



A Quantitative Clinicopathological Signature for Predicting Recurrence Risk of Pancreatic Ductal Adenocarcinoma After Radical Resection

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Recurrence and distant metastases were main reasons of unfavorable outcomes for patients with pancreatic ductal adenocarcinoma (PDAC) after surgery. The aim of this study was to describe the patterns, timing, and predictors of recurrence or metastasis in PDAC patients after curative surgery. Patients with PDAC who underwent radical pancreatectomy were included. Associations between clinicopathological and radiological characteristics and specific pattern of progression were investigated. Least absolute shrinkage and selection operator (LASSO) and Cox regression were applied to assess the prognostic factors for overall survival (OS) and progression-free survival (PFS). A total of 302 patients were included into present study, and 173 patients were documented as recurrence after a median survival of 24.7 months. More than half of patients recurred after 12 months after surgery, and the liver was the most common metastatic site. Decreased time interval to progression, elevated carbohydrate antigen 19-9 (CA19-9) level, and lymph node (LN)16 metastasis were independent predictors for reduced OS. Independent prognostic factors for PFS included elevated carcinoembryonic antigen (CEA) level, local progression, liver or lung-only metastasis, local + distant progression, multiple metastases, LN16 metastasis, imaging tumor size, chemotherapy, and tumor-node-metastasis (TNM) stage. The predictive system showed valuable prediction performance with values of concordance indexes (C-indexes) and the area under the receiver operating characteristic curve (AUC) over 0.80. Different survival curves and predictive factors for specific patterns of disease progression suggested the biological heterogeneity, providing new versions into personal management of recurrence in PDAC patients after surgery.

Keywords: pancreatic ductal adenocarcinoma, recurrence, pattern, timing, predictor

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease and is predicted to become the second leading cause of cancer-specific death by 2030 (1). Surgery followed by adjuvant chemotherapy has been widely established as the best mean to obtain longer survival. However, this combination therapy can only be applied to 20% of patients, whereas most patients suffered from locally

advanced or metastatic diseases, owing to the lack of early clinical symptoms and effective screening methods. Moreover, even after curative resection, up to 80% of patients suffered from recurrence soon after surgery (2–4), and the 5-year survival rate was <6% (5).

Progression had a truly negative effect on prognoses of patients with PDAC. However, the variations of biological behaviors and clinicopathological factors of tumors would contribute to different patterns and timing of progression even when diseases were classified as the same stages. Although multiple studies illustrated the risk factors of progression, such as resection margin status and lymph node (LN) metastasis (6, 7), the relationship between the prognosis and progression was rarely evaluated for patients with PDAC. The prognosis might be changing among patients with different patterns and timing of progression, whereas significant heterogeneity existed among the current reports regarding patterns and timing of recurrence owing to the small sample sizes and limited period of follow-up (8, 9). Understanding both the risk factors and the patterns of progression of PDAC patients can provide an insight into optimization of the treatment, as well as the surveillance strategies. Although recurrence was associated with decreased survival, whether the sites and timing of recurrence had different influences on survival remained controversial. Thus, the aim of this study was to evaluate the risk factors for different patterns of recurrences and compare the survival differences in PDAC patients with varied patterns or timing of disease progression.

MATERIALS AND METHODS

Patients

This study included consecutive patients with PDAC who underwent surgical resection at Sun Yat-sen University Cancer Center (SYSUCC) between 2008 and 2018. Excluded patients were those with metastatic diseases detected at diagnosis by radiological examination, such as computed tomography (CT) and magnetic resonance imaging (MRI). Positron emission tomography/CT (PET/CT) and diagnostic laparoscopy were also selectively performed to detect metastases on the basis of the recommendation of the pancreatic multidisciplinary team. The resection margin for radical margin was defined as 1.5–2 mm, which was the same as that of previous studies (10, 11). Excluded were also patients with microscopic or macroscopic incomplete resection, a history of secondary tumors, period of follow-up <1 year, and missing follow-up records.

Data Collection

Resectability was judged on the basis of CT or MRI, and staging was determined by the pathological factors in accordance with the 8th edition of American Joint Committee on Cancer staging system (12, 13). A team specialized in pancreatic surgery performed all radical pancreatic resection. An experienced pancreatic pathologist assessed all the surgical specimens, made the diagnosis of PDAC, and described the pathological variables, including tumor site, tumor size, tumor differentiation, T-stage, LN status (N-stage), LN total number, positive LN number, macrovascular invasion, microvascular invasion, lymph vessel

invasion, perineural invasion, adjacent organ invasion, and satellite foci. LN ratio (LNR) was defined as the number of LNs with metastases divided by the total number of excised LNs. Several radiological variables, including imaging tumor size, LN metastasis, vascular invasion, and LN size, were analyzed. Inflammation-based indexes, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), modified Glasgow Prognostic Score (mGPS), prognostic nutritional index (PNI), prognostic index (PI), and systemic immune-inflammation index (SII), were included in this study and calculated according to previous studies (14, 15). Clinical data were also analyzed in this study, including age, gender, white blood cell (WBC) count, C-reactive protein (CRP), albumin (ALB), serum levels of carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA).

Follow-Up and Recurrence

The follow-up of patients occurred at the outpatient clinic of our hospital. In general, follow-up strategies consisted of regular chest CT, abdominal CT, and CA19-9 test at least every 2 months during the first year after surgical resection and every 3 months thereafter. Occasional additional imaging modalities, such as MRI and PET/CT, were selectively performed to determine patterns of recurrence. Follow-up data were retrieved at the end of May 2019. The categories of regression patterns in the study conducted by Groot et al. (4) were adopted in this study. When considering patterns of recurrence, only the first location of recurrence was documented, and local recurrence and distant recurrence were registered, separately. In addition, distant recurrences were judged as “liver-only” and “lung-only” recurrences for the isolated hepatic and pulmonary recurrence, respectively, and “others” for isolated recurrence in other less common locations. If both local recurrence and isolated distant metastasis occurred or multiple distant metastases were detected at the same time, recurrences were defined as “local + distant” and “multiple” recurrences, respectively.

Survival Outcomes and Statistical Analysis

Progression-free survival (PFS) and overall survival (OS) were defined as the duration from the date of surgery until the date when tumor progression was diagnosed and death, respectively, or last follow-up. Post-progression survival (PPS) was defined as the time from the first recurrence to either death or last follow-up. Survival time was estimated using the Kaplan–Meier method, and the subgroup differences were compared with log-rank test. Univariate analyses were performed to describe the association between clinical, pathological, and radiological factors and specific patterns of recurrence. For PFS and OS prediction, multivariate logistic regression was conducted on the basis of clinical characteristics and pathological or radiological variables selected by least absolute shrinkage and selection operator (LASSO) logistic regression model. The prediction algorithms were further validated using receiver operating characteristic (ROC) curves. Area under the ROC curve (AUC) and concordance index (C-index) of the multi-marker algorithms were calculated and compared. Two-tailed $P < 0.05$ were considered statistically significant. All statistical

analyses were conducted using R software version 3.2.5 (R Development Core Team; <http://www.r-project.org>).

RESULTS

Patient Characteristic

From 2008 to 2018, a total of 355 patients underwent radical pancreaticoduodenectomy (PD) or distal pancreatectomy for histologically confirmed PDAC. Excluded from this cohort were 10 patients with microscopic or macroscopic incomplete resection, 12 patients with second primary tumors, and 31 patients with incomplete follow-up information. Consequently, 302 patients were included into this study. All patients were followed up at least 1 year. At the end of follow-up, 195 patients (64.6%) were alive after a median follow-up of 24.7 months (95% confidence interval [CI] 20.3–29.1) from surgery. Recurrence was documented in 173 patients (57.3%), whereas 129 patients (42.7%) had no signs of recurrence. The median follow-up time for patients with and without tumor progression was 13.8 and 40.6 months, respectively.

Timing of Recurrence

Among 173 patients who had recurrence, 18 patients had done so within 6 months, 26 within 6–12 months, 57 within 12–24 months, and 72 beyond 24 months after surgery. There were no significant differences in ages and sexes among patients in different recurrent time groups. Primary tumors in early recurrence groups were larger, more likely to be poorly differentiated, and diagnosed at more advanced local stages. Patients with early recurrence had more often T4 tumors, more metastatic LNs, and more often para-aortic LNs (LN16) metastasis than had those in late recurrence groups (Table 1). Median PFS was 11.8 months (95% CI 10.2–15.3) for the whole cohort and 7.0 months (95% CI 6.2–8.4) for those who developed recurrences. For patients who developed recurrences, the comparisons of PPS and OS stratified by different time intervals of recurrences are shown in Figure 1. It was shown that median OS and PPS for patients who developed recurrences beyond 24 months over surgery (OS, 45.1 months, 95% CI 40.2–52.6; PPS, 17.1 months, 95% CI 11.1–17.5) were significantly longer than for those who had recurrence within 24 months since surgery. Also, patients had similar OS and PPS when their recurrences developed within 6, 6 to 12, or 12 to 24 months since surgery.

