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Original Article

Presence of tumor deposits is an indicator of poor prognosis in patients with pancreatic ductal adenocarcinoma

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Abstract: Tumor deposits (TDs) are associated with poor prognosis in several malignancies and have been incorporated into the tumor-node-metastasis (TNM) staging system for colorectal cancer. This study aims to explore the significance of TDs in pancreatic ductal adenocarcinoma (PDAC). All patients who underwent pancreatectomy with a curative intent for PDAC were retrospectively enrolled. Patients were categorized into 2 groups according to the status of TDs: the positive group, in which TDs were present, and the negative group, in which TDs were absent. The prognostic significance of TDs was evaluated. In addition, a modified staging system was developed by incorporating TDs into the eighth edition of the TNM staging system. One hundred nine (17.8%) patients had TDs. Patients with TDs demonstrated significantly lower 5-year overall survival (OS) and recurrence-free survival (RFS) rates than those without TDs (OS: 9.1% *vs.* 21.5%, P=0.001; RFS: 6.1% *vs.* 16.7%, P<0.001). Even after matching, patients with TDs still had significantly worse OS and RFS than those without TDs. In the multivariate analysis, the presence of TDs was an independent prognostic factor in patients with PDAC. The survival of patients with TDs was similar to that of patients with N2 stage disease. The modified staging system had a greater Harrell's C-index than the TNM staging system, which indicates better performance in predicting survival. The presence of TDs was an independent prognostic factor for PDAC. Categorizing patients with TDs into N2 stage improved the accuracy of the TNM staging system in predicting prognosis.

Keywords: Pancreatic ductal adenocarcinoma, tumor deposits, lymph node, staging, prognosis

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy with deaths almost equal to the number of cases and is the seventh in leading cause of cancer-related death worldwide. Over the past several decades, both the incidence and mortality rates have either been stable or have slightly increased in many countries [1, 2]. Despite improvements in diagnosis and treatment, the prognosis of patients with PDAC remains poor. Even after curative resection, the 5-year overall survival (OS) rate has been reported to be approximately 20% [3-5]. The poor prognosis of PDAC is related to many factors, and the identification of associated adverse prognostic factors is vital for prognostic assessment and subsequent treatment.

Tumor deposits (TDs), also known as extranodal metastases, are defined as the irregular aggregation of discrete tumor cells in soft tissue or fat that are discontinuous with the primary lesion. TDs show no evidence of residual lymph node tissue but are within the lymphatic drainage of the primary tumor [6]. TDs have been confirmed to have an adverse impact on the prognosis of many malignancies, including gastric [7-9], colorectal [10, 11], and breast [12, 13] cancers as well as head and neck squamous cell carcinomas [14]. In the latest version

of the tumor-node-metastasis (TNM) staging system for colorectal cancer, the presence of TDs is classified as N1c stage in the absence of regional lymph node metastasis [6]. Recently, several studies have explored the possibility of adding TDs to revise the TNM staging system [7, 15-17]. It has been reported that MRI-diagnosed TDs has superior prognostic accuracy to current clinical TNM staging in rectal cancer [15]. Zhang and his co-workers reveled that classifying patients with TDs into pN3 stage improved the discriminative power of the current TNM staging system for esophageal cancer [16]. In gastric cancer, it was demonstrated that the presence of TDs would upstage N stage and the revised TNM staging system incorporating TDs was more effective in predicting the prognosis of patients with gastric cancer [7, 17]. However, in PDAC, few studies have focused on TDs. The characteristics and clinical significance of TDs have never been well elucidated. Indeed, this study is the first report that specifically focuses on TDs in PDAC.

In the present study, we retrospectively analyzed the data of 612 patients with PDAC who underwent curative resections. The aim of this study was to evaluate the potential impact of TDs on the long-term outcomes of patients with PDAC and to explore the possibility and superiority of incorporating TDs into the eighth edition of the TNM staging system.

Material and methods

Study design and patients

This study was approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital. Given the retrospective design and use of anonymized patient data, informed consent was waived by the Committee of our Institute. Through the pancreatic cancer database of our institute, 836 patients with pancreatic cancer who underwent surgical resection at Tianjin Medical University Cancer Institute and Hospital from January 2011 to December 2018 were eligible for this study. Inclusion criteria included: (i) patients with PDAC, (ii) patients who underwent pancreatic resection with a curative intent, (iii) patients with complete clinical and pathological examination results, (iv) patients who recovered well after surgery and were discharged. And exclusion criteria were: (i) patients with rare pathological histologic subtypes including adenosquamous carcinomas, acinar cell carcinomas and intraductal papillary mucinous neoplasms or mucinous cystic neoplasms with invasive cancer, (ii) patients who underwent bypass surgery or explorative laparotomy without resection, (iii) patients with macroscopical or microscopical tumor residual, (iv) patients with distant metastasis, (v) patients died due to postoperative complications, (vi) patients with history of other malignancy, (vii) patients who were lost to follow-up.

Data collection

Clinicopathological data including sex, age, preoperative serum carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) levels, tumor location, tumor size, pancreatic resection type, tumor differentiation, TNM stage, lymphovascular involvement, perineural invasion, TDs, postoperative complications, and postoperative adjuvant chemotherapy were collected from pancreatic cancer database of our institute. Postoperative complications during hospitalization included those directly related to surgery, such as haemorrhage, anastomotic leak, pancreatic fistula, chyle leak, and abdominal or wound infection.

Tumors were staged according to the eighth edition of the Union for International Cancer Control (UICC) TNM classification system. The levels of preoperative serum tumor markers (CA19-9 and CEA) were detected within 1 week before surgery. For patients with obstructive jaundice, serum CA19-9 was detected again after biliary drainage.

Assessment of TDs

After the surgery, surgeons harvested both lymph nodes and solid structures in adipose connective tissue from fresh surgical specimens. These nodules that were discontinuous with the primary lesion, were grouped according to lymph node stations. Thereafter, all resected specimens including pancreas, lymph nodes, and solid structures in adipose connective tissue were fixed in 10% formalin, embedded in paraffin, and stained with haematoxylin and eosin. Each metastasis was re-examined microscopically on slides for the presence of TDs. Pathological diagnosis was established by two dedicated pathologists. In this study, TDs

were defined as the irregular aggregation of discrete cancer cells in the fat/soft tissue of peripancreatic or locoregional lymph drainage area. Given that PDAC is to grow discontinuously with a lot of stroma between cancer cells aggregates, TDs we defined were macroscopically and microscopically discontinuous from the primary PDAC. Deposits of metastatic adenocarcinoma into soft tissue without a recognizable lymph node were also considered as TDs, unless these metastases were associated with perineural and/or vessel involvement. TDs were also distinguished from peritoneal metastases as they were not located on the peritoneal surface or on the mesentery. **Figure 1** shows the hematoxylin and eosin staining results of three typical TDs.

Outcome measures and statistical analysis

All patients were categorized into 2 groups according to the status of TDs: the positive group, in which TDs were present, and the negative group, in which TDs were absent. Clinicopathological features were compared between the two groups. To overcome bias due to the different distribution of covariates in the two groups, the propensity score analysis according to the nearest-neighbour matching method was used. A caliper width of 0.25 of the standard deviation of the logit of the propensity score was set. Variables including patients' demographic, clinical and tumor characteristics were entered in the propensity model. Survival was compared between the two groups after matching.

The prognostic significance of TDs was evaluated. In addition, a modified staging system was developed by incorporating TDs into the eighth edition of the TNM staging system. The performance of prognostic prediction between the modified staging system and the eighth edition TNM staging system was then compared by Harrell's C-index, hazard ratios (HRs) value and their 95% confidence intervals (CI) related to the Cox regression model. The prognostic discrimination power of the two staging systems was evaluated by the receiver operating characteristic (ROC) curves and decision curve analysis (DCA). The areas under the curve (AUCs) of the two staging systems were compared using the Z test.

Continuous variables were presented as median and interquartile range (IQR), and were compared by means of the Mann-Whitney U test. Categorical variables were expressed as absolute value and relative frequencies (%), and were compared using the Chi-square or Fisher exact test. OS was calculated from the day of surgery until death or last follow-up. RFS was defined as the interval from the operation until tumor recurrence or last follow-up. Date of the last follow-up was March 30, 2022. OS and RFS curves were calculated by the Kaplan-Meier method. Log-rank test was used to assess significant differences between curves. Independent prognostic factors were identified by the Cox proportional hazards regression model. $P<0.050$ with two tails was considered statistically significant. The statistical analysis was performed using the IBM statistical analysis program package SPSS 23.0 and MedCalc v.20. DCA was conducted using R software (version 4.1.2).

