THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2022.33340
Med Bull Sisli Etfal Hosp 2022;56(4):497–502

Original Research

Effects of the Largest Metastatic Lymph Node Size on the Outcomes of Patients who Underwent Pancreaticoduodenectomy for Pancreatic Ductal Adenocarcinoma

Emre Bozkurt,[1] Tutku Tufekci,[1] Serkan Sucu,[1] Cagri Bilgic,[2] Emre Ozoran,[1] Ibrahim Halil Ozata,[1] Mesut Kaya,[1] Gurkan Tellioglu,[1] Orhan Bilge[2]

[1]Department of General Surgery, Koç University Hospital, Istanbul, Türkiye
[2]Department of General Surgery, American Hospital, Istanbul, Türkiye

Abstract

Objectives: Prognostic importance of metastatic lymph nodes in pancreatic cancer is always garnered attention due to dismal prognosis, with some quantitative factors drawing attention for significantly predicting outcomes. Size is one of the easy approach morphological characteristics of the lymph node, and data for effect of largest metastatic lymph node (LMLN) size on survival outcomes are lacking in pancreatic cancer. We aim to evaluate the effect of LMLN size on the prognosis of patients with pancreatic ductal adenocarcinoma (PDAC).

Methods: This retrospective study evaluates the effect of LMLN size on survival outcomes by grouping the patients who were surgically treated for PDAC, according to their lymph node stage and calculated cutoff value for LMLN size, between February 2015 and May 2020.

Results: In the study cohort of 131 patients, the mean age was 63.9±10.8 years and 77 patients were female. Ninety-nine of the patients had pN1, 32 had pN2 stage disease. The optimal cutoff point of LMLN size for predicting the prognosis was calculated as 7.5 mm (sensitivity = 81% and specificity = 81%). 34 (34.3%) of pN1 and 7 (21.9%) of pN2-staged patients had lymph node smaller than 7.5 mm. Three-year survival was significantly longer for patients whose LMLN size was <7.5 mm (56.2–18.2%, p<0.001). Whereas, the patients with LMLN size <7.5 mm had statistically significant longer median survival rate in the subgroup of patients with pN1 lymph node stage, no significant difference in median survival rates was observed between subgroups of pN2 patients (p=0.237).

Conclusion: The present study demonstrated that the LMLN size was one of the potential predictors of survival in patients with PDAC.

Keywords: Lymph node, Metastasis, Pancreatic ductal adenocarcinoma, PDAC, TNM

Please cite this article as "Bozkurt E, Tufekci T, Sucu S, Bilgic C, Ozoran E, Ozata IH, et al. Effects of the Largest Metastatic Lymph Node Size on the Outcomes of Patients who Underwent Pancreaticoduodenectomy for Pancreatic Ductal Adenocarcinoma. Med Bull Sisli Etfal Hosp 2022;56(4):497–502".

Radical surgical resection has currently been the only curative treatment option for pancreatic cancer today, which has a 5-year mortality rate of over 90% and a 5-year overall survival between 5% and 10% based on estimates reported in the literature.[1] Even after curative resection, reports have shown a 5-year disease-free survival rate of only

Address for correspondence: Emre Bozkurt, MD. Koc Universitesi Hastanesi, Genel Cerrahi Klinigi, Istanbul, Türkiye
Phone: +90 532 461 93 39 **E-mail:** dr.emrebozkurt@gmail.com

Submitted Date: April 28, 2022 **Revised Date:** May 26, 2022 **Accepted Date:** July 15, 2022 **Available Online Date:** December 19, 2022

20%.[2] Factors affecting mortality from pancreatic cancer have always garnered attention due to the dismal survival outcomes. Lymph node status, as assessed by the number of metastatic lymph nodes, is one of the most important determinants of survival.[3] The relationship between the number of metastatic lymph nodes and poor survival has been demonstrated in the literature.[4,5]

