Clinical Outcomes of Chemotherapy in Patients with Undifferentiated Carcinoma of the Pancreas: A Retrospective Multicenter Cohort Study

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Abstract

Background: Undifferentiated carcinoma (UC) of the pancreas is a rare subtype of pancreatic cancer. Although UC has been considered a highly aggressive malignancy, no clinical studies have addressed the efficacy of chemotherapy for unresectable UC. Therefore, we performed multicenter retrospective study to investigate the efficacy of chemotherapy in patients with UC of the pancreas.

Methods: This multicenter retrospective cohort study was conducted at 17 institutions in Japan between January 2007 and December 2017. A total of 50 patients treated with chemotherapy were analyzed.

Results: The median overall survival (OS) in UC patients treated with chemotherapy was 4.08 months. The details of chemotherapy in first-line treatment were as follows: gemcitabine (n=24), S-1 (n=12), gemcitabine plus nab-paclitaxel (n=6), and other treatment (n=8). The median progression-free survival (PFS) was 1.61 months in the gemcitabine group, 2.96 months in the S-1 group, and 4.60 months in the gemcitabine plus nab-paclitaxel group. Gemcitabine plus nab-paclitaxel significantly improved PFS compared with gemcitabine (p=0.014). The objective response rate (ORR) was 4.2% in the gemcitabine group, 0.0% in the S-1 group, and 33.3% in the gemcitabine plus nab-paclitaxel group. Gemcitabine plus nab-paclitaxel also showed a significantly higher ORR compared with both gemcitabine and S-1 (gemcitabine plus nab-paclitaxel vs. gemcitabine: p=0.033; gemcitabine plus nab-paclitaxel vs. S-1: p=0.034). A paclitaxel-containing first-line regimen significantly improved OS compared with a non-paclitaxel-containing regimen (6.94 months vs. 3.75 months, respectively; p=0.041). After adjustment, use of a paclitaxel-containing regimen in any line was still an independent predictor of OS (hazard ratio for OS, 0.221; 95% confidence interval, 0.076 – 0.647; p=0.006) in multiple imputation by chained equation.

Conclusions: The results of the present study indicate that paclitaxel-containing regimen would offer relatively longer survival, and it is considered a reasonable option for treating patients with unresectable UC.

Background

Pancreatic cancer (PC) is one of the deadliest cancers and the fourth leading cause of cancer death. It has been estimated that, in 2020, approximately 47,050 patients in the United States will die of this disease [1]. Undifferentiated carcinoma (UC) of the pancreas, also known as anaplastic carcinoma of the pancreas, is a rare subtype of PC and accounts for 0.3-7% of malignant neoplasms of the pancreas [2] [3] [4]. UC is an epithelial neoplasm displaying no particular differentiation such as glandular formation, mucin production, or keratinization.

One population-based study reported that the median age at diagnosis of UC was 67 years, with a slight male predominance (57.5%) [3]. These characteristics are similar to those of PC. On the other hand, UC of the pancreas has been considered more aggressive than PC, and median overall survival (OS) does not exceed 6 months [3] [4]. Clark et al. reported a population-based study comparing patients with UC and PC [3]. The median OS was 11 months in the PC group and 3 months in the UC group, and it was significantly shorter in the UC group than in the PC group (hazard ratio [HR], 1.9; 95% confidence interval [CI], 1.7–2.1). Paal et al. reported 35 patients with UC, and their median OS was 5.2 months [5], although these data were based primarily on surgical series or registry data. Thus, UC has been considered a highly aggressive malignancy. Considering that it was reported that approximately 80% of PC patients were diagnosed at unresectable stages [6] [7], the majority of UC cases potentially have metastases. However, previous reports have rarely mentioned unresectable stage disease, and no clinical studies addressing the efficacy of chemotherapy for UC of the pancreas have been reported. A lack of clinical and treatment data for patients with unresectable UC is a critical issue when considering the therapeutic strategies for UC.

Therefore, clinical and treatment data of patients with unresectable UC were retrospectively collected. The aim of this multicenter retrospective cohort study was to investigate the efficacy of chemotherapy in patients with UC of the pancreas.

Methods

Study design

This retrospective study was conducted at 17 institutions in Japan between January 2007 and December 2017 (Fig. 1). The inclusion criteria were histopathologically diagnosed UC of the pancreas (including UC with osteoclast-like giant cells [UC-OGCs]), recurrent/metastatic or locally advanced disease, and treated with chemotherapy. The study protocol was approved by the institutional review boards of the participating institutions.

Patient evaluation

Data regarding clinical and laboratory features, histological findings, treatment, and outcome measures were collected retrospectively. Histological findings were based on pathology reports and classified into the following subtypes: anaplastic type, sarcomatoid type, carcinosarcoma, UC-OGCs, and not otherwise specified (NOS) [8].