Patterns of Recurrence

Overall, there were six different patterns of recurrence for all radiological or pathological evidence of progression. Most of patients first recurred at the liver ($n = 69$, 39.9%), followed by local progression ($n = 55$, 31.8%), and lung metastases ($n = 17$, 9.8%). There were 20 (11.6%) patients who had both local and distant progression, and multiple recurrences were observed in 12 (6.9%) patients as the first progression. Liver and lung metastases were the most common distant metastases, compared with the local recurrence, and also contributed to most of the multiple progressions. The proportions of recurrence locations

differed significantly at progressive time points. Distribution of these recurrent patterns is shown in Figure 2. Liver-only progressions occupied the majority of all progressions within 6 months, whereas they were responsible for just 12.5% of all recurrences after 24 months since surgery ($P < 0.001$). Also, liver-only progression diminished over time, and recurrences of other sites became more and more common 1 year later since surgery.

Patients with different progression patterns had significantly different cumulative recurrence rates in different time periods after surgery (Supplement Figure 1). It was shown that cumulative rates of liver metastasis were significantly higher than those of local and other sites of progression, whereas the cumulative rates of liver, lung, and local plus distant and multiple metastases were comparable. The pairwise comparisons of OS (Figure 3), PPS (Supplement Figure 2), and PFS (Figure 4) for patients with different recurrence patterns were conducted. Median OS for patients with local recurrence (29.4 months, 95% CI 24.5–39.6) was significantly longer than that of patients with multiple progressions (17.5 months, 95% CI 11.2–19.5), whereas patients with other recurrence patterns of progression had similar OS rates. Similar results of survival comparisons were observed for PPS. In terms of PFS, patients with local (9.0 months, 95% CI 6.4–10.6) and other sites of progressions (12.7 months, 95% CI 9.1–28.7) had similar median survival, whereas they were both higher than those with other patterns of progressions.

Risk Factors for Different Patterns of Recurrence

Results of univariate and multivariate logistic regression models for local recurrence and liver-only metastasis are shown in Tables 2, 3, respectively. Also, risk factors of lung only, other sites of metastasis, local + distant, and multiple metastases are shown in Supplement Tables 1–4, respectively. Age older than 60 years was a strong predictor for both liver-only metastasis (hazard ratio [HR] = 1.35, 95% CI 1.21–1.73, $P = 0.031$) and multiple metastases (HR = 9.82, 95% CI 1.20–80.66, $P = 0.033$). Specific stations of LN metastases were significantly associated with different patterns of progressions, including LN15 metastasis as a predictor for liver-only (HR = 6.39, 95% CI 1.29–31.52, $P = 0.023$) and local + distant metastases (HR = 8.51, 95% CI 1.27–59.11, $P = 0.030$), LN18 metastasis as a predictor for local progression (HR = 8.97, 95% CI 1.48–54.23, $P = 0.017$), LN10 metastasis as a predictor for lung-only metastasis (HR = 15.96, 95% CI 1.89–134.86, $P = 0.011$), and LN14 metastasis as a predictor for multiple metastases (HR = 7.38, 95% CI 1.61–33.74, $P = 0.010$). Patients receiving adjuvant chemotherapy had a decreased likelihood of local progression (HR = 0.18, 95% CI 0.08–0.42, $P < 0.001$) and lung-only metastasis (HR = 0.14, 95% CI 0.02–0.83, $P = 0.031$) than are those who did not receive adjuvant chemotherapy. Also, PLR was the only independent predictor for other sites of metastases (HR = 0.13, 95% CI 0.02–0.87, $P = 0.036$), and enlarged imaging LN size was found to increase the likelihood of local + distant metastases (HR = 4.57, 95% CI 1.34–15.60, $P = 0.015$).

TABLE 1 | Clinicopathological characteristics of patients with PDAC stratified by time of metastases.

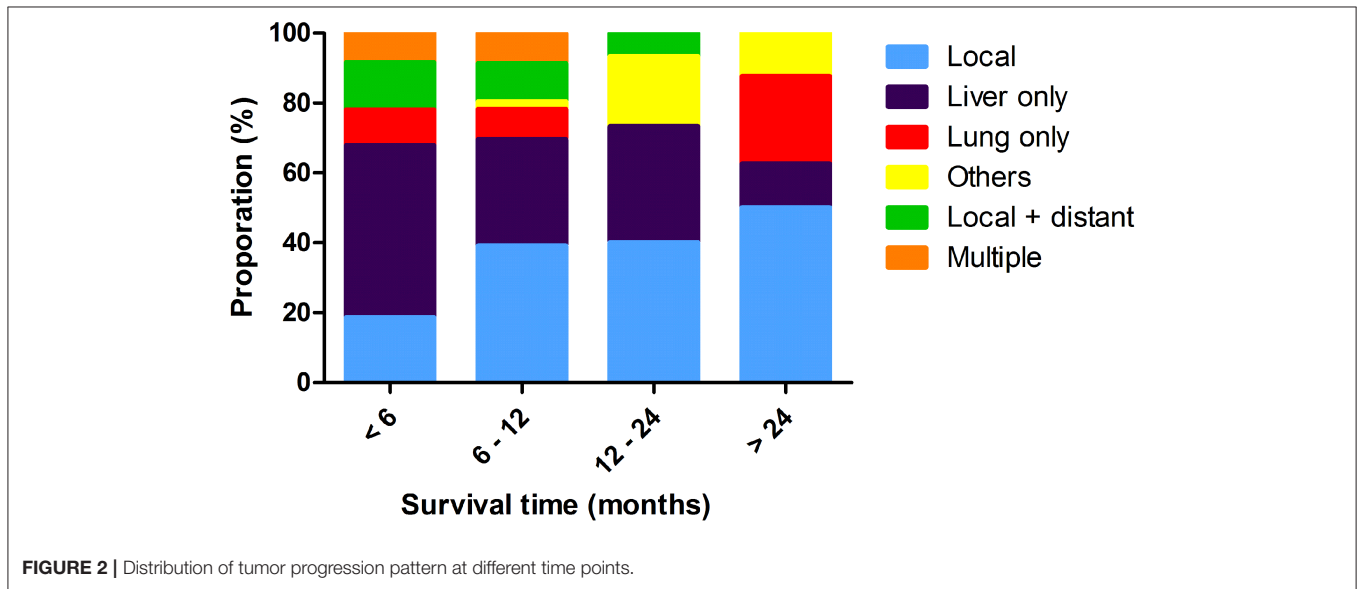
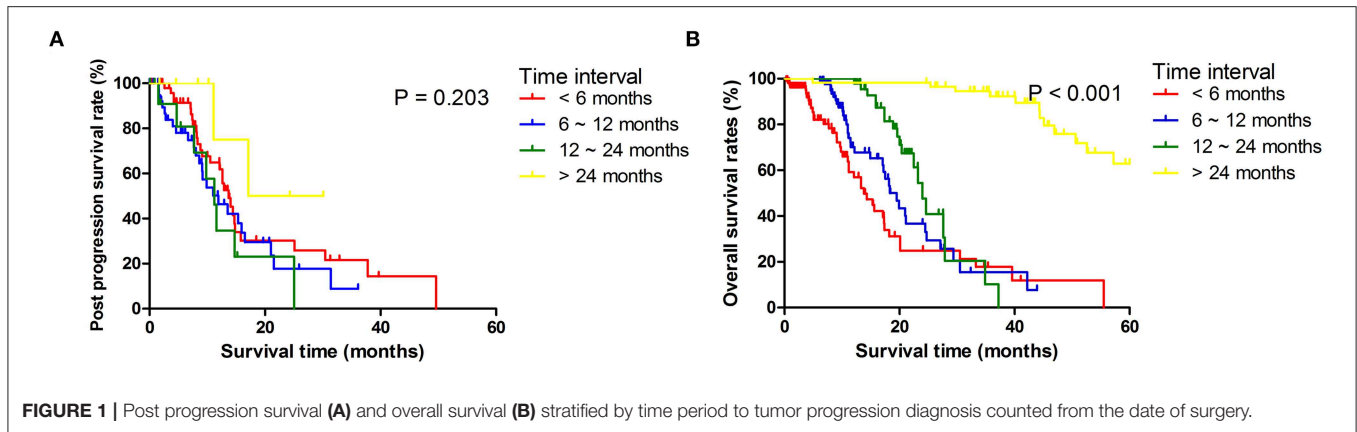
Characteristics	Diagnosis of progression							Characteristics	Diagnosis of progression								
	N	Absence	2-6 M	6-12 M	12-24 M	>24 M	P		N	Absence	2-6 M	6-12 M	12-24 M	>24 M	P		
Whole cohort	302	129	18	26	57	72		Whole cohort	302	129	18	26	57	72			
Age	≤60 years	164	74	8	12	29	41	0.670	Perineural invasion	Absence	146	70	8	13	21	34	0.287
	>60 years	138	55	10	14	28	31			Presence	156	59	10	13	36	38	
Gender	Female	119	53	7	13	25	21	0.286	Adjacent organ invasion	Absence	270	119	15	24	52	60	0.284
	Male	183	76	11	13	32	51			Presence	32	10	3	2	5	12	
Recurrence	Absence	174	129	10	11	11	13	<0.001	LNR	0	173	83	12	17	26	35	0.038
	Presence	128	0	8	15	46	59			0-0.16	66	26	1	7	17	15	
Recurrence patterns	Absence	174	129	10	11	11	13	<0.001	>0.16	63	20	5	2	14	22		
	Local	39	0	4	6	18	11			Satellite foci	Absence	287	123	18	26	55	65
	Liver only	49	0	1	5	14	29		Presence		15	6	0	0	2	7	
	Lung only	12	0	2	0	4	6		T stage	T1	82	46	5	9	8	14	0.023
	Other sites	5	0	1	3	1	0			T2	136	57	8	10	34	27	
	Local + distant	14	0	0	1	5	8			T3	57	18	3	4	12	20	
	Multiple	9	0	0	0	4	5			T4	27	8	2	3	3	11	
LN metastasis	Absence	174	83	13	17	26	35	0.035	Tumor site	Head	247	111	13	23	46	54	0.221
	Presence	128	46	5	9	31	37			Body and tail	55	18	5	3	11	18	
LN5 metastasis	Absence	300	127	18	26	57	72	0.609	TNM stage	IA	54	33	4	7	3	7	0.003
	Presence	2	2	0	0	0	0			IB	74	36	6	7	13	12	
LN6 metastasis	Absence	298	126	18	26	57	71	0.672		IIA	35	11	2	2	10	10	
	Presence	4	3	0	0	0	1			IIB	79	32	3	6	21	17	
LN7 metastasis	Absence	296	128	17	25	56	70	0.582	Imaging tumor size (cm)	III	60	17	3	4	10	26	
	Presence	6	1	1	1	1	2			≤2	104	63	6	5	13	17	0.001
LN8 metastasis	Absence	294	126	17	25	57	69	0.561		2-4	141	45	9	19	31	37	
	Presence	8	13	1	1	0	3		>4	57	21	3	2	13	18		
LN9 metastasis	Absence	292	125	17	25	57	68	0.492	Imaging LN metastasis	Absence	175	73	12	15	34	41	0.944
	Presence	10	4	1	1	0	4			Presence	127	56	6	11	23	31	
LN10 metastasis	Absence	295	127	17	26	56	69	0.566	Imaging vascular invasion	Absence	234	106	16	22	42	48	0.060
	Presence	7	2	1	0	1	3			Presence	68	23	2	4	15	24	
LN11 metastasis	Absence	294	126	18	26	56	68	0.436	Imaging LN size (cm)	≤0.5	177	72	13	16	35	41	0.884
	Presence	8	3	0	0	1	4			0.5-1	64	30	1	5	11	17	
LN12 metastasis	Absence	268	116	18	23	49	62	0.493	PI	>1	61	27	4	5	11	14	
	Presence	34	13	0	3	8	10			0	199	93	12	16	36	42	0.168
LN13 metastasis	Absence	231	103	15	21	40	52	0.473		1	84	31	6	7	19	21	
	Presence	71	26	3	5	17	20			2	19	5	0	3	2	9	

