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Therapeutic Index of Lymphadenectomy Among Patients with Pancreatic Neuroendocrine Tumors: A Multi-Institutional Analysis

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This is the author manuscript accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jso.25689.

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Running title: Benefit of Lymphadenectomy for pNET

Keywords: Lymphadenectomy, Pancreatic neuroendocrine tumor, Therapeutic index

Financial Support: There was no financial support for this study

Synopsis: The study assessed the therapeutic benefit associated with lymphadenectomy among patients with pancreatic neuroendocrine tumors by calculating the therapeutic index. Tumor size, Ki-67, tumor location and the number of LNs evaluated were associated with a meaningful therapeutic index yet a minimal difference in recurrence free survival.

Data Availability Statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abstract

Background: The benefit from lymph node dissection (LND) in patients with pancreatic neuroendocrine tumor (pNET) based on clinicopathologic characteristics remains unclear.

Methods: Patients undergoing surgery for pNET between 1997 and 2016 were identified using a multi-institutional dataset. The therapeutic index of LND relative to patient characteristics was calculated.

Results: Among 647 patients, the median number of LNs evaluated was 10 (IQR:4-16) and approximately one quarter had LNM (N=159, 24.6%). Among patients with LNM, 5-year RFS was 56.0%, reflecting a therapeutic index value of 13.8. The therapeutic index was highest among patients with a moderately/poorly-differentiated pNET (21.5), Ki-67 ≥3% (20.1), tumor size ≥2.0cm (20.0), and location at head of pancreas (20.0). Patients with ≥8 LNs evaluated had a higher therapeutic index than patients who had 1-7 LNs evaluated (≥8: 17.9 vs.1-7: 7.5; difference of index: 11.4).

Conclusion: LND was mostly beneficial among patients with pNETs >2 cm, Ki-67 ≥3%, and lesions located at the pancreatic head as identification of LNM was most common among individuals with these tumor characteristics. Evaluation of ≥8 LNs

was associated with a higher likelihood of identifying LNM as well as a higher therapeutic index, and therefore this number of nodes should be considered the goal.

Introduction

Pancreatic neuroendocrine tumors (pNETs) are rare neoplasms of the gastrointestinal tract with a rising incidence in the United States (US).[1, 2] Resection is the mainstay treatment among patients with resectable pNETs, although several non-surgical techniques have been employed.[3-5] While lymphadenectomy is typically performed at the time of resection to stage the disease, the role of routine lymph node dissection (LND) and the associated oncological therapeutic benefit remains controversial.[4] For example, while data from a single-institution cohort of 136 pNET patients reported that lymph node metastasis (LNM) was associated with shorter disease-free survival (DFS),[6] a separate population-based study of 3,851 patients demonstrated that nodal status was not necessarily associated with overall survival (OS).[7] In light of these data, several investigators have questioned the benefit of routine LND in the treatment of nonfunctional pNET patients with a Ki-67 < 3%.[8] In fact, one recent study noted that patients who had a pNET ≤ 2.0 cm and a Ki-67 < 3% in the distal pancreas had an incidence of LNM as low as 3.4% and, therefore, questioned the need for routine LND.[9]

While many studies support the predictive role of LNM and therefore the role of LND, robust evidence is lacking to support an actual therapeutic benefit for routine LND in pNET patients with resectable disease.[4] To this end, Sasako and colleagues have suggested using “therapeutic index” as a means to determine any potential survival benefit associated with LND among patients undergoing surgical resection.[10]

The rationale of therapeutic index is to identify patients who are most likely to have LNM and, therefore, derive a benefit from LND.[10] The therapeutic index concept has been examined and validated for several other cancers including gastric, colorectal, cholangiocarcinoma and lung.[10-14] Nevertheless, to date, no study has assessed the therapeutic value of LND among patients with pNETs. As such, the objective of the current study was to define the therapeutic index of LND among patients undergoing resection of pNETs. In particular, we sought to identify preoperative patient factors, as well as clinicopathologic features of pNETs, that were associated with a potential clinically relevant therapeutic benefit associated with LND.