Results

Clinicopathological features

The flow chart and exclusion criteria of this study are shown in **Figure 2**. After exclusion of 224 patients, ultimately, 612 patients were eligible for the study. Of the 612 patients with PDAC who underwent pancreatectomy with a curative intent, 260 were females (42.5%), and median age was 61 (IQR: 55-67) years. Most tumors were located in the pancreatic head. A total of 414 (67.6%) patients underwent pancreaticoduodenectomy, 195 (31.9%) patients underwent distal pancreatectomy, and 3 (0.5%) patients underwent total pancreatectomy. Twenty-one patients underwent superior mesenteric vein (SMV)/portal vein (PV) resection and reconstruction. One hundred and sixty-four (26.8%) patients experienced postoperative complications and all recovered after conservative treatment. Thirty patients received neoadjuvant therapy with 5-fluorouracil, leucovorin, gemcitabine and oxaliplatin (mFOLFIRINOX) or albumin-bound paclitaxel and gemcitabine (AG). Three hundred and one (49.2%) patients received postoperative adjuvant chemotherapy with mFOLFIRINOX, capecitabine and gemcitabine (GX), S-1 and gemcitabine (GS), S-1, or gemcitabine. TDs were detected in 109 (17.8%) patients. The median number of

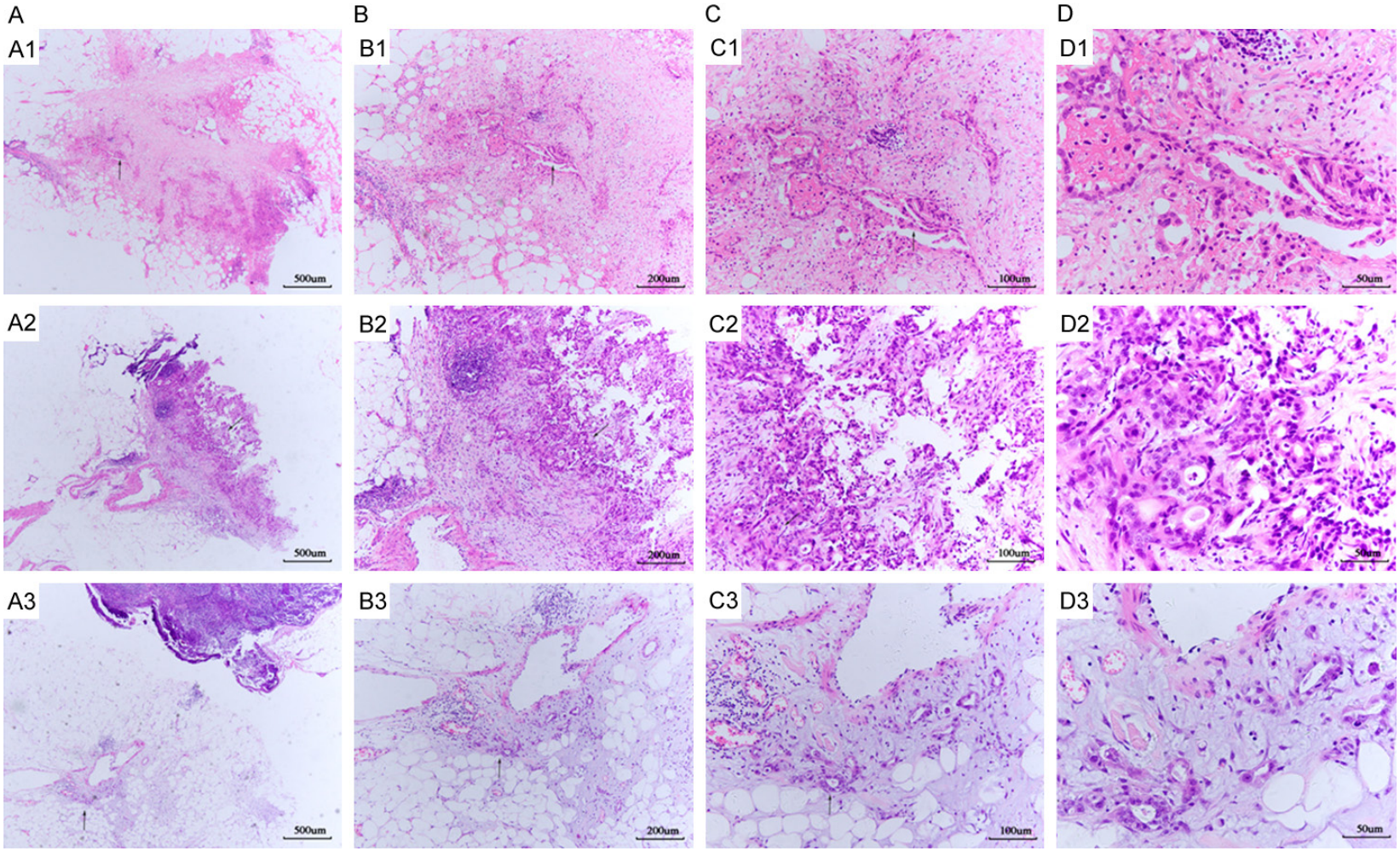

Figure 1. Examples of TDs at different sites in pancreatic ductal adenocarcinoma stained with H&E. Cancer cells scattered in the soft tissue are distinct from those in metastatic lymph nodes. (A1-D1) TDs at station 17; (A2-D2) TDs at station 14v; (A3-D3) TDs at station 12p. (A) Original magnification ×40, (B) ×100, (C) ×200, (D) ×400.

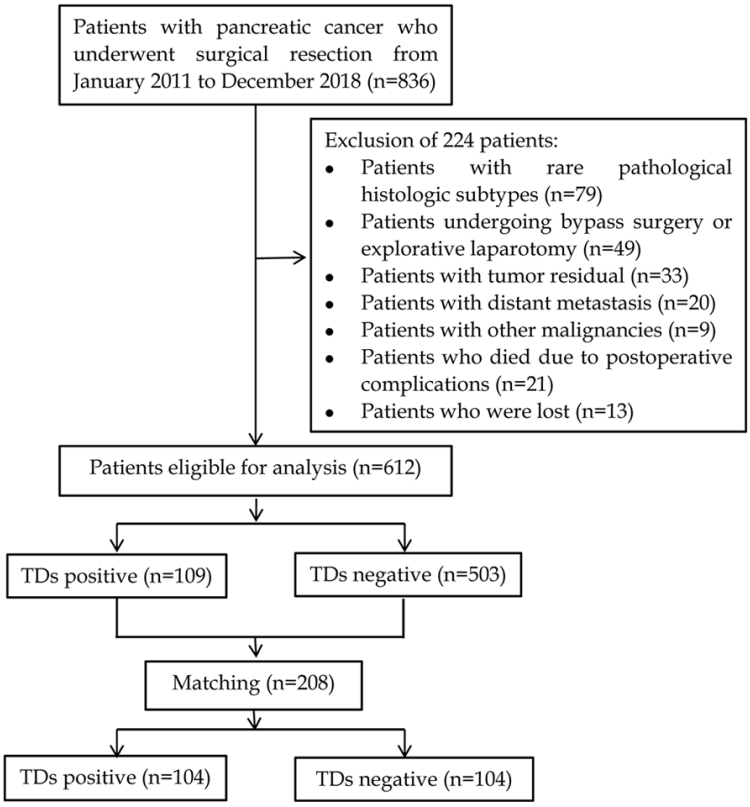

Figure 2. Flow diagram detailing the selection of patients included in this study.

TDs was 1 (range: 1-14). In the 109 patients with TDs, 91 had only one TD, and 18 patients had ≥ 2 TDs.

Clinicopathologic characteristics in the TDs positive and negative groups before and after propensity score matching are shown in **Table 1**. Overall, patients in the TDs positive group were more likely to have preoperative serum CA19-9 levels ≥ 1000 U/ml (22.9% *vs.* 13.9%), a greater number of lymph node metastases (1.6±2.6 *vs.* 1.1±1.9, *P*=0.018), a higher likelihood of lymphovascular invasion (36.7% *vs.* 22.7%, *P*=0.002), a higher incidence of postoperative complications (36.7% *vs.* 24.6%, *P*=0.010) and advanced tumor (T), node (N), and TNM stage than those in the TDs negative group.

After adjusting for sex, age, preoperative serum CA19-9 and CEA levels, tumor location, tumor size, pancreatic resection type, tumor differentiation, number of metastatic lymph nodes, number of retrieved lymph nodes, T stage, N stage, TNM stage, lymphovascular involvement, perineural invasion, postoperative complications and postoperative adjuvant chemotherapy, 104 patients in the TDs negative group were matched with an equal number of patients in the TDs positive group. The adjusted propensity score for patients with TDs was almost identical to that for patients without TDs. The distribution of the propensity scores is displayed in Figure S1. All covariates were equally distributed over the two matched groups.

