Pancreatic Cancer Lymph Node Resection Revisited: A Novel Calculation of Number of Lymph Nodes Required

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BACKGROUND: Pancreatic cancer is the third leading cause of cancer related deaths in the US. Although lymph node (LN) metastasis is a prognostic indicator, the extent of LN resection is still debated. Our goal was to use the distribution of the ratio of positive to negative LNs to derive a more adequate number of necessary examined LNs based on the target LN threshold (TLNT).

STUDY DESIGN: Using the National Cancer Database, we performed a retrospective study of surgically resected pancreatic adenocarcinoma (2010 to 2015). We evaluated the number of positive LNs and total LNs examined and the log of the ratio of positive LNs to negative LNs (LODDS). The distribution of LODDS was examined to determine a target LNs examined threshold sufficient to detect N1 disease. Using the LODDS distribution of N1 cases, target LNs examined threshold were calculated to encompass 90 of the N1 group distribution.

RESULTS: Of the total 24,038 resected patients included in this study, 26% underwent operation only, 18% received neoadjuvant therapy, and 56% underwent adjuvant therapy. In all, 8,144 (34%) patients had N0 disease and 15,894 (66%) had N1 disease. To capture 90% to 95% of the N1 group, the minimum number of LNs examined would be 18 (LODDS −2.74) to 24 (LODDS −3.04), respectively.

CONCLUSIONS: Although previous studies have suggested 11 to 17 LNs required for adequate LN sampling in pancreatic cancer, our findings suggest that to capture 90% of cases with N1 disease, 18 LNs is more appropriate. (J Am Coll Surg 2019;228:662−669. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Pancreatic cancer has recently surpassed breast cancer to become the third leading cause of cancer related deaths in the US. This statistic is discouraging for a cancer that affects only 3% of the population in the US. Equally of note is the abysmal overall 5-year survival rate of 8% in patients with pancreatic adenocarcinoma.[1] Treatment goals for pancreatic cancer are often broken down into 2 categories: treatment for cure, as seen for resectable and borderline resectable early stage disease, or treatment to increase overall survival/palliative care, particularly for those cancer that are unresectable or with distant metastatic disease at time of diagnosis. Operation is essentially the only potential curative treatment in pancreatic cancer. As such, efforts have increased to investigate factors associated with positive surgical outcomes.[2-4]

Surgical resectability for a pancreatic tumor is outlined in National Comprehensive Cancer Network recommendations. These guidelines include resectability based on anatomic relationships with nearby vessels and the absence of distant metastatic disease.[5] Additionally, there are also prognostic factors that portend poor outcomes, even in the setting of resectable disease: lymph node (LN) metastasis, large tumor size, microvascular, perineural and/or vascular invasion, low histologic differentiation, and positive margins.[6,7] Of these, LN metastasis is considered one of the strongest prognostic indicators.[8]

As such, LN staging has become paramount in many cancers, with development of guidelines for acceptable standard minimal LN numbers. Cancer specimens with

Disclosure Information: Nothing to disclose.

Presented at the Southern Surgical Association 130th Annual Meeting, Palm Beach, FL, December 2018.

Received December 14, 2018; Accepted December 17, 2018.

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https://doi.org/10.1016/j.jamcollsurg.2018.12.031
ISSN 1072-7515/19

Abbreviations and Acronyms

AJCC = American Joint Committee on Cancer
LN = lymph node
LNE = total lymph nodes examined
LNR = lymph node ratio
LODDS = log of the ratio of positive lymph nodes to negative lymph nodes
NCDB = National Cancer Database
PLN = positive lymph node
TLNT = target lymph node threshold

no LNs or low numbers of LNs lead to potential understaging of disease. When any cancer is understaged, it leads to an overestimation of long-term outcomes and survival.

For example, the American Joint Committee on Cancer (AJCC) staging system (2010) recommended at least 12 nodes for staging in colon cancer, and the gastric cancer minimum has become 15 lymph nodes.[9] In contrast, consensus has yet to be established for adequate lymphadenectomy in pancreatic cancer with recommendations ranging from 10 to 17 LNs in various studies.[10-12]

There is also controversy about appropriate methodology for determining optimal LN numbers. For pancreatic cancer, AJCC stages LN disease as N0 for LN-negative or N1 for LN-positive disease (1 or more positive LNs). Another methodology to classify and evaluate lymphadenectomy includes lymph node ratio (LNR, calculated by the positive number of LN divided by total number resected).[12-16] However, LNR is not useful in patients with no positive LNs harvested (LNR of 0). In addition, LNR does not distinguish between patients with a larger and smaller number of LNs examined: a patient with 2 positive LNs out of 2 examined has the same LNR as a patient with 20 of 20 (LNR = 1 in both cases). A recently proposed method is the log odds of metastatic (positive) LN (LODDS), which is the log of the ratio of positive LNs to negative LNs[16] as a prognostic indicator. A 2018 study by He and colleagues[17] assessed the prognostic performance of various staging systems, including PLN, LNR, and LODDS, and reported LODDS had the best predictive value of overall survival and progression-free survival.

