 3.1; $p < 0.001$). LN metastases were also present in tumors without these risk factors: < 2 cm (9%), distal location (19%), well-differentiated (23%), and Ki-67 $< 3\%$ (16%). Median LN retrieval was 13 for pancreatoduodenectomy (PD), but only 9 for distal pancreatectomy (DP). Given that PD routinely includes a complete regional lymphadenectomy, a minimum number of LNs to accurately stage patients was not identified. However, for DP, removal of less than seven LNs failed to discriminate 5-year RFS between LN-positive and LN-negative patients (less than seven LNs: 72% vs. 83%, $p = 0.198$; seven or more LNs: 67% vs. 86%; $p = 0.002$).

Conclusions. Tumor size ≥ 2 cm, proximal location, moderate differentiation, and Ki-67 $\geq 3\%$ are preoperative factors that predict LN positivity in resected non-functional PanNETs. Given the 9–23% incidence of LN metastases in patients without such risk factors, routine regional lymphadenectomy should be considered. PD inherently

includes sufficient LN retrieval, while DP should aim to remove seven or more LNs for accurate staging.

INTRODUCTION

Pancreatic neuroendocrine tumors (PanNETs) are a heterogeneous group of tumors that represent a small but increasing proportion of pancreatic neoplasms.[1,2] These tumors can be described as *functional* or *non-functional* based on the presence or absence of hormone secretion, respectively.[3] Approximately 80% of PanNETs are non-functional, which limits their detection until they are either incidentally discovered on axial imaging or until symptoms from mass effect or invasion are present.[1,3,4] Given the behavioral variability of non-functional PanNETs, multidisciplinary oncology teams have struggled to predict individual disease courses.[4] Indeed, 5-year survival for PanNETs in the literature ranges from as low as 15% to as high as 100%.[5–7] As a result, a reliance on other disease factors, such as lymph node (LN) spread, is of paramount importance to anticipate disease progression and intervene accordingly.

LN metastases have been shown to negatively impact survival across most solid organ malignancies, including gastrointestinal malignancies such as colon and gastric cancer.[8–11] Among non-functional PanNETs specifically, the association between positive LNs and poor outcomes has been clearly established.[12–18] The American Joint Committee on Cancer (AJCC) staging system reflects this relationship, as any nodal metastasis in neuroendocrine tumors automatically renders a Stage III diagnosis, regardless of tumor size.[19] Since LN metastases may serve as a surrogate for worse disease, various studies have focused on the ability to predict nodal positivity with other preoperatively available tumor factors, including tumor size and location.[4,15,20] Although conflicting data have caused the predictive reliability of these factors to remain unclear, knowledge of them may be used to both inform and guide patient management.

An important element in the evaluation of neoplasms for nodal metastases is the adequate retrieval of LNs during surgery. The need for sufficient LN sampling to prevent the understaging of tumors has been well studied. For example, in colon cancer, at least 12 nodes are necessary to appropriately stage tumors.[21,22] Likewise, in gastric cancer, guidelines state that at least 16 LNs must be examined to minimize understaging of tumors.[11,23] However, for PanNETs, the number of LNs needed for accurate staging at surgical resection has not been defined. Knowledge of this information may thus prove a valuable addition to the understanding and treatment of these rare and heterogeneous tumors.

Given the value of LN metastases in predicting PanNET behavior, and the current lack of data regarding the target number of LNs needed for PanNET staging, the aim of our study was twofold: (1) to determine preoperative factors associated with LN metastases among resected non-functional PanNETs; and (2) to establish a procedure-specific threshold for the number of LNs needed to be retrieved to enable accurate staging.

METHODS

Study Population

All patients with primary, non-functional PanNETs who underwent curative-intent resection from 1 January 2000 to 31 December 2016 at the eight diverse, high-volume academic institutions (Emory University, Ohio State University, Stanford University, University of Michigan, University of Wisconsin, Vanderbilt University, Virginia Mason, and Washington University in St. Louis) that form the US Neuroendocrine Tumor Study Group (US-NETSG) were identified. Poorly differentiated tumors, metastatic tumors, tumors with a Ki-67 index > 20%, R2 resections, and all 30-day mortalities were excluded from analysis. The primary endpoints were LN metastases and recurrence-free survival (RFS). The aim was to determine preoperative predictors of LN disease, and to utilize serial Kaplan–Meier analysis to determine a procedure-specific target (pancreatoduodenectomy [PD] vs. distal pancreatectomy [DP]) for LN retrieval to accurately stage patients.