OS was measured from the date of start of first-line treatment to the date of death from any cause. OS for patients who were lost to follow-up was censored at the last date they were known to be alive. PFS was measured from the date of start of treatment to the date of first documented disease progression or the date of death from any cause. PFS was censored at the time of the last follow-up if there was no documentation of disease progression or death. Tumor response was based on the best overall response throughout the entire course of the observation period. The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were used to assess tumor responses [9].

Statistical analysis

Univariate analysis was performed using the chi-squared test for categorical variables. The Kaplan-Meier method was used to estimate the time-to-event distribution, and p-values were calculated using the log-rank test. HRs were calculated using the Cox proportional hazards model. Values of $p < 0.05$ were considered statistically significant, and all p-values are two-sided. To analyze predictors of OS in patients with unresectable UC, a multivariate Cox proportional hazards model was used, including predictors ($p < 0.10$) on univariate analysis and clinically relevant variables (Eastern Cooperative Oncology Group performance status [ECOG PS], extent of disease, and histological subtype). Due to the retrospective analysis, covariate data were often missing. Thus, multiple imputation was performed by multiple imputation by chained equation (MICE) to avoid potential bias [10]. A Cox proportional hazards model was estimated in complete-case analysis and MICE. Data were analyzed using STATA version 15.1 (StataCorp, College Station, TX, USA) and R version 3.6.1 (http://www.r-project.org/).

Results

Patient characteristics

A cumulative total of 65 treatments were given to 50 UC patients between January 2007 and December 2017. The baseline characteristics of the patients with UC are shown in Table 1. ECOG PS was 0 in 13 patients (26.0%), 1 in 31 patients (62.0%), and ≥ 2 in 4 patients (8.0%). The median treatment line was 1 (range 1–3). A total of 13 patients received second-line treatment, and 2 patients received third-line treatment. The details of chemotherapy in any treatment line were as follows: gemcitabine (n = 27), S-1 (n = 18), gemcitabine plus nab-paclitaxel (n = 9), FOLFIRINOX (n = 4), gemcitabine plus S-1 (n = 2), paclitaxel (n = 1), and other treatment (n = 4).

Table 1
Patient baseline characteristics

	All patients	
	(n = 50)	Missing
Sex		
Male (%)	34 (68.0)	
Female (%)	16 (32.0)	
Age (y)		
Median (range)	69 (41–83)	
ECOG PS		2 (4.0)
0 (%)	13 (26.0)	
1 (%)	31 (62.0)	
≥ 2 (%)	4 (8.0)	
Prior surgical resection	25 (50.0)	
Tumor location		
Head (%)	24 (48.0)	
Body-Tail (%)	26 (52.0)	
Tumor size (cm)		1 (2.0)
Median (range)	4.5 (2.0–18.0)	
Extent of disease		
Locally advanced (%)	6 (12.0)	
Metastatic (%)	44 (88.0)	
Measurable metastatic sites		
Liver (%)	26 (52.0)	
Lymph node (%)	20 (40.0)	
Lung (%)	4 (8.0)	
Peritoneal (%)	12 (24.0)	
LDH, U/L		2 (4.0)
Median (range)	205 (128–909)	
CRP, mg/L		2 (4.0)
Median (range)	13 (0-178)	
CEA, ng/mL		1 (2.0)
Median (range)	3.0 (0.7–64.1)	
CA19-9, U/mL		1 (2.0)
Median (range)	35.7 (1.0–43,645)	
Histological subtype		
Anaplastic type (%)	16 (32.0)	
Sarcomatoid type (%)	4 (8.0)	
Undifferentiated carcinoma with OGCs (%)	11 (22.0)	
NOS (%)	19 (38.0)	

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; CRP, C-reactive protein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19 – 9; OGCs, osteoclast-like giant cells; NOS, not otherwise specified.

Overall treatment efficacy

For all patients treated with chemotherapy, the median OS was 4.08 months, and the 12-month OS rate was 16.3% (Fig. 2A). The median PFS in patients receiving first-line treatment and in those receiving second-line treatment was 1.84 months and 3.19 months, respectively (Fig. 2B). For the cumulative total of

65 treatments, the median PFS was 2.01 months (Fig. 2C). The individual PFS for them is shown in Fig. 3, and their objective response rate (ORR) was 10.8%.

