Lymph Node Metastatic Patterns and Survival Predictors Based on Tumor Size in Pancreatic Ductal Adenocarcinoma

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Research

Keywords: pancreatic ductal adenocarcinoma, lymph node, tumor size, AJCC, matched curve, survival

Posted Date: September 1st, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-60993/v1>

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Version of Record: A version of this preprint was published at Advances in Therapy on June 26th, 2021. See the published version at <https://doi.org/10.1007/s12325-021-01819-2>.

Abstract

BACKGROUND: Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies. Its larger mass size is widely acknowledged to be associated with increased lymph node (LN) metastatic potential. However, the quantitative relationships between tumor size and LN metastasis or survival remain unclear. Thus, this study aims to quantitatively identify the objective relationship between tumor size and prevalence of LN metastases across primary tumor size spectrums.

METHODS: 9,958 resected PDAC patients without distant metastasis were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database. The prevalence of LN metastases, LN ratio (LNR) and N2/N1 ratio were assessed amongst different tumor sizes, and the relationships were depicted by matched curves.

RESULTS: In the enrolled cohort, age, tumor site, grade, American Joint Committee on Cancer (AJCC) 8th node staging, tumor size, chemotherapy and radiotherapy were identified as significant independent predictors for overall survival (OS) and cancer-specific survival (CSS). For tumors within 1-40 mm in size, the prevalence of node positive disease is closely modelled using a logarithmic formula $[0.249 \times \ln(\text{size}) + 0.452] \times 100\%$, and then fluctuated between 70.0% and 80.0% when beyond 40 mm. The mean LNR increased in a stepwise manner as tumor size increased from 1-5 mm (LNR=0.024) to 41-45 mm (LNR=0.177); then, beyond 45 mm, it plateaued near 0.170. N2/N1 ratio gradually increased along with tumor size from 1-5 mm (N2/N1=0.286) to 41-45 mm (N2/N1=1.016), and when tumor size reached to 41-45 mm or more, the ratio stabilized around 1.000.

CONCLUSION: Regional LN involvement demonstrated a logarithmic growth with increasing tumor sizes in resectable PDAC patients. The probability of metastasis in each regional LN for resectable PDAC patients with tumors greater than 40 mm in size was near 17.0% and their overall prevalence of LN metastasis was 70%-80%. Among which, 50% of patients had an N2 stage.

Introduction

Pancreatic cancer is credited as one of the chief causes of cancer-related deaths worldwide, with a 5-year survival rate of only 9%. The cancer statistics report in 2019 estimated 56,770 new cases and 45,750 cancer-related deaths due to this malignancy[1, 2]. For appropriate patients with resectable pancreatic ductal adenocarcinoma (PDAC), oncologic resection of the primary tumor and regional lymph nodes (LNs) remains the standard for potential cure[3, 4].

Traditionally in resectable PDAC, increasing tumor sizes are generally understood to be a worse prognostic marker, which is directly reflected in current American Joint Committee on Cancer (AJCC) staging guidelines[5, 6]. This guideline and prevailing cognitions conform to the classic model of tumor progression, as the tumor develops, tumor cells obtain additional mutations and finally acquire the capability to metastasize to regional LNs and distant sites[7, 8]. So far, only one report in breast cancer has elucidated the non-linear correlation between the prevalence of LN metastases (% node-positive) and increasing tumor size[9]. However, there is no quantitative statement about the relationships between tumor size and LN metastases in PDAC patients.

PDAC patients with LN metastasis are known to have higher risk of recurrence and shorter survival[4, 10–12]. In general, examined LN (ELN) number and LN ratio (LNR) are considered to be fundamental metrics for quality assessment and prognostic stratification in cancer care[10, 13]. Given the crucial nature of N staging in PDAC, the College of American Pathologists recommends that a minimum of 12 LNs should be examined at the time of pancreaticoduodenectomy. For accurate nodal staging, current guidelines recommend a minimum number of ELNs (minELN) that ranges between 12 and 17 for a pancreatic head tumor and at least 20 for a body and tail carcinoma[14–16]. However, these recommended minELN numbers for accurate staging vary extensively across guidelines, and the optimal examined number, especially to robustly stratify survival, has not yet been formulated. Taken in aggregate, the under sampling of LNs remains a potential error that may impact prognostic value of the current staging paradigm. Thus, a quantitative objective standard is needed to assess LN metastatic ability and assist pathologists with an impression of the presence of LN involvement and tumor metastatic essence.

