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Pathologic Complete Response to Neoadjuvant Therapy in Patients with Pancreatic Ductal Adenocarcinoma Is Associated with Better Prognosis

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Abstract

In patients with pancreatic ductal adenocarcinoma (PDA) who received neoadjuvant therapy and pancreatectomy, pathologic complete response (pCR) is rarely observed and the prognostic significance of pCR is not clear. In this study, we reported 11 patients with pCR (2.5%) from 442 patients with PDA who received neoadjuvant treatment and pancreatectomy from 1995 to 2010. There were 6 men and 5 women with median age of 61 years. Four patients had either synchronous or prior history of extra-pancreatic cancer. Five patients received neoadjuvant chemotherapy followed by chemoradiation, and 6 received chemoradiation alone. Ten patients had pancreaticoduodenectomy and one had distal pancreatectomy. Scar and chronic pancreatitis consistent with therapy effect were present in all cases (100%). Pancreatic intraepithelial neoplasia 3 (Pan IN3)/carcinoma *in situ* was present in 5 cases, PanIN1 and PanIN2 in 5 cases. However, no residual invasive carcinoma or lymph node metastasis was identified in all cases. Follow-up information was available in 10 patients. Follow-up time ranges from 6 to 194 months (median, 63 months). During follow-up, three patients died of other causes and one developed a second primary PDA in the tail of pancreas at 84 months after initial pancreaticoduodenectomy and died at 105 months after the initial diagnosis of PDA. The other 6 patients were alive with no evidence of disease. Patients with pCR had better survival than those who had post-therapy stage I or IIA

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disease ($p<0.001$). Patients with PDA who received neoadjuvant therapy and had pCR in pancreatectomy are rare but have a better prognosis.

Keywords

pathologic complete response; pancreatic cancer; survival; prognosis

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDA) is the fourth leading cause of cancer-related death in the United States [1, 2]. Only 20%–30% of patients with PDA have a resectable disease at the time of diagnosis and 5-year survival rate is less than 5% [3, 4]. Even in patients who undergo surgical resection, the 5-year survival rate is approximately 20% with a median survival of 12 to 20 months [5, 6]. High rate of local recurrence and distant metastasis are the main causes of dismal prognosis in patients with PDA. Neoadjuvant chemoradiation therapy (CRT) has been used as an alternative to “surgery-first” approach in patients with potentially resectable disease due to its potential to reduce in tumor volume, to treat micrometastasis, and to increase the likelihood of a complete resection, especially in borderline resectable cases. In a phase II trial of 86 enrolled patients who received neoadjuvant intravenous infusion of gemcitabine (400 mg/m²/weekly, over 7 weeks) plus external beam of radiation therapy (EBRT) therapy (30 Gy in 10 fractions, 3 Gy/day, over 2 weeks), Evans et al reported a median overall survival (OS) of 34 months in 64 of the 86 enrolled patients who underwent pancreaticoduodenectomy and a median overall survival of 22.7 months in all 86 patients with a 27% 5-year survival rate [7]. Fifty-eight percent of patients in this gemcitabine-based chemoradiation (GEM-XRT) trial showed partial pathologic response and two patients had pathologic complete response (pCR). Similar results have been reported in a phase II trial of neoadjuvant gemcitabine and cisplatin chemotherapy followed by GEM-XRT in 90 patients [8]. The median OS was 31 months for the 52 patients who completed the neoadjuvant therapy and underwent pancreaticoduodenectomy [8]. A large retrospective study of 466 consecutive patients with PDA who underwent R0 resection (all margins negative by histology) at Mayo Clinic showed a median OS of 25.2 in the patients who received neoadjuvant CRT compared to the median OS of 19.2 months in patients who did not receive neoadjuvant CRT ($P=0.001$). Patients who received neoadjuvant CRT had better 5-year OS (28%) than those who had no neoadjuvant CRT (17%) [9].