(Continued)

TABLE 1 | Continued

Characteristics		Diagnosis of progression						P	Characteristics		Diagnosis of progression						P
		N	Absence	2–6 M	6–12 M	12–24 M	>24 M				N	Absence	2–6 M	6–12 M	12–24 M	>24 M	
LN14 metastasis	Absence	281	122	16	26	52	65	0.402	NLR	≤3.32	197	89	13	16	36	43	0.659
	Presence	21	7	2	0	5	7	>3.32		105	40	5	10	21	29		
LN15 metastasis	Absence	294	127	18	26	56	67	0.129	dNLR	≤3.32	100	39	10	9	20	22	0.296
	Presence	8	2	0	0	1	5	>3.32		202	90	8	17	37	50		
LN16 metastasis	Absence	284	127	18	26	52	61	0.001	PLR	≤98.13	36	17	5	1	7	6	0.135
	Presence	18	2	0	0	5	11	>98.13		266	112	13	25	50	66		
LN17 metastasis	Absence	293	124	18	26	54	71	0.498	PNI	0	65	31	6	2	11	15	0.277
	Presence	9	5	0	0	3	1	1		237	98	21	24	46	57		
LN18 metastasis	Absence	296	126	18	26	54	72	0.234	SII	≤1,000	206	90	14	16	26	50	0.706
	Presence	6	3	0	0	3	0	>1,000		96	39	4	10	21	22		
Positive LN number	0	173	83	12	17	26	35	0.046	mGPS	0	202	93	12	16	38	43	0.677
	1–3	95	36	5	8	24	22			1	67	23	4	7	11	22	
	>3	34	10	1	1	7	15			2	33	13	2	3	8	7	
Pancreatic membrane invasion	Absence	184	81	15	13	36	39	0.147	WBC count	≤10	280	124	18	23	53	62	0.061
	Presence	118	48	3	13	21	33	>10		22	5	0	3	4	10		
Tumor size (cm)	≤2	88	48	6	10	9	15	0.012	ALB (g/L)	≤35	46	19	2	4	12	9	0.704
	2–4	146	60	8	10	36	32			>35	256	110	16	22	45	63	
	>4	68	21	4	6	12	25			CRP (ng/L)	≤3	202	93	12	16	38	
Tumor differentiation	Well	2	0	0	0	1	1	0.035	CA19-9 (U/ml)	>3	100	36	6	10	19	29	0.063
	Moderate	153	72	14	12	30	25			≤35	59	34	4	5	5	11	
	Poor	147	57	4	14	26	46			>35	243	95	14	21	52	61	
Macrovascular invasion	Absence	273	120	16	23	54	60	0.161	CEA (ng/ml)	≤5	205	97	14	17	37	40	0.054
	Presence	29	9	2	3	3	12	>5		97	32	4	9	20	32		
Microvascular invasion	Absence	206	87	15	19	40	45	0.493	HBV infection	Absence	283	120	16	25	54	68	0.871
	Presence	96	42	3	7	17	27	Presence		19	9	2	2	3	4		
Lymph vessel invasion	Absence	140	65	8	12	21	34	0.296	Chemotherapy	No	160	78	10	14	21	37	0.061
	Presence	162	62	11	13	38	38			Yes	142	51	8	12	36	35	

M, month; LN, lymph node metastasis; LNR, lymph node ratio; TNM, tumor-node-metastasis; PI, prognostic index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; mGPS, modified Glasgow Prognostic Score; WBC, white blood cell; ALB, albumin; CRP, C-reactive protein; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; HBV, hepatitis B virus; PDAC, pancreatic ductal adenocarcinoma.



Risk Factors for Progression-Free Survival and Overall Survival

For all included patients, 1-, 2-, and 3-year OS and PFS were 81.3, 58.4, and 47.0% and 49.7, 36.0, and 29.7%, respectively. In order to investigate the prognostic factors of survival, a total of 48 high-dimensional radiological and pathological data were incorporated in the LASSO regression (Figure 5). Three best predictors for OS, including LN16 metastasis, tumor differentiation, and imaging tumor size, and another eight predictors for PFS, including the eighth edition tumor-node-metastasis (TNM) stage, liver-only metastasis, lung-only metastasis, local progression, multiple metastases, LN16 metastasis, imaging tumor size, and LNR, were identified. The predictors selected by LASSO regression, along with the associated clinical factors identified by a univariate analysis, were incorporated to the multivariable analysis. Subsequent analyses illustrated that decreased time interval to progression (HR = 4.30, 95% CI 2.57–7.20, $P < 0.001$), elevated CA19-9 level (HR = 1.92, 95% CI 1.03–3.58, $P = 0.039$), and LN16 metastasis (HR = 3.63, 95% CI 1.68–7.82, $P = 0.001$) were independent predictors

for reduced OS (Table 4). Independent prognostic factors for PFS included elevated CEA level (HR = 1.78, 95% CI 1.25–2.53, $P = 0.002$), local progression (HR = 8.84, 95% CI 5.25–14.87, $P < 0.001$), liver-only metastasis (HR = 14.74, 95% CI 9.12–23.84, $P < 0.001$), lung-only metastasis (HR = 9.41, 95% CI 4.45–19.91, $P < 0.001$), local + distant progression (HR = 11.69, 95% CI 5.79–23.58, $P < 0.001$), multiple metastases (HR = 19.51, 95% CI 8.78–43.38, $P < 0.001$), LN16 metastasis (HR = 3.04, 95% CI 1.58–5.99, $P < 0.001$), imaging tumor size (HR = 1.76, 95% CI 1.16–2.67, $P = 0.008$), chemotherapy (HR = 0.60, 95% CI 0.42–0.86, $P = 0.005$), and TNM stage (HR = 2.40, 95% CI 1.17–4.92, $P = 0.017$) (Table 5).