Tumor size is a crucial fundamental indicator of tumor burden and mortality. In breast cancer, an incremental amount of evidence reveal that, rather than the timing of diagnosis within the clinical window, the risk of metastasis is to a great extent determined by intrinsic biology[9]. Marchegiani G *et al.*[17] have reported that in PDAC, larger tumors are significantly associated with more positive LNs, higher LNRs and worse survivals. Therefore, it is interesting to explore the relationship between tumor size and the prevalence of LN metastases within high resolution in PDAC, so as to gain insight into the biological behavior of tumor growth and its impact on LN metastasis.

To quantitatively identify the objective law between prevalence of LN metastases and tumor size across a size range of 1-100 mm, a large population-based cohort of PDAC patients without distant metastasis undergoing resection from the Surveillance, Epidemiology and End Results (SEER) database was analyzed. Stratified by tumor sizes, the prevalence of LN metastases, LNR, N2/N1 ratio were plotted, and survival predictors were analyzed.

Materials And Methods

Patients and data source

All data analyzed in our study were collected from SEER database portal (<https://seer.cancer.gov/>). The up-to-date database, SEER*Stat Database: Incidence - SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975–2016 varying), was used. Access was approved by SEER database for research, and all the data were freely available.

The criteria in this study were included as followings: the column of site and morphology for tumor of pancreas (Site recode ICD-O-3/WHO 2008: Pancreas); carcinoma (8010/3), adenocarcinoma (8140/3), and infiltrating duct carcinoma (8500/3) according to the International Classification of Diseases for Oncology (3rd edition) for tumor of histology/behavior; diagnosis from 2004 to 2016 without distant metastasis. In addition, all patients with unknown tumor size, examined or metastatic lymph node number, distant metastatic information were excluded. Then, only patients with surgical resection were finally included. Given the fundamental nature of T and N staging in PDAC, the College of American Pathologists recommends that a

minimum of 12 LNs should be examined at the time of pancreaticoduodenectomy and since tumor size more than 10 cm is generally in a limited number, only patients with 12–50 (including 12 and 50) examined LNs, and no more than 10 cm in tumor size were analyzed. Explicit data about age, gender, grade, primary site, tumor size, number of examined LNs and positive LNs, chemotherapy, radiotherapy, and survival information were retrieved from the database.

According to AJCC 8th edition of N staging, no regional positive LN was defined as N0, 1–3 regional positive LNs was defined as N1, and at least 4 positive LNs as N2. The AJCC 8th M1 stage was evaluated according to the following codes: derived AJCC M, 7th ed (2010–2015), derived AJCC M, 6th ed (2004–2015), derived SEER Combined M (2016+), SEER Combined Mets at DX-bone (2010+), SEER Combined Mets at DX-brain (2010+), SEER Combined Mets at DX-liver (2010+), SEER Combined Mets at DX-lung (2010+), Mets at DX-Distant LN (2016+), Mets at DX-Other (2016+), CS Mets at DX (2004–2015) and CS Mets Eval (2004–2015). Overall survival (OS) was defined as the time interval between surgery and death or last follow-up, and the time range from surgery to cancer-related death or last follow-up was then defined as cancer specific survival (CSS). The LNR was calculated with the number of positive LNs divided by the number of examined LNs. The prevalence of LN metastases was defined as the proportion of cases with at least one positive regional metastatic LN (N1 + N2) among total included cases (N0 + N1 + N2). The protocol of this study was approved by the ethics committee of Zhongshan Hospital, Fudan University.