Efficacy of first-line treatment

The details of chemotherapy in first-line treatment were as follows: gemcitabine (n = 24), S-1 (n = 12), gemcitabine plus nab-paclitaxel (n = 6), and other treatment (n = 8). The median OS in the first-line gemcitabine group, S-1 group, and gemcitabine plus nab-paclitaxel group was 2.70 months, 8.16 months, and 6.77 months, respectively (Fig. 4A). The median PFS in the first-line gemcitabine group, S-1 group, and gemcitabine plus nab-paclitaxel group was 1.61 months, 2.96 months, and 4.60 months, respectively (Fig. 4B). Tumor responses in first-line treatment are shown in Table 2. There was no significant difference in OS among UC patients treated with gemcitabine, S-1, and gemcitabine plus nab-paclitaxel. However, gemcitabine plus nab-paclitaxel significantly improved PFS compared with gemcitabine (p = 0.014), and it showed significantly higher ORR compared with both gemcitabine and S-1 (gemcitabine plus nab-paclitaxel vs. gemcitabine: p = 0.033; gemcitabine plus nab-paclitaxel vs. S-1: p = 0.034).

Table 2
Tumor response in each line of treatment

	Total number	CR	PR	SD	PD	NE	ORR	DCR
1st-line treatment								
All patients	**50**	**1**	**4**	**12**	**27**	**6**	**10.0%**	**34.0%**
Gemcitabine	24	0	1	5	15	3	4.2%	25.0%
S-1	12	0	0	5	6	1	0.0%	41.7%
Gemcitabine plus nab-paclitaxel	6	0	2	1	2	1	33.3%	50.0%
Gemcitabine plus S-1	2	0	0	0	2	0		
FOLFIRINOX	2	0	1	0	1	0		
S-1 plus radiation	1	0	0	1	0	0		
Paclitaxel	1	1	0	0	0	0		
S-1 plus cisplatin	1	0	0	0	1	0		
Gemcitabine plus radiation	1	0	0	0	0	1		
2nd-line treatment								
All patients	**13**	**0**	**1**	**4**	**4**	**4**	**7.7%**	**38.5%**
S-1	6	0	0	3	1	2	0.0%	50.0%
Gemcitabine	2	0	0	0	1	1		
Gemcitabine plus nab-paclitaxel	2	0	0	0	1	1		
FOLFIRINOX	2	0	1	1	0	0		
FOLFOX	1	0	0	0	1	0		
3rd-line treatment								
All patients	2	0	1	1	0	0		
Gemcitabine	1	0	0	1	0	0		
Gemcitabine plus nab-paclitaxel	1	0	1	0	0	0		
Cumulative total								
All patients	**65**	**1**	**6**	**17**	**31**	**10**	**10.8%**	**36.9%**
Gemcitabine	27	0	1	6	16	4	3.7%	25.9%
S-1	18	0	0	8	7	3	0.0%	44.4%
Gemcitabine plus nab-paclitaxel	9	0	3	1	3	2	33.3%	44.4%

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; PFS, progression-free survival; CI, confidence interval; NR, not reached.

Efficacy of paclitaxel-containing regimens

Two different paclitaxel-containing regimens (gemcitabine plus nab-paclitaxel (n = 6) and paclitaxel monotherapy (n = 1)) were used as first-line treatment. A paclitaxel-containing first-line regimen significantly improved OS compared with a non-paclitaxel-containing regimen (6.94 months vs. 3.75 months, respectively; p = 0.041) (Fig. 5A). For the cumulative total of 65 treatments, a paclitaxel-containing regimen significantly improved PFS compared with a non-paclitaxel-containing regimen (4.60 months vs. 1.81 months, respectively; p = 0.004) (Fig. 5B). ORR was significantly higher with a paclitaxel-containing

regimen than with a non-paclitaxel-containing regimen (40.0% vs. 5.5%, respectively; p = 0.001). In addition, one complete response was observed in patients treated with paclitaxel monotherapy, and this patient achieved long survival.

The results of the Cox proportional hazards model for predicting OS in patients treated with chemotherapy are shown in Table 3. In the univariate Cox proportional hazards model, use of a paclitaxel-containing regimen in any line and absence of liver metastasis were significant factors associated with OS. In the multivariate Cox proportional hazards model, use of a paclitaxel-containing regimen in any line was still an independent predictor of OS (HR for OS, 0.221; 95% CI, 0.076–0.647; p = 0.006) in MICE.