Survival analysis of patients with PDAC

The results of the univariate and multivariate survival analyses are shown in **Table 2**. The following 10 factors evaluated in the univariate analysis had a significant effect on OS and RFS: age at surgery, preoperative serum CA19-9 and CEA levels, tumor differentiation, TNM stage, lymphovascular involvement, perineural invasion, TDs, postoperative complications and postoperative adjuvant chemotherapy. Patients with TDs demonstrated significantly worse OS and RFS (median OS: 13.0 *vs.* 23.0 mo, *P*=0.001; median RFS: 6.0 *vs.* 12.0 mo, *P*<0.001) than those without TDs (**Figure 3A**, **3B**). The analysis of patients grouped according to the number of TDs revealed that the number of TDs did not affect patient survival (**Figure 3C**, **3D**). Even after matching, patients with TDs still had shorter median OS and RFS (OS: 13.0 *vs.* 21.0 mo, *P*=0.025; RFS: 5.0 *vs.* 11.0 mo, *P*=0.014) than those without TDs. In the multivariate analysis, preoperative serum CA19-9 levels, tumor differentiation, TNM stage, TDs and postoperative adjuvant chemotherapy were independently associated with both OS and RFS, while age at surgery was only independently associated with OS. The median follow-up were 51 months (range: 3-126) and 49 months (range: 2-126) for OS and RFS, respectively.

Table 1. Clinicopathological features of patients with pancreatic ductal adenocarcinoma according to the status of TDs, data is reported for the whole study series and for the matched pairs

Characteristics	Whole study series			Matched pairs (Case-control Method)		
	TDs positive (n=109), n (%)	TDs negative (n=503), n (%)	*P*	TDs positive (n=104), n (%)	TDs negative (n=104), n (%)	*P*
Sex			0.622			0.315
Male	65 (59.6)	287 (57.1)		62 (59.6)	69 (66.3)	
Female	44 (40.4)	216 (42.9)		42 (40.4)	35 (33.7)	
Median (IQR)	62 (55-67)	61 (55-67)	0.932	62 (55-67)	61 (56-66)	0.954
Age (Years)			0.881			0.841
<70	94 (86.2)	431 (85.7)		89 (85.6)	90 (86.5)	
≥70	15 (13.8)	72 (14.3)		15 (14.4)	14 (13.5)	
Preoperative CEA (ng/ml)			0.241			0.354
≤5.0	82 (75.2)	350 (69.6)		78 (75.0)	72 (69.2)	
>5.0	27 (24.8)	153 (30.4)		26 (25.0)	32 (30.8)	
Preoperative CA19-9 (U/ml)			0.035			0.746
<200.0	51 (46.8)	290 (57.7)		51 (49.0)	55 (52.9)	
200-1000.0	33 (30.3)	143 (28.4)		33 (31.7)	28 (26.9)	
≥1000.0	25 (22.9)	70 (13.9)		20 (19.2)	21 (20.2)	
Tumor location			0.585			0.739
Head	72 (66.1)	344 (68.4)		69 (66.3)	64 (61.5)	
Body	24 (22.0)	115 (22.9)		23 (22.1)	25 (24.0)	
Tail	13 (11.9)	44 (8.7)		12 (11.5)	15 (14.4)	
Tumor size (cm)			0.065			0.689
Median (IQR)	4.0 (3.0-4.5)	3.5 (2.8-4.5)		3.5 (3.0-4.5)	4.0 (3.0-4.5)	
Pancreatic resection type			0.644			0.470
PD	72 (66.1)	342 (68.0)		69 (66.3)	64 (61.5)	
DP	37 (33.9)	158 (31.4)		35 (33.7)	40 (38.5)	
TP	0 (0.0)	3 (0.6)		0 (0.0)	0 (0.0)	
Number of metastatic lymph nodes			0.008			0.487
Median (IQR)	1 (0-2)	0 (0-2)		0 (1-2)	0 (1-2)	
Number of retrieved lymph nodes			0.523			0.877
Median (IQR)	10 (8-17)	10 (8-14)		10 (8-17)	10 (9-14)	
T stage			0.014			0.419
T1	9 (8.3)	90 (17.9)		9 (8.7)	13 (12.5)	
T2	60 (55.0)	263 (52.3)		59 (56.7)	57 (54.8)	
T3	34 (31.2)	141 (28.0)		30 (28.8)	32 (30.8)	
T4	6 (5.5)	9 (1.8)		6 (5.8)	2 (1.9)	
N stage			0.006			0.857
N0	47 (43.1)	296 (58.8)		46 (44.2)	50 (48.1)	
N1	47 (43.1)	144 (28.6)		44 (42.3)	41 (39.4)	
N2	15 (13.8)	63 (12.5)		14 (13.5)	13 (12.5)	
TNM stage			0.006			0.519
I	27 (24.8)	206 (41.0)		27 (26.0)	31 (29.8)	
II	60 (55.0)	225 (44.7)		56 (53.8)	58 (55.8)	
III	22 (20.2)	72 (14.3)		21 (20.2)	15 (14.4)	
Differentiation			0.055			0.058
Well	0 (0.0)	23 (4.6)		0 (0.0)	5 (4.8)	
Moderate	41 (37.6)	200 (39.8)		40 (38.5)	33 (31.7)	
Poor	68 (62.4)	280 (55.7)		64 (61.5)	66 (63.5)	

Perineural invasion			0.772			0.569
Present	66 (60.6)	297 (59.0)		62 (59.6)	66 (63.5)	
Absent	43 (39.4)	206 (41.0)		42 (40.4)	38 (36.5)	
Lymphovascular invasion			0.002			0.462
Present	40 (36.7)	114 (22.7)		37 (35.6)	32 (30.8)	
Absent	69 (63.3)	389 (77.3)		67 (64.4)	72 (69.2)	
Postoperative complications			0.010			0.656
Present	40 (36.7)	124 (24.7)		35 (33.7)	32 (30.8)	
Absent	69 (63.3)	379 (75.3)		69 (66.3)	72 (69.2)	
Postoperative adjuvant chemotherapy			0.581			0.405
Yes	51 (46.8)	250 (49.7)		47 (45.2)	53 (51.0)	
No	58 (53.2)	253 (50.3)		57 (54.8)	51 (49.0)	

IQR, interquartile range; TDs, tumor deposits; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy.

Incorporation of the TDs status into the eighth edition of the N staging system

Based on strata analysis, significant prognostic differences between the two groups were observed in patients at the N0-N1 stages or TNM I-II stages. TDs did not affect the OS and RFS of patients with N2 or TNM III stage disease (Table S1; Figure S2A-L). The survival of N0 or N1 patients with TDs was similar to that of N2 patients regardless of TDs status (**Figure 4A**, **4B**). According to the results of the stratified analysis, we incorporated TDs into the eighth edition of the N staging system and introduced the newly modified N (mN) stages. The mN stages were defined as follows: mN0, no regional lymph node metastasis and no TDs; mN1, 1-3 regional lymph node metastases and no TDs; mN2, 4 or more regional lymph node metastases regardless of the presence of TDs or 0-3 regional lymph node metastases and presence of TDs.

Predictive performance of the modified staging system

The prognostic values of the N stage, mN stage, TNM stage and mTNM stage were evaluated and the differences in prognostic prediction were compared (**Table 3**). The median OS was 25.0, 18.0 and 16.0 months in patients with N0, N1 and N2 stage disease, respectively (χ^2=28.365, *P*<0.001). The median OS was 27.0, 20.0 and 14.0 months in patients in the mN0, mN1 and mN2 stages, respectively (χ^2=49.916, *P*<0.001) (**Figure 5A**, **5B**). The median RFS was 14.0, 9.0 and 6.0 months in patients in the N0, N1 and N2 stages, respectively (χ^2=40.512, *P*<0.001), and the median RFS was 15.0, 10.0 and 6.0 months in patients in the mN0, mN1 and mN2 stages, respectively (χ^2=61.044, *P*<0.001) (**Figure 5C**, **5D**). The mN classification system (OS: HR=1.471; RFS: HR=1.487) was confirmed to be a more accurate prognostic classification for predicting the OS and RFS of patients with PDAC than the N stage of the eighth edition of the TNM staging system (OS: HR=1.419; RFS: HR=1.474). The Harrell's C-index values of the mN stage were greater than those of the N stage (OS: 0.595 *vs.* 0.564; RFS: 0.600 *vs.* 0.577), which indicated a better performance in predicting survival. The ROC curves also demonstrated superior AUC values for mN stage compared with N stage for OS and RFS at 3 years after surgery (Table S2; Figure S3A, S3B). According to the DCA of N stage and mN stage, the net benefit for mN stage was larger over the N stage, which means that mN stage is the optimal staging system (Figure S4A).