To date, there is little examination of the frequency at which a low number of positive LNs (PLN) are found relative to larger lymph nodes examined (LNE), among N1 cases, which is critical in evaluating the minimal number of LNs needed for accurate staging. In this study, we examine current surgical practice (2010 to 2015) to examine the differences in LNE for N1 vs N0 cases. We hypothesize a target number of LNs that need to be examined for accurate staging (target LN threshold [TLNT]) can be derived based on LODDS (the distribution of positive to negative LNR) among N1 cases.

METHODS

Patient characteristics

The National Cancer Database (NCDB) is a joint program of the American College of Surgeons and the American Cancer Society that accounts for approximately 75% of all newly diagnosed pancreatic cancers every year.[18,19] The NCDB collects data from more than 1,440 hospitals in the US and thereby provides information on more than 20 million patients. Our cohort selection is depicted in Figure 1. Our cohort included patients with a diagnosis of primary adenocarcinoma of the pancreas (ICD for Oncology codes 8140 and 8500), diagnosed between 2010 and 2015, who received surgical treatment of the primary tumor with LN dissection. Patients with non-adenocarcinoma pancreatic tumors were excluded, as were those with adenocarcinoma from another site that was metastatic to the pancreas. We included patients undergoing surgical resection with or without neoadjuvant chemotherapy, neoadjuvant chemoradiation, adjuvant chemotherapy, or adjuvant chemoradiation. We excluded patients who received intraoperative radiation or neoadjuvant radiation without chemotherapy. Patients with missing or non-numerical PLN count or total LNE were excluded. Patients missing both a clinical and pathologic AJCC stage category were not included in analyses. American Joint Committee on Cancer pathologic staging was used unless missing, in which case, AJCC clinical staging was used. Stage I, IA, and IB were categorized as stage I. Lymph node positivity (N1) was defined as having any regional LN classified as positive based on pathologic examination. Patients whose operations were performed at an unknown cancer center facility type were classified as "unknown." Patients at "community" and "comprehensive community" facilities were classified as "community." This study was reviewed and deemed exempt by University of Arizona IRB (IRB# 1804468234), as all data were deidentified.

Statistical analysis

Patient characteristics, such as demographics and treatment patterns, were summarized with descriptive statistics, such as means, SDs, frequencies, and percentages. When used, statistical tests were 2-sided.

Calculation of log of the ratio of positive lymph nodes to negative lymph nodes

We use the distribution of LODDS for this calculation because it had been shown to have the best predictive

