Oncological outcome of surgical resection for anaplastic carcinoma of the pancreas

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Abstract. Anaplastic carcinoma of the pancreas (ACP) is a rare disease with rapid growth. Therefore, the significance of surgery for ACP remains unknown. The present study aimed to elucidate the oncological outcome following surgical resection for ACP and investigated pathological features associated with prognosis. In the present study, 12 patients who underwent surgical resection for ACP at Chiba University Hospital (Chiba, Japan) were retrospectively analyzed. Among the 12 patients, 7 had anaplastic undifferentiated carcinoma, 1 had sarcomatoid undifferentiated carcinoma, 2 had carcinosarcoma and 2 had undifferentiated carcinoma with osteoclast-like giant cells (OCGC). A total of 7 cases exhibited early recurrence within 6 months postoperatively, and the median overall survival (OS) time of the patients with curative resection was 15.0 months, which was shorter than that of patients with pancreatic ductal adenocarcinoma. The median OS time of patients with pT3 was significantly shorter than that of those with pT1 or pT2 (2.2 vs. 24.5 months; P<0.01). pT3 tumors frequently exhibited a high Ki-67 proliferative index with tumor necrosis and intratumoral hemorrhage. These cases exhibited high serum inflammatory marker levels, including white blood cells, C-reactive protein and neutrophil-to-lymphocyte ratio. On the other hand, 4 patients survived for ≥2 years without recurrence after surgery. These patients included 2 cases with undifferentiated carcinoma with OCGC and 2 pT1 cases with undifferentiated carcinoma who did not exhibit tumor necrosis or intratumoral hemorrhage. The present study demonstrated that a number of ACP cases exhibited early recurrence with poor survival, whereas limited cases experienced long-term survival. The tumor subtype and pathological features, such as tumor diameter, tumor necrosis and intratumoral hemorrhage, may be associated with the postoperative prognosis of patients with ACP.

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Abbreviations: ACP, anaplastic carcinoma of the pancreas; OCGC, osteoclast-like giant cell; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; MDCT, multidetector-row computed tomography; MRI, magnetic resonance imaging; DFS, disease-free survival; EUS-TA, ultrasonography-tissue acquisition; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; DUPAN-2, duke pancreatic monoclonal antigen type 2; Span-1, s-pancreas-1 antigen; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; GEM, gemcitabine; UICC, Union for International Cancer Control; WBC, white blood cell; CRP, C-reactive protein

Key words: anaplastic carcinoma, pancreas, pancreatic cancer, surgery, prognosis, undifferentiated carcinoma

Introduction

Anaplastic carcinoma of the pancreas (ACP), also known as undifferentiated carcinoma, is an extremely rare pancreatic neoplasm. Previous reports revealed the frequency of ACP at 0.1-0.9% of all pancreatic cancers (1,2). The Japan Pancreas Society categorized ACP into pleomorphic type, spindle cell type, and osteoclast-like giant cell (OCGC) type (3). On the other hand, WHO classification distinguished undifferentiated carcinoma with OCGC from undifferentiated carcinoma, and categorized undifferentiated carcinoma into anaplastic undifferentiated carcinoma, sarcomatoid undifferentiated carcinoma, and carcinosarcoma (4). ACP is frequently observed as a large tumor with distant metastases upon diagnosis because of the rapid progression and high invasiveness. The prognosis is significantly worse in patients with ACP than in those with pancreatic ductal adenocarcinoma (PDAC) (5). Conversely, a previous report that analyzed only surgical resection cases revealed compatible overall survival (OS) of resected ACP cases to that of resected PDAC cases (6). Surgical resection may be the only curative treatment strategy for ACP, but there was no consensus about surgical indication for patients with ACP. Furthermore, the significance of multidisciplinary therapy for ACP has not been determined.

The role and the optimal candidates of surgical resection for ACP require clarification. ACP exhibits undifferentiated carcinoma characterized by positive staining for vimentin and Snail, and negative staining for E-cadherin in pathological

examination, indicating that the tumor cells of ACP undergo epithelial-mesenchymal transition (7-9). Accordingly, previous case reports revealed that ACP commonly had poor prognosis even after radical pancreatic resection (10,11). On the other hand, surgical resection provided prolonged survival without disease recurrence for some cases (1,12-14). Indeed, undifferentiated carcinoma with OCGC is a subtype that exhibited a preferable prognosis after surgery (15,16). The effect of surgical resection on survival may be different according to the tumor characteristics and its progression. Selecting the patients with survival benefits from surgery is important for deciding the optimal treatment strategy for pancreatic cancer. However, only a few case studies reported surgical outcomes for ACP due to the rarity of the disease, and prognostic factors affecting survival after surgery for ACP remain unknown. Therefore, clinicopathological features of ACP and prognosis after surgery warrant further investigation. We conducted pancreatectomy for 12 patients with ACP in our department. The current study aimed to determine the oncological outcome of surgery for ACP and clinicopathological factors that were associated with survival after surgery.