Study Variables

Each institution obtained Institutional Review Board approval prior to any data retrieval. Retrospective chart review captured baseline demographic, preoperative, operative, pathologic, and postoperative data. The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) risk calculator was used to define patient comorbidities, and cancer staging was assigned according to the AJCC 7th edition guidelines.[24] Disease recurrence data were also collected; recurrence of disease was ascertained by review of patient medical records, radiographic reports of surveillance imaging, and/or biopsy results.

Statistical Analyses

Descriptive and comparative analyses were performed for the entire cohort. Categorical variables were compared using Chi square analyses and Fisher's exact tests, and continuous variables were compared using Student's *t* test,

TABLE 1 Baseline demographics and clinicopathologic variables of patients with low/intermediate grade non-functional pancreatic neuroendocrine tumors from the US-NETSG Database who underwent curative-intent resection from 2000 to 2016 [n = 695]

Baseline variables	All patients [n = 695]
Age, years [mean ± SD]	57 ± 13
Male	358 (52)
BMI, kg/m^2 [mean ± SD]	29.3 ± 6.8
Comorbidities[a]	
0	264 (39)
1	190 (28)
≥ 2	229 (33)
Race	
White	533 (78)
African American	61 (9)
Other	87 (13)
ASA class	
1	23 (3)
2	311 (46)
3	333 (49)
4	10 (2)
Operative/pathologic variables	
Tumor size, cm [mean ± SD]	3.1 ± 2.8
Tumor location in the pancreas	
Head/uncinate (proximal)	227 (33)
Neck/body/tail (distal)	466 (67)
Type of resection	
Enucleation	35 (5)
Classic pancreatoduodenectomy	92 (13)
Pylorus-preserving pancreatoduodenectomy	116 (17)
Central pancreatectomy	26 (4)
Distal pancreatectomy	417 (60)
Total pancreatectomy	8 (1)
Positive margins	97 (14)
AJCC T stage	
T1/T2	536 (78)
T3/T4	154 (22)
Tumor differentiation	
Well	548 (89)
Moderate	68 (11)
Ki-67 index	
< 3%	205 (62)
3–20%	185 (38)
Mitotic rate category	
< 2	366 (86)
2–20	59 (14)
Lymph node-positive	158 (26)
Number of positive nodes [median (IQR)]	0 (0–1)

TABLE 1 continued

Baseline variables	All patients [n = 695]
Lymph node yield [median (IQR)]	
Pancreatoduodenectomy	13 (8–20)
Distal pancreatectomy	9 (4–14)
Enucleation/central pancreatectomy	1 (1–2.25)
Lymphovascular invasion	177 (30)
Perineural invasion	125 (23)

Data are expressed as n (%) unless otherwise specified

SD standard deviation, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *AJCC* American Joint Committee on Cancer, *IQR* interquartile range

[a]Comorbidities are defined as any concurrent medical condition, including but not limited to, heart disease, chronic pulmonary disease, diabetes, renal disease, and liver disease as per the American College of Surgeons National Surgical Quality Improvement Program risk calculator

where indicated. Kaplan–Meier log-rank plots were calculated for RFS, which was defined as the time between the date of operation and the date of recurrence diagnosis. Binomial logistic regression was used to evaluate clinicopathologic variables associated with LN metastases. All statistical analyses were conducted using SPSS version 23.0 (IBM Corporation, Armonk, NY, USA), with statistical significance predefined as $p < 0.05$.