Table 3
Predictors of survival in patients treated with chemotherapy

	Complete-case analysis (n = 44)						Multiple imputation by chained equation (n = 50)				
		Unadjusted HR			Adjusted HR			Unadjusted HR			Adjuste HR
	Estimate	95% CI	*P*	Estimate	95% CI	*P*	Estimate	95% CI	*P*	Estimate	95% CI
Sex											
Male (Reference)	1.000						1.000				
Female	0.537	0.255 — 1.131	0.102				0.606	0.303 — 1.213	0.157		
Age, y											
< 65 (Reference)	1.000			1.000			1.000			1.000	
≥ 65	1.982	0.981 — 4.004	0.057	3.404	1.472 — 7.875	0.004	1.877	0.981 — 3.591	0.057	2.242	1.119 – 4.494
ECOG PS											
0 (Reference)	1.000			1.000			1.000			1.000	
≥ 1	1.384	0.626 — 3.060	0.422	1.709	0.752 — 3.885	0.201	1.292	0.638 — 2.619	0.477	1.293	0.627 – 2.667
Prior surgical resection											
No (Reference)	1.000						1.000				
Yes	0.798	0.414 — 1.537	0.500				0.760	0.413 — 1.397	0.377		
Tumor location											
Head (Reference)	1.000						1.000				
Body-Tail	1.124	0.574 — 2.200	0.733				1.153	0.619 — 2.145	0.654		
Extent of disease											
Locally advanced (Reference)	1.000			1.000			1.000			1.000	
Metastatic	0.820	0.316 — 2.132	0.685	0.630	0.210 — 1.891	0.410	0.820	0.319 — 2.107	0.681	0.606	0.204 – 1.805
Location of metastases											
Liver	2.173	1.111 — 4.248	0.023	2.373	1.086 — 5.184	0.030	1.919	1.034 — 3.559	0.039	1.721	0.856 – 3.457
Lymph node	0.805	0.413 — 1.570	0.525				0.831	0.442 — 1.563	0.566		
Peritoneal	0.865	0.406 — 1.842	0.707				0.933	0.458 — 1.901	0.849		
LDH, U/L											
≤ 250 (Reference)	1.000						1.000				
> 250	0.715	0.324 — 1.576	0.405				0.829	0.407 — 1.686	0.604		
CRP, mg/L											
≤ 10 (Reference)	1.000						1.000				

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; CRP, C-reactive prot carcinoembryonic antigen; CA19-9, carbohydrate antigen 19 – 9; UC, undifferentiated carcinoma; OGCs, osteoclast-like giant cells

	Complete-case analysis (n = 44)						Multiple imputation by chained equation (n = 50)					
> 10	1.624	0.846 — 3.116	0.145				1.650	0.898 — 3.031	0.106			
CEA, ng/mL												
≤ 5.0 (Reference)	1.000						1.000					
> 5.0	1.239	0.600 — 2.559	0.562				1.337	0.675 — 2.650	0.405			
CA19-9, U/mL												
≤ 37.0 (Reference)	1.000						1.000					
> 37.0	1.032	0.537 — 1.981	0.926				1.143	0.620 — 2.107	0.669			
Histological subtype												
UC without OGCs (Reference)	1.000			1.000			1.000			1.000		
UC with OGCs	0.935	0.385 — 2.268	0.882	2.372	0.848 — 6.635	0.100	0.857	0.378 — 1.943	0.713	0.826	0.354 – 1.930	
Use of paclitaxel-containing regimen in any line												
No (Reference)	1.000			1.000			1.000			1.000		
Yes	0.216	0.076 — 0.620	0.004	0.181	0.062 — 0.534	0.002	0.218	0.077 — 0.621	0.004	0.221	0.076 – 0.647	

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; CRP, C-reactive prot carcinoembryonic antigen; CA19-9, carbohydrate antigen 19 – 9; UC, undifferentiated carcinoma; OGCs, osteoclast-like giant cells

Discussion

Using a retrospective cohort design, the present study examined the efficacy of chemotherapy in patients with UC of the pancreas. The most frequently used first-line treatment regimens were gemcitabine, S-1, and gemcitabine plus nab-paclitaxel. Although there was no significant difference in OS among these first-line regimens, gemcitabine plus nab-paclitaxel significantly improved PFS compared with gemcitabine, and it showed a significantly higher ORR compared with both gemcitabine and S-1. In addition, one complete response was observed in a patient treated with paclitaxel. A paclitaxel-containing first-line regimen significantly improved OS compared with a non-paclitaxel-containing regimen. After adjustment, use of a paclitaxel-containing regimen in any line was still an independent predictor of OS. All these observations indicate that a paclitaxel-containing regimen is a reasonable option for treatment of patients with unresectable UC of the pancreas.