Furthermore, we established an mTNM staging system by replacing the N stage of the eighth edition of the UICC TNM staging system with the mN stage. As presented in Figure S5, the patients were more evenly distributed among the mTNM stages than among the TNM stages. The median OS of patients at TNM stage I, II and III was 28.0, 19.0 and 15.0 months, respectively (χ^2=39.719, *P*<0.001). The median OS of patients at mTNM stage I, II and III was 29.0, 20.0 and 14.0 months, respectively (χ^2= 55.142, *P*<0.001) (**Figure 6A**, **6B**). The median

Table 2. Univariate and multivariate analyses of factors associated with OS and RFS in patients with pancreatic ductal adenocarcinoma

Characteristics	N	Overall Survival						Recurrence-Free Survival					
		5-year OS (%)	MST	Univariate analysis		Multivariate analysis		5-year RFS (%)	MRT	Univariate analysis		Multivariate analysis	
				HR (95% CI)	*P*	*HR (95% CI)*	*P*			*HR (95% CI)*	*P*	*HR (95% CI)*	*P*
Sex													
Male	352	19.5	20.0	1 (ref)				14.0	10.0	1 (ref)			
Female	260	18.6	24.0	0.899 (0.739-1.092)	0.282			15.7	12.0	0.908 (0.756-1.091)	0.305		
Age at surgery													
<70	525	19.9	22.0	1 (ref)		1 (ref)		15.1	11.0	1 (ref)		1 (ref)	
≥70	87	14.3	15.0	1.408 (1.083-1.832)	0.011	1.576 (1.204-2.064)	0.001	12.5	8.0	1.201 (0.930-1.551)	0.160	1.286 (0.992-1.668)	0.058
Tumor location													
Head	416	19.7	21.0	1 (ref)				14.5	10.0	1 (ref)			
Body and tail	196	18.2	21.0	1.001 (0.814-1.231)	0.993			14.7	10.0	0.985 (0.811-1.197)	0.881		
Preoperative serum CEA (ng/ml)													
≤5.0	432	21.8	24.0	1 (ref)		1 (ref)		16.5	12.0	1 (ref)		1 (ref)	
>5.0	180	12.2	17.0	1.416 (1.150-1.745)	0.001	1.194 (0.946-1.506)	0.135	10.6	8.0	1.402 (1.151-1.708)	0.001	1.170 (0.939-1.458)	0.161
Preoperative serum CA19-9 (U/ml)													
<200.0	341	22.2	25.0	1 (ref)		1 (ref)		19.5	15.0	1 (ref)		1 (ref)	
200.0-1000.0	176	18.1	19.0	1.339 (1.074-1.668)	0.009	1.423 (1.130-1.793)	0.003	10.5	10.0	1.382 (1.123-1.700)	0.002	1.350 (1.0866-1.678)	0.007
≥1000.0	95	12.6	14.0	2.013 (1.547-2.620)	<0.001	1.560 (1.172-2.076)	0.002	4.7	5.0	2.274 (1.772-2.919)	<0.001	1.823 (1.389-2.391)	<0.001
Differentiation													
Well	23	46.3	45.0	1 (ref)		1 (ref)		43.7	23.0	1 (ref)		1 (ref)	
Moderate	241	21.8	27.0	1.807 (0.922-3.542)	0.085	1.314 (0.664-2.600)	0.433	15.1	15.0	1.832 (0.995-3.370)	0.052	1.336 (0.719-2.482)	0.359
Poor	348	15.7	16.0	2.854 (1.468-5.551)	0.002	2.001 (1.018-3.932)	0.044	12.5	8.0	2.756 (1.508-5.036)	0.001	1.947 (1.054-3.596)	0.033
TNM stage													
I	233	28.5	28.0	1 (ref)		1 (ref)		22.0	17.0	1 (ref)		1 (ref)	
II	285	14.9	19.0	1.544 (1.245-1.914)	<0.001	1.335 (1.066-1.671)	0.012	12.4	9.0	1.494 (1.220-1.829)	<0.001	1.251 (1.013-1.545)	0.037
III	94	7.7	15.0	2.323 (1.753-3.078)	<0.001	1.914 (1.396-2.624)	<0.001	3.3	6.0	2.349 (1.798-3.068)	<0.001	1.723 (1.280-2.318)	<0.001
Lymphovascular invasion													
Absent	458	21.0	23.0	1 (ref)		1 (ref)		17.2	12.0	1 (ref)		1 (ref)	
Present	154	14.0	17.0	1.436 (1.158-1.780)	0.001	1.063 (0.837-1.350)	0.618	7.8	6.0	1.622 (1.327-1.983)	<0.001	1.206 (0.964-1.509)	0.102
Perineural invasion													
Absent	249	25.3	23.0	1 (ref)		1 (ref)		20.0	12.0	1 (ref)		1 (ref)	
Present	363	13.4	20.0	1.217 (1.212-1.481)	0.046	1.011 (0.824-1.241)	0.914	10.5	9.0	1.286 (1.067-1.549)	0.008	1.059 (0.872-1.285)	0.563
Tumor deposits													
Negative	503	21.5	23.0	1 (ref)		1 (ref)		16.7	12.0	1 (ref)		1 (ref)	
Positive	109	9.1	13.0	1.755 (1.391-2.213)	<0.001	1.583 (1.238-2.024)	<0.001	6.1	6.0	1.777 (1.420-2.222)	<0.001	1.553 (1.226-1.967)	0.001
Postoperative complications													
No	448	21.0	24.0	1 (ref)		1 (ref)		16.2	12.0	1 (ref)		1 (ref)	
Yes	164	14.2	17.0	1.416 (1.146-1.751)	0.001	1.220 (0.978-1.522)	0.078	10.6	8.0	1.303 (1.065-1.594)	0.010	1.099 (0.890-1.356)	0.381
Postoperative adjuvant chemotherapy													
No	311	14.1	17.0	1 (ref)		1 (ref)		13.3	9.0	1 (ref)		1 (ref)	
Yes	301	24.4	26.0	0.598 (0.493-0.726)	<0.001	0.576 (0.473-0.701)	<0.001	16.2	12.0	0.780 (0.651-0.934)	0.007	0.782 (0.651-0.939)	0.008

Ref, reference category; HR, hazard ratio; MST, median survival time; MRT, Median recurrence time; OS, overall survival; RFS, recurrence-free survival.

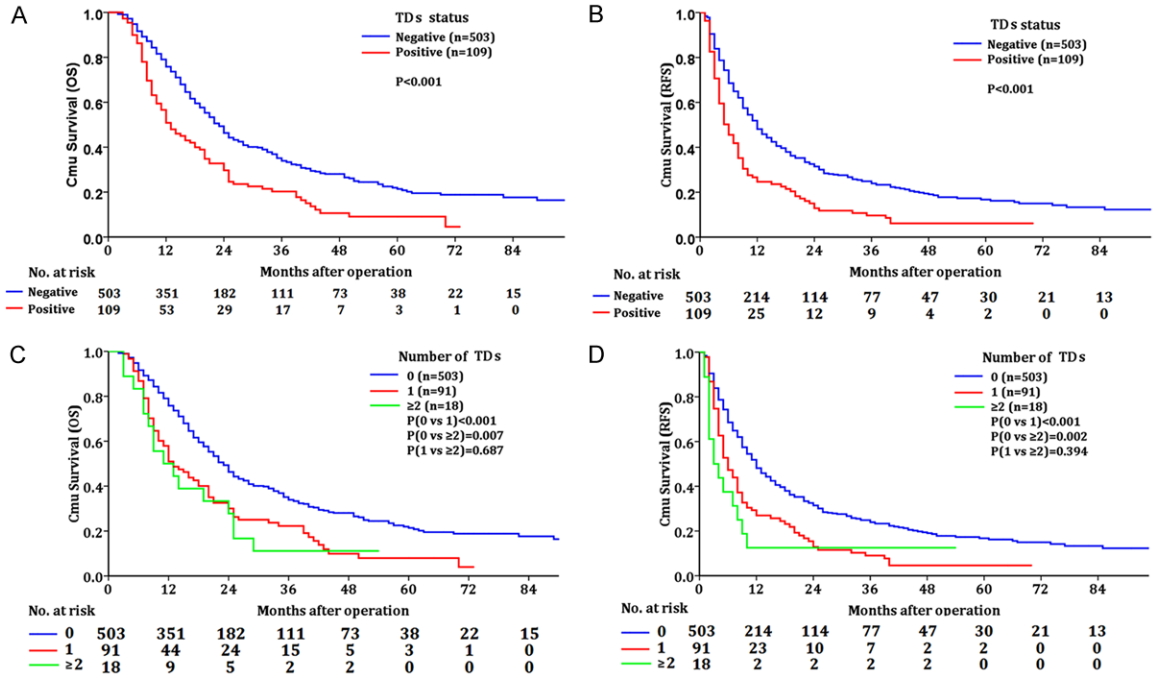

Figure 3. Kaplan-Meier estimates of overall survival and recurrence free survival in patients with PDAC after curative resection according to the status and number of TDs. A. OS of patients with and without TDs. B. RFS of patients with and without TDs. C. OS according to the number of TDs. D. RFS according to the number of TDs.