Statistical analysis

In this study, statistical software of SPSS 21.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analyses. Continuous variables were presented as medians with interquartile range (IQR). The correlation between tumor size and prevalence of LN metastases was assessed using a logarithmic regression. Cox proportional hazards regression model was used for the univariate and multivariate analyses to identify independent risk factors for OS and CSS. Statistical significance was defined as $P < 0.05$.

Results

Clinicopathological characteristics

A final 9,958 patients with histologically confirmed resected PDAC without distant metastasis were identified after applying the inclusion and exclusion criteria mentioned in Fig. 1. Among this retrieved cohort, the median age was 67 (ranging from 17 to 95) years, and female patients accounted for 50.4%. Lesions located in the head of the pancreas were almost ten times more common than those in the body or tail. Based on the pathological examinations, approximately 9%, 49%, and 34% of PDAC patients were confirmed as well, moderately and poorly or undifferentiated, respectively. The median number of examined and positive LNs was 20.8 (IQR 15.0–25.0) and 3.0 (IQR 0–4.0), respectively. N0 stage was found in 2,891 patients while 3,985 were stage N1 and 3,082 were stage N2. In addition, the median tumor diameter of the total cohort was 31.0 mm (IQR 25.0–40.0 mm), and the population of each 5 mm segment is displayed in Table 1. According to the National Comprehensive Cancer Network (NCCN) guideline, radiotherapy was administered in 34.1% of patients while 72.3% received chemotherapy.

Table 1

Univariate and multivariate analysis of prognostic indicators for overall survival and cancer-specific survival in resected PDAC patients.

Variables	No. of patients (N = 9958)	Overall survival		Cancer-specific survival			
		Univariate P value	Multivariate P value	Hazard Ratio (95% CI)	Univariate P value	Multivariate P value	Hazard Ratio (95% CI)
Age (years)	4523	< 0.001	< 0.001	1.203	< 0.001	< 0.001	1.156
≤65	5435			1.145– 1.263			1.097– 1.217
≥65							
Gender	5015	0.012	0.130	1.038	0.022	0.296	1.028
Female	4943			0.989– 1.089			0.977– 1.081
Male							
Location	7672	0.016	0.001	0.955	0.003	0.001	0.952
Head	674			0.931– 0.980			0.926– –
Body	751						0.919
Tail	861						
Others							
Grade	906	< 0.001	< 0.001	1.169	< 0.001	< 0.001	1.188
Well differentiated (I)	4911			1.132– 1.206			1.149– 1.228
Moderately differentiated (II)	3404						
Poorly differentiated or Undifferentiated (III or IV)	737						
Unknown							
Radiotherapy	6563	< 0.001	0.006	0.925	< 0.001	0.009	0.925
None/Unknown	3395			0.875– 0.978			0.872– 0.980
Yes							

PDAC, pancreatic ductal adenocarcinoma; CI, confidence interval.

Variables	No. of patients (N = 9958)	Overall survival			Cancer-specific survival		
		Univariate P value	Multivariate P value	Hazard Ratio (95% CI)	Univariate P value	Multivariate P value	Hazard Ratio (95% CI)
Chemotherapy	2758	< 0.001	< 0.001	0.548	< 0.001	< 0.001	0.577
None/Unknown	7200			0.518– 0.580			0.543– 0.613
Yes							
AJCC 8th N staging	2891	< 0.001	< 0.001	1.456	< 0.001	< 0.001	1.527
	3985			1.410–			1.476–
N0				1.504			1.580
N1	3082						
N2							

PDAC, pancreatic ductal adenocarcinoma; CI, confidence interval.

Variables	No. of patients (N = 9958)	Overall survival		Cancer-specific survival			
		Univariate P value	Multivariate P value	Hazard Ratio (95% CI)	Univariate P value	Multivariate P value	Hazard Ratio (95% CI)
Tumor size (mm)	63	< 0.001	< 0.001	1.050	< 0.001	< 0.001	1.051
1–5	115			1.040– 1.059			1.041– 1.061
6–10	424						
11–15	957						
16–20	1643						
21–25	1677						
26–30	1549						
31–35	1236						
36–40	779						
41–45	556						
46–50	319						
51–55	236						
56–60	134						
61–65	89						
66–70							
71–85							
86–100							
	119						
	62						
PDAC, pancreatic ductal adenocarcinoma; CI, confidence interval.							