In recent phase 3 trials for metastatic PC [11] [12], the median OS has reached approximately 1 year. On the other hand, that for UC patients treated with chemotherapy did not exceed 5 months. The present study clearly showed that UC was refractory to chemotherapy. However, of chemotherapeutic regimens used for UC, paclitaxel-containing regimens may have a relatively high anti-tumor effect on UC. Paclitaxel has shown activity in anaplastic carcinoma of the thyroid [13] [14] and sarcoma (*e.g.* angiosarcoma and Kaposi's sarcoma) [15] [16]. It has been reported that UC of the pancreas expressed the same mesenchymal marker, Vimentin, as anaplastic carcinoma of the thyroid and sarcoma [5] [17]. Drug sensitivity of UC of the pancreas may be similar to these neoplasms because they show similar pathological features. On the other hand, although gemcitabine monotherapy was the most frequently used regimen for unresectable UC in this study, it provided a limited response, with median PFS and ORR of 1.61 months and 3.7%, respectively. Most patients with unresectable UC had lower ECOG PS at the time of diagnosis, and the majority of patients received only one line of treatment. Although gemcitabine monotherapy still remains a therapeutic option for frail and elderly patients with PC [18] [19] [20], the benefit of gemcitabine monotherapy may be limited for UC patients.

In addition to the efficacy of paclitaxel-containing regimens, a multivariate Cox proportional hazard model showed that age ≥ 65 years was independent predictor of OS in patients treated with chemotherapy. Fundamentally, chemotherapy provides modest survival benefit in patients with unresectable UC. However, some patients had a good response to chemotherapy and achieved relatively long survival. In such a situation, there is a critical need to identify high-risk patients and select patients who will potentially benefit from treatment based on predictors. For example, for patients who are not expected to respond to chemotherapy, it is possible to avoid highly invasive treatments and focus on quality of life. By predicting the chemotherapeutic response, it makes a significant contribution to the selection of treatment for UC. Age is a widely accepted prognostic factor for PC, and Clark et al. reported that age was an independent prognostic factor for survival in UC (HR per 10 years, 1.1; 95% CI, 1.04–1.2) in their population-based study [3]. This report supports the present findings. It should be noted that survival benefit of chemotherapy for UC may be limited in patients aged ≥ 65 years.

This study has some limitations. The first limitation is the fact that the present analysis was a retrospective study that lacked adequate statistical power. Therefore, the study should be considered only an exploratory investigation. However, UC of the pancreas is a rare malignant neoplasm, and this could complicate the recruiting for and completion of clinical trials for UC of the pancreas. The retrospective design and relatively small sample size limit the

strength of this study. However, the result is not negligible since our results will benefit patients with UC who have had difficulty in establishing therapeutic strategies due to its rarity. The second limitation is missing values. Due to the retrospective nature of this study, missing data were unavoidable, which may lead to bias and loss of information in the study [21]. It may undermine the value of such a small-sized study for a rare disease. Thus, multiple imputation was used to account for missing values. The prognostic factors obtained by multiple imputation may be useful in decision-making for the treatment of UC of the pancreas. The final limitation is the small number of patients treated with FOLFIRINOX. Of the 4 patients treated with FOLFIRINOX, two had partial response. FOLFIRINOX may be potentially effective for UC of the pancreas. However, even so, UC patients are often in poor condition. Thus, less invasive treatment than FOLFIRINOX, gemcitabine plus nab-paclitaxel, is a reasonable choice for UC of the pancreas [18].

Conclusions

The results of the present retrospective multicenter cohort study show that paclitaxel-containing regimen would offer relatively longer survival, and it is considered a reasonable option for treating patients with unresectable UC.

Abbreviations

CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: hazard ratio; MICE: multiple imputation by chained equation; NOS: not otherwise specified; ORR: objective response rate; OS: overall survival; PC: pancreatic cancer; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors; UC: undifferentiated carcinoma; UC-OGCs: undifferentiated carcinoma with osteoclast-like giant cells.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of National Cancer Center (reference number, 2018-242). Approval for the review of hospital records was obtained from the Institutional Review Board of National Cancer Center and the patients' informed consent was waived given the retrospective nature of the study.

Consent for publicaion

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable requet.

Competing Interests

Yasuyuki Kawamoto has received speaking honoraria from Taiho Pharmaceutical and Lilly. Makoto Ueno has received research funding from Taiho Pharmaceutical and Yakult Honsha, and speaking honoraria from Taiho Pharmaceutical and Yakult Honsha. The other authors have no conflict of interest.

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Authors' contributions

Conception and design: HI and MI. Acquisition of data: HI, KM, KU, MO, SK, TT, HI, CS, KT, KS, KO, YK, RS, HS, and HN. Analysis and interpretation of data: HI, MI, SK, MU, CM, and JF. Writing, review, and revision of the manuscript: HI, MI, KM, KU, MO, SK, TT, HI, CS, KT, KS, KO, YK, RS, HS, HN, MU, CM, and JF. Study supervision: MI, MU, CM, and JF. All authors have read and approved the manuscript.