Methods

Study Population and Data Collection

Patients who underwent pancreatectomy for pNETs between 1997 and 2016 were identified using a multi-institutional database from eight tertiary institutions (The Ohio State University Comprehensive Cancer Center, Columbus, OH; University of Michigan, Ann Arbor, MI; Stanford University, Palo Alto, CA; Virginia Mason Medical Center, Seattle, WA; Winship Cancer Institute, Emory University, Atlanta, GA; Washington University, School of Medicine, St. Louis, MO; University of Wisconsin, School of Medicine and Public Health, Madison, WI; Vanderbilt University, Nashville, TN).[15] All patients included in the study had a histologically proven pNET and underwent a curative intent pancreatectomy along with LND. Patients with metastatic disease, as well as individuals with macroscopically positive surgical margins (R2 resection), missing follow-up data and individuals who died within 30-days of surgery were excluded from the analysis. The study was approved by the Institutional Review Board of all participating institutions.

Patient demographic and clinicopathologic data included age, sex, race, American Society of Anesthesiologist (ASA) class, functional status, type of resection, tumor size, tumor location, tumors number, number of LNs examined, number of LNM, tumor grade, resection margin status, Ki-67 status, presence of lympho-vascular or perineural invasion and receipt of adjuvant therapy. Functional tumors were defined as lesions with hormone overproduction (i.e. insulinoma, gastrinoma, somatostatinoma and VIPoma).[16] LND was defined as removal of LNs from regional nodal stations. All resected specimens were submitted for histopathologic analysis by an experienced pathologist at each institution.

Calculation of Therapeutic Index

The frequency of LNM was calculated by dividing the number of patients with LNM in a particular group by the total number of patients in that subgroup.[14] The therapeutic index of LND was calculated by multiplying the frequency of LNM in a particular group by the 5-year recurrence-free survival (RFS) rate of patients with LNM in that specific subgroup of patients, as previously reported;[17] the 5-year endpoint was based on previous studies.[11, 18, 19] Similar to previous reports, a therapeutic index difference of more than ten was considered meaningful.[14, 17, 18]

Statistical Analysis

Continuous and categorical variables were presented as median (inner quartile range [IQR]) and frequency (%), respectively. Logistic regression was utilized to detect independent predictors of LNM. RFS was defined as time duration from the date of surgery to tumor recurrence. Recurrence was defined as identification of suspicious imaging findings or biopsy-proven tumor. Overall survival (OS) was calculated from the date of surgery to date of death or last follow-up. Survival curves were estimated using the Kaplan-Meier method and differences between curves were investigated with the log-rank test. Statistical significance was assessed at $\alpha = 0.05$. All statistical analyses were performed using SPSS, version 25 (IBM Corp. Armonk, NY, USA).

Results

Characteristics of patients undergoing lymphadenectomy

Among 1,125 patients who underwent curative-intent resection of pNETs, 647 (57.5%) patients underwent LND and were included in the final analysis **(Table 1)**. Median patient age at the time of surgery was 58 years old (IQR 48-66); roughly one-half of patients were male (N=343, 53.0%) and had an ASA score of 3 (N=328, 52.6%). Most patients were white (N=480, 80.7%), had a non-functional tumor (N=559, 88.0%), had a tumor located in the body or tail of the pancreas (N=385, 59.6%) and underwent a distal pancreatectomy (N=392, 60.6%) through an open surgical approach (N=491, 75.9%). Most patients had unifocal disease (N=590, 92.0%) and a median tumor size of 2.2 cm (IQR 1.4-3.8). The median number of LNs evaluated was 10 (IQR 4-16) and approximately one quarter of patients had LNM (N=159, 24.6%). Most patients underwent an R0 resection (N=537, 83.8%) (**Table 1**).

Preoperative Factors associated with LNM

On bivariate analysis, male sex [Odds ratio (OR) 1.54, 95% confidence interval (CI) 1.07-2.22], functional pNET status (OR, 0.48; 95%CI 0.25-0.94), symptomatic pNET (OR 1.53; 95%CI 1.05-2.23), primary location of tumor in the head of pancreas (OR 2.41; 1.67-3.47), tumor size ≥ 2.0 cm (OR 5.90; 3.78-9.21), number of LNs evaluated ≥ 8 (OR 3.04; 1.99-4.64), moderately (OR 2.78; 1.62-4.79) or poorly differentiated (OR 6.67; 2.19-20.33) tumors, and Ki-67 between 3% and 20% (OR 3.34; 2.11-5.30), or Ki-67 > 20% (OR 7.84; 2.97-20.69) were associated with LNM. On multivariable analysis, only presence of symptoms (OR 2.03; 1.17-3.51), primary tumor in head of pancreas (OR, 1.83; 1.10-3.06), tumor size ≥ 2.0 cm (OR, 4.59; 2.57-8.20), and Ki-67 between 3% and 20% (OR, 1.83; 1.04-3.22) remained associated with a higher likelihood of LNM (**Table 2**).