The median OS of this cohort was 21.0 months (IQR 11.0–43.0 months), and its accumulative 5-year OS rate was 17.9%. Referring to CSS, its median was 23.0 months (IQR 12.0–49.0 months), and the accumulative 5-year CSS rate was 21.2%.

Prognostic Indicators For Resected PDAC

Many indicators have been verified as predictors of resected PDAC. Univariate analysis revealed that age ($P < 0.001$), gender ($P = 0.012$), tumor site ($P = 0.016$), tumor grade ($P < 0.001$), AJCC 8th N staging ($P < 0.001$), tumor size ($P < 0.001$), radiotherapy ($P < 0.001$) and chemotherapy ($P < 0.001$) were all significant prognostic factors for OS, as well as those for CSS (Table 1). Furthermore, multivariate analysis showed that age [$P < 0.001$; hazard ratio (HR), 1.203; 95% confidence interval (CI), 1.145–1.263], tumor site ($P = 0.001$; HR, 0.955; 95% CI, 0.931–0.980), tumor grade ($P < 0.001$; HR, 1.169; 95% CI, 1.132–1.206), AJCC 8th N staging ($P < 0.001$; HR, 1.456; 95% CI, 1.410–1.504), tumor size ($P < 0.001$; HR, 1.050; 95% CI, 1.040–1.059), radiotherapy ($P = 0.006$; HR, 0.925; 95% CI, 0.875–0.978) and chemotherapy ($P < 0.001$; HR, 0.548; 95% CI, 0.518–0.580) remained as significant independent predictors for OS, as well as those for CSS (Table 1).

Correlations between tumor sizes and prevalence of lymph node metastases

The prevalence of LN metastases in this cohort was 71.0%. There was a non-linear relation between increasing tumor sizes and the prevalence of LN metastases across the tumor size spectrum (Fig. 2). Patients with tumors between 1 and 5 mm in size had the lowest prevalence of LN metastases (less than 15%). Then, the prevalence increased in a stepwise fashion as tumor size increased from 6–10 mm (40.0%) to 36–40 mm (75.7%); however, beyond 40 mm, the prevalence of LN metastases plateaued between 70.0% and 80.0%. Observing the tracing pattern of the initial part of the curve (1–40 mm), which conformed to non-linear correlation, we tried to use the logarithmic regression to match this non-linear curve. As expected, the established curve was highly matched (**Figure S1**), and its formula was

$$Y = [0.249 \times \ln(X) + 0.452] \times 100\%$$

Correlation coefficient $R^2 = 0.991$ (Y, prevalence of LN metastases; X, tumor size in centimeter)

Thus, the prevalence of LN metastases was limited within 80% no matter the size of tumors. The probability for PDAC patients with tumors within 1–40 mm in size to be detected with positive LN metastasis was subjected to the formulated matched curve, and when tumors larger than 40 mm, its probability was steadily within 70%-80%.

Patterns Between Tumor Sizes And Lymph Node Metastatic Status

LNR measures the metastatic ability of each examined LN. The global LNR of the total cohort was 0.145 (IQR 0-0.214), and in patients with at least one positive LN metastasis was 0.205 (IQR 0.077–0.278). Following the tracing pattern of average LNR across the tumor size spectrum, the average LNR increased stepwise as tumor size rose from 1–5 mm (LNR = 0.024) to 41–45 mm (LNR = 0.177); then, beyond 45 mm, it too plateaued near 0.170 (Fig. 2). Thus, when tumor size reaches 41–45 mm or more, the probability of metastasis in each regional LN was steadily near 17.0%.