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Figures

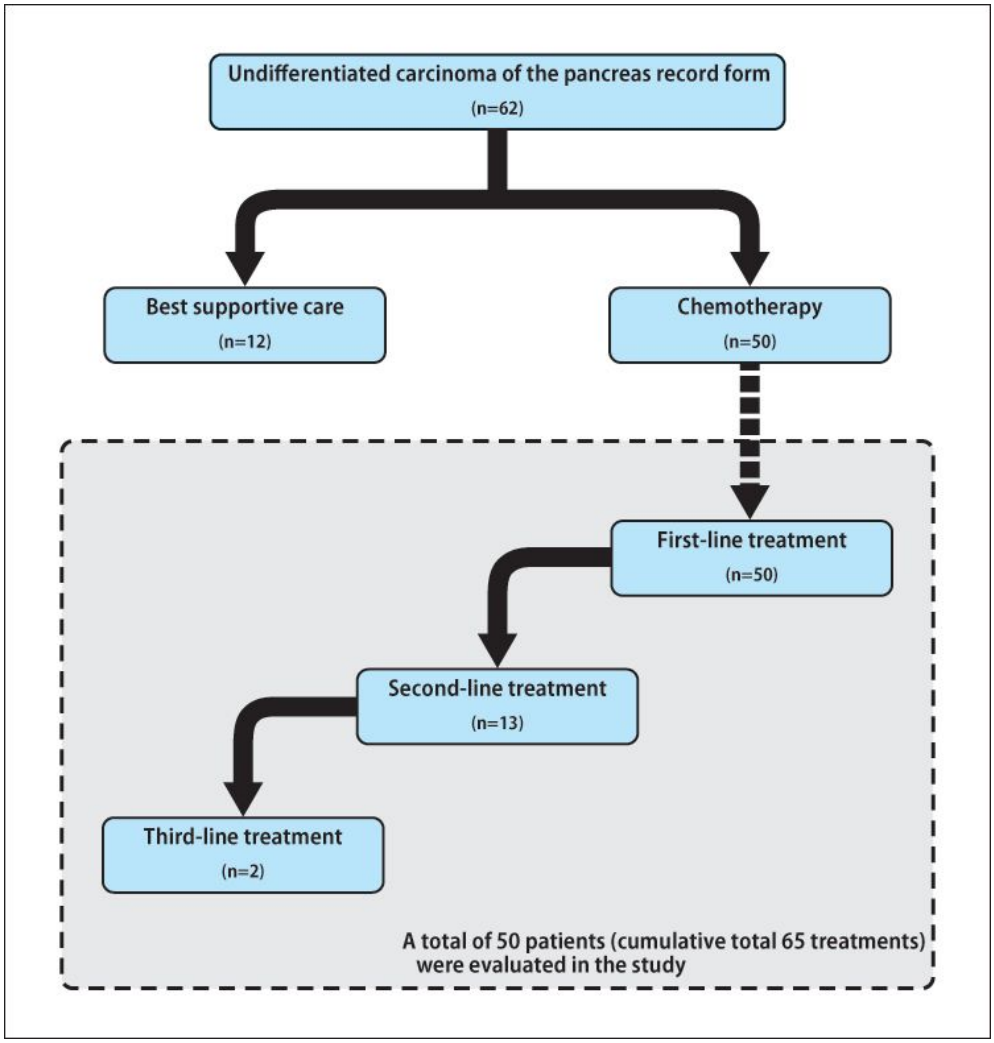

Figure 1

Selection of patients for the study

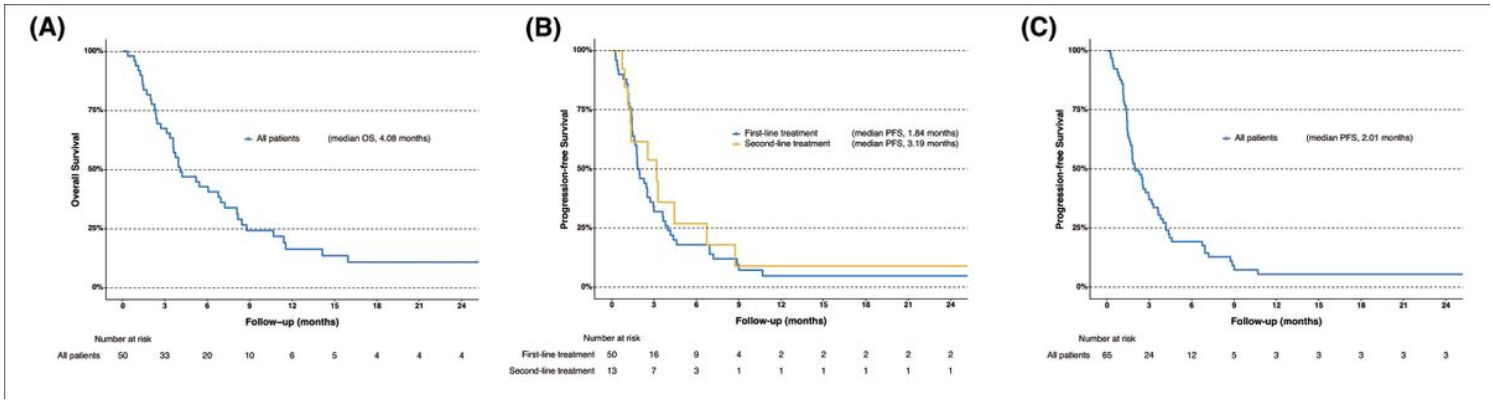

Figure 2

Kaplan-Meier curves of overall survival for all patients with undifferentiated carcinoma of the pancreas (A), progression-free survival with first-line and second-line treatments (B), and progression-free survival for the cumulative total of 65 treatments (C). OS, overall survival; PFS, progression-free survival.