Survival and Therapeutic Index by preoperative factors

After a median follow-up of 33.9 months (IQR 11.9-62.6), 5-year OS was 84.1% (95%CI 74.9-90.3) among patients with LNM versus 93.8% (95%CI 90.1-96.1) among patients with negative LNs (P < 0.001; **Figure 1A**). Similarly, 5-year RFS was 56.0% (95%CI 44.7-66.7) versus 83.3% (95%CI 77.9-87.6) among patients who did and did not have LNM, respectively (P < 0.001; **Figure 1B**).

Irrespective of other factors, patients with poor to undifferentiated tumor grade had the worst 5-year RFS (46.0%) followed by symptomatic patients (49.3%) (**Table 3**). The highest therapeutic value of lymphadenectomy was noted among patients with moderately to poorly differentiated tumor grade (21.5), Ki-67 ≥ 3% (20.1), tumor size ≥ 2.0 cm (20.0), and primary tumor location in the head of pancreas (20.0). An index difference of more than 10 points was noted when examining tumor size (index difference: 13.4; <2.0: 6.6 vs. ≥ 2.0: 20.0), Ki-67 (index difference: 12.6; <3%: 7.5 vs. ≥ 3%: 20.1), location of tumor (index difference: 10.3; body/tail: 9.7 vs. head: 20.0) as well as the number of LNs evaluated (index difference: 10.4; 1-7: 7.5 vs. ≥ 8: 17.9; **Table 3**). Of note, patients who had ≥8 LNs evaluated had a higher therapeutic index than patients who had 1 to 7 LNs evaluated (≥8: 17.9 vs. 1-7: 7.5; difference of index: 11.4).

Discussion

The prognostic impact of LNM and the therapeutic role of LND to remove LNM among patients with pNETs remains a topic of debate. Several studies have reported that LNM was not associated with OS among patients undergoing resection of pNET.[7,20] While several other studies reported that the presence of LNM was associated with worse RFS,[6, 21, 22] other investigators have noted that 5-and and 10-year OS were comparable among patients who did and did not have LNM.[6,22] As such, the therapeutic value of routine LND still remains controversial among patients undergoing surgery with pNETs, despite the possibility that removal of LNM may decrease locoregional recurrence.[4] The current study was important because we identified patients who may have the most benefit from LND by calculating the therapeutic index based on clinicopathological characteristics.[10] Of note, a difference in the therapeutic index above 10 was identified among patients who had a tumor size larger than 2 cm (≥2: 20.0 vs. <2: 6.6; difference of index: 13.4), patients who had a Ki-67 ≥3% (≥3%: 20.1 vs. <3%; difference of index: 12.6), as well as patients with a pNET located in the head of the pancreas (head: 20.0 vs. body/tail: 9.7; difference of index: 10.3). Of note, therapeutic index was also associated with total number of nodes evaluated as patients who had ≥8 LNs evaluated had a higher therapeutic index than patients who had 1 to 7 LNs evaluated. To the best of our knowledge, this is the first study to examine the therapeutic benefit associated with LND among patients who underwent a curative-intent resection for a pNET.