Performance of Prediction for Overall Survival and Progression-Free Survival

The comparisons of ROC curves of the predictive systems on the basis of the risk factors and TNM stage system are shown in Figure 6. The values of AUC for 1-, 2-, and 3-year OS and PFS prediction were 0.823, 0.844, and 0.858 and 0.789, 0.829, and 0.863, respectively, which were significant higher than those

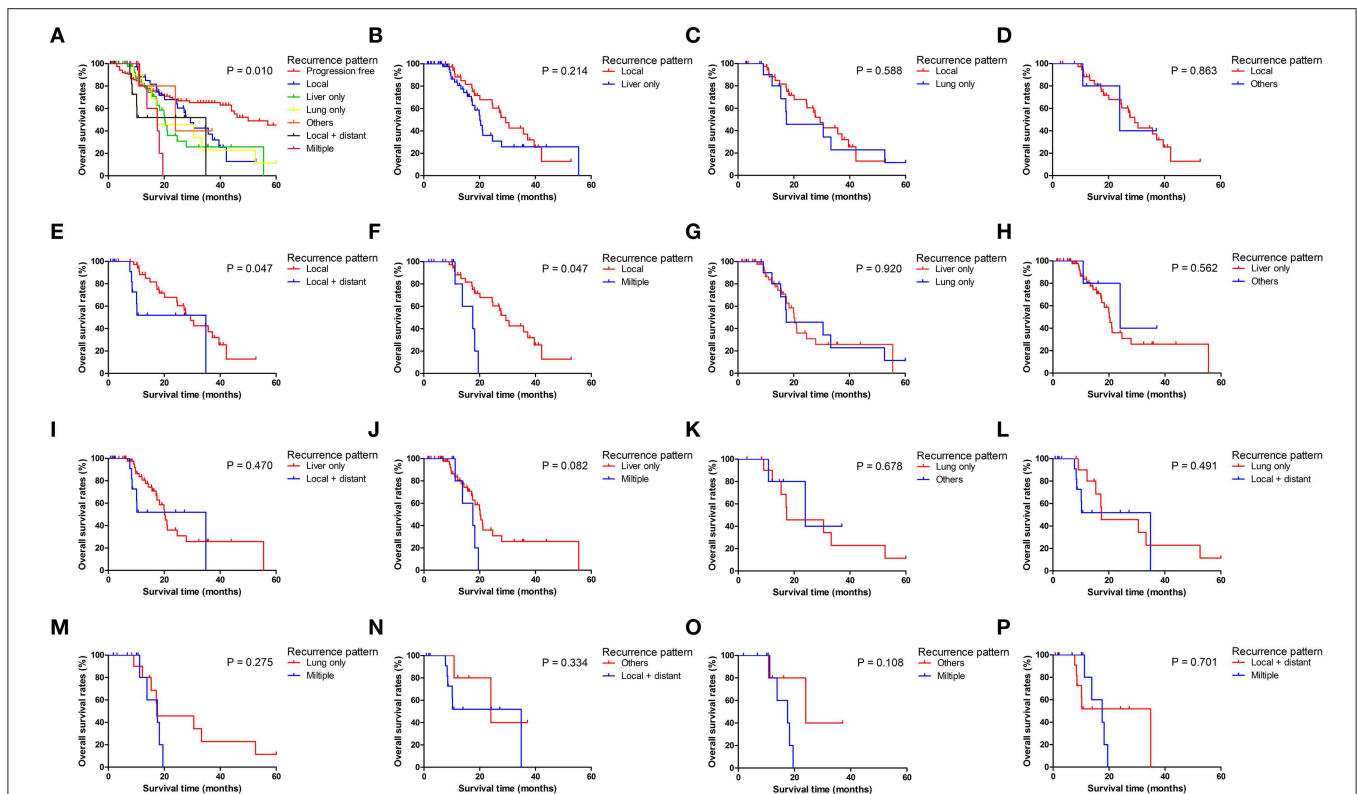


FIGURE 3 | Pairwise comparison of overall survival for different tumor progression patterns. **(A)** Stratification of patients using different progression patterns of progression free, local, liver only, lung only, others, local and distant and multiple progressions. **(B–P)** Stratification of patients by comparing the following patterns of progression: local vs. liver only, local vs. lung only, local vs. others, local vs. local + distant, local vs. multiple, liver only vs. lung only, liver only vs. others, liver only vs. local + distant, liver only vs. multiple, lung only vs. others, lung only vs. local + distant, lung only vs. multiple, others vs. local + distant, others vs. multiple and local + distant vs. multiple.

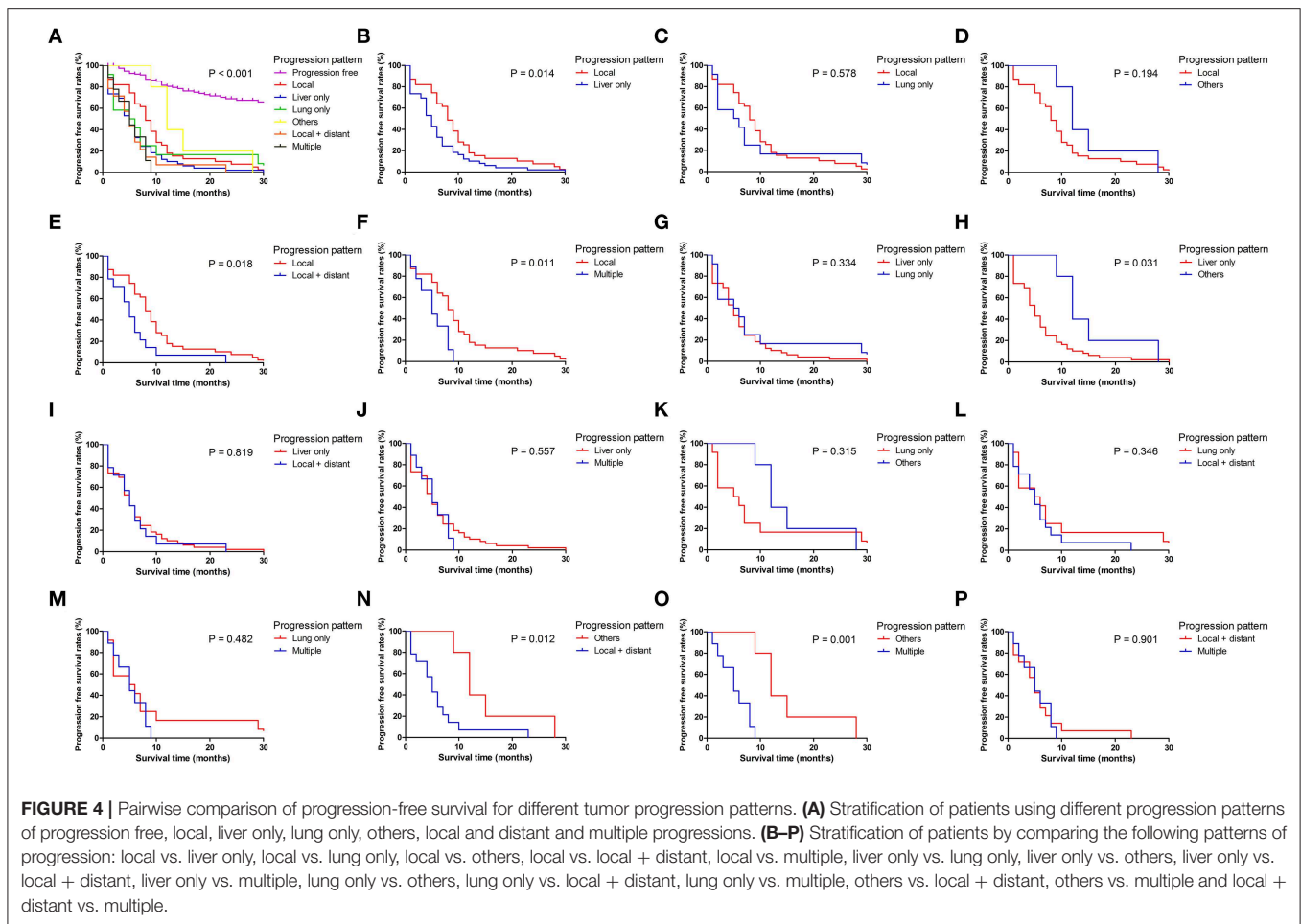
of the TNM stage system (OS, 1 year, 0.614; 2 years, 0.592; 3 years, 0.599; PFS, 1 year, 0.669; 2 years, 0.647; 3 years, 0.630). The predictive system also demonstrated significantly more valuable prediction performance with the C-indexes of 0.829 (95% CI 0.760–0.898) for OS and 0.797 (95% CI 0.723–0.871) for PFS, respectively, than did the TNM stage system (C-index, OS, 0.588 [95% CI 0.465–0.711]; PFS, 0.619 [95% CI 0.524–0.713]).