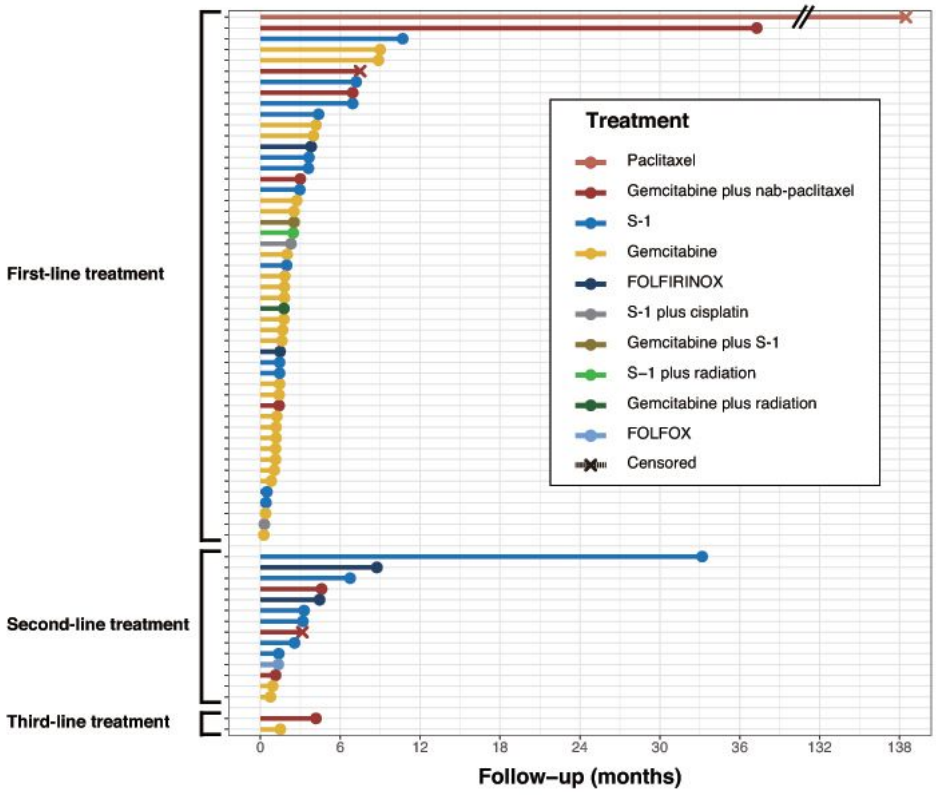

Figure 3

Individual progression-free survival of patients treated with chemotherapy

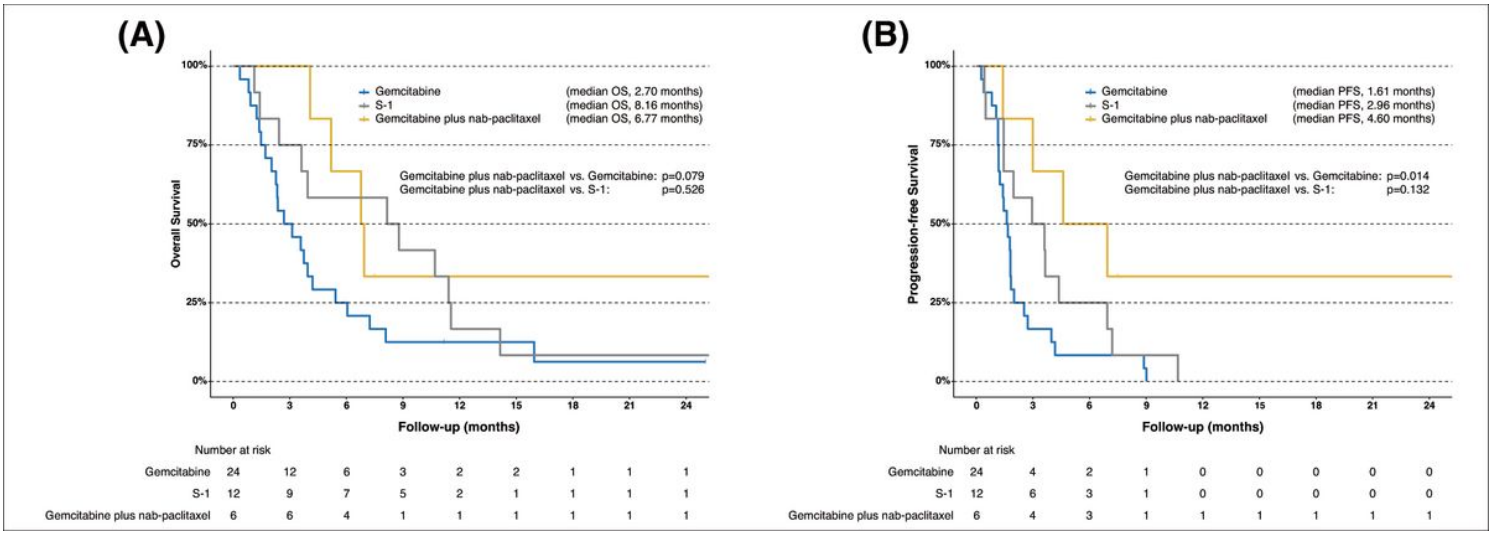

Figure 4

Kaplan-Meier curves of overall survival in the first-line gemcitabine group, S-1 group, and gemcitabine plus nab-paclitaxel group (A); and progression-free survival in the first-line gemcitabine group, S-1 group, and gemcitabine plus nab-paclitaxel group (B). OS, overall survival; PFS, progression-free survival.