pCR has been shown to be associated with lower frequencies of local recurrence and better survival in patients with adenocarcinoma of several anatomic sites who received neoadjuvant therapies [10–14]. In patients with esophageal and gastroesophageal junction adenocarcinoma who received neoadjuvant therapy, 21.7% to 40.5% patients have been reported to have pCR in their subsequent esophagectomy specimens, and pCR is associated with better 5-year survival rate and lower risk of recurrence [12, 14]. Similarly, the rates of pCR in patients with rectal cancer who received neoadjuvant therapy are reported to be 13% to 16% [10, 11]. Overall survival and distant recurrence are significantly improved for patients with rectal cancer who achieved pCR [10, 11]. However, the frequency and the prognostic value of pCR in patients with PDA who received neoadjuvant CRT are not clear. In this study, we identified 11 patients with pCR among 442 consecutive patients who had confirmatory tissue diagnoses of PDA and received neoadjuvant CRT and pancreatectomy at our institution from 1995 to 2010. The radiological, clinical and pathologic features of the patients with pCR were reviewed. The survival of patients with pCR was compared to 15 patients with post-treatment American Joint Committee on Cancer (AJCC) stage I disease and 85 patients with post-treatment stage IIA disease. Our study showed that pCR was

associated with better overall survival and lower frequency of recurrence in patients with PDA who received neoadjuvant therapy.

MATERIALS AND METHODS

Study population and histologic evaluation

To identify the patients who had pCR in patients with PDA who received neoadjuvant therapy and pancreatectomy, we searched the computerized databases of the Department of Pathology and the prospective pancreatic cancer database maintained at Department of Surgical Oncology at our institution from 1995–2010. We searched for patients who had treatment effect, but no residual invasive carcinoma in the pancreatectomy specimen. During this period of time, 442 patients who had histologically confirmed diagnosis of PDA and received neoadjuvant therapy and pancreatectomy were identified. Among these patients, 11 patients with pCR were identified.

All pancreatectomy specimens had been fixed in 10% neutral buffered formalin and paraffin-embedded sections were processed routinely for hematoxylin-eosin (H&E) stain. To be included in this study, the potential patients with pCR in pancreatectomy specimens had to be reviewed and independently confirmed by two gastrointestinal pathologists (H.W. and A.R.) and the diagnosis of adenocarcinoma in the pre-treatment FNA or bile duct brushing specimens had to be confirmed by a cytopathologist (Y.G.) in correlation with the findings by computed tomography (CT) imaging. The following features were recorded: age, gender, clinical presentation, radiologic findings/diagnosis, type of neoadjuvant chemotherapy and radiation therapy, presence or absence scar (tumor bed), chronic pancreatitis, pancreatic intraepithelial neoplasia (PanIN lesions), lymph node metastasis, and the margin status of resection. The pCR was defined as area of scarring in pancreatic parenchyma and/or peripancreatic soft tissue with chronic inflammation, with or without acellular mucin pools and histiocytic infiltrates, but no residual viable invasive adenocarcinoma cells in the pancreatectomy specimen. These criteria are based on the grading system for the extent of residual tumor proposed by Evans et al: grade I, little (<10%) or no tumor cell destruction is evident; grade IIa, destruction of 10%–50% of tumor cells; grade IIb, destruction of 51%–90% of tumor cells; grade III, few (<10%) viable-appearing tumor cells are present; grade IV, no viable tumor cells are present; and IVM, only acellular pools of mucin, but not viable tumor cells are present [15]. Cases with either microscopic or gross viable residual tumor were staged based on the AJCC Cancer Staging Manual, 7th edition. The grading of PanIN lesions were based on the previously published criteria [16–19]. The study was approved by the Institutional Review Board of The University of Texas M. D. Anderson Cancer Center.