DISCUSSION

Pancreatic cancer has an extremely poor prognosis even after surgical resection. Recurrence was observed in more than 60% of all PDAC patients after surgery (4, 16) and remained the main reason of poor prognosis in these patients. In this study, recurrence was observed in 57.3% of patients. In addition, 68.2% of recurrences occurred at a distant site, illustrating that there were systemic diseases in these patients at the time of surgery. Also, 41.6% of recurrences occurred 2 years after surgery. Maybe recurrence-free survival for 2 years did not mean cure, and regular follow-up was also needed for these patients. Furthermore, it was shown that different time intervals or patterns of recurrence would both have different survival. These results suggested that maybe recurrence time interval

and patterns were important aspects of recurrence, and the evaluation of factors associated with time intervals and patterns of recurrence opened the door to the exploration of unique biological behaviors of PDAC.

Although the prognostic value of recurrence in survival had been illustrated by previous studies, the current published results differed considerably. For instance, the recurrence rates of PDAC patients after surgery ranged from 38 to 88% in previous studies (17–21). The discrepancies might differ greatly owing to the variations of neoadjuvant treatment regimen and differences of time periods of follow-up. Additionally, the patterns and timing of recurrence of PDAC patients were also not clearly illustrated owing to small population size and limited period of follow-up (22, 23). Moreover, only “local,” “distant,” and “local + distant” groups were analyzed in most of these studies (8, 9, 24–26), and specific recurrence sites were seldom illustrated. In the present study, our detailed recurrence data allowed for further stratification of recurrence patterns in six separated groups: local, liver-only, lung-only, other, local + distant, and multiple metastases. Similar with those in other studies (27, 28), liver-only metastasis and local recurrence contributed to most of the disease progressions. Considering the time period to tumor progress, our study further illustrated that liver-only metastasis



occurred mainly in early phase after surgery and diminished over time. Oppositely, other patterns of progressions, including local recurrence and lung metastasis, were more and more common along with time. Following the variations of progression patterns over time, patients might benefit from changes of therapy focus during the period of follow-up.

Progression patterns and time period were two important natural aspects of progression. Apart from the changes of progression patterns over time, it was shown that survival differences were significant when they were stratified by different sites of first recurrence and time periods to tumor progression. In the current study, liver-only metastasis led to the shortest median PFS of only 5.1 months, which was comparable with that of local + distant progression or multiple metastases. Owing to the high rates of occurrence, liver-only metastasis contributed to most of the local + distant progression and multiple metastases. This may partly explain the similar PFS among these three patterns of progression. Similar results were also observed in a study conducted by Suenaga et al. (3), which reported that the median PFS of PDAC patients after surgery was 6.0 months. Apart from liver-only and lung-only metastases, other sites of sole metastasis contributed the longest median PFS (median 12.7 months) among all patterns of progression, followed by local recurrence

with a median PFS of 9.0 months. A similar result was also achieved in Vincent's study (4). Additionally, survival differences of OS and PPS were also explored in the present study. Compared with patients with liver-only metastasis, although patients with other sites of distant metastases had slightly short median PPS, they finally achieved longer median OS owing to the significantly extended PFS. Moreover, compared with other patterns of progression, local recurrence contributed to better OS, followed by other sites of sole metastasis, and better PPS, followed by lung-only metastasis. A complete understanding of why local recurrence and lung-only metastasis were associated with relatively favorable PPS remains elusive. A hypothesis assumed that the large capacity of tumor bed and lung allowed patients to endure a greater tumor burden, leading to extended survival (29). Considering the slow growth pattern and apparently less aggressive tumor biology of local progression and lung-only metastasis, maybe locally advanced pancreatic cancer (LAPC) patients can benefit from additional treatment of the subsequent lung and local recurrence after surgery. Additionally, the inherent nature of organ-specific metastasis might be explained by the distinct genetic signatures of both primary PDAC and metastatic lesions. The analysis of biological mechanisms would potentially provide personal therapeutic approaches.

TABLE 2 | Risk factors for local recurrence in PDAC patients after surgery.

Characteristics	Univariate analysis			Multivariate analysis			Characteristics	Univariate analysis			Multivariate analysis			
	HR	95%	P	HR	95%	P		HR	95%	P	HR	95%	P	
Age	≤60 years	Reference	0.951				NI	Perineural invasion	Absence	Reference	0.188			NI
	>60 years	1.02	0.52–2.01						Presence	1.59	0.80–3.16			
Gender	Female	Reference	0.897					Adjacent organ invasion	Absence	Reference	0.941			NI
	Male	1.05	0.52–2.09						Presence	0.96	0.32–2.90			
LN metastasis	Absence	Reference	0.060				NI	LNR	0	Reference				NI
	Presence	1.92	0.97–3.28						0–0.16	1.36	0.91–2.04	0.135		
LN5 metastasis	Absence	Reference					NI		>0.16	1.50	0.70–3.22	0.302		
	Presence	–						Satellite foci	Absence	Reference	0.470			NI
LN6 metastasis	Absence	Reference					NI		Presence	0.47	0.06–3.66			
	Presence	–						Tumor site	Head	Reference	0.964			NI
LN7 metastasis	Absence	Reference	0.783				NI		Body and tail	0.98	0.41–2.35			
	Presence	1.36	0.15–11.94					Imaging tumor size (cm)	≤2	Reference				NI
LN8 metastasis	Absence	Reference					NI		2–4	1.74	0.79–3.85	0.173		
	Presence	–							>4	1.32	0.48–3.67	0.600		
LN9 metastasis	Absence	Reference					NI	Imaging LN metastasis	Absence	Reference	0.213			NI
	Presence	–							Presence	1.54	0.78–3.01			
LN10 metastasis	Absence	Reference	0.913				NI	Imaging vascular invasion	Absence	Reference	0.203			NI
	Presence	1.13	0.13–9.62						Presence	1.62	0.77–3.40			
LN11 metastasis	Absence	Reference	0.315				NI	Imaging LN size (cm)	≤0.5	Reference				NI
	Presence	2.32	0.45–11.90						0.5–1	0.63	0.23–1.75	0.374		
LN12 metastasis	Absence	Reference	0.163				NI		>1	2.01	0.94–4.32	0.073		
	Presence	1.91	0.77–4.75					PI	0	Reference				NI
LN13 metastasis	Absence	Reference	0.460				NI		1	0.94	0.43–2.06	0.878		
	Presence	1.33	0.63–2.83						2	1.86	0.57–6.04	0.304		
LN14 metastasis	Absence	Reference	0.389				NI	NLR	≤3.32	Reference	0.203			NI
	Presence	1.65	0.53–5.29						>3.32	0.61	0.29–1.31			
LN15 metastasis	Absence	Reference					NI	dNLR	≤3.32	Reference	0.067			NI
	Presence	–							>3.32	0.53	0.27–1.05			
LN16 metastasis	Absence	Reference	0.814				NI	PLR	≤98.13	Reference	0.731			NI
	Presence	0.83	0.18–3.78						>98.13	1.21	0.40–3.64			

(Continued)

TABLE 2 | Continued

Characteristics	Univariate analysis			Multivariate analysis			Characteristics	Univariate analysis			Multivariate analysis		
	HR	95%	P	HR	95%	P		HR	95%	P	HR	95%	P
LN17 metastasis	Absence	Reference	0.870				NI	PNI	0	Reference	0.076		NI
	Presence	0.84	0.10–6.90						1	2.64	0.90–7.73		
LN18 metastasis	Absence	Reference	0.018	Reference		0.017	SII	≤1,000	Reference	0.110			NI
	Presence	7.22	1.40–37.15		8.97	1.48–54.23			>1,000	0.51	0.23–1.16		
Positive LN number	0	Reference					NI	mGPS	0	Reference			NI
	1–3	1.72	0.82–3.63	0.154					1	0.92	0.39–2.14	0.843	
	>3	1.82	0.66–5.06	0.250					2	1.21	0.43–3.41	0.720	
Pancreatic membrane invasion	Absence	Reference	0.432				NI	WBC count	≤10	Reference	0.162		NI
	Presence	0.75	0.37–1.53						>10	2.13	0.74–6.14		
Tumor size (cm)	≤2	Reference					NI	ALB (g/L)	≤35	Reference	0.977		NI
	2–4	1.17	0.52–2.64	0.711					>35	0.99	0.39–2.51		
	>4	1.35	0.53–3.44	0.537				CRP (ng/L)	≤3	Reference	0.975		NI
Tumor differentiation	Well	Reference					NI		>3	1.01	0.50–2.07		
	Moderate	1.21	0.54–2.53	0.542				CA19-9 (U/ml)	≤35	Reference	0.485		NI
	Poor	1.46	0.76–3.68	0.286					>35	1.39	0.55–3.49		
Macrovascular invasion	Absence	Reference	0.882				NI	CEA (ng/ml)	≤5	Reference	0.204		NI
	Presence	1.09	0.36–3.31						>5	1.56	0.78–3.12		
Microvascular invasion	Absence	Reference	0.555				NI	HBV infection	Absence	Reference	0.288		NI
	Presence	1.24	0.61–2.50						Presence	1.87	0.59–5.97		
Lymph vessel invasion	Absence	Reference	0.462				NI	Chemotherapy	No	Reference	0.001	Reference	<0.001
	Presence	1.21	0.59–2.74						Yes	0.19	0.08–0.43	0.18	0.08–0.42

PDAC, pancreatic ductal adenocarcinoma; HR, hazard ratio; LNR, lymph node ratio; LN, lymph node metastasis; NLR, neutrophil-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; mGPS, modified Glasgow Prognostic Score; WBC, white blood cell; ALB, albumin; CRP, C-reactive protein; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; HBV, hepatitis B virus.