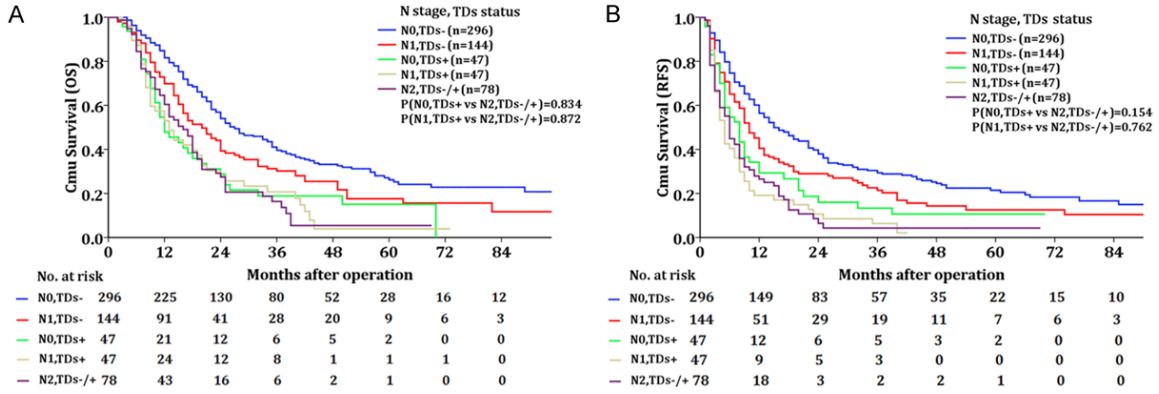

Figure 4. Survival curves of PDAC patients according to N stage and TDs status. The OS and RFS of patients with TDs at the N0 and N1 stages were similar to those of patients at the N2 stage. A. OS. B. RFS.

RFS of patients with TNM stage I, II and III disease was 17.0, 9.0 and 6.0 months, respectively (χ^2=43.565, *P*<0.001). The median RFS of patients with mTNM stage I, II and III disease was 19.0, 10.0 and 6.0 months, respectively (χ^2=63.666, *P*<0.001) (**Figure 6C**, **6D**). The capacity to predict OS and RFS was also compared between the mTNM and TNM staging systems (**Table 3**). We found that the mTNM staging system could better predict OS and RFS than the TNM staging system. The Harrell's C-index values of mTNM staging were greater than those of TNM staging (OS: 0.606 *vs.* 0.585; RFS: 0.608 *vs.* 0.587). The ROC curves also demonstrated superior AUC values for mTNM staging compared with TNM staging for OS and RFS at 3 years after surgery (Table S2; Figure S3C, S3D). According to the DCA of TNM stage and mTNM stage, the net benefit for mTNM stage was larger over the TNM stage, which means that mTNM stage is the optimal staging system (Figure S4B).

Table 3. Definitions of N and TNM categories and their impact on the prognostic value of staging

Character-istics	N	Overall Survival							Recurrence-free Survival						
		5-y OS (%)	MST	Univariate analysis		Multivariate analysis		C-Index (95% CI)	5-y RFS (%)	MRT	Univariate analysis		Multivariate analysis		C-Index (95% CI)
				χ^2	*P*	HR (95% CI)	*P*				χ^2	*P*	HR (95% CI)	*P*	
N stage				27.998	<0.001	1.419 (1.243-1.620)	<0.001	0.564 (0.537-0.590)			40.512	<0.001	1.474 (1.300-1.672)	<0.001	0.577 (0.551-0.602)
N0	343	24.8	25.0			1 (ref)			20.0	14.0			1 (ref)		
N1	191	14.1	18.0			1.444 (1.167-1.786)	0.001		9.4	9.0			1.472 (1.204-1.799)	<0.001	
N2	78	5.5	16.0			1.992 (1.498-2.649)	<0.001		4.3	6.0			2.176 (1.663-2.849)	<0.001	
mN stage				49.340	<0.001	1.471 (1.316-1.645)	<0.001	0.595 (0.569-0.622)			61.044	<0.001	1.487 (1.337-1.655)	<0.001	0.600 (0.574-0.625)
mN0	296	26.4	27.0			1 (ref)			21.5	15.0			1 (ref)		
mN1	144	17.6	20.0			1.423 (1.113-1.818)	0.005		12.5	10.0			1.368 (1.087-1.723)	0.008	
mN2	172	8.1	14.0			2.169 (1.736-2.711)	<0.001		5.1	6.0			2.227 (1.802-2.752)	<0.001	
TNM stage				39.122	<0.001	1.526 (1.330-1.750)	<0.001	0.585 (0.558-0.611)			44.833	<0.001	1.520 (1.333-1.732)	<0.001	0.587 (0.561-0.614)
I	233	28.5	28.0			1 (ref)			22.0	17.0			1 (ref)		
II	285	14.9	19.0			1.544 (1.245-1.914)	<0.001		12.4	9.0			1.494 (1.220-1.829)	<0.001	
III	94	7.7	15.0			2.323 (1.753-3.078)	<0.001		3.3	6.0			2.349 (1.798-3.068)	<0.001	
mTNM stage				54.377	<0.001	1.558 (1.379-1.759)	<0.001	0.606 (0.580-0.633)			63.666	<0.001	1.552 (1.381-1.743)	<0.001	0.608 (0.582-0.633)
I	206	30.1	29.0			1 (ref)			23.2	19.0			1 (ref)		
II	225	17.2	20.0			1.553 (1.221-1.975)	<0.001		15.6	10.0			1.420 (1.134-1.777)	0.002	
III	181	8.7	14.0			2.425 (1.900-3.095)	<0.001		4.5	6.0			2.396 (1.905-3.014)	<0.001	

OS, overall survival; RFS, recurrence free survival; MST, median survival time; MRT, median recurrence time; HR, hazard ratio; Ref, reference category.

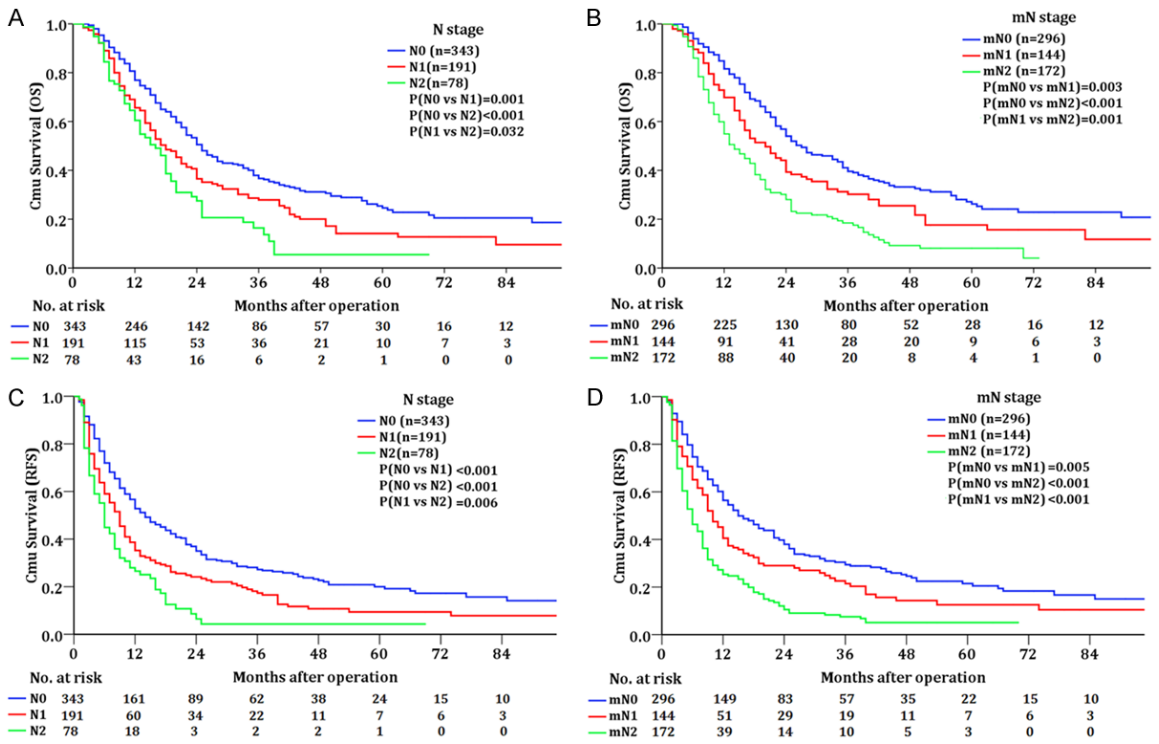

Figure 5. Survival curves according to the eighth edition of the N staging system and the modified N staging system. There were significant differences in OS and RFS with N or mN stages. A. N stage, OS. B. mN stage, OS. C. N stage, RFS. D. mN stage, RFS.