RESULTS

Patient Variables

Among 2182 patients with neuroendocrine tumors from the US-NETSG database, 695 patients underwent curative-intent surgical resection of low-to-intermediate grade, non-functional PanNETs. Table 1 summarizes the baseline demographics and clinicopathologic features of the study cohort. Fifty-two percent of patients were male (n = 358), 78% were Caucasian (n = 533), and the mean age was 57 years. Mean tumor size was 3.1 cm, with 67% (n = 466) of tumors located distally in the neck, body, or tail of the pancreas, and 33% (n = 228) of tumors located proximally in the head or uncinate. Fourteen percent (n = 97) had positive margins, 89% (n = 548) had well-differentiated tumors, 62% (n = 205) had a Ki-67 index < 3% (of patients with available data), and 26% (n = 158) of the entire cohort had LN-positive disease (Table 1).

When separated by procedure performed, 417 patients (60%) underwent DP, of which the median number of LNs retrieved was 9 (interquartile range [IQR] 4–14) and the number of patients with node-positive disease was 70
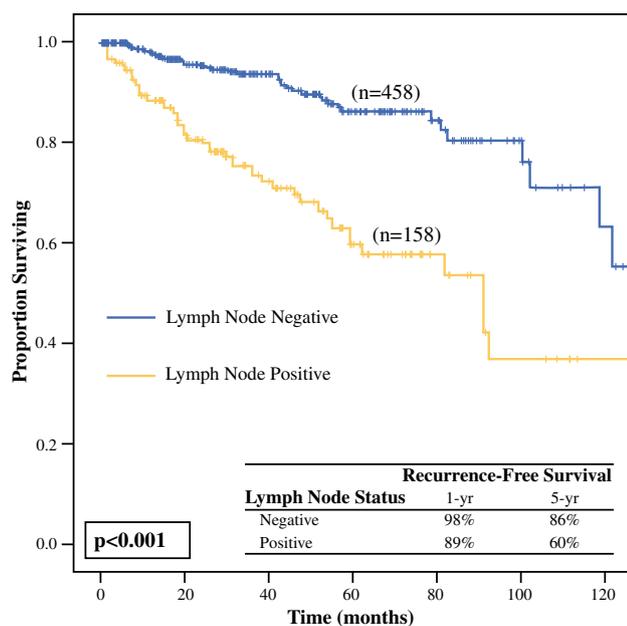
FIG. 1 Kaplan–Meier survival curve for recurrence-free survival in lymph node-positive versus lymph node-negative patients with low/intermediate grade non-functional pancreatic neuroendocrine tumors

(18%). Conversely, 208 patients (30%) underwent PD, of whom a median of 13 (IQR 8–20) LNs were retrieved, with 79 (39%) being LN-positive. The remaining patients underwent enucleation ($n = 35$; 5%), central pancreatectomy ($n = 26$; 4%), or total pancreatectomy ($n = 8$; 1%) (Table 1). There was no difference in the median number of LNs retrieved when comparing open versus minimally invasive surgical technique (median of 10 vs. 9 LNs; $p = 0.260$).

Recurrence-Free Survival (RFS) Analysis

Median follow-up was 36 months (IQR 14.9–62.6 months), and 89 patients (13%) had disease recurrence following resection. The 5-year RFS for patients with LN-positive disease was 60% versus 86% for patients with node-negative disease on Kaplan–Meier analysis ($p < 0.001$) (Fig. 1). On univariable Cox regression, LN-positive disease was associated with a 3.7-fold increase in risk for recurrence compared with node-negative disease (hazard ratio [HR] 3.7, 95% confidence interval [CI] 2.4–5.6; $p < 0.001$). The increasing number of positive LNs was not associated with worse RFS as the majority of LN-positive patients had only one positive node ($n = 56$).

Other clinicopathologic factors associated with decreased RFS included tumor size ≥ 2 cm (HR 5.4, 95% CI 3.0–9.7; $p < 0.001$), Ki-67 index ≥ 3% (HR 2.9, 95% CI 1.7–5.2; $p < 0.001$), positive margins (HR 2.0, 95% CI 1.2–3.2; $p = 0.008$), advanced T stage (T3/T4: HR 3.8,

95% CI 2.5–5.9; $p < 0.001$), lymphovascular invasion (HR 4.5, 95% CI 2.7–7.4; $p < 0.001$), and perineural invasion (HR 2.4, 95% CI 1.5–4.0; $p = 0.001$).