TABLE 3 | Risk factors for liver metastases in PDAC patients after surgery.

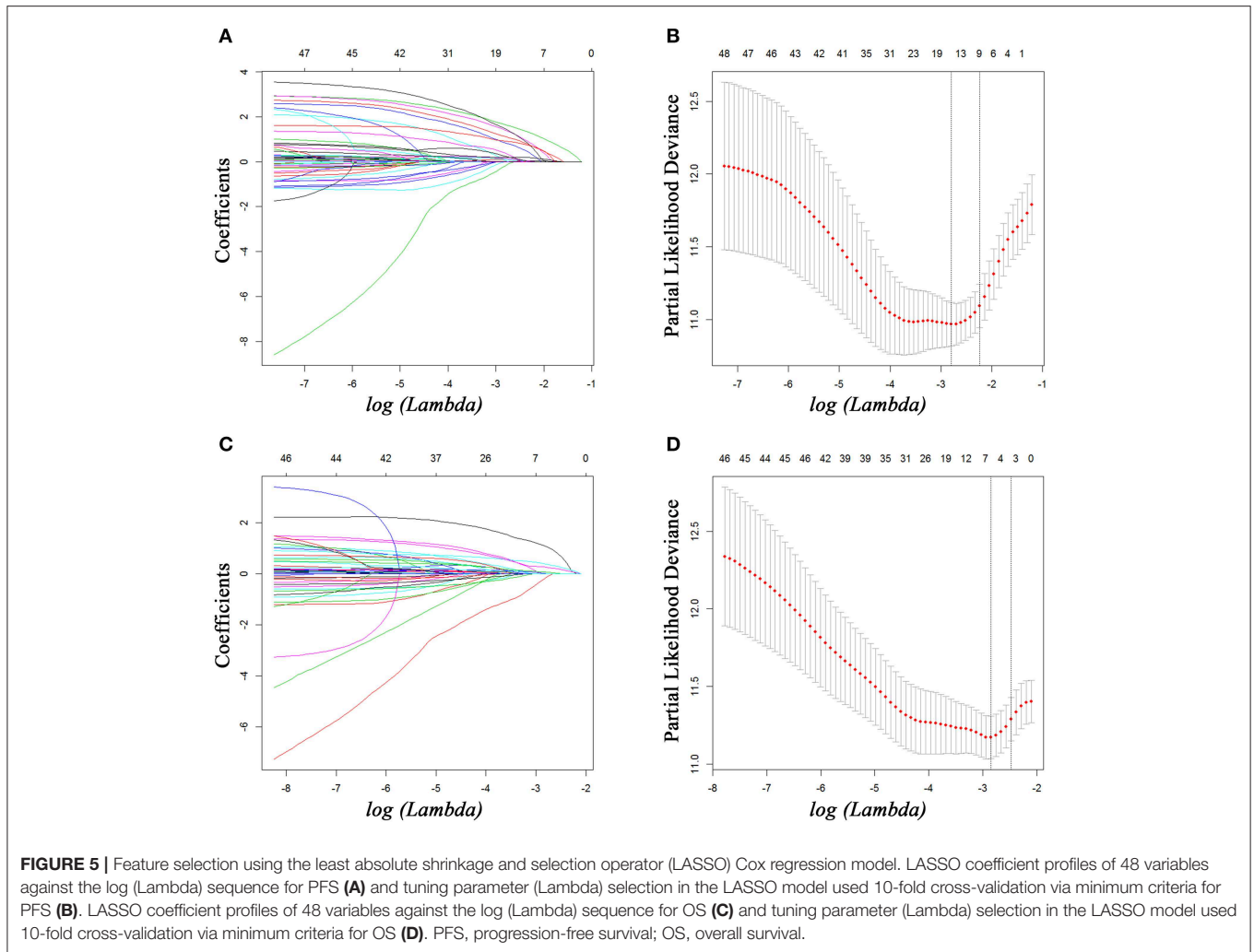
Characteristics	Univariate analysis			Multivariate analysis			Characteristics	Univariate analysis			Multivariate analysis		
	HR	95%	P	HR	95%	P		HR	95%	P	HR	95%	P
Age	≤60 years	Reference	0.030	Reference	0.031	Perineural invasion	Absence	Reference	0.145	NI			
	>60 years	1.32	1.11–2.23	1.35	1.21–1.73		Presence	1.59	0.85–2.97				
Gender	Female	Reference	0.922	NI	NI	Adjacent organ invasion	Absence	Reference	0.160	NI			
	Male	1.03	0.55–1.93				Presence	1.86	0.78–4.43				
LN metastasis	Absence	Reference	0.901	NI	NI	LNR	0	Reference	0.165	NI			
	Presence	1.04	0.56–1.93				0–0.16	1.311			0.90–1.92		
LN5 metastasis	Absence	Reference	0.636	NI	NI	Satellite foci	Absence	Reference	0.076	NI			
	Presence	–					Presence	2.76	0.90–8.47				
LN6 metastasis	Absence	Reference	0.269	NI	NI	Tumor site	Head	Reference	0.614	NI			
	Presence	1.74					0.18–17.04	Body and tail	1.22		0.57–2.62		
LN7 metastasis	Absence	Reference	0.500	NI	NI	Imaging tumor size (cm)	≤2	Reference	0.489	NI			
	Presence	2.65					0.47–14.88	2–4			1.28	0.64–2.57	
LN8 metastasis	Absence	Reference	0.743	NI	NI	Imaging LN metastasis	2–4	1.11	0.45–2.73	0.816			
	Presence	1.75					0.34–8.95	>4	1.11		0.45–2.73		
LN9 metastasis	Absence	Reference	0.031	NI	NI	Imaging vascular invasion	Absence	Reference	0.031	0.053			
	Presence	1.30					0.27–6.33	Presence	2.07		1.07–4.03	2.08	0.99–4.38
LN10 metastasis	Absence	Reference	0.773	NI	NI	Imaging LN size (cm)	≤0.5	Reference	0.353	NI			
	Presence	–					0.5–1	0.67			0.29–1.55		
LN11 metastasis	Absence	Reference	0.466	NI	NI	PI	>1	0.92	0.42–2.02	0.842			
	Presence	0.73					0.09–6.09	0	Reference		0.186	NI	
LN12 metastasis	Absence	Reference	0.363	NI	NI	NLR	1	1.27	0.64–2.52	0.487			
	Presence	1.40					0.57–3.41	2	2.09		0.70–6.25		
LN13 metastasis	Absence	Reference	0.803	NI	NI	dNLR	≤3.32	Reference	0.106	NI			
	Presence	0.85					0.24–3.01	>3.32	1.67		0.90–3.11		
LN14 metastasis	Absence	Reference	0.018	0.023	0.023	PLR	≤3.32	Reference	0.087	NI			
	Presence	5.53					1.34–22.93	>3.32	1.88		0.91–3.85		
LN15 metastasis	Absence	Reference	0.050	0.252	0.252	PLR	≤98.13	Reference	0.379	NI			
	Presence	2.80					1.00–7.87	>98.13	1.63		0.55–4.83		
LN16 metastasis	Absence	Reference	0.623	NI	NI	PNI	0	Reference	0.836	NI			
	Presence	1.50					0.30–7.42	1	1.08		0.51–2.31		

(Continued)