First proposed by Sasako et al., the therapeutic index has been used in assessing the role of LND in the surgical management of gastric,[10] rectal,[11] esophageal,[12] and lung cancer. [13] In addition, our own group recently examined the therapeutic benefit associated with LND among patients with intrahepatic cholangiocarcinoma and identified particular groups of patients who were most likely to derive a benefit from LND.[14, 23] The rationale of the therapeutic index is that the utilization of LND would be most effective when it is employed among patients who have the highest risk for LNM and therefore the greatest chance of a therapeutic benefit.[10] Given the conflicting results about the role of LND for patients undergoing surgery for pNET, the therapeutic index could be a relevant way to identify which specific subgroups of patients may particularly warrant LND.[10] Indeed, the goal of LN harvesting may not only be for accurate staging, but also as a means to reduce locoregional disease among patients with LNM. To this end, the current study noted that certain clinicopathological characteristics were associated with a reasonable therapeutic index difference, including primary tumor location, tumor size, Ki-67 and number of LNs evaluated (Table 3). Of note, while 5-year RFS was not different among these groups of patients, the higher rates of LNM in each particular subgroup of patients (i.e. patients with tumor located at the head of pancreas, LNM: 34.5%; tumor size ≥ 2 cm, LNM: 37.9%; Ki-67 >3%, 39.1% and >8 LN harvested, LNM: 32.3%) led to a higher therapeutic index value **(Table 3)**. The reason for the comparable RFS among these subgroups of patients may be that LND not only facilitated identification of LNM, but also provided an oncological benefit for patients with seemingly worse characteristics (and higher LNM rates) by eliminating locoregional disease and reducing the risk of local recurrence. In addition, data from the current study demonstrated that an increase in the number of LNs evaluated was associated with a concomitant increase in the number of LNM detected. Specifically, removing >8 LNs was associated with a higher therapeutic index compared with harvesting 7 or fewer LNs (index difference of more than 10), suggesting that 8 LN is the appropriate goal LND threshold.[24, 25]

Previous studies have attempted to evaluate the role of LND in pNET patients to identify subgroups of individuals who might benefit the most from LND. For example, Harimoto and colleagues reported that the presence of LNM was associated with DFS, but not OS.[22] In turn, these authors recommended that patients with Ki-67 ≥3% should have routine LND since these patients were at high risk for locoregional recurrence.[22] In a separate study, Lopez-Aguiar et al. noted that less than 10% of patients with a tumor less than 2 cm had LNM; in addition, patients with a Ki-67 < 3% and pNET location in the distal pancreas had a particularly low risk of LNM (3.4%).[9] In line with these reports, data from our study suggest that LND could be more meaningful among patients with pNET >2 cm and among patients with pNET located in the pancreatic head with Ki-67 >3%. As such, surgeons should weigh the potential benefit and related risks prior to deciding on the extent of LND. Data from the current study strongly suggest that routine LND and evaluation of ≥8 LNs should be performed among these patients at high risk of LNM. In contrast, among patients with a tumor < 2 cm (therapeutic index: 6.6), Ki-67 < 3% (7.5) or pNET located at the pancreatic body or tail (9.7) the therapeutic benefit of LND appeared to be much more modest.

Several limitations should be taken into consideration when interpreting the results of the current study. Due to its retrospective nature, the current study may be subject to selection bias. In addition, while the multi-institutional database may serve to minimize the inter-institutional bias, the inclusion of multiple centers could have introduced some bias related to unstandardized surgical operations, pathological analysis of surgical specimen, and variation of follow-up protocols at individual institutions. In addition, while the cut-off value of therapeutic index associated with LND has not been standardized, the valued used in the current study facilitated comparison to the relative therapeutic value of LND among subgroups of patients who did or did not have certain characteristics.[14]

In conclusion, LND was mostly beneficial among patients with pNETs >2 cm, Ki-67 $\geq$ 3%, and lesions located at the pancreatic head as identification of LNM was most common among individuals with these tumor characteristics. In addition, evaluation of $\geq$8 LNs was associated with a higher likelihood of identifying LNM, as well as a higher therapeutic index, and therefore this number of nodes should be considered the goal to evaluate.

Acknowledgments: none

Conflict of interest: none

Funding: none

U.S. Neuroendocrine Tumor Study Group; Jordan Cloyd, MD[2], Mary Dillhoff, MD[2], Alexandra G. Lopez-Aguiar, MD[4], Eleftherios Makris, MD[5], Zaheer Kanji, MD[6], Alexander Fisher, MD[7], Bradley A. Krasnick, MD[8], Paula M. Smith, MD[9], Megan Beems, MD[10]

References

1. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol. 2017;3:1335-42.

2. Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. Ann Oncol. 2008;19:1727-33.

3. Rindi G, Wiedenmann B. Neuroendocrine neoplasms of the gut and pancreas: new insights. Nat Rev Endocrinol. 2011;8:54-64.

4. Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology. 2016;103:153-71.