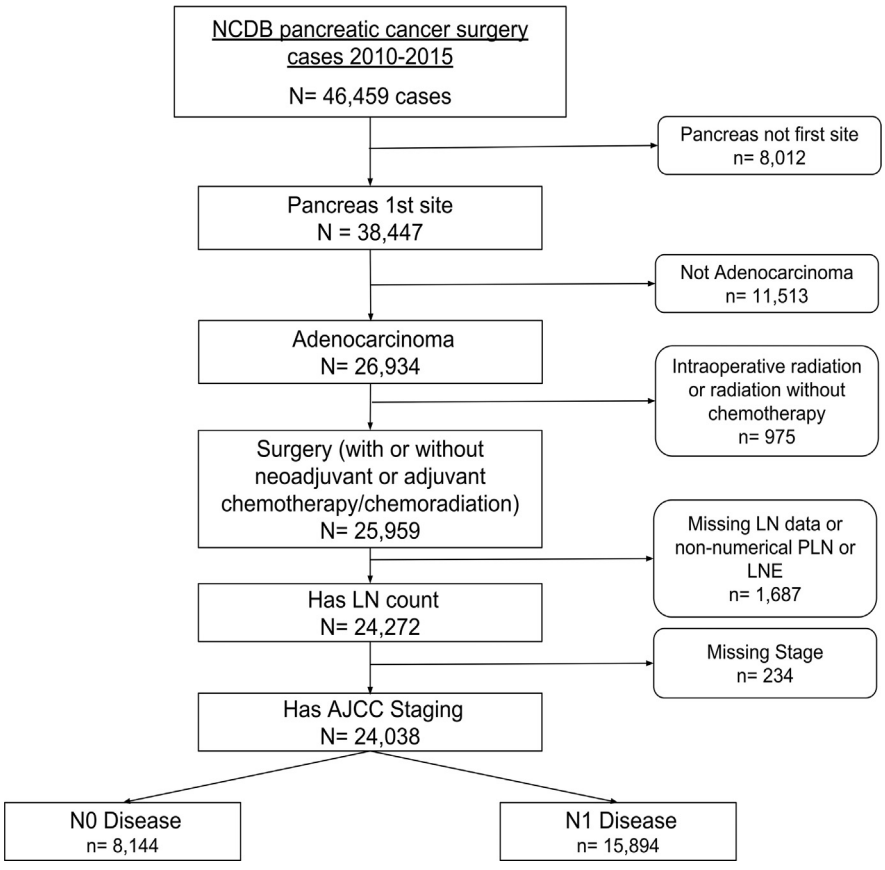

Figure 1. Exclusion criteria flowchart.

value of survival in previous studies[15] and because it allows a direct visual comparison of N1 and N0 LNE distributions. The LODDS was calculated with the following formula:

$$\text{LODDS} = \log[(\text{PLN} + 0.1)/(\text{LNE} - \text{PLN} + 0.1)]$$

In this calculation, PLN is number of positive LNs and LNE is number of LNs examined. To avoid singularity in the case where PLN = 0 or PLN = LNE, a constant of 0.1 was added to the numerator and denominator.

Calculation of target lymph nodes examined threshold count

This calculation uses the empirical distribution of positive LN frequency among N1 cases to estimate what minimum number of LNE would need to be examined to capture 90% of pancreatic cancers that would have positive LNs if the lymphadenectomy is adequate. The bottom 10% of the LODDS distribution represents those cases with the lowest frequency of positive LNs relative to the total number of LN examined. We use the distribution of the log of the odds of PLN (LODDS) to identify a TLNT at the 10th percentile. By assuming 1 positive LN within the LODDS equation, we calculated the proportion of positive LN to total LNE, for any given quantile percentage, x, of the LODDS distribution. This calculation is represented by:

$$\text{LODDS} = \log[(\text{PLN} + 0.1)/(\text{LNE} - \text{PLN} + 0.1)] \rightarrow$$

$$\log[(1 + 0.1)/(\text{TLNT} - 1 + 0.1)] = \text{LODDSx or}$$

$$1.1 + \left(\left(0.9 * e^{\text{LODDSx}}\right)/\left(e^{\text{LODDSx}}\right)\right) = \text{TLNT}$$

Where PLN is positive LNs, LNE is LNs examined, and LODDS_x it the LODDS value at a given distribution percentile, x, and TLNT is the target LN threshold. We report the TLNT estimate across the quantile distribution of LODDS for N1, as well as the TLNT threshold that encompasses 90% of N1 cases. The lowest 10% of this distribution represents those cases with the lowest proportion of positive LNs relative to the number of LNs examined.

Differences between the groups were assessed using Student's *t*-test or Wilcoxon rank sum test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. A general linear regression model

was used to evaluate the effect of time on the number of LNE for N1 and N0 cases. All tests used a 2-tailed p value. SAS software, version 9.4 (SAS Institute) was used for all statistical analysis.

RESULTS

Patient and disease characteristics

A total of 24,038 patients were identified based on our study inclusion criteria (Fig. 1 and Table 1). Of those, 33.9% (8,144) had LN-negative (N0) disease and 66.1% (15,894) had LN-positive (N1) disease (Table 1). Mean age was 65.4 years and 51.2% were male.

Of all patients, 82.9% (19,928) had stage II and 2,482 (10.3%) had stage I disease (Table 1). There were 755 (3.1%) stage III and 824 (3.4%) stage IV disease patients. Discrepancy between stage category and LN positivity reflects the available clinical and pathologic staging and the accuracy of the NCDB records.

Of the total cohort, 18.1% of patients underwent neoadjuvant therapy. Of these, 12.1% received neoadjuvant only, and 6.0% (1,451) underwent perioperative therapy with neoadjuvant therapy followed by operation and then adjuvant therapy. There were 13,372 (61.7%) patients that received adjuvant therapy, and 26.2% of patients underwent operation only. In an unadjusted analysis, patients who underwent neoadjuvant therapy were more likely to have N0 disease time of resection compared with those who underwent operation alone or adjuvant therapy (51.6% neoadjuvant vs 30.0% no neoadjuvant, chi-square = 745; $p < 0.0001$). Patients with N0 disease had clinically similar rates of multimodality therapy compared with patients with N1 disease (72.7% vs 74.4%, chi-square = 7.8; $p < 0.005$), although in the latter group, it was more often delivered in the adjuvant setting.