Materials and methods

Patients. This study retrospectively analyzed the medical records of 12 patients with ACP who underwent pancreatic resection at the Department of General Surgery in Chiba University (Chiba, Japan) from 2003 to 2021. All patients underwent multidetector-row computed tomography (MDCT), magnetic resonance imaging (MRI), and positron emission tomography upon diagnosis to assess the clinical stage and resectability status as presented in the National Comprehensive Cancer Network guideline for pancreatic adenocarcinoma version 2 (2021). Endoscopic ultrasonography-tissue acquisition (EUS-TA) was conducted for preoperative diagnosis in some cases. Some recent cases received neoadjuvant chemotherapy. Surgical resection of pancreatic tumors was performed with the standard method and technique, as described in previous studies (17). The patients underwent routine adjuvant chemotherapy for 6 months. Adjuvant chemotherapy regimens include gemcitabine (GEM) monotherapy or S-1 monotherapy. Regarding follow-up, patients underwent blood tests, including tumor markers, every 3 months, and MDCT every 6 months. Systemic chemotherapy was administrated once they were deemed medically fit for it when patients had tumor recurrence postoperatively. Only patients who underwent macroscopic curative pancreatic resection were included in the survival analyses. In some analyses, we compared patients with ACP who underwent curative pancreatic resection to those with resectable PDAC who received curative surgery at our institution between 2008 and 2021. The inclusion criteria of resectable PDAC were as follows: i) histologically confirmed PDAC, ii) no evidence of distant metastases, except for para-aortic lymph node metastases, at the time of surgery. The exclusion criteria included: i) patients diagnosed with unresectable or metastatic disease based on preoperative examinations, ii) patients who received only palliative surgery, and iii) patients with insufficient follow-up data. The PDAC cohort included 305 patients, comprising 170 males and 135 females. The median age was 63.5 years (range: 31-89 years). The committee on Human Research of Chiba University School of Medicine approved the study protocol (approval code: #3302). Informed consent was obtained using an opt-out method, as approved by the institutional ethics committee.

Preoperative parameters. All patients underwent blood tests before treatment to assess preoperative parameters including tumor markers, inflammatory markers, and nutritional parameters. Carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), duke pancreatic monoclonal antigen type 2 (DUPAN-2), and s-pancreas-1 antigen (Span-1) were measured as tumor markers. Upper normal limits of CEA (≤5.0 ng/ml), CA19-9 (≤37.0 U/ml), DUPAN-2 (≤150 U/ml), and Span-1 (≤30 U/ml) in our institution were used as cutoff values of these tumor markers. The neutrophil-to-lymphocyte ratio (NLR) and prognostic nutritional index (PNI) were calculated as previously presented regarding inflammatory and nutritional parameters (18).

Pathological examination. Tissue samples were fixed in 10% neutral buffered formalin for 24 to 48 h at room temperature. Following fixation, the specimens were dehydrated through ethanol, cleared in xylene, and embedded in paraffin. Sections (4 μm thick) were cut, mounted on glass slides, deparaffinized, and stained with hematoxylin and eosin (H&E) using standard protocols. Histological diagnoses were made using H&E staining, and tumor subtypes were classified according to the WHO Classification of Pancreatic Tumors, 5th Edition (4) (Fig. S1). TNM classification was examined based on the Union for International Cancer Control (UICC) classification. Tumor necrosis and intratumoral hemorrhage were evaluated by H&E staining (Fig. S2A). The resection margin status was microscopically assessed and resection margin positive (R1) was defined as tumors with cancer cells at the transection line. Tumor cell proliferation was investigated by Ki-67 immunohistochemical staining (Fig. S2B). For immunohistochemical staining, ACP tissue specimens were sliced from FFPE blocks. After microwave antigen retrieval and non-specific protein binding, the sections were incubated overnight with Ki-67 primary antibody (Proteintech; 27309-1-AP, dilution 1:2,000) at 4˚C. Subsequently, the goat anti-rabbit IgG secondary antibody (Invitrogen; 65-6120, dilution 1:500) were applied for 30 min at room temperature, and then stained with a peroxidase DAB kit (Nacalai Tesque, Inc.). Tumor Ki-67 immunostaining evaluation was performed based on the percentage of positive nuclei of tumor cells from a positive field at high power (x200). Based on the median percentage of Ki-67 positive tumor cells in the cohort, a high Ki-67 proliferative index was defined as ≥10% of positive Ki-67 tumor cells.