Predictors of Lymph Node Positivity

Preoperatively measurable clinicopathologic factors associated with LN positivity on binomial logistic regression were tumor size ≥ 2 cm (odds ratio [OR] 6.6, 95% CI 4.1–10.7; $p < 0.001$), proximal tumor location in the head/uncinate of the pancreas (OR 2.5, 95% CI 1.7–3.6; $p < 0.001$), moderate versus well differentiation (OR 2.1, 95% CI 1.2–3.7; $p = 0.006$), and Ki-67 index ≥ 3% (OR 3.1, 95% CI 2.0–4.9; $p < 0.001$) (Table 2). When placed in a multivariable model, tumor size ≥ 2 cm (OR 4.9, 95% CI 2.7–8.8; $p < 0.001$), proximal tumor location (OR 1.9, 95% CI 1.2–3.2; $p = 0.008$), and Ki-67 ≥ 3% (OR 2.2, 95% CI 1.3–3.7; $p = 0.004$) all remained independently significant (Table 2). Proximally located tumors were nearly twice as likely to have positive LNs compared with distally located tumors (37% vs. 19%; $p < 0.001$); tumors ≥ 2 cm were nearly fourfold as likely to have LN metastasis compared with tumors < 2 cm (38% vs. 9%; $p < 0.001$); nearly double the amount of moderately differentiated tumors had nodal spread versus well-differentiated PanNETs (39% vs. 23%; $p = 0.009$); and tumors with a Ki-67 index ≥ 3% were more than twofold as likely to have positive LNs compared with a Ki-67 index < 3% (38% vs. 16%; $p < 0.001$) (Table 3). However, patients without such individual high-risk clinicopathologic factors still had a rate of LN positivity that ranged from 9 to 23% (Table 3). Even among the 131 patients in the cohort with < 2 cm, distally located, and well-differentiated tumors with a Ki-67 < 3%, a 4% rate of LN metastases was still observed.

Procedure-Specific Lymphadenectomy and RFS

When performing a procedure-specific, serial Kaplan–Meier analysis of the association between node-positive disease and RFS, stratified by the number of LNs retrieved during surgical resection, less than seven LNs removed during DP failed to discriminate RFS between node-positive and node-negative patients ($p = 0.198$) (Fig. 2a). Conversely, when a threshold of seven nodes was reached during serial analysis of patients who underwent DP, accurate discrimination between LN-positive and LN-negative patients became feasible. Eighty-five percent of patients who underwent DP also had simultaneous splenectomy ($n = 353$), with a median LN retrieval of nine nodes. Among the 63 patients who underwent DP without concomitant splenectomy, median LN retrieval was only 4 ($p < 0.001$). The 5-year RFS for patients with LN

TABLE 2 Logistic binary regression analysis of risk factors associated with lymph node positivity among patients with low/intermediate grade non-functional pancreatic neuroendocrine tumors

Clinicopathologic variables	Logistic regression			
	Lymph node positivity			
	Univariable		Multivariable	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Age, years	1.00 (1.0–1.0)	0.388	–	–
Sex				
Female	Ref	–	–	–
Male	1.3 (0.9–1.8)	0.217		
Race				
White	Ref	–	–	–
African American	1.6 (0.9–3.0)	0.107		
Other	0.9 (0.5–1.6)	0.670		
Tumor size, cm				
< 2	Ref	–	Ref	–
≥ 2	**6.6 (4.1–10.7)**	**< 0.001**	**4.9 (2.7–8.8)**	**< 0.001**
Tumor location in the pancreas				
Distal	Ref	–	Ref	–
Proximal	**2.5 (1.7–3.6)**	**<0.001**	**1.9 (1.2–3.2)**	**0.008**
Type of resection				
Enucleation[a]	Ref	–	–	–
Classic pancreatoduodenectomy	2.3 (0.6–9.0)	0.222		
Pylorus-preserving pancreatoduodenectomy	2.0 (0.5–7.6)	0.323		
Central pancreatectomy[a]	0.3 (0.0–2.9)	0.268		
Distal pancreatectomy	0.8 (0.2–2.8)	0.669		
Total pancreatectomy	3.3 (0.5–22.1)	0.213		
Tumor differentiation				
Well	Ref	–	Ref	–
Moderate	**2.1 (1.2–3.7)**	**0.006**	0.9 (0.5–1.9)	0.883
Ki-67 index				
< 3%	Ref	–	Ref	–
3–20%	**3.1 (2.0–4.9)**	**< 0.001**	**2.2 (1.3–3.7)**	**0.004**