For surgical facilities, 30.6% of operations were performed in community cancer programs, and the majority, 51.2%, were performed at academic/research programs, 10.0% were performed at integrated network facilities, and 8.2% were unknown (Table 1). There was no difference between N0 and N1 rates among the known facility-types (chi-square = 1.8; $p = 0.41$).

Table 1. Demographics and Treatment

Characteristic	All (n = 24,308)	N0 (n = 8,144)	N1 (n = 15,894)
Age, y, mean (SD)	65.4 (10.3)	66.0 (10.4)	65.3 (10.2)
Race, ethnicity, n (%)			
White	19,367 (80.6)	6,495 (79.7)	12,872 (80.1)
Black	2,493 (10.4)	863 (10.6)	1,630 (10.3)
Hispanic	1,114 (4.8)	397 (4.9)	748 (4.7)
Other/unknown	1,033 (4.3)	389 (4.8)	644 (4.1)
Sex, n (%)			
Male	12,314 (51.2)	4,058 (49.8)	8,256 (51.9)
Female	11,724 (48.9)	4,086 (50.2)	7,638 (48.1)
American Joint Committee on Cancer stage, n (%)			
0	49 (0.2)	47 (0.6)	2 (0.01)
1	2,482 (10.3)	2,390 (29.4)	92 (0.6)
2	19,928 (83.0)	5,229 (64.2)	14,699 (92.5)
3	755 (3.1)	263 (3.2)	492 (3.1)
4	824 (3.4)	215 (2.6)	609 (3.8)
No. of nodes examined median (interquartile range)	16 (11–23)	14 (8–20)	17 (12–24)
Treatment, n (%)			
Surgery only	6,301 (26.2)	2,225 (27.3)	4,076 (25.6)
Adjuvant chemo/XRT	13,372 (55.6)	3,668 (45.0)	9,704 (61.1)
Neoadjuvant chemo/XRT	2,914 (12.1)	1,647 (20.2)	1,267 (8.0)
Neoadjuvant and adjuvant therapy	1,451 (6.0)	604 (7.4)	847 (5.3)
Facility/program, n (%)			
Community	7,348 (30.6)	2,440 (30.0)	4,908 (30.9)
Academic	12,318 (51.2)	4,303 (52.8)	8,015 (50.4)
Integrated network	2,398 (10.0)	804 (9.9)	1,594 (10.0)
Unknown	1,974 (8.2)	597 (7.3)	1,377 (8.7)

XRT, radiation therapy.

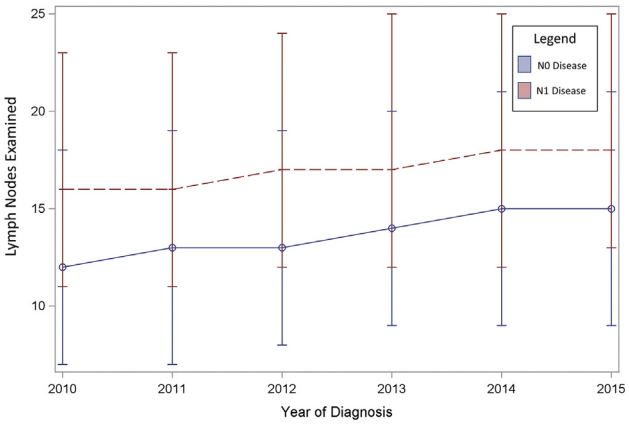

Figure 2. Median, interquartile number of lymph nodes examined over time, by lymph node disease status.

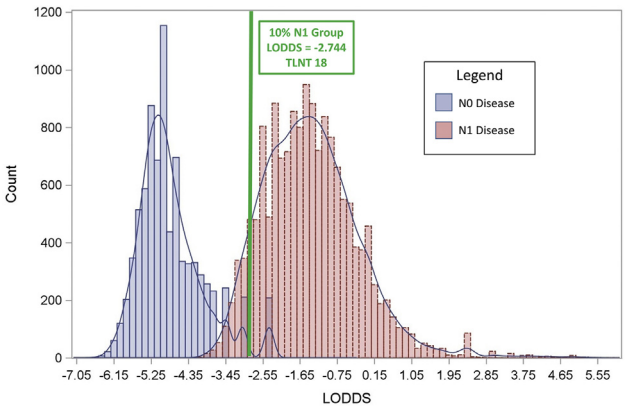

Figure 3. Distribution of log of the ratio of positive lymph nodes to negative lymph nodes by positive lymph node status. TLNT, target lymph node threshold.