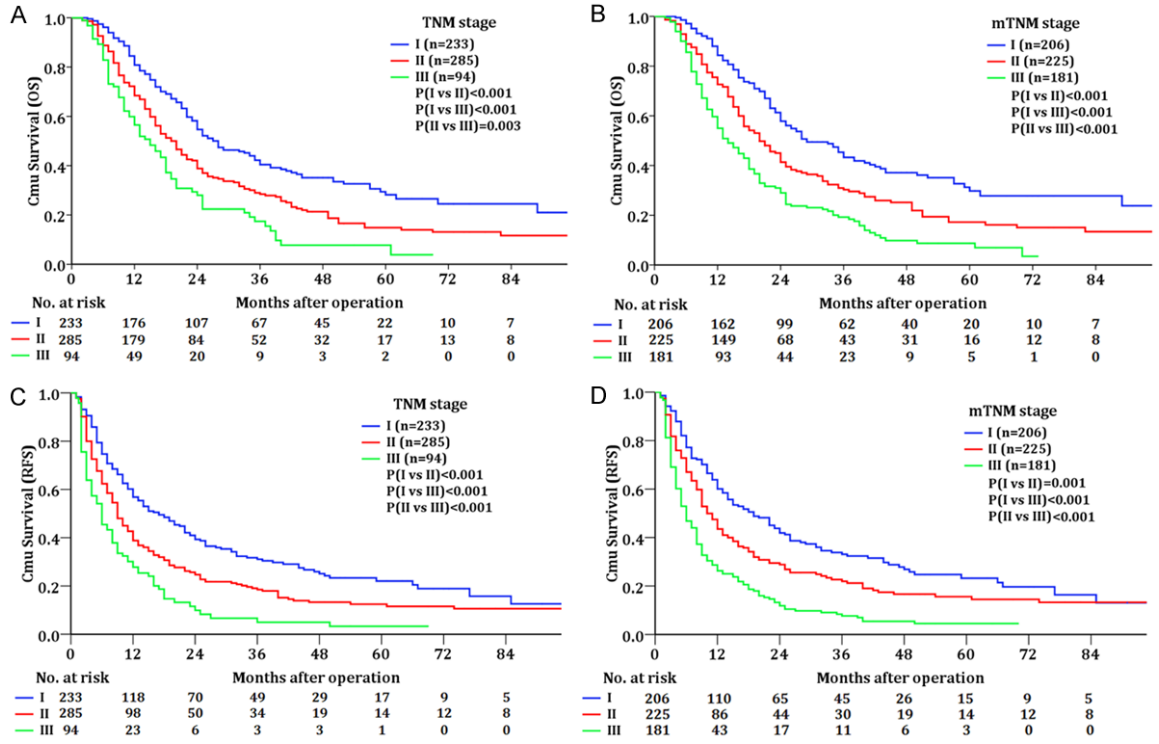

Figure 6. Survival curves according to the eighth edition of the TNN staging system and the modified TNM staging system. There were significant differences in OS and RFS with TNM or mTNM stages. A. TNM stage, OS. B. mTNM stage, OS. C. TNM stage, RFS. D. mTNM stage, RFS.

Discussion

In recent years, TDs have attracted increased attention from clinicians. Many studies have demonstrated that the presence of TDs is associated with poor prognosis in a variety of malignancies, such as gastric cancer and colorectal cancer [7-11]. However, TDs have not been investigated in PDAC. In the present study, we investigated TDs in PDAC patients who underwent curative resection. The presence of TDs was confirmed to be an independent prognostic factor for PDAC, and the classification of patients with TDs into N2 stage could improve the accuracy of the TNM staging system in predicting prognosis.

TDs have been widely studied in gastrointestinal cancer. In 1997, this concept was first introduced into the 5th edition of the TNM staging system for colorectal cancer; a TD greater than 3 mm was considered similar to a metastatic lymph node and was classified as N stage, while TDs less than or equal to 3 mm were defined as discontinuous extensions of the primary tumor and were categorized as T3 stage [18]. According to the eighth edition of the TNM staging system, TDs are defined as irregularly discrete tumor deposits in the pericolic or perirectal fat that show no evidence of residual lymph node tissue but are within the lymphatic drainage of the primary tumor, moreover, the presence of TDs is classified as N1c stage in the absence of regional lymph node metastasis [6]. The criteria, histological features and clinical value of TDs have been gradually clarified. In other malignancies, the incidence of TDs has been reported to be approximately 10% to 27% [7-14]. The presence of TDs is associated with decreased survival. It was reveled that gastric cancer patients with TDs exhibited aggressive characteristics and poorer prognosis [7]. Zhang and his co-workers confirmed that the presence of TDs was an independent prognostic factor for oesophageal cancer and that the classification of patients with TDs into N3 stage improved the discriminative power of the TNM staging system [16]. Nevertheless, no study has focused on TDs in patients with PDAC. Discontinuous nodules far from the primary tumor are frequently detected in the lymphatic drainage pathways of PDAC specimens. Unlike metastatic lymph nodes, these nodules have no lymph node structure. They are also distinct from the peripancreatic soft tissue (PST) invasion. Previous studies defined PST involvement as the presence of tumor cells in the peripancreatic soft tissues, including the anterior and posterior surfaces of adipose and fibrous tissues [19, 20]. In several studies, PST involvement was found in 91% of the cases and was not correlated with survival [19, 21]. In this study, we defined these nodules as TDs since they are very similar to TDs in colorectal cancer. As a result, one hundred and nine (17.8%) patients had TDs. Patients with TDs were more likely to have lymphovascular invasion, and advanced T, N, and TNM stage than those without TDs. We believe that the presence of TDs in PDAC indicates higher aggressiveness and a more advanced stage.

Regarding the prognostic value of TDs, previous studies have confirmed the adverse impact of TDs on survival in various types of malignancies [7-17]. In our study, PDAC patients with TDs demonstrated a significantly lower 5-year OS and RFS rates than those without TDs (OS: 9.1% *vs.* 21.5%, P=0.001; RFS: 6.1% *vs.* 16.7%, P<0.001). To overcome bias, a one-to-one propensity score matching method was used. Even after matching, patients with TDs still had significantly worse OS and RFS than those without TDs. In the multivariate analysis, the presence of TDs was found to be an independent prognostic factor. However, the number of TDs did not affect patient survival, and a sharp slope was noted in survival curves if only one TD was present. This is consistent with a previous study showing that TDs are more similar to peritoneal metastases than to lymph node metastases [22]. Patients with TDs who exhibited long-term survival were not uncommon, which was different from what was observed in patients with peritoneal disease [7]. Wang and his co-workers considered that the presence of TDs was a special type of metastasis and reported that the prognosis of patients with TDs was better than that of patients with peritoneal metastasis [23]. These results suggest that the presence of TDs is a poor prognostic indicator in PDAC and is of great value in predicting prognosis, monitoring recurrence and determining post-surgery treatment strategies.

As the presence of TDs was a strong indicator of poor prognosis in patients with PDAC, we

hypothesized that the incorporation of TDs into the TNM staging system would improve the accuracy of the system in predicting prognosis. It was recommended that TDs be included in the staging system for gastric cancer, as the N classification including TDs was superior to the N stage of the eighth edition TNM staging system in predicting OS in patients with gastric cancer [7]. In the present study, we found that the OS and RFS of PDAC patients with TDs who were at stages pN0 and pN1 were similar to those of patients at stage pN2 regardless of TDs status. Although TDs status was an independent prognostic factor for the whole study series, the presence of TDs did not affect the OS and RFS of patients with PDAC at the pN2 stage. The presence of TDs was as important as the pN2 stage. Based on these results, we suggest that patients with TDs should be assigned to stage pN2 and that a new staging system should be established. The new staging system was confirmed to be a better prognostic predictor than the eighth edition of the TNM staging system. It is therefore necessary to include more patients to determine how the incorporation of TDs will change the PDAC staging system in the future.