OR odds ratio, *CI* confidence interval

Bold values indicate *p* < 0.05

[a]Patients with enucleation or central pancreatectomy who were included in the analysis had separate lymphadenectomies performed during surgery

metastases who underwent DP was 67%, compared with 86% for those without nodal metastases (*p* = 0.002) (Fig. 2b). There was no difference in RFS among patients who underwent DP, based solely on the number of LNs retrieved.

Given that PD routinely includes a complete regional lymphadenectomy, and with the median number of nodes removed via PD in this cohort being 13, a minimum number of LNs needed to accurately stage patients undergoing this procedure for PanNETs was not identified. There was also no difference in RFS among patients who underwent PD, based solely on the number of LNs retrieved.

DISCUSSION

Non-functional PanNETs are a group of increasingly diagnosed neoplasms known for their unpredictable behavior and disease course. In this multi-institutional study of 695 patients with non-functional PanNETs, we showed that not only are LN metastases associated with decreased 5-year RFS but also that tumor size ≥ 2 cm, proximal tumor location in the head/uncinate of the pancreas, moderate tumor differentiation, and Ki-67 index ≥ 3% all preoperatively predict locoregional nodal spread. However, even in patients without such high-risk clinicopathologic factors, there was still a rate of LN positivity that ranged

TABLE 3 Distribution of preoperative risk factors associated with lymph node positivity among patients with low/intermediate grade nonfunctional pancreatic neuroendocrine tumors

Risk factors	Lymph node-negative [n =462]	Lymph node-positive [n = 158]	p Value[a]
Tumor size, cm			< 0.001
< 2	238 (92)	22 (9)	
≥ 2	223 (62)	136 (38)	
Tumor location in the pancreas			< 0.001
Distal	328 (81)	78 (19)	
Proximal	133 (63)	79 (37)	
Tumor differentiation			0.009
Well	373 (77)	112 (23)	
Moderate	39 (61)	25 (39)	
Ki-67 index			< 0.001
< 3%	224 (84)	43 (16)	
3–20%	110 (63)	66 (38)	

Data are expressed as n (%)

[a]Statistical significance is indicated by a p value < 0.05

from 9% to as high as 23%. When using a procedure-based approach to LN retrieval for accurate tumor staging, removal of less than seven LNs during DP failed to distinguish RFS between LN-positive and LN-negative patients. Conversely, when seven or more LNs were removed, a nearly 20% decrease in 5-year RFS was demonstrated between patients with node-positive and node-negative disease. However, for patients undergoing PD, a threshold for LN retrieval could not be reached, given that the median number of LNs removed was 13. As such, complete regional lymphadenectomy during PD likely inherently includes sufficient LN retrieval for accurate PanNET staging.

The negative prognostic role that regional LN spread plays in cancer, particularly in abdominal solid organ malignancies, is well-established. LN involvement has been shown to correlate with an increased risk in disease recurrence, even at the micrometastatic level.[19] Indeed, in the study of patients with stage I/II colon cancer by Sloothaak et al., micrometastasis in the sentinel nodes was found to be associated with decreased 3-year disease-free survival (DFS) compared with patients with node-negative disease (75% vs. 95%; p = 0.005).[25] Similarly, in a study of patients with early-stage gastric cancer, patients with LN metastasis had a 79% 3-year overall survival compared with 94% in those without nodal spread.[26] This association with decreased survival has also been demonstrated in nonfunctional PanNETs, as Partelli et al. reported a 5-year DFS of 70% versus 97% for patients with N1 versus N0 disease, respectively.[15] The current study supports these previous findings, with node-positive patients displaying a nearly fourfold increase in risk for recurrence compared

with node-negative patients. Furthermore, our study shows that tumor size ≥ 2 cm, proximal tumor location, moderate differentiation, and Ki-67 ≥ 3% can all preoperatively predict risk for nodal metastases. This information may influence the future management of PanNETs, including the decision to resect or observe tumors and what type of resection to perform. However, given the 9–23% incidence of nodal metastasis, even among patients without these high-risk factors, a low threshold for performing a lymphadenectomy should be considered.