For the patients with post-therapy stage I (n=15, 14 with ypT1 disease and one patient with ypT2 disease) and stage IIA (ypT3) disease (n=85), there were 48 males and 52 females with age ranging from 38.5 years to 83.8 years (median: 66.3 years). Eighteen patients (18%) received neoadjuvant fluoropyrimidine-based chemoradiation, 36 patients (36%) received neoadjuvant gemcitabine-based chemoradiation, 29 patients (29%) received systemic chemotherapy followed by gemcitabine-based chemoradiation, 14 patients (14%) received systemic chemotherapy followed by fluoropyrimidine-based chemoradiation and the remaining three patients (3%) received neoadjuvant systemic chemotherapy alone. The follow-up of these patients ranging from 7.6 to 122.3 months (median: 34.2 months).

Follow-up and statistical analysis

Clinical follow-up information through May of 2011 was extracted from patient medical records and review of the U.S. Social Security Index. Overall survival (OS) was calculated

as the time from the date of diagnosis to the date of death or the date of last follow-up (if death did not occur). The overall survival of patients with pCR was compared to the patients who had post-treatment stage I disease (n=15) and the patients who had post-treatment stage IIA disease (n=85). Survival curves were constructed using the Kaplan-Meier method and the log-rank test was used to evaluate the statistical significance of differences. Two-tailed P values <0.05 were considered significant. Statistical analysis was performed using Statistical Package for Social Sciences software (for Windows 12.0, SPSS Inc., Chicago, IL).

RESULTS

Among the 442 patients who completed neoadjuvant therapy and underwent pancreatectomy from 1995 to 2010, 11 patients (2.5%) with pCR in pancreatectomy specimens were identified. The summary of the clinical presentations, prior or synchronous cancer history, radiological findings, values of carbohydrate antigen 19.9 (CA 19.9), pretreatment diagnosis by cytology fine needle aspiration, the types of neoadjuvant therapies, OS and outcomes of these 11 patients are listed in Table 1. These patients included six males and five females with ages ranging from 43 to 75 year-old (median age: 61 year-old). Three patients presented with jaundice, four with abdominal pain, one with weight loss, one with recurrent pancreatitis, and the remaining two were asymptomatic and the pancreatic lesions were identified incidentally by imaging studies for other causes. By imaging studies, a mass lesion was identified in the head or neck of pancreas in 10 patients, and the body in one patient. Representative images of pre- and post-treat CT scans of patients #9 and #11 are shown in Figure 1. Three patients also had obstruction of the common bile duct by endoscopic retrograde cholangiopancreatography (ERCP). Among the nine patients whose serum carbohydrate antigen 19.9 (CA19.9) were available, six patients had significant elevation ranging from 76 to 607 u/ml (average 249 u/ml). Three patients (27%) had prior history of extrapancreatic malignancies, including lung, breast, and prostate cancers diagnosed 22 months, 168 months and 120 months, respectively, prior to the diagnosis of PDA (Table 1). Another patient had a synchronous renal cell carcinoma (conventional type, Furhman nuclear grade 1) and underwent right nephrectomy at the time of pancreaticoduodenectomy.

The diagnosis of adenocarcinoma prior to neoadjuvant therapy was confirmed in all patients either by fine needle aspiration (FNA) in 10 patients or biliary fluid aspiration in one patient. For the three patients who had prior history of extrapancreatic carcinomas, the diagnosis of PDA was made based on the comparison of cytology specimens to the extra-pancreatic carcinoma, immunohistochemical stains and correlation with clinical and radiological findings. For the patient who had a prior history of the prostatic adenocarcinoma, a FNA was performed on the subcarinal lymph node at the time of FNA for the pancreatic mass. Representative micrographs of the FNA specimens of pancreatic mass and the subcarinal lymph node are shown in Figure 2A–2D and 2E–2H respectively. The tumor in pancreatic FNA was positive for cytokeratin 7 and CA19.9, but negative for PSA and PAP (Figure 2C–2D). In contrast, the tumor in the FNA from subcarinal lymph node was positive for prostate specific antigen (PSA) and prostatic acidic phosphatase (PAP), but negative for cytokeratin 7 and thyroid transcription factor 1 (TTF-1) confirming metastatic prostatic adenocarcinoma (Figure 2G–2H). For the patient with a prior history of lung cancer, the tumor in pancreatic FNA was morphologically different from the lung primary and was negative for TTF-1. For the patient who had a prior history of breast cancer, the diagnosis of PDA on pancreatic FNA was based on the different tumor morphology, no other site of breast cancer metastasis at the time of pancreatic FNA, and increase serum level of carbohydrate antigen 19.9 (76 U/ml). Among the 11 patients, five patients received systemic chemotherapy with gemcitabine and cisplatin followed by gemcitabine-based chemoradiation (Gem-Cis-XRT) as reported by Varadhachary, G.R., *et al* [8]; three patients received gemcitabine-based chemoradiation