This study has several limitations. First, this study was retrospective in nature and was conducted at a single institution. Although a propensity score matching method was implemented to reduce confounding factors, selection bias was inevitable. Second, the origin and formation mechanism of TDs were not explored. Generally, cancer nodules can be divided into 5 types according to their origins, namely, nodules continuous with the primary tumor, nodules around organs, nodules formed by perineural invasion, nodules formed by lymph node metastasis and nodules formed by lymphovascular infiltration [24]. Recently, it was reported that extranodal extension significantly predicted poor prognosis in patients with pancreatic head cancer, especially those with lymph node metastasis [25]. In previous studies, extranodal extension, which was defined as cancer cells penetrating into the perinodal adipose tissue, had been reported to be associated with poor prognosis in patients with PDAC [26-28]. In fact, extranodal extension is a type of TDs that originate from lymph node metastasis. The mechanism of TDs still requires exploration by pathologists and is vital for a better understanding of the clinical value and significance of TDs. Finally, the characteristics of TDs, such as size, contour and texture, were not described because it was difficult to distinguish TDs from lymph nodes at the macro level.

In conclusion, the presence of TDs is an independent prognostic factor for PDAC. Patients with TDs usually have a poorer prognosis, and the survival of these patients is similar to that of patients at the N2 stage. The presence of TDs should be considered in PDAC staging. Moreover, pathologists should be aware of this important clinicopathological feature and should carefully examine PDAC specimens to determine the presence of TDs by histological examination; additionally, the status of TDs should also be recorded in the pathology report. Given the single-center retrospective nature of this study and that this is the first validation of TDs in PDAC, multicenter prospective trials are warranted to confirm our findings.

Disclosure of conflict of interest

None.

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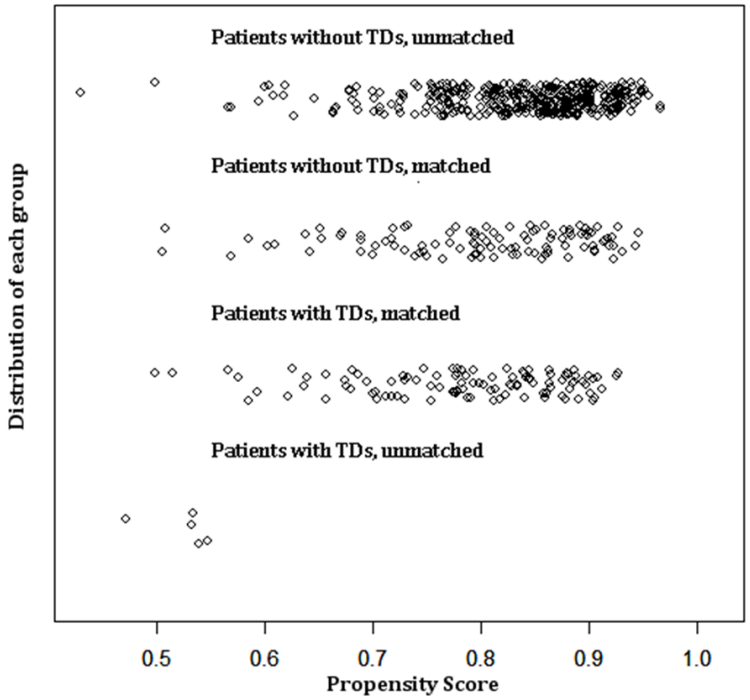

Figure S1. Distribution of the propensity scores. Each circle represents one patients.

Table S1. Strata survival analysis of pancreatic cancer patients according to tumor stage

Tumor stage	5-year OS (%)/MST		χ^2	P	5-year RFS (%)/MRT		χ^2	P
	TDs negative	TDs positive			TDs negative	TDs positive		
N stage								
N0	26.4/27.0	15.1/12.0	18.519	<0.001	21.5/15.0	10.7/8.0	11.764	0.001
N1	17.6/20.0	3.9/13.0	6.507	0.011	12.5/10.0	NA/5.0	13.645	<0.001
N2	4.8/15.0	NA/20.0	0.536	0.464	3.0/6.0	NA/4.0	0.006	0.938
TNM stage								
I	30.1/29.0	15.5/15.0	12.503	<0.001	23.2/19.0	11.9/8.0	7.609	0.006
II	17.2/20.0	4.1/13.0	8.412	0.006	15.6/10.0	NA/5.0	16.328	<0.001
III	8.6/16.0	NA/9.0	0.208	0.504	2.1/6.0	NA/4.0	0.029	0.697

TDs: Tumor deposits; MST: Median survival time; MRT: Median recurrence time; NA: not applicable.

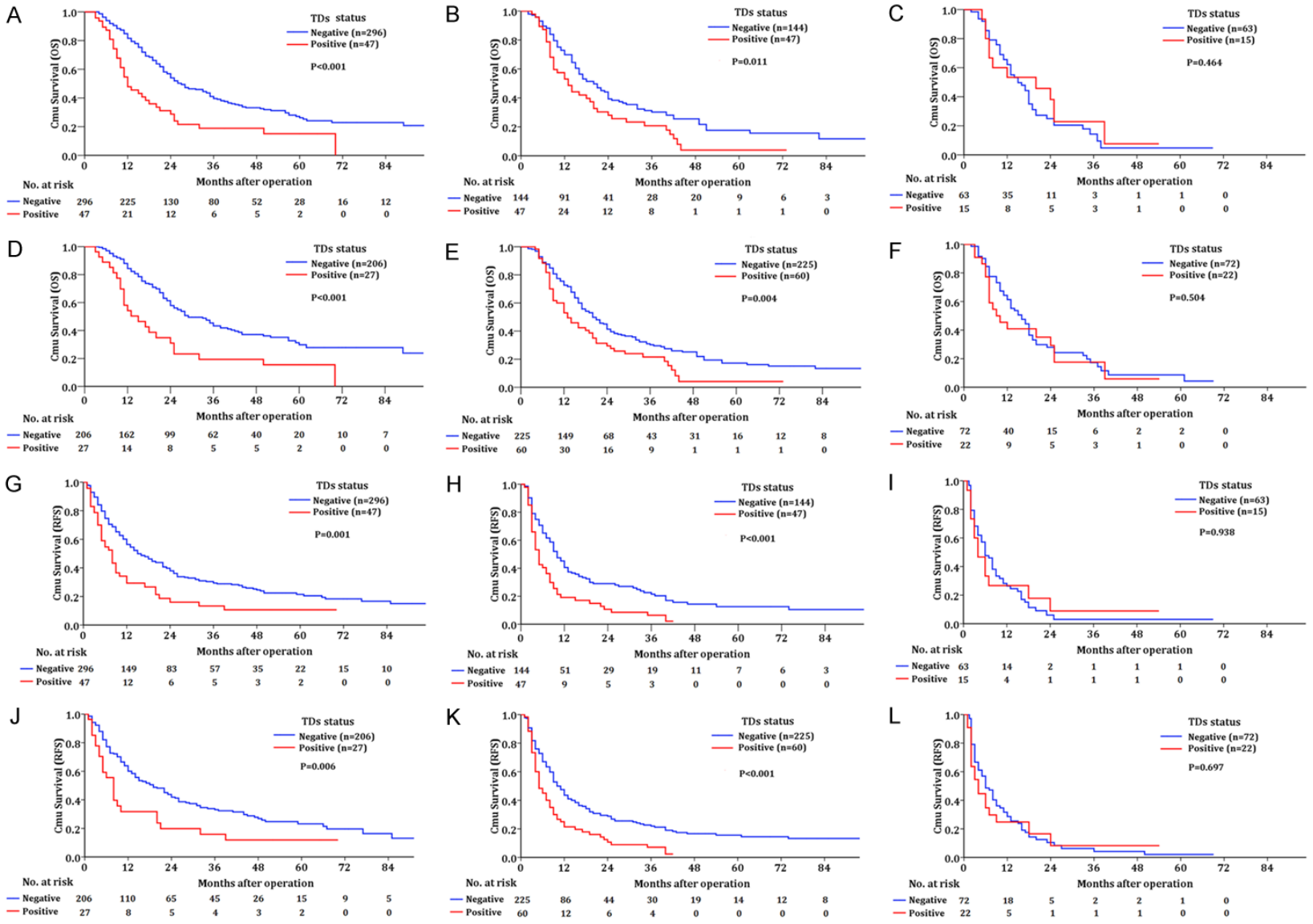

Figure S2. Overall survival and recurrence-free survival curves stratified by N stage and TNM stage. The survival differences were only observed in PC patients with N0-1 or TNM I-II stage. (A) OS of N0 stage, (B) OS of N1 stage, (C) OS of N2 stage, (D) OS of TNM I stage, (E) OS of TNM II stage, (F) OS of TNM III stage, (G) RFS of N0 stage, (H) RFS of N1 stage, (I) RFS of N2 stage, (J) RFS of TNM I stage, (K) RFS of TNM II stage, (L) RFS of TNM III stage.