While LN metastases may serve as a surrogate for worse disease, the ability to detect nodal spread relies heavily on the surgical removal of an adequate number of LNs for tumor staging. When the number of retrieved LNs is insufficient, a patient's prognosis can be underestimated by the AJCC staging designation due to an understaging phenomenon.[10] Studies in colon cancer and gastric cancer have shown that a high LN count at resection is associated with improved outcomes, regardless of tumor stage.[8,10,27–29] Not only does the higher node removal improve the accuracy of staging, which may help guide management, but it also enables discrimination between node-positive and node-negative groups. In the study of patients with gastric cancer by Marchet et al., when > 15 LNs were removed, discrimination between the N1 (1–6 metastatic nodes) and N2 (7–15 metastatic nodes) prognostic categories according to the AJCC 7th edition was achieved.[30] Thus, determining a target number of LNs to remove is of critical importance in the optimization of cancer management accurate staging; however, no such target currently exists for staging PanNETs.
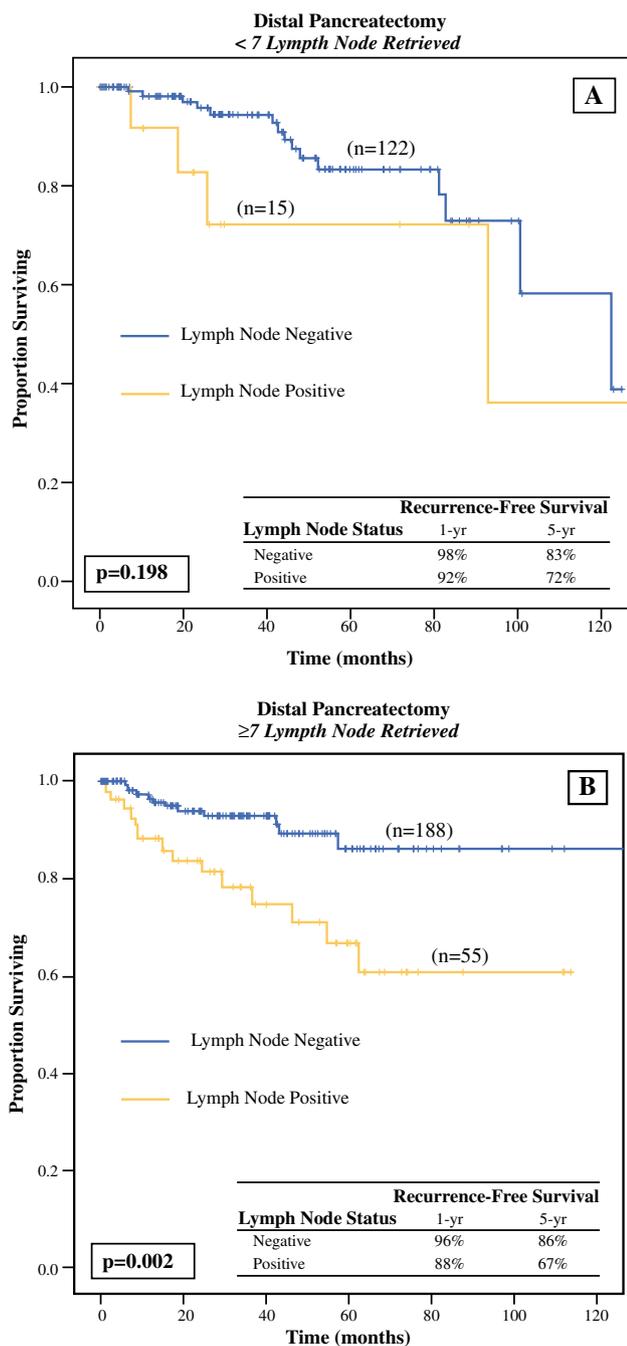
Distal Pancreatectomy
< 7 Lympth Node Retrieved