Expectedly, patients with a higher N stage revealed a higher metastatic presence. The number of stage N2 patients/the number of stage N1 patients (N2/N1) represents the distribution of patients with different LN metastatic severity. The tracing pattern of N2/N1 was similar to the curve for average LNR. N2/N1 ratio gradually increased along with greater tumor size from 1–5 mm (0.286) to 41–45 mm (1.016), and when

tumor size reached 41–45 mm or more, the ratio stably wavered around 1.000 except for size group 61–65 mm. Therefore, nearly half of LN positive patients may have an N2 stage when tumor size reaches 40 mm.

Prognostic significance of AJCC 8th N staging in different tumor sizes

In the analysis of the prognostic significance of AJCC 8th N staging for OS, there was no significant difference in patients with tumor between 1 and 5 mm in size. Additionally, no significant difference was obtained between stage N2 and N1 when tumor size from 6 to 15 mm. However, once tumor sizes ranged from 16 to 45 mm, the survival curves could be stratified significantly based on N stage. Again, when tumor size ranged between 46 and 65 mm, there was no significant difference between stage N1 and N0. Furthermore, no significant difference was reached when tumor size was greater than 66 mm except for stage N2 and N0 in size group 86–100 mm (Table 2).

Table 2
Prognostic significance of AJCC 8th N staging in different tumor sizes.

Tumor size (mm)	JACC 8th N staging	No. of patients	Overall survival P value			Cancer-specific survival P value		
			N0	N1	N2	N0	N1	N2
1–5	N0	54	0.14	0.14	0.21	0.031	0.031	0.003
	N1	6	0.21	0.683	0.683	0.003	0.683	0.683
	N2	3						
6–10	N0	69	0.001	0.001	< 0.001	< 0.001	< 0.001	< 0.001
	N1	35	< 0.001	0.525	0.525	< 0.001	0.315	0.315
	N2	11						
11–15	N0	211	0.012	0.012	< 0.001	0.003	0.003	< 0.001
	N1	158	< 0.001	0.051	0.051	< 0.001	0.127	0.127
	N2	55						
16–20	N0	372	0.030	0.030	< 0.001	0.008	0.008	< 0.001
	N1	391	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
	N2	194						
21–25	N0	508	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
	N1	688	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
	N2	447	< 0.001	< 0.001	< 0.001			
26–30	N0	451	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
	N1	717	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
	N2	509						
31–35	N0	381	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
	N1	637	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
	N2	531	< 0.001	< 0.001	< 0.001			

Tumor size (mm)	JACC 8th N staging	No. of patients	Overall survival P value			Cancer-specific survival P value		
			N0	N1	N2	N0	N1	N2
36–40	N0	300	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
			< 0.001	0.002	0.002			
	N1	478				< 0.001	< 0.001	< 0.001
	N2	458						
41–45	N0	160	0.001	0.001	< 0.001	< 0.001	< 0.001	< 0.001
	N1	307	< 0.001	0.036	0.036	< 0.001	0.018	0.018
	N2	312						
46–50	N0	134	0.072	0.072	< 0.001	0.115	0.115	< 0.001
	N1	203	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
	N2	219			< 0.001			
51–55	N0	73	0.372	0.372	0.033	0.478	0.478	0.021
	N1	123	0.033	0.179	0.179	0.021	0.081	0.081
	N2	123						
56–60	N0	62	0.044	0.044	0.001	0.032	0.032	< 0.001
	N1	88	0.001	0.227	0.227	< 0.001	0.065	0.065
	N2	86						
61–65	N0	39	0.698	0.698	0.025	0.318	0.318	0.003
	N1	55	0.025	0.023	0.023	0.003	0.012	0.012
	N2	40						
66–70	N0	28	0.124	0.124	0.074	0.077	0.077	0.047
	N1	31	0.074	0.808	0.808	0.047	0.905	0.905
	N2	30						

Tumor size (mm)	AJCC 8th N staging	No. of patients	Overall survival P value			Cancer-specific survival P value		
			N0	N1	N2	N0	N1	N2
71–85	N0	31	0.124	0.124	0.074	0.185	0.185	0.017
	N1	46	0.074	0.808	0.808	0.017	0.233	0.233
	N2	42						
86–100	N0	18	0.445	0.445	0.008	0.356	0.356	0.018
	N1	22	0.008	0.234	0.234	0.018	0.292	0.292
	N2	22						
AJCC, American Joint Committee on Cancer.								