Studies investigating the prognostic importance of lymph node involvement have mostly focused on parameters, such as harvested lymph node, the number of metastatic lymph nodes, pN-stage, ratio of metastatic lymph nodes to the total examined lymph nodes, and log odds of metastatic lymph nodes.[6,7] Among these parameters, the ratio of metastatic lymph nodes and log odds of metastatic lymph nodes has been identified as the important prognostic factors in addition to the American Joint Committee on Cancer (AJCC) TNM classification system.[8,9] In addition, John et al. reported that the metastatic lymph node rate and the metastatic lymph node number are prognostic factors for cancer specific survival in patients with pancreatic adenocarcinoma.[10]

All aforementioned studies relied on lymph node number and metastatic status instead of morphological features, suggesting the need for more studies in this field to subclassify the patients based on lymph node status. Size is one of the easy approach morphological characteristics of the lymph node. The studies already demonstrate a relationship between the largest metastatic lymph node (LMLN) size and prognosis of patients with colorectal and gastric cancers.[11,12] However, to the best of our knowledge, there has been no data in the relation of LMLN size and outcomes of patients with pancreatic cancer. Based on the available data, the present study aimed to determine effects of the size of the LMLN on the prognosis of patients with pancreatic ductal adenocarcinoma (PDAC).

Methods

Data from patients who underwent surgery for pancreatic cancer between February 2015 and May 2020 at the Vehbi Koç Foundation Hospitals (Koç University Hospital and American Hospital) were reviewed retrospectively. Our study protocol was approved by the Ethics Committee of the Koç University Hospital (approval code: 2021.142. IRB1.046). All methods were carried out in accordance with the Declaration of Helsinki, relevant guidelines, and regulations of the Institutional Review Board.

Lymph node dissection for pancreaticoduodenectomy included lymph nodes around the pancreatic head, common hepatic artery, the hepatoduodenal ligament, superior mesenteric artery, distal part of the superior mesenteric vein, and the area located right of the celiac artery. The inclusion criteria were as follows: Histopathologically confirmed PDAC, R0 resection margin, and pN1 and pN2 lymph node status. The exclusion criteria were pN0 lymph node status, distant metastasis, patients with duodenal, ampullary, and extrahepatic bile duct tumors, secondary tumor, and missing follow-up data.

Data related to patient demographics, clinicopathological features, and follow-up were retrospectively collected and recorded. Detailed histopathological data, including harvested lymph node, metastatic lymph node number, pT stage, pN stage, and the size of the LMLN, were recorded. Initially, two groups were created according to their lymph node stage, namely, pN1 and pN2; following this, they were subdivided according to the calculated cutoff value for LMLN size, with each having two new groups.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) software package (version 21.0, SPSS-IBM, Armonk, NY, USA) was used for statistical analyses, with $p<0.05$ indicating statistical significance. Data were obtained by retrospectively reviewing the maintained database. Continuous and normally distributed data will be reported as mean with standard deviation and compared between groups using an unpaired t-test. Continuous data, not normally distributed, will be reported as median with interquartile range and compared between groups using the Kruskal–Wallis test. Qualitative variables were presented as numbers and percentages. Differences between categorical variables were assessed using Fisher's exact test or Chi-square test. Receiver operating curve analyses were performed to determine the establishment between the LMLN size and mortality. The sensitivity and specificity for predicting the prognosis were 81% and 81%, respectively, when the LMLN was 7.5 mm in size, which yielded the highest ratio (Fig. 1). Patients were also classified into two groups according to this cutoff value, namely, those whose LMLN was ≥7.5 or <7.5 mm in size. Overall survival was defined as the time from surgery to event of death, as well as was analyzed using the Kaplan–Meier method, and Log-rank (Mantel-cox) was applied to compare survival differences. Cox proportional hazards and regression models were used for identifying independent factors for survival.