TABLE 3 | Continued

Characteristics		Univariate analysis			Multivariate analysis			Characteristics		Univariate analysis			Multivariate analysis					
		HR	95%	P	HR	95%	P			HR	95%	P	HR	95%	P			
LN18 metastasis	Absence	Reference			NI	SII	≤1,000	Reference	0.140	NI								
	Presence	–									>1,000	1.61	0.86–3.02					
Positive LN number	0	Reference			NI	mGPS	0	Reference		NI								
	1–3	1.53	0.75–3.11	0.245							1	1.38	0.67–2.83	0.380				
	>3	2.15	0.85–5.44	0.105							2	1.27	0.49–3.35	0.623				
Pancreatic membrane invasion	Absence	Reference			NI	WBC count	≤10	Reference	0.152	NI								
	Presence	1.79	0.97–3.32								>10	2.07	0.77–5.58					
Tumor size (cm)	≤2	Reference			Reference			ALB (g/L)	≤35	Reference	0.840	NI						
	2–4	2.37	1.03–5.47	0.043	1.97	0.83–4.68	0.124						>35	1.09	0.46–2.61			
	>4	2.36	0.92–6.08	0.074	1.48	0.53–4.19	0.457						CRP (ng/L)	≤3	Reference		0.359	NI
Tumor differentiation	Well	Reference			NI		>3	CA19-9 (U/ml)	≤35	Reference	0.079	NI						
	Moderate	0.11	0.01–1.83	0.123									>35	2.39	0.90–6.32			
	Poor	0.29	0.02–4.75	0.385									CEA (ng/ml)	≤5	Reference		0.673	NI
Macrovascular invasion	Absence	Reference			NI		>5	HBV infection	Absence	Reference	0.210	NI						
	Presence	1.40	0.54–3.63										Presence	0.27	0.04–2.09			
Microvascular invasion	Absence	Reference			NI		No	Chemotherapy	No	Reference	0.031	Reference	0.170					
	Presence	1.17	0.61–2.23										Yes	0.50	0.27–0.94	0.63	0.32–1.22	
Lymph vessel invasion	Absence	Reference			NI		No	Chemotherapy	No	Reference	0.031	Reference	0.170					
	Presence	1.42	0.58–1.67										Yes	0.50	0.27–0.94	0.63	0.32–1.22	

PDAC, pancreatic ductal adenocarcinoma; HR, hazard ratio; LNR, lymph node ratio; LN, lymph node metastasis; PI, prognostic index; NLR, neutrophil-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; mGPS, modified Glasgow Prognostic Score; WBC, white blood cell; ALB, albumin; CRP, C-reactive protein; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; HBV, hepatitis B virus.



The exploration of risk factors for organ-specific recurrences and predictive factors for survival formed another important finding of this study. Several characteristics were risk factors for liver-only metastasis, such as age older than 60 years and LN15 metastasis. Presence of specific stations of LN metastases could be interpreted as signs of increasing probabilities of progressions. LN18, LN15, and LN14 metastases were identified as predictors for local progression, local + distant metastases, and multiple metastases, respectively. Additionally, as an effective adjuvant therapy to increase survival, the effects of chemotherapy on patterns of progression were poorly understood. Similar with previous study (4), the current study showed that chemotherapy significantly reduced the likelihood of recurrence, especially for local recurrence and lung-only metastasis. Additionally, the prognostic factors were also explored. Apart from the conventional recurrence patterns, elevated levels of CEA, enlarged imaging tumor size, poor differentiation, and advanced TNM stages were all predictive factors of decreased PFS. The exact relation of poor differentiation and poor PFS remained unclear. Maybe this could be partly explained by the ability of PDAC to

develop distant metastases, which could be enhanced by the molecules released by the poorly differentiated tumor, including epidermal growth factor, E-cadherin (24). On the other hand, an increasing time prior to tumor progression was also a predictive factor of improved OS, indicating more favorable tumor behavior in patients with late progression. After other risk factors were controlled, the multivariate analysis also illustrated that elevated level of CA19-9 and LN16 metastasis were significantly associated with decreased OS, suggesting that patients with these unfavorable characteristics needed to receive adjuvant therapy after surgery to earn prolonged survival. Similar with study conducted by Groot et al. (30), our results showed that chemotherapy was associated with less local progression and lung-only metastasis and was an independent predictor for PFS. However, the significant associations between chemotherapy and other patterns of recurrences were not observed, and chemotherapy failed to act as a predictor of OS in this study. Owing to the heterogeneity in the length and regimen of the chemotherapy, data on the adjuvant or neoadjuvant chemotherapy in the current literatures were often limited and contradictory. A previous study based on 1,375 patients did not

TABLE 4 | Independent prognostic factors for OS.

Characteristics		Univariate analysis			Multivariate analysis		
		HR	95%	P	HR	95%	P
Age	≤60 years		Reference				NI
	>60 years	1.40	0.96–2.04	0.084			
Gender	Female		Reference				NI
	Male	0.89	0.61–1.31	0.556			
WBC count	≤10		Reference		Reference		0.234
	>10	2.43	1.38–4.29	0.002	1.73	0.70–4.26	
NLR	≤3.32		Reference				NI
	>3.32	1.16	0.79–1.72	0.447			
dNLR	≤3.32		Reference				NI
	>3.32	1.03	0.69–1.54	0.903			
PLR	≤98.13		Reference				NI
	>98.13	1.16	0.65–2.08	0.612			
PNI	0		Reference				NI
	1	1.30	0.81–2.08	0.285			
SII	≤1,000		Reference				NI
	>1,000	0.93	0.61–1.40	0.712			
mGPS	0		Reference				NI
	1	1.40	0.89–2.21	0.143			
	2	1.03	0.58–1.83	0.927			
PI	0		Reference				NI
	1	1.20	0.78–1.83	0.412			
	2	2.24	1.18–4.26	0.014			
ALB (g/L)	≤35		Reference				NI
	>35	0.97	0.59–1.59	0.897			
CRP (ng/L)	≤3		Reference				NI
	>3	1.24	0.84–1.84	0.275			
CA19-9 (U/ml)	≤35		Reference		Reference		0.039
	>35	2.72	1.52–4.87		1.92	1.03–3.58	
CEA (ng/ml)	≤5		Reference		Reference		0.840
	>5	1.01	1.00–1.02	0.019	1.05	0.68–1.61	
HBV infection	Absence		Reference				NI
	Presence	1.23	0.54–2.81	0.624			
Chemotherapy	No		Reference				NI
	Yes	0.81	0.56–1.19	0.288			
Time period to recurrence (month)	≤6		Reference		Reference		
	6–12	2.45	1.34–3.57	<0.001	2.67	1.52–4.69	<0.001
	12–24	3.33	1.35–4.37	<0.001	3.29	2.00–5.43	<0.001
	>24	4.23	2.34–6.45	<0.001	4.30	2.57–7.20	<0.001
LN16 metastasis	Absence				Reference		
	Presence				3.63	1.68–7.82	0.001
Tumor differentiation	Well				Reference		
	Moderate				1.37	0.91–2.05	0.130
	Poor				1.45	0.87–2.98	0.13
Imaging tumor size (cm)	≤2				Reference		
	2–4				1.15	0.84–1.56	0.389
	>4				1.34	0.76–1.78	0.267

OS, overall survival; HR, hazard ratio; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; mGPS, modified Glasgow Prognostic Score; PI, prognostic index; ALB, albumin; CRP, C-reactive protein; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; HBV, hepatitis B virus.

TABLE 5 | Independent prognostic factors for PFS.

Characteristics		Univariate analysis			Multivariate analysis		
		HR	95%	P	HR	95%	P
Age	≤60 years		Reference				NI
	>60 years	1.15	0.85–1.55	0.365			
Gender	Female		Reference				NI
	Male	1.15	0.85–1.56	0.375			
WBC count	≤10		Reference		Reference		0.052
	>10	1.73	1.05–2.85	0.032	1.74	0.99–3.05	
NLR	≤3.32		Reference				NI
	>3.32	1.14	0.84–1.56	0.390			
dNLR	≤3.32		Reference				NI
	>3.32	0.94	0.69–1.29	0.717			
PLR	≤98.13		Reference				NI
	>98.13	1.32	0.82–2.13	0.256			
PNI	0		Reference				NI
	1	1.25	0.86–1.82	0.244			
SII	≤1,000		Reference				NI
	>1,000	0.96	0.70–1.32	0.813			
mGPS	0		Reference				NI
	1	1.34	0.95–1.91	0.099			
	2	1.01	0.62–1.62	0.987			
PI	0		Reference				NI
	1	1.19	0.85–1.66	0.298			
	2	1.68	0.96–2.93	0.069			
ALB (g/L)	≤35		Reference				NI
	>35	1.05	0.69–1.58	0.825			
CRP (ng/L)	≤3		Reference				NI
	>3	1.22	0.89–1.66	0.216			
CA19-9 (U/ml)	≤35		Reference		Reference		0.997
	>35	1.87	1.22–2.86	0.004	0.99	0.62–1.62	
CEA (ng/ml)	≤5		Reference		Reference		0.002
	>5	1.60	1.18–2.18	0.003	1.78	1.25–2.53	
HBV infection	Absence		Reference				NI
	Presence	0.98	0.52–1.86	0.95			
Chemotherapy	No		Reference		Reference		0.005
	Yes	1.35	1.00–1.82	0.050	0.60	0.42–0.86	
Local recurrence	Absence				Reference		<0.001
	Presence				8.84	5.25–14.87	
Liver metastasis	Absence				Reference		<0.001
	Presence				14.74	9.12–23.84	
Lung metastasis	Absence				Reference		<0.001
	Presence				9.41	4.45–19.91	
Local + distant metastasis	Absence				Reference		<0.001
	Presence				11.69	5.79–23.58	
Multiple metastasis	Absence				Reference		<0.001
	Presence				19.51	8.78–43.38	
LN16 metastasis	Absence				Reference		0.001
	Presence				3.04	1.58–5.99	
Imaging tumor size (cm)	≤2				Reference		
	2–4				1.76	1.16–2.67	0.008
	>4				1.47	0.83–2.58	0.185

(Continued)

TABLE 5 | Continued

Characteristics		Univariate analysis			Multivariate analysis		
		HR	95%	P	HR	95%	P
LNR	0				Reference		
	0–0.16				0.96	0.46–1.98	0.900
	>0.16				1.03	0.51–2.10	0.928
TNM stage	IA				Reference		
	IB				0.92	0.52–1.64	0.782
	IIA				2.40	1.17–4.92	0.017
	IIB				1.21	0.49–3.01	0.674
	III				1.12	0.50–2.50	0.789
Tumor differentiation	Well				Reference		
	Moderate				1.24	0.78–1.95	0.330
	Poor				1.65	1.21–3.67	0.032

PFS, progression-free survival; HR, hazard ratio; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; mGPS, modified Glasgow Prognostic Score; PI, prognostic index; ALB, albumin; CRP, C-reactive protein; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; HBV, hepatitis B virus; LNR, lymph node ratio; TNM, tumor-node-metastasis.