Lymphadenctomy parameters

The range of LNE was not different between N0 and N1 groups (1 to 81 vs 1 to 90, respectively). A Wilcoxon signed-rank test indicates that the median LNE for N0 cases (14 LNE) was significantly lower than the median LNE for N1 cases (17 LNE) ($Z = -29$; $p < 0.0001$) (Table 1). A linear regression analysis of the effect of time and node status on LNE showed a significant increase in LNE over time ($t = 9.0$; $p < 0.0001$). The estimated linear increase in LNE per year was 0.41 for N1 and 0.55 for N0. As shown in Figure 2, N0 cases have a consistently lower median number of LNs examined compared with N1 disease through the entire time period analyzed, implying possible understaging in this group.

Log of the ratio of positive lymph nodes to negative lymph nodes distribution

As shown in Figure 3, LODDS creates a normal distribution to evaluate N0 and N1 disease. The LODDS of the lower 10% of N1 disease was −2.744, which calculates to a TLNT of 18 (see Methods section, Table 2, and Fig. 3). To capture 90% of pancreatic cancers with positive LNs at the time of operation, 18 LNs (the TLNT) need to be examined and to miss <5% of cases with positive LNs, 24 nodes would be the minimum to examine (Table 2). Examining this N1 population in light of previous LN count recommendations, 27.8% had fewer than 1 in 10 positive LNs and 12.4% had fewer than 1 in 17 positive LNs.

Of note, the majority of all N1 cases (78%) had <5 total positive LNs, regardless of the total LNE (Fig. 4). However, of the N1 patients with a PLN/LNE ratio of 1 of 18 or fewer (10% TLNT cases with LODDS < −2.744), 91% had only 1 positive LN harvested (Table 2 and Fig. 4). For this particular group, the cases that had >1 PLN harvested (9%) also had a significantly higher number of LNE and, therefore, correspondingly a similar PLN/LNR ratio as those in the group with only 1 positive LN harvested.

DISCUSSION

Compared with other cancers, pancreatic cancer continues to have dismal long-term outcomes because of its late presentation and limited effective treatment regimens. Lymph node disease has been shown to be a prognostic indicator of both outcomes and survival in several cancers.[8,14,16,20-22] The aim of our current study was to identify the number of LNs needed to ensure adequate staging in pancreatic cancer. The value of evaluating PLN frequency among N1 cases to identify a minimum number of resected LNs needed is to accurately identify N1 disease. Based on our result, 10% of N1 cases had a frequency of 1 in 18 positive LNs or fewer. The findings in our study align with much of the recent literature suggesting current recommendations are underestimating the number of resected LNs required in a pancreatic surgical resection.[9,10] Our results prompt the question of whether patients with the lower LNE and shorter survival in previous studies were truly node-negative or whether PLN were not discovered due to inadequate resection.

Accurate staging requires removing enough LNs to evaluate for node-positive disease. Valsangkar and colleagues[12] reported in Surveillance, Epidemiology, and End Results data set analysis that 75% of patients had <12 LNE, with a median LNE of 8. Additionally, Slidell and colleagues[23] used the Surveillance, Epidemiology, and End Results database to show that nodal disease alone or the absolute number of positive LNs can fail to stratify survival secondary to an inadequate LN dissection (though in their

Table 2. Log of the Ratio of Positive Lymph Nodes to Negative Lymph Nodes Quantiles Table, and Target Lymph Node Threshold Estimate Across N1 Disease Distribution

Quantiles table	LODDS	TLNT	PLN/LNE ratio
100% Maximum	5.525453	1	1/1
75% Q3	−0.683295	3	1/3
50% Median	−1.466337	6	1/6
25% Q1	−2.217225	11	1/11
10%*	−2.743768	18	1/18
5%	−3.044522	24	1/24
1%	−3.433987	35	1/35

LNE, total lymph nodes examined; LODDS, log of the ratio of positive lymph nodes to negative lymph nodes; PLN, positive lymph node; Q, quantile; TLNT, target lymph node examined threshold.
*Target lymph node examined threshold at the 10th percentile.

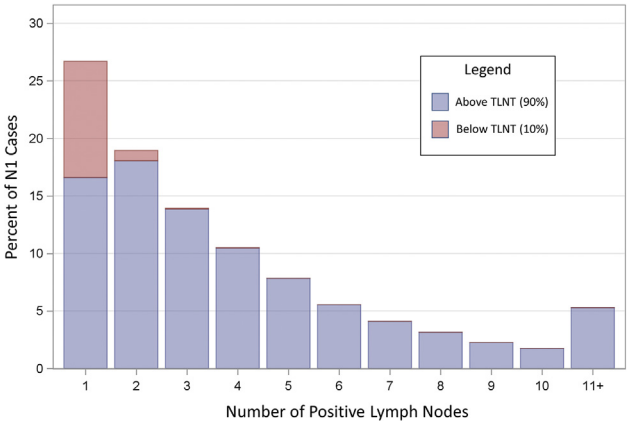

Figure 4. Number of positive lymph nodes in N1 disease. TLNT, target lymph node threshold.

study, the median number of LNs evaluated was 7). In addition, multiple studies have shown that node-negative patients have better overall survival compared with N1 patients after operation.[8,24-27] In a study of stage III colon cancer patients, both LNR and LODDS stratifications affected survival regardless of total LNE.[28] Many others, including Le Voyer and colleagues,[24] reported that in colon cancer, higher numbers of LNE in the node-negative population are associated with increased survival. Some of that effect might be due to failing to detect N1 disease in the patients with a low LNE. With a higher number of LNs examined in the N0 group, the likelihood of missing a positive LN, and thereby correctly stage a patient, decreases.