Results

A total of 235 pancreatic resections were performed during the defined study period. Among them, 60 patients who were N0; 41 who had duodenal, ampullary, and extrahepatic bile duct tumors; three who had missing follow-up data were excluded from the study. Then, the remaining 131 pa-

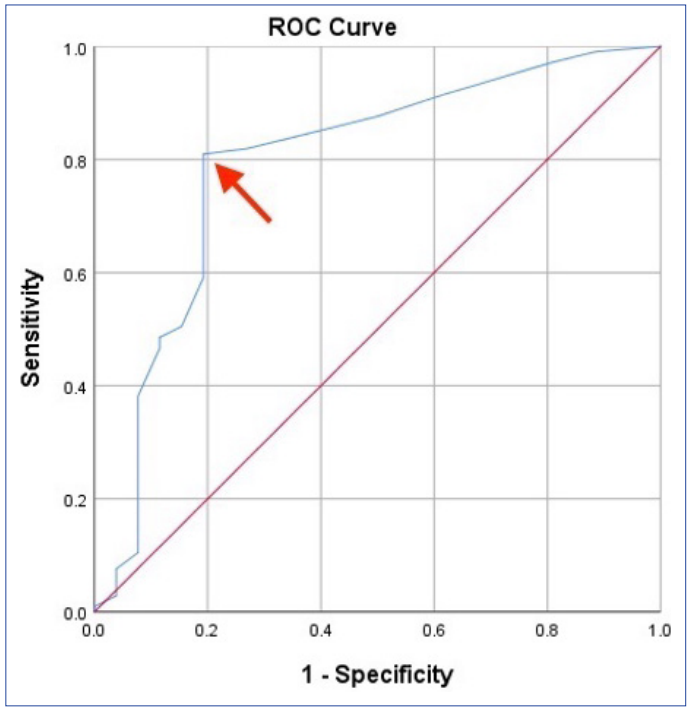

Figure 1. ROC curve analysis for largest metastatic lymph node size to calculate optimal cutoff point that predict survival outcomes. Red arrow indicates the optimal cutoff points of largest metastatic lymph node size as 7.5 mm (sensitivity = 81% and specificity = 81%). Area under the curve [SE] = 0.792 [0.055], 95% confidence limits range = 0.683–0.900, p<0.001.

tients were included in this study cohort. The mean age of the patients was 63.9±10.8 (range: 39–86) years old; 58.8% (n=77) were female and 41.2% (n=54) were male. Among the included patients, 87 (66.4%) underwent pylorus-preserving pancreaticoduodenectomy, 11 underwent distal pancreatectomy (8.4%), and 33 underwent total pancreatectomy (25.2%). All patients had a tumor free resection margin and all resections were R0. Moreover, 99 (75.6%) and 32 (24.4%) patients were staged as pN1 and pN2, respectively. The median number of harvested lymph nodes and metastatic lymph nodes was 26 (range: 7–90) and 3 (range: 1–28), respectively. The median harvested lymph node number for total pancreatectomy, distal pancreatectomy, and pancreaticoduodenectomy was 39 (range: 14–90), 27 (range: 13–50), and 24 (range: 7–54), respectively. As expected, among the procedures, total pancreatectomy had the highest amount of harvested lymph node (p<0.001). The median LMLN size was 13 mm (range: 1–45 mm) and 10 mm (range: 3–23 mm) for N1 and N2 patients, respectively. Meanwhile, 34 (34.3%) pN1 and 7 (21.9%) pN2 patients had lymph node smaller than 7.5 mm (Table 1).

Univariate and multivariate Cox hazard analyses were performed for to determining the effects of age, gender, ASA score, T stage, N stage, harvested lymph node, metastatic lymph node number, metastatic lymph node ratio, and LMLN size (<7.5 mm–≥7.5 mm) on survival. Accordingly, in

Table 1. Demographic features,and surgical and pathological data

	N1 stage	N2 stage	p
Gender, n			
Male	40	14	0.89
Female	59	18	
Age, years (mean±SD)	64.9±10.9	60.6±10	0.048
ASA, n, (%)			
1–2	63 (63.6)	21 (65.6)	0.99
3–4	36 (36.4)	11 (34.4)	
Surgical Procedure, n, (%)			
Pancreaticoduodenectomy	65 (65.7)	22 (68.8)	0.45
Distal pancreatectomy	10 (10.1)	1 (3.1)	
Total pancreatectomy	24 (24.2)	9 (28.1)	
T stage, n			
pT1-T2	14	17	<0.001
pT3-T4	85	15	
Median number of harvested lymph nodes, n (min-max)	24 (7–65)	34 (11–90)	<0.001
Median metastatic lymph node size, mm, (range)	13 (1–45)	10 (3–23)	0.10
Largest metastatic lymph node, n, (%)			
<7.5 mm	34 (34.3)	7 (21.9)	0.18
≥7.5 mm	65 (65.7)	25 (78.1)	