A

(n=122)

(n=15)

Lymph Node Negative

Lymph Node Positive

	Recurrence-Free Survival	
Lymph Node Status	1-yr	5-yr
Negative	98%	83%
Positive	92%	72%

p=0.198

Distal Pancreatectomy
≥7 Lympth Node Retrieved

B

(n=188)

(n=55)

Lymph Node Negative

Lymph Node Positive

	Recurrence-Free Survival	
Lymph Node Status	1-yr	5-yr
Negative	96%	86%
Positive	88%	67%

p=0.002

FIG. 2 Kaplan–Meier survival curve for recurrence-free survival in lymph node-positive versus lymph node-negative patients with low/intermediate grade non-functional pancreatic neuroendocrine tumors who underwent distal pancreatectomy, stratified by the number of lymph nodes retrieved. **a** Less than seven lymph nodes; **b** seven or more lymph nodes

To our knowledge, this study was the first to examine a procedure-specific threshold for the number of LNs needed to enable accurate PanNET staging. Similar to the findings by Dolan and Marchet, discrimination between node-

positive and node-negative groups was achieved when seven or more LNs were removed during DP. Moreover, to reach the threshold of seven LNs for DP, it seems that concomitant splenectomy was necessary in this cohort. As a result, DP with splenectomy may be preferred over splenectomy-preserving techniques to optimize the chance of accurately staging patients undergoing PanNET resection. However, for PD, due to the inherently sizeable amount of LNs routinely obtained during this procedure, no minimum retrieval threshold was detected, and thus no difference in RFS was found based solely on the number of LNs retrieved.

This study was limited by its retrospective design, as well as by missing data for several pathologic variables. Moreover, given the relative indolent nature of the PanNETs in this population, we were unable to evaluate LN ratios as the median number of positive nodes was zero. Nonetheless, this study represents one of the largest cohorts of PanNETs to date, and its multi-institutional design supports the generalizability of its findings.

CONCLUSIONS

Tumor size, location, differentiation, and Ki-67 index can all preoperatively predict nodal metastases and inform the use of regional lymphadenectomy at resection of non-functional PanNETs. Given the 9–23% incidence of LN metastases in patients without known risk factors, routine regional lymphadenectomy should still be considered. While PD inherently provides sufficient nodes to stage PanNETs, a minimum of seven or more LNs should be removed when performing a DP to enable accurate staging.

REFERENCES

1. Haynes AB, Deshpande V, Ingkakul T, et al. Implications of incidentally discovered, nonfunctioning pancreatic endocrine tumors: short-term and long-term patient outcomes. *Arch Surg*. 2011;146:534–8
2. Strosberg JR, Cheema A, Weber JM, et al. Relapse-free survival in patients with nonmetastatic, surgically resected pancreatic neuroendocrine tumors: an analysis of the AJCC and ENETS staging classifications. *Ann Surg*. 2012;256:321–5
3. Cherenfant J, Stocker SJ, Gage MK, et al. Predicting aggressive behavior in nonfunctioning pancreatic neuroendocrine tumors. *Surgery*. 2013;154:785–91 (**discussion 791–3**)

4. Postlewait LM, Ethun CG, Baptiste GG, et al. Pancreatic neuroendocrine tumors: preoperative factors that predict lymph node metastases to guide operative strategy. *J Surg Oncol.* 2016;114:440–5

5. Bilimoria KY, Talamonti MS, Tomlinson JS, et al. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients. *Ann Surg.* 2008;247:490–500

6. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology.* 2008;135:1469–92

7. Ekeblad S, Skogseid B, Dunder K, et al. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. *Clin Cancer Res.* 2008;14:7798–803

8. Dolan RD, McSorley ST, Horgan PG, et al. Determinants of lymph node count and positivity in patients undergoing surgery for colon cancer. *Medicine (Baltimore).* 2018;97:e0185