5. Frilling A, Modlin IM, Kidd M, Russell C, Breitenstein S, Salem R, et al. Recommendations for management of patients with neuroendocrine liver metastases. Lancet Oncol. 2014;15:e8-21.

6. Hashim YM, Trinkaus KM, Linehan DC, Strasberg SS, Fields RC, Cao D, et al. Regional lymphadenectomy is indicated in the surgical treatment of pancreatic neuroendocrine tumors (PNETs). Ann Surg. 2014;259:197-203.

7. Bilimoria KY, Talamonti MS, Tomlinson JS, Stewart AK, Winchester DP, Ko CY, et al. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients. Ann Surg. 2008;247:490-500.

8. Yoo YJ, Yang SJ, Hwang HK, Kang CM, Kim H, Lee WJ. Overestimated Oncologic Significance of Lymph Node Metastasis in G1 Nonfunctioning Neuroendocrine Tumor in the Left Side of the Pancreas. Medicine (Baltimore). 2015;94:e1404.

9. Lopez-Aguiar AG, Ethun CG, Zaidi MY, Rocha FG, Poultsides GA, Dillhoff M, et al. The conundrum of < 2-cm pancreatic neuroendocrine tumors: A

preoperative risk score to predict lymph node metastases and guide surgical management. Surgery. 2019;166:15-21.

10. Sasako M, McCulloch P, Kinoshita T, Maruyama K. New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. Br J Surg. 1995;82:346-51.

11. Ueno H, Mochizuki H, Hashiguchi Y, Ishiguro M, Miyoshi M, Kajiwara Y, et al. Potential prognostic benefit of lateral pelvic node dissection for rectal cancer located below the peritoneal reflection. Ann Surg. 2007;245:80-7.

12. Soeno T, Harada H, Hosoda K, Mieno H, Ema A, Ushiku H, et al. Lymph Node Progression and Optimized Node Dissection of Middle Thoracic Esophageal Squamous Cell Carcinoma in the Latest Therapeutic Surgical Strategy. Ann Surg Oncol. 2019;26:996-1004.

13. Kuroda H, Sakao Y, Mun M, Uehara H, Nakao M, Matsuura Y, et al. Lymph Node Metastases and Prognosis in Left Upper Division Non-Small Cell Lung Cancers: The Impact of Interlobar Lymph Node Metastasis. PLoS One. 2015;10:e0134674.

14. Sahara K, Tsilimigras DI, Merath K, Bagante F, Guglielmi A, Aldrighetti L, et al. Therapeutic Index Associated with Lymphadenectomy Among Patients with Intrahepatic Cholangiocarcinoma: Which Patients Benefit the Most from Nodal Evaluation? Ann Surg Oncol. 2019; 26:2959-68.

15. Zhang XF, Wu Z, Cloyd J, Lopez-Aguiar AG, Poultsides G, Makris E, et al. Margin status and long-term prognosis of primary pancreatic neuroendocrine tumor after curative resection: Results from the US Neuroendocrine Tumor Study Group. Surgery. 2019;165:548-56.

16. Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology. 2016;103:153-71.

17. Lin J-X, Huang C-M, Zheng C-H, Li P, Xie J-W, Wang J-b, et al. Is All Advanced Gastric Cancer Suitable for Laparoscopy-Assisted Gastrectomy With Extended Lymphadenectomy? A Case–Control Study Using a Propensity Score Method. Annals of Surgical Oncology. 2016;23:1252-60.

18. Tokunaga MM, Ohyama MS, PhD, Hiki MN, PhD, Fukunaga MT, et al. Therapeutic Value of Lymph Node Dissection in Advanced Gastric Cancer with Macroscopic Duodenum Invasion: Is the Posterior Pancreatic Head Lymph Node Dissection Beneficial? Annals of Surgical Oncology. 2009;16:1241-6.

19. Kosuga T, Ichikawa D, Okamoto K, Komatsu S, Shiozaki A, Fujiwara H, et al. Survival benefits from splenic hilar lymph node dissection by splenectomy in gastric cancer patients: relative comparison of the benefits in subgroups of patients. Gastric Cancer. 2011;14:172-7.

20. Taki K, Hashimoto D, Nakagawa S, Ozaki N, Tomiyasu S, Ohmuraya M, et al. Significance of lymph node metastasis in pancreatic neuroendocrine tumor. Surg Today. 2017;47:1104-10.