Statistical analysis. Postoperative disease-free survival (DFS) and OS were analyzed with the Kaplan-Meier curve, and statistical significance was investigated with log-rank test. The association between groups stratified by pathological T factor was evaluated using Fisher's exact test and Wilcoxon rank sum test because the data were not normally distributed and the sample size was small. All tests were two-tailed, and p-values of <0.05 indicated a statistically significant difference. JMP software (SAS Institute) was used for data analysis.

Results

Patient characteristics. Table I shows clinical and preoperative information of the patients who underwent pancreatectomy for ACP. Of the 12 patients who underwent pancreatic resection, 9 were male and 3 were female, with a median age of 65 years (range: 45-81). Of the 12 patients, 7 experienced tumor-related symptoms upon diagnosis, including epigastralgia (n=4) and back pain (n=3). Intratumoral or gastrointestinal bleeding which required surgical intervention was observed in three cases. The tumors were located in the pancreatic head, pancreatic body and pancreatic tail in 6, 4 and 2 cases, respectively. The tumor size in MDCT upon diagnosis ranged from 12 to 108 mm, with a median of 30.5 mm. The pancreatic tumor of seven cases demonstrated a hypodense lesion with a peripheral contrast enhancement in MDCT. Radiological investigation revealed that 11 patients were resectable state and 1 patient was unresectable state with distant metastases. EUS-TA was performed for 5 cases, among which 3 were preoperatively diagnosed as ACP.

Treatment strategy for ACP and its outcome. Table I also shows treatment for the patients with ACP. Of 12 patients, 3 received 2 cycles of neoadjuvant chemotherapy by gemcitabine plus S-1 based on a previous study (19). According to the RECIST criteria, all 3 cases were classified as stable disease, and all patients underwent surgical resection because no tumor progression including distant metastases was detected during preoperative chemotherapy. Curative pancreatic resection and palliative pancreatic resection due to bleeding from the tumor were performed on 11 patients and 1 patient, respectively. Surgical procedures included pancreaticoduodenectomy for 6 patients and distal pancreatectomy for 6 patients. One case required combined portal vein resection. There was no mortality after surgery. Adjuvant chemotherapy was performed for 9 cases (gemcitabine monotherapy: 4 cases, S-1 monotherapy: 5 cases). Table II presents pathological results of the patients. All of the cases were diagnosed as ACP. The subtypes included 7 cases of anaplastic undifferentiated carcinoma, 1 case of sarcomatoid undifferentiated carcinoma, 2 cases of carcinosarcoma, and 2 cases of undifferentiated carcinoma with OCGC. Lymph node metastases were detected in 11 cases, and R0 resection was achieved in 8 (66.7%) cases. We then analyzed the prognosis of patients with ACP who underwent macroscopic curative pancreatic resection using the Kaplan-Meier survival analyses. The DFS curve demonstrated that the median DFS time was 5.8 months (Fig. 1A). Table II also presents the prognosis of each patient. The initial recurrence site after resection included liver metastases (n=3), local recurrence (n=2), distant lymph node metastases (n=2), and bone metastases (n=1). Seven (63.6%) cases had early recurrence within 6 months after surgery, whereas 4 cases were alive ≥2 years after surgery with no evidence of recurrence. We next compared the OS of patients with ACP who underwent macroscopic curative resection to that of patients with resectable PDAC. Clinicopathological factors are summarized in Table SI. Even though the resectability of all ACP cases was assessed as resectable preoperatively, the proportion of patients with M1 disease was significantly higher in the ACP group than in the PDAC group. Patients with ACP had significantly shorter OS compared to those with PDAC (median OS: 15.0 vs. 39.7 months, χ^2=8.60, P<0.01; Fig. 1B). The 2-year OS rate of the patients with ACP was 36.4% (Fig. 1B).

Clinicopathological factors associated with survival postoperatively for ACP. To determine pathological factors of the patients which influence their prognosis, the association between pathological findings and OS after surgery was investigated (Table II). Regarding the subtype of ACP, both cases with undifferentiated carcinoma with OCGC experienced long survival postoperatively. On the other hand, among ten cases diagnosed with undifferentiated carcinoma, only two cases survived over 2 years without recurrence. With respect to the pathological features of these two cases, pathological tumor diameter was ≤2 cm (pT1), and tumor necrosis or intratumoral hemorrhage was not observed in H&E staining. Furthermore, Ki67 immunohistochemical staining revealed low proliferative potential of these two cases. Regarding local factor and lymph node metastases, Kaplan-Meier survival analyses revealed that the median OS time of the patients with pT3 was significantly shorter than that with pT1 or pT2 (2.2 vs. 24.5 months, χ^2=12.77, P<0.01), whereas pathological lymph node metastases were not significantly correlated to OS (Fig. 2A).