protocol as reported by Evans D. B. *et al* [7] and the remaining three patients received 5-fluorouracil-based chemoradiation [15] (Table 1).

After the completion of neoadjuvant therapy, all patients underwent restaging evaluation and pancreatotomy was performed only in patients with resectable disease who had no disease progression or metastasis and no contraindications to major abdominal surgery. Ten patients underwent pancreaticoduodenectomy and one had distal pancreatectomy with splenectomy. On gross examination, four patients (36.4%) had a mass lesion in the pancreas, two patients (18.2%) had a scar in the pancreas and the other five patients (45.4%) showed diffuse fibrosis of the pancreas, but no mass lesion identified. The pancreatectomy specimens were extensively sampled in all patients. In nine patients the entire pancreas and bile duct were submitted for histologic evaluation. Twelve and 26 sections of pancreas were submitted from the remaining two patients. The total number of dissected regional lymph nodes ranged from 15 to 41 (median, 22). On histologic review, chronic pancreatitis and area of scar with fibrosis were identified in all patients (Table 2 and Figure 3). PanIN3/Carcinoma *in situ* was present in five cases (45%), and PanIN1 or PanIN2 were identified in five patients (45%). Other histologic findings in the tumor beds included multifocal acellular mucin pools in tumor bed and perineural location in one patient (patient #9), foreign body giant cell reactions in two patients, infiltration of foamy histiocytes in two patients, prominent lymphocytic infiltrates in two patients, hemosiderin-laden macrophages and cholesterol cleft in one patient. However, no residual invasive adenocarcinoma or lymph node metastasis was identified in all the eleven cases (Table 2).

Follow-up information was available in ten patients (91%). The follow-up time ranged from 6 to 194 months (median, 63.1 months). During the follow-up, four patients died, including one of brain metastasis from lung cancer, one of bone metastasis from breast cancer, one of complication from sepsis, and one developed a second primary PDA in the tail of the pancreas 84 months after the initial pancreaticoduodenectomy and died of the second PDA 105 month after the initial diagnosis. The last patient has multifocal PanIN3/carcinoma *in situ* in the initial pancreaticoduodenectomy specimen (Figure 3F), but no residual viable invasive adenocarcinoma identified. A secondary primary of PDA is favored in this patient because of the long disease-free period after the initial pancreaticoduodenectomy (84 months). The other six patients were alive with no evidence of disease with a follow-up of 10 to 194 months (median: 68 months, Table 1). Patients with pCR in pancreatectomy specimen had significant better disease-specific OS than the patients who had post-treatment stage I or stage IIA disease in pancreaticoduodenectomy specimens after neoadjuvant therapy ($p < 0.001$, Figure 4).

DISCUSSION

In this study, we report the clinical and pathologic features of 11 patients with PDA, who completed neoadjuvant chemoradiation and had pCR in post-therapy pancreatectomy specimens. We found that patients with pCR had better survival than those patients who had post-treatment stage I or stage IIA disease. Our findings highlight the importance of careful pathologic evaluation of post-therapy pancreatectomy specimen in predicting the prognosis in this group of patients.