21. Partelli S, Gaujoux S, Boninsegna L, Cherif R, Crippa S, Couvelard A, et al. Pattern and clinical predictors of lymph node involvement in nonfunctioning pancreatic neuroendocrine tumors (NF-PanNETs). JAMA Surg. 2013;148:932-9.

22. Harimoto N, Hoshino K, Muranushi R, Hagiwara K, Yamanaka T, Ishii N, et al. Significance of Lymph Node Metastasis in Resectable Well-differentiated Pancreatic Neuroendocrine Tumor. Pancreas. 2019;48:943-47.

23. Sahara K, Tsilimigras DI, Pawlik TM. ASO Author Reflections: Which Patients Benefit the Most From Lymphadenectomy During Resection for Intrahepatic Cholangiocarcinoma? Ann Surg Oncol. 2019;26:2969-70.

24. Lopez-Aguiar AG, Zaidi MY, Beal EW, Dillhoff M, Cannon JGD, Poultsides GA, et al. Defining the Role of Lymphadenectomy for Pancreatic Neuroendocrine Tumors: An Eight-Institution Study of 695 Patients from the US Neuroendocrine Tumor Study Group. Ann Surg Oncol. 2019;26:2517-24.

25. Zhang XF, Xue F, Dong DH, Lopez-Aguiar AG, Poultsides G, Makris E, et al. New Nodal Staging for Primary Pancreatic Neuroendocrine Tumors: A Multi-institutional and National Data Analysis. Ann Surg. 2019.[Epub ahead of print]

Figure

Figure 1 Kaplan Meier curves demonstrating OS (A) and RFS (B) among patients who underwent LND stratified by the presence of LNM.

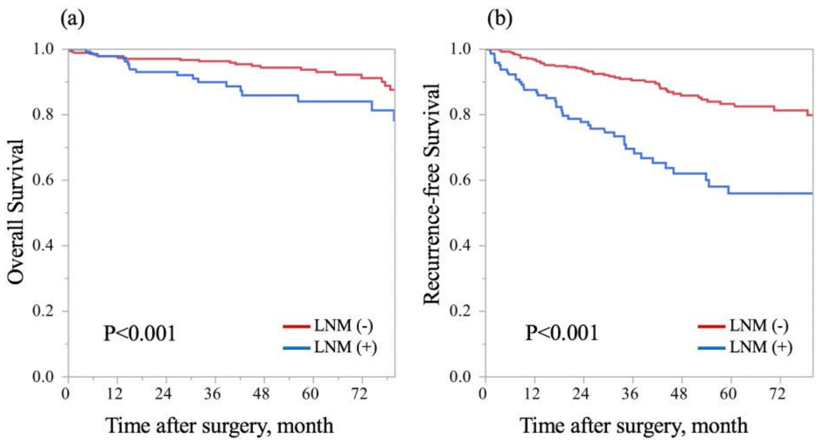

Table 1 Demographic and patient characteristics in the entire cohort (n=647).

Variable	N (%)
Age, median (IQR)	58 (48-66)
Sex	
Male	343 (53.0%)
Female	304 (47.0%)
Race	
White	480 (80.7%)

Variable	N (%)
African American	51 (8.6%)
Asian	39 (6.6%)
Hispanic	23 (3.8%)
Other	2 (0.3%)
ASA classification	
1	11 (1.8%)
2	273 (43.8%)
3	328 (52.6%)
4	12 (1.8%)
Tumor functional status	
Nonfunctional	559 (88.0%)
Functional	76 (12.0%)
Symptomatic	
No	273 (43.0%)
Yes	362 (57.0%)
Type of resection	

Variable	N (%)
Enucleation	28 (4.3%)
Classic PD	76 (11.7%)
Pylorus-preserving PD	129 (19.9%)
Central pancreatectomy	10 (1.5%)
Distal pancreatectomy	392 (60.6%)
Total pancreatectomy	12 (1.9%)
Surgical approach	
Open	491 (75.9%)
MIS	156 (24.1%)
Primary location	
Head	261 (40.4%)
Body/Tail	385 (59.6%)
Largest tumor size (cm), median (IQR)	2.2 (1.4-3.8)
Tumor number	
Single	590 (92.0%)
Multiple	51 (8.0%)