Preoperative prediction of survival is important for selecting an optimal treatment strategy for pancreatic cancer. We assessed whether tumor markers were associated with OS after surgery with Kaplan-Meier survival analyses (Fig. 2B). The median OS time of the patients with an elevated DUPAN-2 level have significantly shorter OS than that of the patients with a normal range of DUPAN-2 (3.0 vs. 24.5 months, χ^2=4.62, P=0.03), and there was a trend toward an association between CA19-9 level and overall survival (χ^2=3.77, P=0.05).

Clinicopathological characteristics of the patients with large ACP and poor prognosis. Our data so far indicated that pathological tumor diameter may be one of the crucial factors correlating to prognosis. Clinicopathological factors of the ACP cases with pT3 were compared to those of ACP cases with pT1 or pT2 to determine the characteristics of large ACP which exhibited a poor prognosis (Table III). No significant difference was observed in patient characteristics, such as age, gender, and tumor location among the groups. Regarding the preoperative laboratory test, no difference was observed in the preoperative tumor marker levels between the tumor with pT3 and the tumor with pT1 or pT2. On the other hand, patients with pT3 demonstrated significantly higher levels of white blood cell (WBC), C-reactive protein (CRP), and NLR than patients with pT1 or pT2 (P=0.04, P=0.04, and P=0.02). The results indicated that patients with pT3 ACP suffered systemic inflammation at the time of diagnosis. We then assessed the pathological findings of the tumor with pT3. Most of the ACP with pT3 were concomitant with tumor necrosis and intratumoral hemorrhage, both of which may be attributed to the rapid tumor progression. Indeed, all ACP cases with pT3 demonstrated high Ki-67 proliferative index.

Discussion

This study elucidated the oncological outcomes of the surgical resection for ACP and examined the histopathological

Table I. Perioperative characteristics of the patients with anaplastic carcinoma of the pancreas.

				MDCT findings upon diagnosis							
Case	Age, years	Sex	Symptoms	Tumor location	Tumor size, mm	Hypodense lesions with peripheral enhancement	Resectability	Diagnosis by EUS-TA	Neoadjuvant therapy	Operative method	Adjuvant therapy
1	45	M	Epigastralgia; tumor bleeding	Tail	70	+	Unresectable	-	None	DP	None
2	81	M	Epigastralgia	Tail	108	+	Resectable	-	None	DP	None
3	66	M	Epigastralgia; gastrointestinal bleeding	Head	60	+	Resectable	-	None	PD + PVR	None
4	61	M	Back pain	Body	75	+	Resectable	-	None	DP	GEM
5	79	M	None	Body	12	-	Resectable	Atypical cells	None	DP	S-1
6	64	M	Back pain	Head	31	+	Resectable	-	None	PD	GEM
7	60	M	None	Body	19	-	Resectable	Undifferentiated carcinoma	None	DP	S-1
8	68	M	None	Head	26	-	Resectable	-	GS	PD	S-1
9	83	F	Back pain; gastrointestinal bleeding	Head	33	+	Resectable	Anaplastic carcinoma	None	PD	GEM
10	53	F	Epigastralgia	Head	30	+	Resectable	-	None	PD	GEM
11	65	M	None	Head	20	-	Resectable	Anaplastic carcinoma	GS	PD	S-1
12	65	F	None	Body	16	-	Resectable	Adenocarcinoma	GS	DP	S-1

M, male; F, female; MDCT, multidetector-row computed tomography; EUS-TA, endoscopic ultrasonography-tissue acquisition; GS, gemcitabine plus S-1 therapy; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; PVR, portal vein resection; GEM, gemcitabine.

Table II. Pathological findings and prognosis of the patients with anaplastic carcinoma of the pancreas.