*ASA: The American society of anesthesiologists (ASA) physical status classification system.

univariate analyzes, T stage and N stage, number of metastatic lymph nodes, metastatic lymph node ratio and LMLN size (<7.5 mm–≥7.5 mm) were found to have a significant effect on survival, whereas the multivariate Cox hazard analyses revealed that the only LMLN size (<7.5mm–≥7.5 mm) was a significant predictor of survival (HR [95% CI]: 2.76 [1.62–4.60], p<0.001) (Table 2).

The median follow-up period of the patients included in the study was 20 months and a 1- and 3-year survival of 78.7% and 28.4%, respectively. The survival rates for 1- and 3-year were 86.7% and 56.2% for patients whose LMLN size was <7.5 mm and 75.6% and 18.2% for those whose LMLN size was ≥7.5 mm, (p<0.001) (Fig. 2). Whereas the patients with LMLN size <7.5 mm had statistically significant longer median survival rate in subgroup of patients with pN1 lymph node stage, statistical significance in median survival rates was not observed between subgroups of pN2 patients (p=0.237) (Fig. 3).

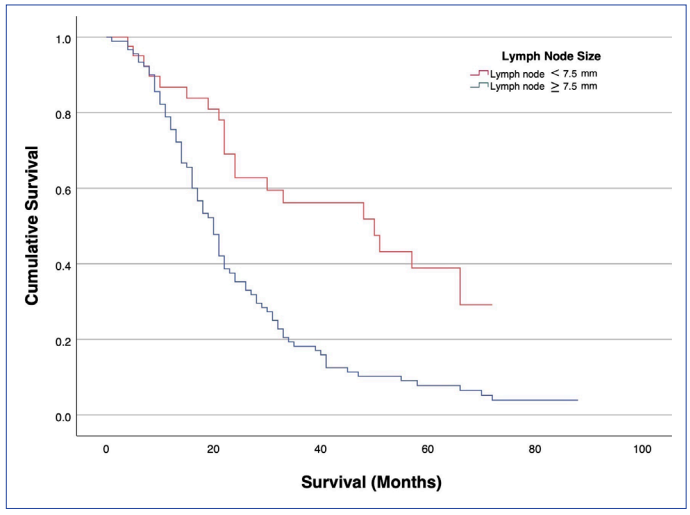

Figure 2. Kaplan-Meier survival curves stratified by largest metastatic lymph node size. Patients with largest metastatic lymph node size <7.5 mm had a better prognosis than patients with largest metastatic lymph node size ≥7.5 mm (56.2% versus 16.2%, p<0.001).

Discussion

Although the lymph node status provides important information on survival among patients with PDAC, some controversy remains regarding evidence on the prognostic effects of lymph node status.[13-14] Several factors associated with lymph node characteristic were investigated, such as harvested lymph node, metastatic lymph node ratio, or logarithm of the odds of metastatic lymph node.[5,15,16] The seventh edition of AJCC TNM system classified the Node stage only as N0 and N1. As suggested and validated by the previous studies, the eight edition of the staging system was updated and subdivided the lymph node status into N0 (no metastatic lymph node), N1 (1–3 metastatic lymph node), and N2 (≥4 metastatic lymph node).[3,17-19] The aforementioned data support the need for more investigations into lymph node status to estimate its prognostic effect.