Concurrently, in the analysis for CSS, significant differences and discriminations by N stage were found in tumor size of 16–45 mm, similar to OS. The other detailed descriptions when tumor size was less than 16 mm or more than 45 mm are displayed in Table 2. Overall, remarkable stratification and discrimination was only achieved in tumors ranging between 16 and 45 mm in size. Furthermore, other detailed prognostic indicators, such as age, gender, grade, chemotherapy and radiotherapy in different tumor sizes, were analyzed and displayed in **Supplementary Tables 1–3**.

Discussion

In this retrospective population-based analysis, 9,958 resected PDAC patients without distant metastasis were analyzed to investigate the impact of tumor size on LN metastatic status and survival indicators. As expected, tumor size and the AJCC 8th N staging were both independent predictors of OS and CSS for resected PDAC patients without distant metastasis. Both tumor size and LN status have been integral parts of staging according to the AJCC guidelines. A retrospective study of 6,145 PDAC patients by Park H *et al.*[18] sought to confirm whether the AJCC 7th TNM staging system accurately represented tumor size versus extrapancreatic extension, and demonstrated that tumor size was more determinant of prognosis than extrapancreatic extension. A large number of other studies, besides our previous report, also confirmed that tumor size was an independent risk factor in PDAC patients[6, 17, 19]. As a result, the most recent AJCC 8th TNM staging guidelines, as of January 1, 2018, solely utilizes tumor size in its T-stage classification[20]. In addition, our previous study addressed the controversy of the current AJCC staging [21] and showed that a modified stage IIIA (T1-2N2M0) had a significantly more prolonged survival than a modified stage IIIB (T3N2M0, T4NxM0). This is similar to a report that N2 patients had a better survival rate than T4 patients[22]. Thus, tumor size may have a wider effect on survival stratification than LN metastasis, and the predictive power of N assessment may be limited, just like the regional LN metastatic ability may tend to plateau when reaching a certain tumor size threshold.

Muralidhar V *et al.*[7] have reported that LN involvement has significantly interacted with tumor T stage, thus indicating that a relationship may exist between them. Interestingly, our study supports the existence of trends and where a nonlinear development from 1 to 40 mm and be stable (70–80%) once beyond 40 mm occurs. Meanwhile, the non-linear variation between 1 and 40 mm was almost perfectly matched by a formulated logarithmic regression equation. Additionally, we found that the probability of metastasis in each regional LN steadily plateaued near 17%, and the stage N2/N1 ratio was nearly 50% in node-positive patients when tumor size reached 40 mm. Therefore, the general prevalence of LN metastases could be assessed by radiologists via tumor sizes measured by preoperative radiological examinations and then surgeons and pathologists could be more confident about the likelihood of LN metastasis from pathological specimens.

Ma C *et al.*[23] and Kassardjian A *et al.*[24] reported that preoperative contrast-enhanced CT or MRI scan could underestimate the tumor sizes when compared to pathological specimens. Thus, when clinicians want to estimate the prevalence of LN metastases in resectable PDAC patients before surgery, a bias of about 5 mm between imaging modalities and gross examinations should be considered. In our study, a tumor size of 40 mm is the potential demarcation point for the prevalence of LN metastases, the probability of metastasis in each regional LN and N2/N1 ratio in node-positive patients. Takahashi C *et al.*[25] determined that a tumor size of 20 mm as the ideal cut-off and found that patients with tumors > 20 mm were more likely to have positive LNs. This was consistent with our findings that the prevalence of LN metastases, the probability of metastasis in each regional LN and the N2/N1 ratio in node-positive patients for tumor size more than 20 mm were all absolutely higher than tumors < 20 mm. Meanwhile, international validations have proved that the AJCC 8th TNM staging guideline demonstrated a modestly increased prognostic accuracy and more equal distribution among stages[26, 27]. This new staging system includes a tumor size of 40 mm as one cut-off value for T staging, and Cing L *et al.*[28] have validated that the pT classification in the 8th edition is significantly superior to that in the 7th edition at stratifying patients by OS when compared to N staging, which indicates tumor size of 40 mm plays an important stratified role in tumor progression. Petermann D *et al.*[29] tried to illustrate the impact of tumor sizes on LN metastasis, and limited PDAC cases (n = 114) similarly showed patients with tumor sizes of ≤ 20 mm had the prevalence of LN metastases of 41%, which is consistent with our large population-based study and formulated equation.