	Pathological findings							
Case	Histology	pStage	Tumor necrosis	Intratumoral hemorrhage	Ki-67, %	Curability	Recurrence	Overall survival
1	Anaplastic undifferentiated carcinoma	T3N1M1(PER)	+	+	20.9	R2	-	0.5 M; DD
2	Sarcomatoid undifferentiated carcinoma	T3N2M0	+	+	11.1	R0	0.9 M; liver	2.0 M; DD
3	Anaplastic undifferentiated carcinoma	T3N2M0	+	+	28.7	R1	1.8 M; local	2.2 M; DD
4	Anaplastic undifferentiated carcinoma	T3N2M1(ADR)	+	-	15.0	R0	1.6 M; local	3.0 M; DD
5	Anaplastic undifferentiated carcinoma	T1N1M0	+	-	2.1	R0	3.3 M; LYM	4.7 M; DD
6	Anaplastic undifferentiated carcinoma	T2N1M1(LYM)	+	-	34.0	R1	5.8 M; LYM	11 M; DD
7	Anaplastic undifferentiated carcinoma	T1N2M0	-	-	23.0	R0	4.4 M; bone	15 M; DD
8	Carcinosarcoma	T2N2M1(LYM)	-	-	1.0	Rx	4.9 M; liver	17 M; DD
9	Undifferentiated carcinoma with OCGC	T2N2M0	+	+	1.0	R0	24 M; no recurrence	24 M; AW
10	Undifferentiated carcinoma with OCGC	T2N1M0	-	-	0.7	R0	25 M; liver	30 M; DD
11	Anaplastic undifferentiated carcinoma	T1N1M0	-	-	1.7	R0	31 M; no recurrence	31 M; AW
12	Carcinosarcoma	T1N0M0	-	-	1.0	R0	45 M; no recurrence	45 M; AW

OCGC, osteoclast-like giant cell; M, months, PER, peritoneal dissemination; ADR, adrenal grand; LYM, lymph node; DD, dead with disease; AW, alive without recurrence.

features associated with prognoses. As previous reports demonstrated the aggressive biological behavior of ACP (8), even patients with resectable ACP experienced significantly worse survival compared to those with resectable PDAC. 63.6% of the patients with radical resection had early recurrence within 6 months after surgery and all of the pT3 cases in our cohort had poor prognosis postoperatively. Conversely, limited cases that experienced prolonged survival without recurrence included two cases with undifferentiated carcinoma with OCGC and two pT1 cases with undifferentiated carcinoma. We demonstrated that tumor necrosis and intratumoral hemorrhage, both indicative of rapid growth, are associated with tumor diameter, which may influence patient prognosis. The results of this study are useful for predicting postoperative prognosis for ACP.

ACP frequently exhibits activation of epithelial-mesenchymal transition and is clinically characterized by rapid progression as well as concomitant lymphatic and distant metastases (8,20). Therefore, the tumor diameter of ACP upon diagnosis is relatively large and the prognosis of ACP is worse compared to that of PDAC (5,20,21). Since only a few reports investigated the oncological outcome of the surgery for ACP, the survival benefits and optimal candidates of surgery for ACP remain unclear.

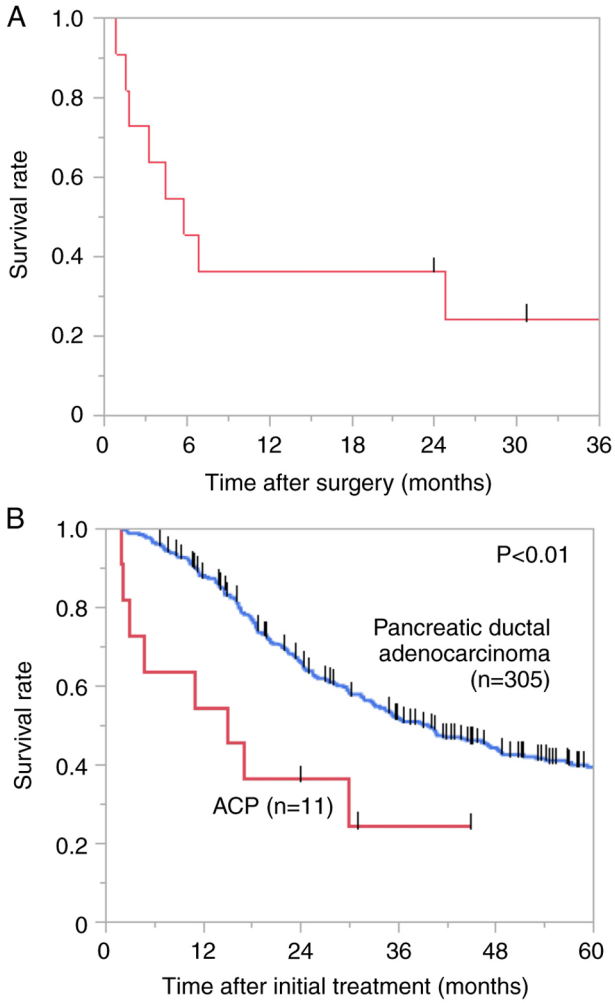

Figure 1. Prognosis of patients with ACP after surgery. (A) Disease-free survival rate after surgery in patients with ACP. (B) Overall survival rate after surgery in patients with ACP compared with that in patients with pancreatic ductal adenocarcinoma. ACP, anaplastic carcinoma of the pancreas.