The current staging systems on lymph node status have mainly been based on metastatic lymph node number rather than its morphological features. Only a limited number of studies have evaluated to predict the lymph node metastases by radiologically measured lymph node size, with one concluding that larger lymph nodes are more prone to be metastatic for PDAC patients.[15] The studies have already evaluated the LMLN size in various gastrointestinal system cancers, with their results concluding that the LMLN size has prognostic importance in patients with colorectal and gastric cancers.[11,12] However, no study has shown that such findings remain true for PDAC. The present study showed differences in survival according to the LMLN size in pN1-stage patients, when setting the estimated cutoff size to 7.5 mm. Nonetheless, the lack of significant

Table 2. Univariate and multivariate cox regression analysis of variables associated with mortality

	Univariate analysis		Multivariate analysis	
Factor	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**
Age (10 years, 1 IU)	0.701	0.97 (0.82–1.15)	-	-
Gender	0.901	0.98 (0.66–1.45)	-	-
ASA	0.639	0.93 (0.69–1.26)	-	-
pT stage	0.023	0.62 (0.41–0.94)	0.077	0.63 (0.38–1.05)
pN stage	0.005	1.87 (1.21–2.91)	0.217	1.70 (0.73–3.99)
Harvested lymph node	0.175	1.01 (1.00–1.02)	-	-
Metastatic lymph node number	0.036	1.05 (1.00–1.11)	0.168	0.92 (0.82–1.04)
Metastatic lymph node ratio	0.009	1.03 (1.01–1.04)	0.165	1.02 (0.99 –1.05)
Largest metastatic lymph node size <7.5 mm–≥7.5 mm	<0.001	2.74 (1.68–4.48)	<0.001	2.76 (1.62–4.60)

*ASA: The American society of anesthesiologists (ASA) Physical status, classification system.

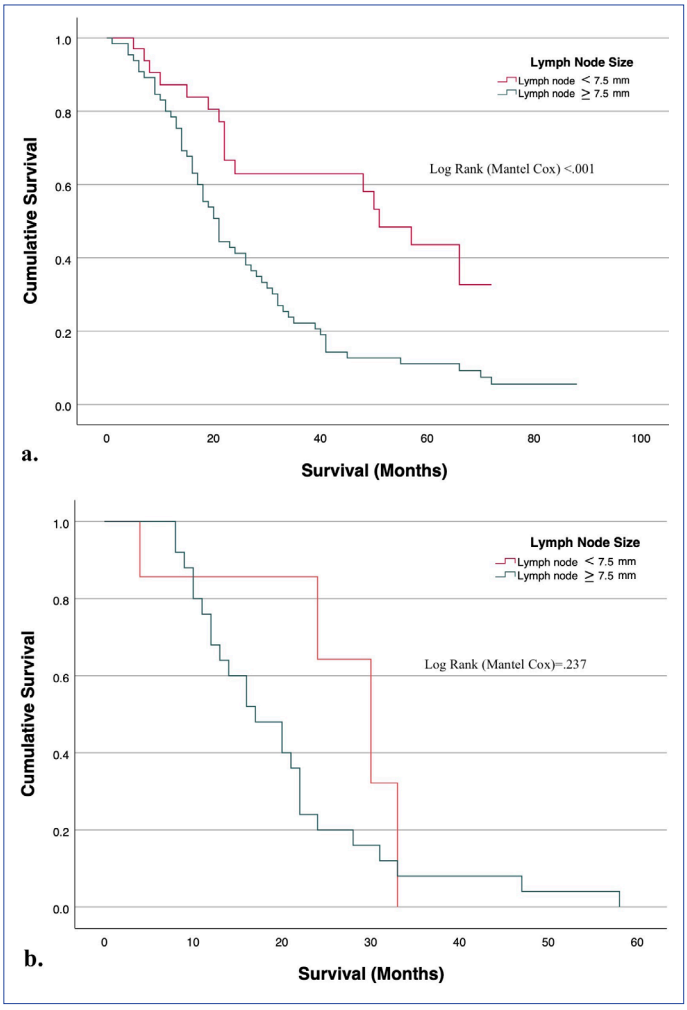

Figure 3. (a, b) Kaplan–Meier survival curves stratified by largest metastatic lymph node size in each N stage. **(a)** Patients with pN1-stage, largest metastatic lymph node <7.5 mm had a better prognosis than patients with the largest metastatic lymph node ≥7.5 mm (62% vs. 22%, p<0.001). **(b)** Patients with pN2-stage, no statistically significant survival difference between groups.

findings in pN2-stage patients may have been due to the small sample size (n=7–25) in each group.