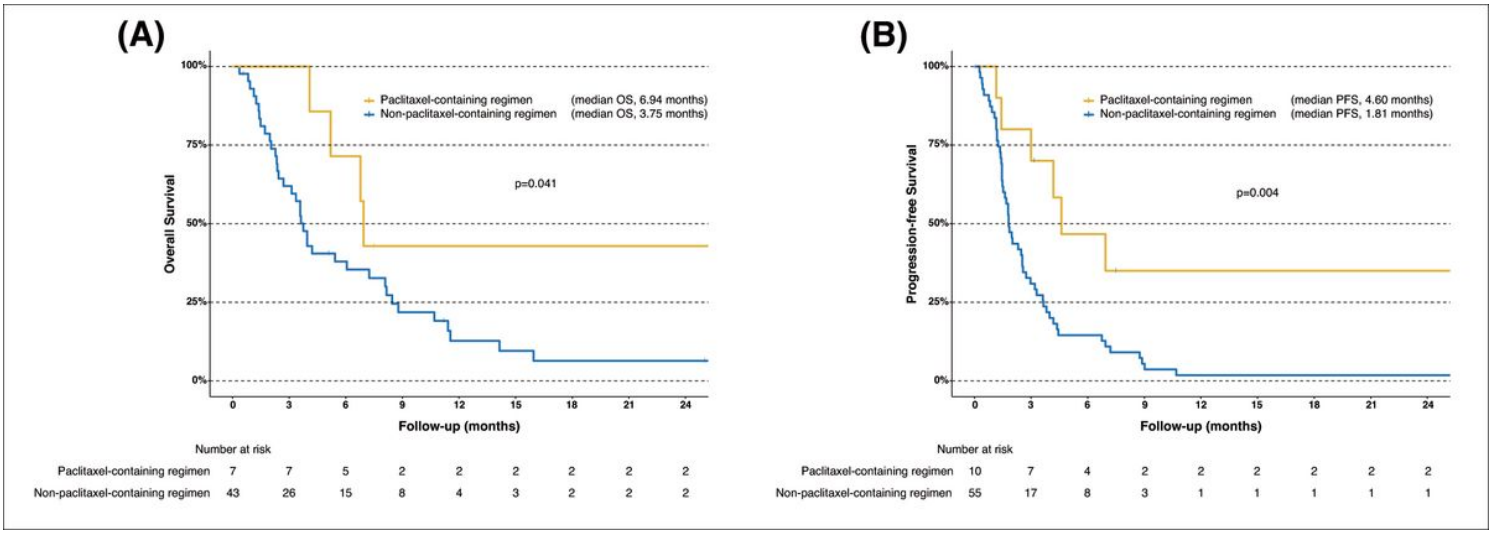

Figure 5

Kaplan-Meier curves comparing overall survival in patients treated with a first-line paclitaxel-containing regimen and a non-paclitaxel-containing regimen (A), and comparing progression-free survival in patients treated with a paclitaxel-containing regimen and a non-paclitaxel-containing regimen in any line (B). OS, overall survival; PFS, progression-free survival.