The postoperative survival time of the patients with ACP varies in our cohort. Of 11 patients who underwent macroscopical curative pancreatic resection, 7 experienced early recurrence within 6 months after surgery, resulting in poor prognosis. Conversely, 4 could survived over 2 years without recurrence after surgery. These results indicated that many patients experienced early tumor recurrence after surgery and poor prognosis, but there was a patient cohort with long-term survival without recurrence postoperatively. Previous studies also revealed that the survival of the patients with ACP during the first year after operation was worse than that of the patients with PDAC, but some ACP cases experienced long-term survival (13).

The WHO classification recognizes the undifferentiated carcinoma with OCGC as a distinct subtype of undifferentiated carcinoma of the pancreas. In our cohort, both patients with undifferentiated carcinoma with OCGC achieved long-term survival without recurrence even though these cases had concomitant lymph node metastases. Previous studies have reported that the prognosis of undifferentiated carcinoma with OCGC was more favorable than that of PDAC with a 5-year survival rate of 59.1% following surgical resection (15,22). Furthermore, the majority of the ACP patients with long-term survivors were reported to be undifferentiated carcinoma with OCGC (21,23). These findings suggest that tumor subtype may be associated with prognosis following radical resection. Additionally, we revealed that two cases with undifferentiated carcinoma experienced long-term survival. Tumor necrosis and intratumoral hemorrhage are frequently observed in ACP caused by the rapid progression (24). However, two long-term survival cases with undifferentiated carcinoma were pathological T1 tumor with low Ki-67 proliferative index and did not have tumor necrosis or intratumoral hemorrhage, indicating that these cases may not have highly proliferative potential and were diagnosed in the early diseases stage. These data suggested that early disease detection and surgical resection of the ACP at an early stage may contribute to prolong survival. Conversely, the patients with pT3 had short OS postoperatively in our cohort. These cases frequently demonstrated tumor necrosis and intratumoral hemorrhage with a high Ki-67 proliferative index, indicating that the patients with large tumors had poor prognosis possibly caused by the rapid tumor progression. We could not observe the oncological survival benefits of the surgery for these cases, but surgical resection achieved control of tumor-related symptoms, such as tumor bleeding, in two patients.

Preoperative prediction of prognosis after surgery is important to select the appropriate candidates for surgical resection of pancreatic cancer. Among the patients with unresectable ACP, performance status, CRP level, and age were reported to be associated with poor prognoses (25). Conversely, the prognostic factors for the resected ACP remain unknown. This study indicated that tumor diameter may affect the prognosis of patients with ACP after surgical resection. Specifically, patients with pT3 in our cohort, who experienced poor prognosis, exhibited tumor necrosis in the tumor with systemic inflammation. These results indicated that high serum inflammatory marker levels, such as WBC, CRP, and NLR, may be associated with the poor oncological outcome after surgical resection for ACP. Our results also suggested that hypodense lesions with peripheral contrast enhancement in MDCT may be important radiological findings that reflect tumor necrosis observed in histopathological examination. In PDAC, tumor markers were also associated with OS postoperatively and important decision-making factors for the treatment. Previous reports revealed that increased CEA and CA19-9 levels were not commonly observed in patients with ACP (26). In this study, the patients with elevated DUPAN-2 levels experienced poor survival and CA19-9 tended to be associated with overall survival after surgery. These results indicated that tumor markers may also be potential candidates for predicting prognosis of the patients with ACP. Further research is required to identify robust preoperative prognostic markers for ACP patients undergoing surgical resection.

Moreover, this study included critical information regarding preoperative diagnosis and preoperative treatment for patients with ACP. Clinical diagnosis may be important in determining the treatment strategy for patients with ACP, particularly in the era of multidisciplinary treatment for pancreatic cancer. According to the radiological results of

Table III. Characteristics of patients with anaplastic carcinoma of the pancreas stratified by pathological tumor diameter.