Table S2. AUC values of the modified staging system compared to the AUC values of the UICC eighth staging system regarding OS and RFS at 3 years after surgery

Staging system	Overall Survival			Recurrence-free Survival		
	AUC value	95% CI	*P*	AUC value	95% CI	*P*
N stage	0.570	0.529-0.609		0.598	0.558-0.637	
mN stage	0.646	0.607-0.684	<0.0001*	0.644	0.605-0.682	0.0008*
TNM stage	0.592	0.552-0.631		0.611	0.571-0.650	
mTNM stage	0.665	0.626-0.702	<0.0001**	0.661	0.622-0.699	<0.0001**

AUC, area under the curves; CI, confidence interval; *compared to the N stage; **compared to the TNM stage.

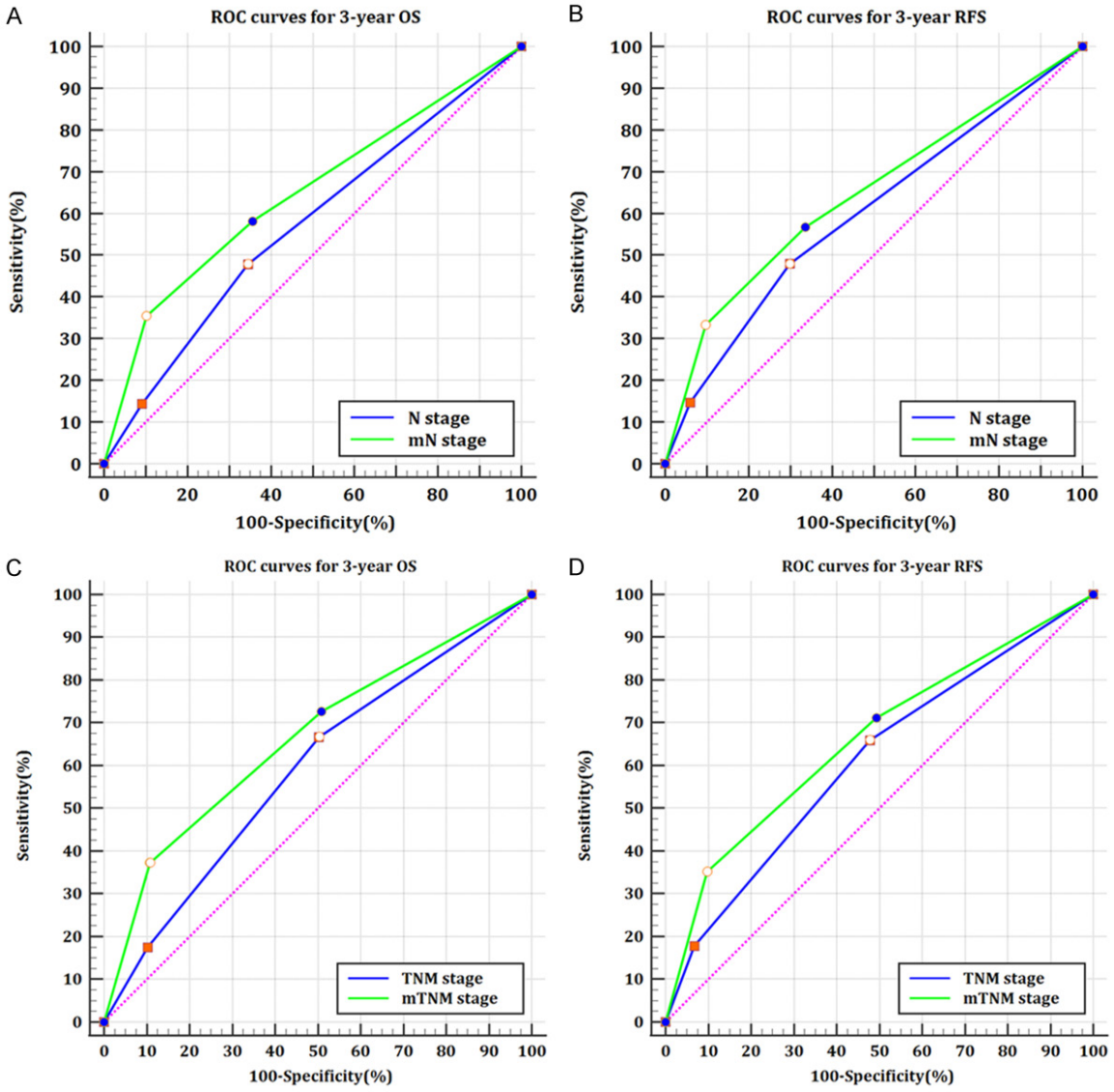

Figure S3. The ROC curves demonstrated superior AUC values for the modified staging system compared with the TNM staging system for OS and RFS at 3 years after surgery. (A) N stage and mN stage for OS, (B) N stage and mN stage for RFS, (C) TNM stage and mTNM stage for OS, (D) TNM stage and mTNM stage for RFS.

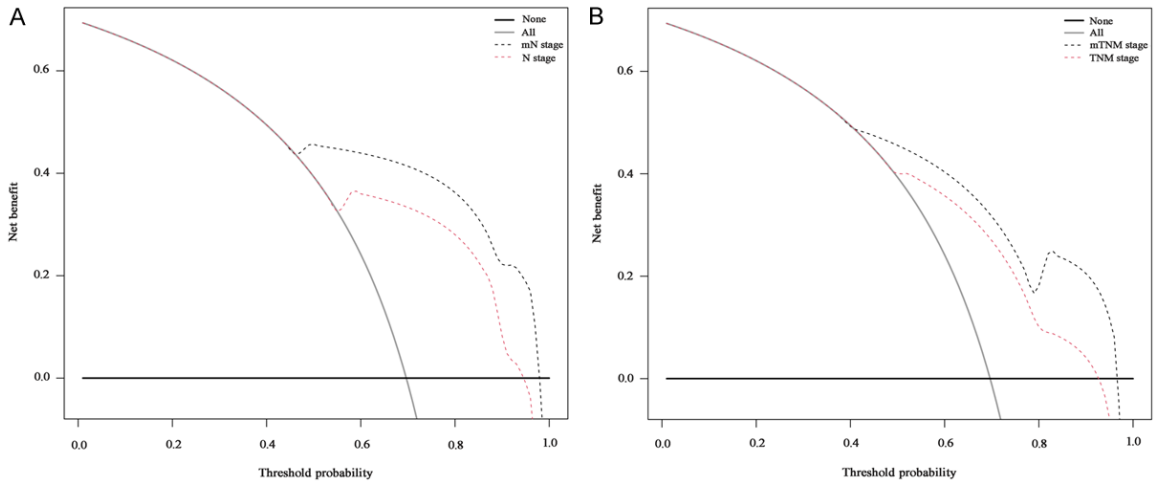

Figure S4. Decision curve analysis (DCA) of the two staging models. The net benefit curves for the two staging models are shown. A. The preferred model is the mN stage, the net benefit of which was larger over the N stage. B. The preferred model is the mTNM stage, the net benefit of which was larger over the TNM stage.

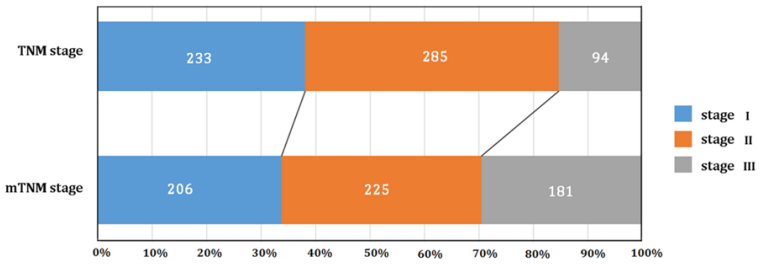

Figure S5. Patients distribution. The largest subgroup in the two staging system is II, whereas the stage migration is most obvious in the III subgroup.