Despite significant improvements in operative techniques and mortality rates related to pancreatectomy and the advance of adjuvant chemoradiation therapy, the prognosis for patients with PDA remains unchanged in the last four decades. Neoadjuvant CRT has been increasingly used in patients with potentially resectable PDA and has been shown to improve the survival and locoregional metastatic disease [15, 20–23]. In this group of patients, the frequency of pCR in subsequent pancreatectomy specimens is largely unknown.

In a phase II trial of 86 enrolled patients who received neoadjuvant gemcitabine-based chemoradiation, two patients were reported to have pCR in their subsequent pancreatectomy specimens [7]. Another study from Germany [24] reported pCR in three of 38 patients (7.9%) with locally advanced PDA who received neoadjuvant chemoradiation. In our study, we found only 11 patients (2.5%) with pCR in a large consecutive cohort of 442 patients with PDA who completed neoadjuvant chemoradiation and subsequently underwent pancreatectomy at our institution from 1995 to 2010. All 11 patients (100%) with pCR in pancreatectomy specimens had a mass lesion in the pancreas on pre-treatment CT scans, and were histologically confirmed to be PDA before treatment. All patients showed marked response to the treatment by restaging CT scans after the completion of the neoadjuvant chemoradiation. No residual invasive carcinoma was identified in these patients even with extensive sampling or complete submission of the entire pancreas. In addition, pCR was independently confirmed by two gastrointestinal pathologists in all patients. None of our patients had lymph node metastasis or treatment effect involving the lymph nodes suggesting treated tumor with adequate numbers of lymph nodes examined in all cases.

The extent of residual invasive adenocarcinoma in post-therapy specimens has been shown to correlate with the prognosis in patients with several types of carcinomas, including PDA, esophageal cancer, and rectal cancer [24–29]. In our previous study of 240 patients with PDA who received neoadjuvant CRT and pancreaticoduodenectomy, we showed that post-therapy tumor stage (ypT), lymph node status (ypN), and the post therapy AJCC pathologic stage were independent prognostic factors of both disease-free and overall survivals in this group of patients [30]. However, the significance of pCR in patients with PDA after neoadjuvant CRT has not been addressed. In other tumor sites, patients who achieved pCR after neoadjuvant therapy have better prognosis. Patients with pCR in rectal specimens who received neoadjuvant chemoradiation have better disease-free and overall survival than patients with residual rectal adenocarcinoma [24–29]. Similarly, patients with pCR in esophagectomy specimens after neoadjuvant therapy also had better prognosis than those with residual disease [12, 14]. In this study, we compared the disease-specific survival of 10 patients with pCR to those patients who had lymph node negative residual PDA (stage I and stage IIA) in pancreaticoduodenectomy after neoadjuvant therapy. We found that patients with pCR had better disease-specific survival than those with either post-treatment stage I or stage IIA disease. Our data is consistent with the previous findings from other carcinoma sites that pCR is associated with better prognosis [24–29]. Given the rarity and the limited number of patients with PDA who received neoadjuvant CRT had pCR in pancreatectomy reported in this study, future collaborative studies of a larger patient population is needed to confirm the prognostic values of pCR in patients with PDA. Since the prognostic significance of the grading of the extent of residual tumor in patients with PDA who receive neoadjuvant therapy and pancreatectomy remains unclear, it would be also important to evaluate the prognostic significance of pathologic response to neoadjuvant therapy in future studies.

It was interesting that four of our patients in this study had a prior or synchronous extra-pancreatic carcinoma including prostatic, lung, breast, and renal cell carcinoma. These are the most frequent carcinomas in our patient population and this age group of patients. However, none of our patients had a known history of genetic disease or syndrome which would predispose to increased risk of pancreatic cancer. The significance of the high frequency of second malignancy observed in this study is unknown.