Variable	N (%)
Presence of LN metastasis	159 (24.6%)
Number of LN examined, median (IQR)	10 (4-16)
Number of LN metastasis, median (IQR)	0 (0-1)
Margin status	
R0	537 (83.8%)
R1	104 (16.2%)
Tumor differentiation	
Well differentiated	499 (86.6%)
Moderately differentiated	63 (10.9%)
Poorly differentiated	14 (2.4%)
Ki-67	
<3%	268 (59.3%)
3%-20%	165 (36.5%)
>20%	19 (4.2%)
Lympho-vascular invasion	
Absent	370 (66.4%)

Variable	N (%)
Present	187 (33.6%)
Perineural invasion	
Absent	408 (75.7%)
Present	131 (24.3%)
Adjuvant therapy	
No	606 (93.7%)
Yes	41 (6.3%)

IQR: interquartile range; ASA: American Society of Anesthesiologist; PD: pancreatoduodenectomy; MIS: minimally invasive surgery; LN: lymph node

Table 2 Logistic regression analysis of clinicopathological factors associated with lymph node metastasis.

	Bivariate analysis		Multivariable analysis	
Variable	OR	95% CI	OR	95% CI
Age				
<65	*Ref*			
≥65	0.95	0.63-1.42		

	Bivariate analysis		Multivariable analysis	
Variable	OR	95% CI	OR	95% CI
Sex				
Female	*Ref*		*Ref*	
Male	1.54	1.07-2.22	1.50	0.90-2.52
Functional status				
Nonfunctional	*Ref*		*Ref*	
Functional	0.48	0.25-0.94	0.43	0.17-1.07
Symptomatic				
No	*Ref*		*Ref*	
Yes	1.53	1.05-2.23	**2.03**	**1.17-3.51**
Primary location				
Body/Tail	*Ref*		*Ref*	
Head	2.41	1.67-3.47	**1.83**	**1.10-3.06**
Tumor size (cm)				
<2.0	*Ref*		*Ref*	
≥2.0	5.90	3.78-9.21	**4.59**	**2.57-8.20**

	Bivariate analysis		Multivariable analysis	
Variable	OR	95% CI	OR	95% CI
Tumor number				
Single	*Ref*			
Multiple	0.72	0.35-1.48		
Number of LN examined				
1-7	*Ref*		*Ref*	
≥8	3.04	1.99-4.64	1.61	0.90-2.90
Tumor differentiation				
Well differentiated	*Ref*		*Ref*	
Moderately differentiated	2.78	1.62-4.79	1.80	0.85-3.80
Poorly differentiated	6.67	2.19-20.33	0.96	0.10-9.59
Ki-67				
<3%	*Ref*		*Ref*	
3%-20%	3.34	2.11-5.30	**1.83**	**1.04-3.22**
>20%	7.84	2.97-20.69	2.28	0.37-14.03

LN: lymph node

Table 3 Therapeutic index stratified by preoperative acquirable clinicopathological factors.

Variable	Frequency of LNM	5-y RFS (%)	Therapeutic index	Difference of index
Overall	0.246	56.0	13.8	
Functional status				
Nonfunctional	0.259	56.0	14.5	5.8
Functional	0.145	60.0	8.7	
Symptomatic				
No	0.202	71.1	14.4	0.6
Yes	0.279	49.3	13.8	
Primary location				
Body/Tail	0.179	54.0	9.7	
Head	0.345	58.0	**20.0**	**10.3**
Tumor size (cm)				
<2.0	0.094	69.9	6.6	
≥2.0	0.379	52.7	**20.0**	**13.4**
Tumor number				

Variable	Frequency of LNM	5-y RFS (%)	Therapeutic index	Difference of index
Single	0.253	53.5	13.5	
Multiple	0.196	85.7	16.8	2.7
Grade				
Well	0.212	60.2	12.8	
Moderate to poor	0.468	46.0	**21.5**	8.7
Ki-67				
<3%	0.149	50.1	7.5	
≥3%	0.391	51.4	**20.1**	**12.6**
Number of LNs harvested				
1-7	0.136	55.1	7.5	
≥8	0.323	55.4	17.9	**10.4**

LNM: lymph node metastasis; RFS: recurrence-free survival,