In 2017, Contreras and colleagues[29] performed a retrospective analysis of NCDB data on LN retrieval and concluded that there is an incremental positive relationship between LN retrieval and survival in patients undergoing pancreatic cancer resection. They also evaluated multiple cutoff points for minimum LN retrieval in node-negative patients, and showed that those cases below a given cutoff point consistently had significantly lower median survival times compared with those at or above the nodal cutoff threshold. This difference persisted even at the highest cutoff evaluated (24 LNs). Supporting this is also our finding of consistently lower median LNE for N0 compared with N1 cases, even in this era of minimum LN recommendations. If N0 cases were receiving sufficient LN dissection, there is little reason for a difference in median LNE between N0 and N1 groups. Even within this contemporary cohort of 2010 to 2015, more than 38% of N0 cases had fewer LNs extracted than even the lowest guideline recommendation of 12 by the International Study Group on Pancreatic Surgery compared with 23% of N1 cases.[10] Together these results suggest that a higher minimum number of LNs might need to be extracted to avoid false N0 diagnoses and to accurately capture true N1 cases. This is important because currently there is no widely agreed on guideline dictating the standard of care for LN resection in patients with pancreatic adenocarcinoma undergoing surgical resection. Clinical nodal staging has been reported to be <50% sensitive, with understaging occurring in almost half of cN0 patients undergoing operations.[30] Additionally, data in earlier studies have demonstrated there is increased survival in patients with >15 LNE for both node-negative and -positive disease.[31,32] Again, this highlights the importance of a more concrete retrieval guideline, such as our proposed TLNT.

The National Comprehensive Cancer Network recommends multimodality therapy with operation and chemotherapy (with or without chemoradiation) for the treatment for resectable pancreatic cancer regardless of nodal status.[33] Despite these recommendations, >25% of patients who underwent operation alone did not receive multimodality therapy. When stratified by nodal status, our study shows that a similar proportion of patients get multimodality therapy (neoadjuvant and/or adjuvant chemotherapy); however, those who receive neoadjuvant therapy are more likely to have negative nodes at resection, and those who are node-positive more often get chemotherapy in the adjuvant setting. Although 66.4% of N1 patients underwent adjuvant chemotherapy, 52.5% of N0 patients received adjuvant therapy (chi-square = 442; $p < 0.0001$).

Our study is not without limitations. Beyond its retrospective nature, we were limited in which variables could be assessed due to only having available the information collected through the NCDB. In addition, not all fields in the NCDB database are uniformly populated, which leads to missing variables and incorrect data. Another limitation was that we do not have detailed information about the LN dissection. Specifically, the relationship of the

positive LNs resected to the order of resection is unknown. We also cannot determine how pathologic examination of resected LNs might be contributing to low LNE counts. Having this information would give more information related to number of LNs necessary to ensure capturing PLN. Nevertheless, these results provide a benchmark for the surgical and pathology teams to collectively evaluate surgical care by. Lastly, as this study includes a large population of more than 24,000 patients, the study is highly powered and can overestimate statistically significant, yet clinically irrelevant, small differences. Regardless of potential limitations, our study is novel in that it uses the most sensitive evaluation of lymphadenectomy (in relation to survival).[10,16,17,34] to determine the minimum number of LNs examined to find 90% to 95% of LN-positive disease.

CONCLUSIONS

Because LN status is a key prognostic indicator in many cancers, many studies have looked at the LN dissection and LNE. Our study uses LODDS in a novel way to determine the frequency of PLNs found among N1 disease and, accordingly, to determine what minimal LNE number should be considered.