In summary, our study identified 2.5% of patients with pCR in a large cohort of 442 patients with PDA who completed neoadjuvant CRT and subsequently underwent pancreatectomy. Patients with pCR had better overall survival than those with post-therapy stage I and stage IIA residual invasive PDA. Therefore, complete and thorough examinations of the post-

therapy pancreatectomy specimen to identify patients with pCR play an important role in predicting a better prognosis of patients with PDA who received neoadjuvant CRT and pancreatectomy.

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FIGURE 1.

Pre- and post-therapy computer tomography (CT) scans of patient #9 (A & B) and patient #11 (C & D). The pre-treatment CT scans are shown in A and C and post-treatment scans are shown in B and D. Both patients show marked tumor shrinkage as indicated by the arrow after neoadjuvant chemoradiation.

FIGURE 2.

Representative micrographs of the pretreatment fine needle aspiration (FNA) specimens from the pancreas and the subcarinal lymph node of patient #9. Papanicolaou cell smear (A & E), cell block (B & F), and immunohistochemical staining for cytokeratin 7 (CK7, C & G) and prostate specific antigen (PSA, D & H) are shown. The pancreatic carcinoma stains for CK7 (C), but does not stain for PSA (D), TTF-1 and PAP (not shown). In contrast, the metastatic prostatic adenocarcinoma in subcarinal lymph node does not stain for CK 7 (G) and TTF-1 (not shown) but stains for PSA (H) and PAP (not shown).

FIGURE 3.

Representative micrographs show the post-treatment tumor bed and PanIN lesions, but no residual invasive adenocarcinoma. Tumor bed of patient #9 shows fibrosis, chronic pancreatitis and acellular mucin pools in the pancreas (A) and perineural spaces (B). Tumor bed from patients #7 show large area of fibrosis with foreign body giant cell reactions and cholesterol clefts (C). Tumor bed from patient #4 show a collection of histiocytes associated with scar (D). PanIN2 lesion with chronic pancreatitis from patients #10 (E) and PanIN3/ carcinoma *in situ* from patient #3 (F). Original magnification 40× for A, B, C, E, F and 100× for D.

Figure 4. Kaplan-Meier estimates of disease-specific overall survivals in patients with pCR (n=10), patients with post-treatment stage I PDA (ypT1 & ypT2, n=15) and patients with post-treatment stage IIA PDA (ypT3, n=85) who received neoadjuvant chemoradiation and post-therapy pancreaticoduodenectomy.

Summary of Clinical Information, Neoadjuvant Therapies and Outcomes

TABLE 1

Cases	Age (yrs)	Gender	Clinical Presentation	Prior or synchronous cancer	Radiographic Findings	CA 19.9 (u/ml)	Cytology Dx	Pre-op CRT	Dose of XRT	OS (months)	Outcome
1	57	M	Abdominal pain		Mass [§] , head	n/a	ACA	5-FU/XRT	50.4 Gy	194	Alive, NED
2	43	M	Weight loss	Renal cell carcinoma ^a	4–5 cm mass, head	n/a	ACA	5-FU/XRT	50.4 Gy	22	Alive, NED
3	62	F	Recurrent pancreatitis		1.1 cm mass, head	< 8	ACA	GEM/XRT	30.0 Gy	105	Died of second PDA
4	57	F	Abdominal pain, diarrhea		3.4 cm mass, head	30	ACA	5-FU/XRT	30.0 Gy	106	Alive, NED
5	75	F	Diarrhea, abdominal pain	Breast ACA ^b	2.0 cm mass, head	76	ACA	GEM/XRT	30.0 Gy	80	Died of breast ACA
6	72	M	Jaundice	Lung ACA ^c	2.7 cm mass, head	8	ACA	GEM/XRT	30.0 Gy	6	Died of lung ACA
7	53	F	Jaundice		4.0 cm mass, head	607	ACA	GEM-CIS-XRT	50.4 Gy	62	Alive, NED
8	69	M	Jaundice		2.0 cm mass, head	207	ACA	GEM-CIS-XRT	50.4 Gy	31	Died of sepsis
9	61	M	Asymptomatic	Prostatic ACA ^d	3.1 cm mass, body	380	ACA	GEM-CIS-XRT	50.4 Gy	0.6	Lost follow-up
10	65	F	Abdominal pain		2.6 cm mass, neck	130	ACA	GEM-CIS-XRT	50.4 Gy	15	Alive, NED
11	60	M	Asymptomatic		3.5 cm mass, head	94	ACA	GEM-CIS-XRT	30.0 Gy	10	Alive, NED