Parameters	pT1, 2 (n=8)	pT3 (n=4)	P-value
Age, years	65 (53-83)	64 (45-81)	0.59
Sex, n (male/female)	5/3	4/0	0.49
Tumor location, n (Ph/Pbt)	5/3	1/3	0.55
Preoperative laboratory test			
CEA, U/ml	3.4 (1.4-11.1)	3.5 (0.7-5.5)	0.93
CA19-9, U/ml	107.2 (24.1-1,621.0)	241.2 (0.4-780.0)	>0.99
DUPAN-2, U/ml	32 (25-1,300)	215 (86-1,000)	0.15
Span-1, U/ml	34 (12-290)	13 (1-100)	0.41
WBC, /μl	7,350 (4,500-10,500)	11,800 (6,400-14,400)	0.04
Hb, g/dl	11.3 (9.3-15.9)	8.8 (5.5-14.9)	0.17
CRP, mg/dl	0.3 (0.1-0.7)	4.9 (0.6-20.8)	0.04
NLR	2.92 (1.53-5.30)	15.45 (5.89-182.00)	0.02
PNI	47.8 (38.3-56.7)	18.9 (14.3-46.7)	0.08
Pathological findings			
Tumor necrosis, n (+/-)	3/5	4/0	0.08
Intratumoral hemorrhage, n (+/-)	1/7	3/1	0.07
Ki-67 proliferative index, n (high/low)	2/6	4/0	0.06

Fisher's exact test was applied for categorical variables and the Wilcoxon rank sum test was used for continuous variables. Continuous data are presented as the mean (range). Ph, pancreas head; Pbt, pancreas body or tail; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; DUPAN-2, duke pancreatic monoclonal antigen type 2; Span-1, s-pancreas-1 antigen; WBC, white blood cell; Hb, hemoglobin; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutrition index.

MDCT and MRI, the differential diagnosis includes PDAC, solid pseudopapillary neoplasm, and neuroendocrine tumor. EUS-TA enables the diagnosis of pancreatic cancer with high sensitivity and specificity (27). In our cohort, 5 cases underwent EUS-TA of the pancreatic tumor and 3 cases were preoperatively diagnosed as ACP. Recent studies have also reported that EUS-TA facilitated accurate diagnosis of ACP before treatment (28,29). Our survival analyses revealed that ACP cases had a high frequency of early recurrence even in the resectable state according to the UICC criteria, indicating that multidisciplinary treatment may be necessary to improve the prognosis of the patients with ACP. In our cohort, adjuvant chemotherapy was administered whenever the patient's condition was considered suitable for treatment based on the clinical trials for pancreatic cancer (30,31). There are few reports on the efficacy of neoadjuvant therapy for ACP. Two of three patients in our cohort who underwent surgical resection after neoadjuvant chemotherapy experienced a prolonged OS without recurrence. Neoadjuvant chemotherapy may prolong the survival and also select the optimal candidates for operation by excluding patients with rapid growth and distant metastases (32,33). Paclitaxel-containing regimens have been reported to be effective for ACP (34). The indication of neoadjuvant therapy and appropriate multidisciplinary treatment warrants further investigation.

This study has a couple of potential limitations. First, this study investigated a small number of patients and multivariate analysis for evaluating prognostic factors was not feasible in this study. However, a limited number of reports have analyzed the outcome of surgical resection for ACP. This is the first study to conduct detailed analyses regarding the clinicopathological features of long-term survivors and the patients with poor prognosis. Further studies with a large number of patients are required to confirm our results. Second, patients who received neoadjuvant therapy were analyzed together with those who underwent upfront surgery for survival analysis. But there is currently no established evidence demonstrating the survival benefit of neoadjuvant therapy for ACP. While the efficacy of neoadjuvant therapy in resectable PDAC remains controversial, some clinical trials have shown potential benefits recently (35). The impact of neoadjuvant therapy on the prognosis of ACP should be investigated in future studies. In addition, this study included patients with ACP over an extended period from 2003 to 2021, despite recent advances in multidisciplinary treatment for pancreatic cancer. However, our survival data on upfront surgery followed by adjuvant therapy for ACP are crucial in determining whether preoperative therapy should be introduced. Furthermore, aside from our study, there are few case series reporting ACP patients who received neoadjuvant chemotherapy followed by surgical resection.

In conclusion, ACP cases frequently exhibited early recurrence after surgery, resulting in poor survival, whereas a limited number of cases achieved long-term survival. Tumor subtype and pathological features, such as tumor diameter, tumor necrosis, and intratumoral hemorrhage, may be crucial factors associated with postoperative prognosis for ACP.