Author Contributions

Study conception and design: Arrington, Price
Acquisition of data: Arrington, Price
Analysis and interpretation of data: Arrington, Price, Golisch, Riall
Drafting of manuscript: Arrington, Price, Golisch, Riall
Critical revision: Arrington, Price, Golisch, Riall

REFERENCES

1. Gordon-Dseagu VL, Devesa SS, Goggins M, Stolzenberg-Solomon R. Pancreatic cancer incidence trends: evidence from the Surveillance, Epidemiology and End Results (SEER) population-based data. Int J Epidemiol 2018;47:427–439.
2. Gall TM, Thompson Z, Dinneen EP, et al. Surgical techniques for improving outcomes in pancreatic ductal adenocarcinoma. Expert Rev Gastroenterol Hepatol 2014;8:241–246.
3. Zhan HX, Xu JW, Wang L, et al. Lymph node ratio is an independent prognostic factor for patients after resection of pancreatic cancer. World J Surg Oncol 2015;13:105.
4. Nakamura T, Asano T, Okamura K, et al. A preoperative prognostic scoring system to predict prognosis for resectable pancreatic cancer: who will benefit from upfront surgery? J Gastrointest Surg 2018 Sep 21 [Epub ahead of print].
5. Isaji S, Mizuno S, Windsor JA, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology 2018;18:2–11.
6. Yeo CJ, Sohn TA, Cameron JL, et al. Periampullary adenocarcinoma: analysis of 5-year survivors. Ann Surg 1998;227:821–831.
7. Yeo CJ, Cameron JL. Prognostic factors in ductal pancreatic cancer. Langenbecks Arch Surg 1998;383:129–133.
8. House MG, Gonen M, Jarnagin WR, et al. Prognostic significance of pathologic nodal status in patients with resected pancreatic cancer. J Gastrointest Surg 2007;11:1549–1555.
9. 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;17:1471–1474.
10. Tol JA, Gouma DJ, Bassi C, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery 2014;156:591–600.
11. Eskander MF, de Geus SW, Kasumova GG, et al. Evolution and impact of lymph node dissection during pancreaticoduodenectomy for pancreatic cancer. Surgery 2017;161:968–976.
12. Valsangkar NP, Bush DM, Michaelson JS, et al. N0/N1, PNL, or LNR? The effect of lymph node number on accurate survival prediction in pancreatic ductal adenocarcinoma. J Gastrointest Surg 2013;17:257–266.
13. National Comprehensive Cancer Network. Pancreatic Adenocarcinoma: NCCN Clinical Practice Guidelines in Oncology, version 3.2017. Fort Washington, PA: National Comprehensive Cancer Network; 2015.
14. Berger AC, Watson JC, Ross EA, Hoffman JP. The metastatic/examined lymph node ratio is an important prognostic factor after pancreaticoduodenectomy for pancreatic adenocarcinoma. Am Surg 2004;70:235–240; discussion 240.
15. Tol JA, Brosens LA, van Dieren S, et al. Impact of lymph node ratio on survival in patients with pancreatic and periampullary cancer. Br J Surg 2015;102:237–245.
16. La Torre M, Nigri G, Petrucciani N, et al. Prognostic assessment of different lymph node staging methods for pancreatic cancer with R0 resection: pN staging, lymph node ratio, log odds of positive lymph nodes. Pancreatology 2014;14:289–294.
17. He C, Mao Y, Wang J, et al. Surgical management of periampullary adenocarcinoma: defining an optimal prognostic lymph node stratification schema. J Cancer 2018;9:1667–1679.
18. American College of Surgeons. National Cancer Database: Tools, Reports, and Resources. Chicago IL: American College of Surgeons; 2018.
19. National Cancer Database 2018. Available at: https://www.facs.org/quality-programs/cancer/ncdb. Accessed November 26, 2018.
20. La Torre M, Nigri G, Cavallini M, et al. The Glasgow prognostic score as a predictor of survival in patients with potentially resectable pancreatic adenocarcinoma. Ann Surg Oncol 2012;19:2917–2923.
21. La Torre M, Ramacciato G, Nigri G, et al. Post-operative morbidity and mortality in pancreatic surgery. The role of surgical Apgar score. Pancreatology 2013;13:175–179.
22. Lorenzon L, Mercantini P, Ferri M, et al. Lymph-node ratio classification strongly correlates with cancer survivals of patients who underwent r0 resection for gastric cancer with more than 15 nodes harvested. Eur Surg Res 2014;53:1–10.
23. Slidell MB, Chang DC, Cameron JL, et al. Impact of total lymph node count and lymph node ratio on staging and survival after pancreatectomy for pancreatic adenocarcinoma: a large, population-based analysis. Ann Surg Oncol 2008;15:165–174.
24. 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;21:2912–2919.
25. Kang MJ, Jang JY, Chang YR, et al. Revisiting the concept of lymph node metastases of pancreatic head cancer: number of metastatic lymph nodes and lymph node ratio according to N stage. Ann Surg Oncol 2014;21:1545–1551.
26. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. Ann Surg 2003;237:74–85.
27. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg 2000;4:567–579.
28. Lee CW, Wilkinson KH, Sheka AC, et al. The log odds of positive lymph nodes stratifies and predicts survival of high-risk individuals among stage III rectal cancer patients. Oncologist 2016;21:425–432.
29. Contreras CM, Lin CP, Oster RA, et al. Increased pancreatic cancer survival with greater lymph node retrieval in the National Cancer Data Base. Am J Surg 2017;214:442–449.
30. Tran Cao HS, Zhang Q, Sada YH, et al. Value of lymph node positivity in treatment planning for early stage pancreatic cancer. Surgery 2017;162:557–567.
31. Mirkin KA, Hollenbeak CS, Wong J. Greater lymph node retrieval improves survival in node-negative resected gastric cancer in the United States. J Gastric Cancer 2017;17:306–318.
32. Mirkin KA, Hollenbeak CS, Wong J. Greater lymph node retrieval and lymph node ratio impacts survival in resected pancreatic cancer. J Surg Res 2017;220:12–24.
33. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Pancreatic Cancer 2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed November 24, 2018.
34. Ramacciato G, Nigri G, Petrucciani N, et al. Prognostic role of nodal ratio, LODDS, pN in patients with pancreatic cancer with venous involvement. BMC Surg 2017;17:109.