Concurrently, we found that the AJCC 8th N staging could have a significant survival prediction and risk stratification in patients with tumor sizes from 16 to 45 mm. Researchers reported that very small primary tumors might be correlated with decreased OS among LN-positive PDAC patients, which raises the possibility that small tumors are more capable of LN metastasis and hence may represent more biologically aggressive cancers[7]. However, in resectable PDAC patients, the prevalence of LN metastases, LNR and N2/N1 ratio were relatively stable as tumor size approached 40 mm. This could explain the reason why a lack of significance existed in survival stratification. It was reported that the correlation between tumor size and survival was linear for patients with localized tumors, but stochastic in patients with regional and distant stages. Increased tumor size was associated with worse CSS among patients with resected tumors, rather than that in patients with unresected tumors[6].

This study is limited by its retrospective nature. Data retrieved from the SEER database have limited information about patients' clinicopathological characteristics, so its retrospective nature needs a prospective, international, and large-scale cohort for future validation. Meanwhile, the number of ELNs might be influenced

by other confounders not available in data provided, including patient immune status, body mass index, surgical standards, tumor biological behaviors, difficulties in separating individual LNs in dissected specimens, and evaluators' expertise.

Conclusion

In conclusion, this study is the first time to formulate the associations between tumor sizes and prevalence of LN metastases in PDAC using real-world cohorts with generalizable and representative results by robust statistics. The relationship curves suggest that the probability of metastasis in each regional LN for resectable PDAC patients with tumors > 40 mm in size is near 17.0% and their prevalence of LN metastasis is 70%-80%. Among which, 50% of patients may have a higher stage (stage N2).

Abbreviations

PDAC: pancreatic ductal adenocarcinoma; LN: lymph node; SEER: Surveillance, Epidemiology, and End Results; LNR: lymph node ratio; AJCC: American Joint Committee on Cancer; OS: overall survival; CSS: cancer-specific survival; ELN: examined lymph node; minELN: minimum number of ELN; NCCN: National Comprehensive Cancer Network

Declarations

Ethics approval and consent to participate

The protocol of this study was approved by the ethics committee of Zhongshan Hospital, Fudan University.

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

There are no conflicts of interest to report from these authors.

Funding

This work was supported by grants from: the National Natural Science Foundation of China (81773068), Zhongshan Clinical Trial (2016ZSLC14), Clinical Science and Technology Innovation Project, Shengkang Hospital Development Center of Shanghai (SHDC12017X04) and Project of Shanghai Municipal Health Commission (201940409).

Authors' contributions

NP, QC, WW, and WL conceived and designed the research. NP, QC, BKK, HY, JRH, MC, YD, JL, SG and MN collected and analyzed data. NP, WW, LL, JY, and WL participated in evaluation of results. NP, QC, and JY wrote the manuscript, and all authors reviewed and approved the manuscript for publication.

Acknowledgements

Not applicable

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Figures

Figure 1

Flowchart showing the enrolled cohort according to the inclusion and exclusion criteria.

Figure 2

The relationships depicted by trend charts between tumor sizes and (A) prevalence of lymph node metastases, (B) average lymph node ratio and (C) N2/N1 ratio.

Supplementary Files

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