Measuring LMLN size is one of the easy to measure parameter related with morphological features of the lymph node and is routinely reported in the pathology reports. Although LMLN size was shown to be an independent prognostic factor for colorectal and gastric cancer in multivariate analyses, the lower odds ratio supports that it may be a complementary prognostic factor.[11,12] Considering literature data, the detection of LMLN size as the only factor on survival in our study should be interpreted with caution.

Another controversial point on lymph nodes in PDAC is harvested lymph nodes. Although there is a consensus on the recommendation that more than 12 lymph nodes should be dissected for definitive nodal classification, no consensus exists on the prognostic and clinical significance of an increased number of dissected nodes.[20,21] In this study, median harvested lymph nodes were 24, which was similar to, and even higher than, those reported from most experienced institutions. In addition, only 8 (6.1%) patients in this study did not satisfy the lymph node number that is required for staging, which can be considered a strength of our study.

Besides the retrospective nature of the study, small sample size and single-center design are the major limitations of this study. The study demonstrates significant relation of LMLN size and survival, except for patients with pN2-stage. Therefore, additional, multicenter, and prospective studies with more patients are warranted to obtain a clear statement, particularly in patients with stage pN2.

In conclusion, the present study showed that the LMLN size was one of the predictors of survival in patients with PDAC. Moreover, to the best of our knowledge, this has been the first study to show the potentially significant relation of LMLN size and survival, in PDAC patients. This has also been the first study to subclassify pN1 and pN2 Node stages on the basis of the LMLN size for determining prognostic differences.

Congress presentation: The preliminary results of this study was presented in part at the 15th Turkish Hepatopancreatobiliary Congress as an oral presentation, and get the 1st degree best oral presentation award. Istanbul/Turkey, 2021, (Abstract S-092).

Disclosures

Ethics Committee Approval: Study protocol was approved by the Institutional Review Board and Ethics Committee of the Koç University Hospital (approval code: 2021.142.IRB1.046).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – E.B., S.S., E.Ö., İ.H.Ö., M.K., G.T., O.B.; Design – E.B., S.S., T.T., İ.H.Ö., E.Ö.; Supervision – E.B., C.B., M.K., E.Ö., İ.H.Ö., G.T., O.B.; Materials – E.B., S.S., T.T., C.B., M.K.; Data collection &/or processing – E.B., S.S., C.B., M.K., E.Ö., İ.H.Ö.; Analysis and/or interpretation – E.B., S.S.; Literature search – E.B., S.S., T.T., E.Ö., C.B., M.K., İ.H.Ö.; Writing – E.B., T.T., S.S., C.B., M.K., E.Ö., İ.H.Ö., G.T.; Critical review – E.B., G.T., O.B.

References

1. Oncology ASCO. Pancreatic Cancer: Statistics 2021 [updated Feb 2021]. Available at: https://www.cancer.net/cancer-types/pancreatic-cancer/statistics. Accessed Nov 28, 2022.
2. Janssen QP, van Dam JL, Bonsing BA, Bos H, Bosscha KP, Coene PPLO, et al; Dutch Pancreatic Cancer Group. Total neoadjuvant FOLFIRINOX versus neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine for resectable and borderline resectable pancreatic cancer (PREOPANC-2 trial): study pro-