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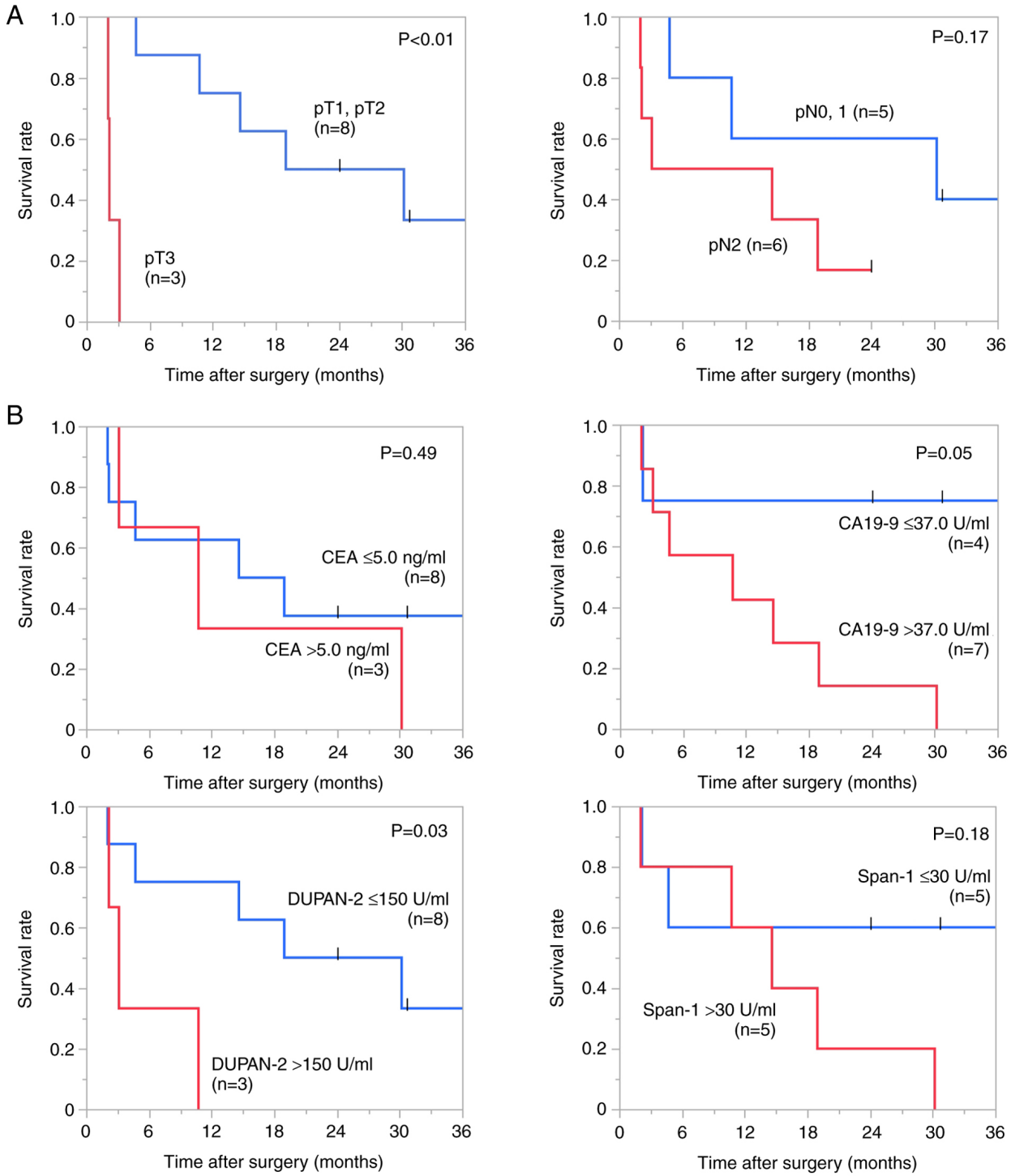

Figure 2. Clinicopathological factors associated with OS of patients with ACP after surgery. (A) OS rate after surgery stratified according to pathological T factor and lymph node metastases in patients with ACP. (B) OS rate after surgery stratified according to the CEA level, CA19-9 level, DUPAN-2 level and Span-1 level in patients with ACP. ACP, anaplastic carcinoma of the pancreas; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; DUPAN-2, duke pancreatic monoclonal antigen type 2; OS, overall survival; Span-1, s-pancreas-1 antigen.

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Availability of data and materials

The data generated in the present study may be requested form corresponding author.

Authors' contributions

IS, TK, ST and MO contributed to the study design. IS, TK and KS contributed to the data acquisition. ST and TM confirmed the authenticity of all the raw data. IS, TK, ST, TT, DS, NS, IH, HN, TM and SN contributed to analysis and interpretation of data. IS and TK drafted the manuscript. ST and MO critically revised the manuscript.

All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Committee on Human Research of Chiba University School of Medicine (approval no. 3302; Chiba, Japan). Informed consent was obtained using an opt-out method, as approved by the institutional ethics committee.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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