Abbreviations: yrs: years; Dx: diagnosis; NED: no evidence of disease; ACA: adenocarcinoma; PDA: pancreatic adenocarcinoma; OS: overall survival calculated from the time of the diagnosis of PDA to death or last follow-up; n/a: not available; CRT: chemoradiation therapy; XRT: radiation treatment; 5-FU/XRT: 5-fluorouracil with radiation; GEM/XRT: gemcitabine with radiation; GEM-CIS-XRT: Gemcitabine-based chemotherapy followed by chemoradiation; Gy: Gray.

[§]Tumor size is not available.

^asynchronous renal cell carcinoma and underwent right nephrectomy at the time of pancreaticoduodenectomy.

^bbreast cancer diagnosed at 168 months prior to the diagnosis of PDA, status post left total mastectomy and chemotherapy.

^clung adenocarcinoma diagnosed at 22 months prior to the diagnosis of PDA, status post neoadjuvant chemoradiation and right pneumonectomy and chest wall resection.

^dprostatic adenocarcinoma diagnosed 120 months prior to the diagnosis of PDA, status post radical prostatectomy.

TABLE 2

Summary of Pathological Findings in Pancreatectomy Specimens

Cases	Specimen	Gross findings	Microscopic findings				LN status*
			Scar	CP	Precursor lesion	Others	
1	PDE	3.0 cm, ill-defined mass in the pancreas	present	present	Absent	Focal foreign body giant cell reactions	0/22
2	PDE	Diffuse fibrosis of the pancreas, no mass lesion identified	present	present	Absent		0/15
3	PDE	2.0 cm, ill-defined mass in the pancreas	present	present	Multifocal PanIN3/CIS	Focal foreign body giant cell reactions	0/21
4	PDE	2.5 cm, ill-defined mass in the pancreas	present	present	Focal PanIN3/CIS	Infiltration of foaming histiocytes	0/22
5	PDE	Diffuse fibrosis of the pancreas, no mass lesion identified	present	present	Focal PanIN3/CIS		0/28
6	PDE	Diffuse fibrosis of the pancreas, no mass lesion identified	present	present	Focal PanIN 1		0/21
7	PDE	2.0 cm, ill-defined mass in the pancreas	present	present	Absent	Hemosiderin-laden macrophages, cholesterol clefts and calcification	0/41
8	PDE	Diffuse fibrosis of the pancreas, no mass lesion identified	present	present	Focal PanIN 2–3	Prominent lymphocytic infiltrates	0/24
9	DPE	3.0 cm area of scar in the pancreas	present	present	Focal PanIN 1	Acellular mucin with foamy histiocytes	0/16
10	PDE	1.5 cm area of scar in the pancreas	present	present	Focal PanIN 1–2		0/26
11	PDE	Diffuse fibrosis of the pancreas, no mass lesion identified	present	present	Focal PanIN 1B, 2, 3	Prominent lymphocytic infiltrates	0/18

Abbreviations: PDE: pancreaticoduodenectomy; DPE: Distal pancreatectomy; LN: lymph node; PanIN: pancreatic intraepithelial neoplasia; CIS: carcinoma *in situ*; CP: chronic pancreatitis.
LN status, expressed as number of involved LN/number of total LNs examined