Discussion

DR STEVEN J HUGHES (Gainesville, FL): This study stands on a vast body of previous work that establishes that the presence or absence of lymph node metastases from solid organ malignancies provides very important prognostic information. Therefore, this information drives cohort definitions (staging), and from this, treatment recommendation. This concept is rather advanced in melanoma and breast disease with sentinel lymph node analysis, but unfortunately, lymphatic drainage networks within the abdomen have proven a challenge to such approaches for gastrointestinal malignancy. This study speaks to our collective desire as surgeons to have a "magical" number that defines adequacy of the surgical lymphadenectomy. This has been realized for colon and rectal cancer, but the authors appropriately note that adequacy of lymphadenectomy for pancreatic ductal adenocarcinoma remains poorly understood.

This is intriguing use of the National Cancer Database (NCDB). They report that the average number of lymph nodes analyzed in the setting of node negative disease is consistently lower than that when lymphatic metastases are present. They use a novel statistical strategy using the log of the ratio of positive lymph nodes to the number of negative lymph nodes to evaluate the distribution of total lymph nodes analyzed in these negative and positive cohorts. It is complicated. They then assign a cutoff to the minimum nodes needed to be analyzed in order to capture 90% of the N1 group, and this magical number proves to be 18 or 19 lymph nodes.

The question being addressed here centers on the adequacy of sampling. This is one of the reasons that lymph node ratios probably provide superior prognostic information. A ratio provides an understanding of the volume of metastatic burden in a total volume of specimens analyzed; number of positive nodes alone does not give one an understanding of the overall volume sampled. Further, the sampling is dependent on the fact that the standard of care involves the bi-valving of the lymph node, an analysis of 1 or at most 2 thin sections of said lymph node. This is the reason that sentinel lymph node biopsies involve multiple sections through the node of interest. In fact, one uses a very sensitive tool like reverse transcription-polymerase chain reaction in the setting of pancreatic cancer, virtually all lymph nodes are proven to be positive. The authors offer significant value to our current understanding.

The question germane to this audience is whether an adequate lymphadenectomy has been performed, but this data source and methodology places the entire lymph node count on the shoulders of the surgeon and cannot assess bias or variability within the surgical pathology suite or the reading room. These important variables cannot be addressed with a database analysis.

How would you suggest validating this number of 18 or 19 lymph nodes as an essential quality assessment tool akin to what is being done for colon and rectal cancer? What happens when you apply these criteria to your current or unique data set? Is there, in fact, a poorer survival in patients in whom fewer than 19 lymph nodes were analyzed? If there are fewer than 19 lymph nodes, would additional sampling of the available lymph nodes suffice to overcome this inadequate sampling? Have you considered presenting your data as a continuous variable rather than as a categorical variable?

You demonstrated, as others have, that neoadjuvant therapy is associated with a reduction in the percentage of cases in which lymph node metastases are identified. This is particularly intriguing to me in this era of immunotherapy because it may suggest that neoadjuvant therapy is particularly effective at sterilizing lymphatic metastases. However, you did not exclude these patients from your analysis. So please explain or further explain to me why you chose to include these patients in the analysis. Clearly, you have plenty of patients. And then would you give us a little more rationale as to why you excluded patients who received intraoperative radiation or radiation therapy alone? A total of 92% of your study population proved to be in stage II. This is a strong skewing to a stage, and I ask, does this really matter? Or is there value in refining the data set to incorporate a greater percentage of Stage 1 and Stage 3 patients in your training set?