tocol for a nationwide multicenter randomized controlled trial. BMC Cancer 2021;21:300. [CrossRef]
3. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumors. 8th ed. Oxford: Wiley-Blackwell; 2017. p. 93–6.
4. Orci LA, Meyer J, Combescure C, Bühler L, Berney T, Morel P, et al. A meta-analysis of extended versus standard lymphadenectomy in patients undergoing pancreatoduodenectomy for pancreatic adenocarcinoma. HPB (Oxford) 2015;17:565–72. [CrossRef]
5. Karjol U, Chandranath A, Jonnada P, Cherukuru S, Annavarjula V, Morla SA. Lymph node ratio as a prognostic marker in pancreatic cancer survival: a systematic review and meta-analysis. Cureus 2020;12:e9597. [CrossRef]
6. La Torre M, Cavallini M, Ramacciato G, Cosenza G, Rossi Del Monte S, Nigri G, et al. Role of the lymph node ratio in pancreatic ductal adenocarcinoma. Impact on patient stratification and prognosis. J Surg Oncol 2011;104:629–33. [CrossRef]
7. You MS, Lee SH, Choi YH, Shin BS, Paik WH, Ryu JK, et al. Lymph node ratio as valuable predictor in pancreatic cancer treated with R0 resection and adjuvant treatment. BMC Cancer 2019;19:952.
8. Aoyama T, Yamamoto N, Kamiya M, Murakawa M, Tamagawa H, Sawazaki S, et al. The lymph node ratio is an independent prognostic factor in pancreatic cancer patients who receive curative resection followed by adjuvant chemotherapy. Anticancer Res 2018;38:4877–82. [CrossRef]
9. La Torre M, Nigri G, Petrucciani N, Cavallini M, Aurello P, Cosenza G, 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;14:289–94. [CrossRef]
10. John BJ, Naik P, Ironside A, Davidson BR, Fusai G, Gillmore R, et al. Redefining the R1 resection for pancreatic ductal adenocarcinoma: tumour lymph nodal burden and lymph node ratio are the only prognostic factors associated with survival. HPB (Oxford) 2013;15:674–80. [CrossRef]
11. Cheong O, Oh ST, Kim BS, Yook JH, Kim JH, Im JT, et al. Large metastatic lymph node size, especially more than 2 cm: independent predictor of poor prognosis in node-positive gastric carcinoma. World J Surg 2008;32:262–6. [CrossRef]
12. Dhar DK, Yoshimura H, Kinukawa N, Maruyama R, Tachibana M, Kohno H, et al. Metastatic lymph node size and colorectal cancer prognosis. J Am Coll Surg 2005;200:20–8. [CrossRef]
13. Allen PJ, Kuk D, Castillo CF, Basturk O, Wolfgang CL, Cameron JL, et al. Multi-institutional validation study of the American Joint Commission on Cancer (8th Edition) changes for T and N staging in patients with pancreatic adenocarcinoma. Ann Surg 2017;265:185–91. [CrossRef]
14. Liu ZQ, Xiao ZW, Luo GP, Liu L, Liu C, Xu J, et al. Effect of the number of positive lymph nodes and lymph node ratio on prognosis of patients after resection of pancreatic adenocarcinoma. Hepatobiliary Pancreat Dis Int 2014;13:634–41. [CrossRef]
15. Shin J, Shin S, Lee JH, Song KB, Hwang DW, Kim HJ, et al. Lymph node size and its association with nodal metastasis in ductal adenocarcinoma of the pancreas. J Pathol Transl Med 2020;54:387–95. [CrossRef]
16. Ren H, Wang CF. The relationship between the index of lymph node metastasis and the prognosis of pancreatic cancer patients after R0 resection. Zhonghua Zhong Liu Za Zhi 2020;42:474–9.
17. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer-Verlag; 2009.
18. Basturk O, Saka B, Balci S, Postlewait LM, Knight J, Goodman M, et al. Substaging of lymph node status in resected pancreatic ductal adenocarcinoma has strong prognostic correlations: proposal for a revised N classification for TNM staging. Ann Surg Oncol 2015;22 Suppl 3:S1187–95. [CrossRef]
19. van Roessel S, Kasumova GG, Verheij J, Najarian RM, Maggino L, de Pastena M, et al. International Validation of the Eighth Edition of the American Joint Committee on Cancer (AJCC) TNM staging system in patients with resected pancreatic cancer. JAMA Surg 2018;153:e183617. [CrossRef]
20. Slidell MB, Chang DC, Cameron JL, Wolfgang C, Herman JM, Schulick RD, 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;15:165–74. [CrossRef]
21. Sierzega M, Bobrzyński Ł, Matyja A, Kulig J. Factors predicting adequate lymph node yield in patients undergoing pancreatoduodenectomy for malignancy. World J Surg Oncol 2016;14:248.