9. Reha J, Mukkamalla SKR, Rathore R, et al. Adequate lymph node evaluation in the elderly is associated with improved survival in patients with stage I–III colon cancer: a validation study using the National Cancer Data Base. *Eur J Surg Oncol.* 2018;44:148–156

10. Lu J, Zheng CH, Cao LL, et al. The effectiveness of the 8th American Joint Committee on Cancer TNM classification in the prognosis evaluation of gastric cancer patients: a comparative study between the 7th and 8th editions. *Eur J Surg Oncol.* 2017;43:2349–2356

11. Alatengbaolide, Lin D, Li Y, et al. Lymph node ratio is an independent prognostic factor in gastric cancer after curative resection (R0) regardless of the examined number of lymph nodes. *Am J Clin Oncol.* 2013;36:325–30

12. Scarpa A, Mantovani W, Capelli P, et al. Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. *Mod Pathol.* 2010;23:824–33

13. Hochwald SN, Zee S, Conlon KC, et al. Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. *J Clin Oncol.* 2002;20:2633–42

14. Sarmiento JM, Farnell MB, Que FG, et al. Pancreaticoduodenectomy for islet cell tumors of the head of the pancreas: long-term survival analysis. *World J Surg.* 2002;26:1267–71

15. Partelli S, Gaujoux S, Boninsegna L, et al. Pattern and clinical predictors of lymph node involvement in nonfunctioning pancreatic neuroendocrine tumors (NF-PanNETs). *JAMA Surg.* 2013;148:932–9

16. Tomassetti P, Campana D, Piscitelli L, et al. Endocrine pancreatic tumors: factors correlated with survival. *Ann Oncol.* 2005;16:1806–10

17. Bettini R, Boninsegna L, Mantovani W, et al. Prognostic factors at diagnosis and value of WHO classification in a mono-institutional series of 180 non-functioning pancreatic endocrine tumours. *Ann Oncol.* 2008;19:903–8

18. Schindl M, Kaczirek K, Kaserer K, et al. Is the new classification of neuroendocrine pancreatic tumors of clinical help? *World J Surg.* 2000;24:1312–8

19. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin.* 2017;67:93–99

20. Hashim YM, Trinkaus KM, Linehan DC, et al. Regional lymphadenectomy is indicated in the surgical treatment of pancreatic neuroendocrine tumors (PNETs). *Ann Surg.* 2014;259:197–203

21. Chin CC, Wang JY, Yeh CY, et al. Metastatic lymph node ratio is a more precise predictor of prognosis than number of lymph node metastases in stage III colon cancer. *Int J Colorectal Dis.* 2009;24:1297–302

22. Zare Mirzaei A, Abdorrazaghi F, Lotfi M, et al. Prognostic value of lymph node ratio in comparison to lymph node metastases in stage III colon cancer. *Iran J Pathol.* 2015;10:127–35

23. Smith DD, Schwarz RR, Schwarz RE: Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. *J Clin Oncol.* 2005;23:7114–24

24. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol.* 2010;17:1471–4

25. Sloothaak DAM, van der Linden RLA, van de Velde CJH, et al. Prognostic implications of occult nodal tumour cells in stage I and II colon cancer: the correlation between micrometastasis and disease recurrence. *Eur J Surg Oncol.* 2017;43:1456–1462

26. Zhao BW, Chen YM, Jiang SS, et al. Lymph node metastasis, a unique independent prognostic factor in early gastric cancer. *PLoS One.* 2015;10:e0129531

27. McDonald JR, Renehan AG, O'Dwyer ST, et al. Lymph node harvest in colon and rectal cancer: current considerations. *World J Gastrointest Surg.* 2012;4:9–19

28. Le Voyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *J Clin Oncol.* 2003;21:2912–9

29. Zhou Y, Zhang J, Cao S, et al. The evaluation of metastatic lymph node ratio staging system in gastric cancer. *Gastric Cancer.* 2013;16:309–17

30. Marchet A, Mocellin S, Ambrosi A, et al. The prognostic value of N-ratio in patients with gastric cancer: validation in a large, multicenter series. *Eur J Surg Oncol.* 2008;34:159–65