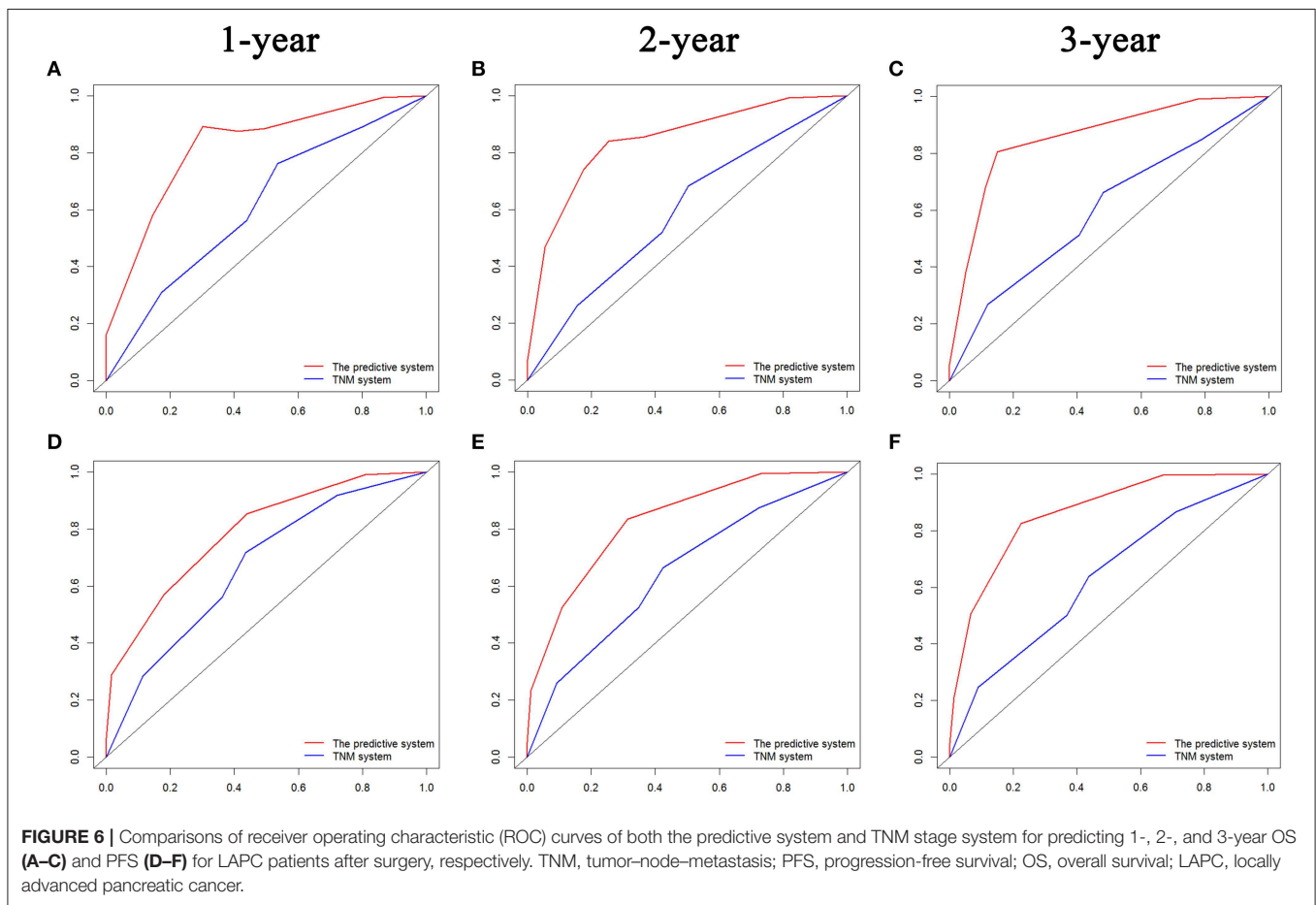


FIGURE 6 | Comparisons of receiver operating characteristic (ROC) curves of both the predictive system and TNM stage system for predicting 1-, 2-, and 3-year OS (A–C) and PFS (D–F) for LAPC patients after surgery, respectively. TNM, tumor-node-metastasis; PFS, progression-free survival; OS, overall survival; LAPC, locally advanced pancreatic cancer.

show survival benefit from adjuvant chemotherapy (31), whereas in another study, the additional survival benefit from adjuvant chemotherapy was reported in PDAC patients (32). The selection bias partly contributed to this discrepancy in retrospective study,

and maybe more insights concerning the survival benefit of chemotherapy were available from prospective studies.

It is important to note that the precise prediction of progression is essential for the individual treatment. An

important advantage of this study was the use of a relatively large cohort to determine the risk factors for different patterns of recurrences and survival. Several independent prognostic factors were selected by evaluating high-dimensional radiological and clinicopathological variables in the current study. In addition, analyses of ROC curves and comparisons of the associated values of AUC and C-indexes of the predictive system and TNM stage system showed a strong predictive strength of the predictive system on the basis of risk factors for OS and PFS. The inclusion of additional clinicopathological variables guaranteed that the established predictive system was better in predicting OS and PFS than did the eighth edition of the TNM stage system. On the other hand, the different clinicopathological features of progression patterns and timing suggested that there might be unique biological features in different progressions. Currently, the molecular feature, *SMAD4*, was shown to have a close relationship with progression patterns. Tumors with *SMAD4* up-regulated tended to be localized, whereas the down-regulation or silence of this gene was likely to promote metastasis (33). Moreover, different regulation of specific genes was associated closely with different patterns of progressions in an animal model (34, 35). Therefore, maybe the combination of clinicopathological characteristics and genetic features would have more meaningful implications in predicting progressions. Clinicians could perform evaluation of recurrence risks and survival on the basis of individual risk factors of patients and specialize the adjuvant therapy, which fitted the current trend to personalized medicine.

This study has several limitations. First, the specific adjuvant therapies after surgery and the associated response to adjuvant therapy were unavailable. More detailed information of length and regimen of chemotherapy would further illustrate the association between therapy and progression. Second, this study only focused on the first recurrence, and subsequent progressions were not taken into account. Third, it was well-known that more progressions would be observed over time. In this study, the period of follow-up for all included patients was longer than 1 year, but this time period was not relatively long enough. Although patients were followed up with a median time of 2 years in this study, the whole view of progression in patients could be changed if patients were followed up even longer. A prospective study with an even longer period of follow-up is also needed to validate results of this study. Last, sometimes diagnoses of progression on the basis of imaging were challenging, and it was possible to overestimate the probabilities of progression in PDAC patients after surgery.

In conclusion, for PDAC patients after radical operation, the different patterns and timing of recurrence were accurately described in the present study. This study further identified the risk factors of different recurrence patterns, which could

help to predict the occurrence of first tumor progression. Furthermore, individual predictors of OS and PFS were also identified and validated for these patients. These findings further suggested the linkages between different progression patterns and biological heterogeneity, and the exploration might provide new versions into the prediction of tumor progression, prognosis stratification, and a more personalized management for PDAC patients after surgery.

DATA AVAILABILITY STATEMENT

The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (<http://www.researchdata.org.cn>), with the Approval Number as RDDA2019001267.

ETHICS STATEMENT

This study was approved by the Institutional Review Board of SYSUCC. All procedures performed in present study involving human participants were in accordance with the ethical standards of institutional and/or national research committees and the 1964 Declaration of Helsinki and its later amendments or similar ethical standards. Written informed consent for inclusion in this study was obtained from patients prior to treatment.

AUTHOR CONTRIBUTIONS

SL was responsible for conception, design, and quality control of this study. CH, XH, and YZ performed the study selection, data extraction, statistical analyses and were major contributors in writing the manuscript. CH and XH participated in study selection and statistical analyses. CH, XH, YZ, ZC, and XL contributed in classification criteria discussion. CH, XH, and YZ contributed to the writing of manuscript. SL reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2019.01197/full#supplementary-material>

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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