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Original article

Prognostic significance of intraoperative peritoneal washing cytology for patients with potentially resectable pancreatic ductal adenocarcinoma

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ABSTRACT

Background: The prognostic significance of intraoperative peritoneal washing cytology (IPWC) in pancreatic ductal adenocarcinoma (PDAC) remains controversial, and the treatment strategy for PDAC patients with positive cytology has not been established.
Objectives: The objective of this study was to evaluate the clinical significance of IPWC in PDAC patients.
Methods: This study included a retrospective cohort of 166 patients with curatively resected PDAC who underwent IPWC.
Results: Overall, 17 patients (10%) had positive cytology (CY+), and 149 (90%) patients were negative (CY−). Tumor location in the pancreatic body and/or tail and pancreatic anterior capsular invasion were independent predictors of a CY+ status (P = 0.012 and 0.041, respectively). The initial recurrence occurred at the peritoneum with a significantly higher frequency in CY+ patients (50%) than in CY− patients (12%) (P = 0.003). The median overall survival (OS) for CY+ patients was 12 months. The OS rates at 1 and 3 years were significantly higher for CY− patients (75.1% and 35.3%, respectively) versus CY+ patients (47.1% and 17.6%, respectively; P = 0.012). However, one CY+ patient survived for 66 months, and another two CY+ patients have survived for more than three years after surgery without evidence of peritoneal recurrence. In the multivariate analysis, the independent predictors of OS were a CY+ status, lymph node metastasis, and adjuvant chemotherapy.
Conclusions: This study demonstrates that positive IPWC predicts early peritoneal recurrence and a poor prognosis for PDAC patients. However, a small but not insignificant subset of CY+ patients with PDAC may avoid peritoneal carcinomatosis.

1. Introduction

Pancreatic carcinoma is the fifth and fourth leading cause of death in Japan and Western countries, respectively, and is associated with an extremely poor prognosis [1,2]. Despite recent advances in radiological imaging modalities, pancreatic cancers are frequently detected late in the disease course. Successful surgical resection offers the only chance for cure in patients with pancreatic cancer, but the 5-year survival rate for patients undergoing complete resection is low (20–25%) even when combined with adjuvant chemotherapy [3–5]. Peritoneal metastasis is one of the most frequent causes of treatment failure following curative resection for pancreatic cancer, with an incidence of 14–33% for patients with recurrence [6,7]. Intraoperative peritoneal washing cytology (IPWC) can detect subclinical peritoneal spread of the disease by directly detecting free cancer cells in the peritoneal cavity. IPWC has been included in the guidelines for tumor staging and is currently a routine procedure for several intra-abdominal malignancies, such as gastric and ovarian cancer [8–10]. However, the prognostic significance of free intra-peritoneal cancer cells in pancreatic ductal adenocarcinoma (PDAC) remains controversial because no randomized controlled trials or prospective follow up studies have investigated this issue. Therefore, the treatment

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strategy for PDAC patients with positive peritoneal cytology has not been established. Several earlier studies demonstrated that PDAC patients with positive peritoneal washing cytology had a poorer prognosis than patients with negative cytology [11–13], whereas conflicting survival data that demonstrated comparable survival of PDAC patients with positive peritoneal washing cytology and patients with negative cytology were presented in other reports [14–16]. However, the number of patients with positive cytology in most previous studies was 20 or less. Recently, Satoi et al. [17] reported a multi-institutional study of 69 PDAC patients with positive peritoneal washing cytology who underwent curative resection. The authors demonstrated that positive peritoneal cytology was an independent prognostic factor for PDAC patients, with a median survival time of 16 months and a 3-year overall survival (OS) rate of 6%. Due to the controversy regarding the prognostic impact of IPWC, the role of peritoneal washing in the staging of pancreatic cancer is still debatable. The current National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma indicate that positive cytology from washings obtained at laparoscopy or laparotomy is equivalent to M1 disease [18]. In addition, the current American Joint Committee on Cancer (AJCC) staging system for pancreatic cancer classifies positive peritoneal cytology as stage IV disease [8]. However, to date, the Union for International Cancer Control (UICC) TNM classification system and the Japanese General Rules for the Study of Pancreatic Cancer do not include peritoneal cytology for tumor staging [10,19]. The objective of this study was to evaluate the clinical significance of IPWC in patients with potentially resectable PDAC by comparing the IPWC status with the corresponding clinicopathological parameters and clinical outcomes.

2. Patients and methods

2.1. Patients

Between February 1995 and September 2015, a total of 195 patients underwent macroscopically curative resection for PDAC at our institution. This study included a retrospective cohort of 166 patients who underwent IPWC in addition to resection. Patients with visible peritoneal metastases or liver metastases were excluded from this study. This study was approved by the Institutional Review Board. The data obtained from the medical records included clinical characteristics, surgical procedures, IPWC results, histopathological findings, administration of adjuvant chemotherapy, and clinical outcomes. For each patient, the tumor stages were assigned according to the UICC classification system and were based on the surgical and pathological findings. Since 2003, adjuvant chemotherapy was administered to 94 patients (57%) who underwent surgery. The adjuvant chemotherapy regimens were gemcitabine alone (1000 mg/m^2, intravenously administered on days 1, 8, and 15 every 4 weeks [one cycle] for up to six cycles) in 37 patients, S-1 alone (80–120 mg/day according to the body surface area for 28 days followed by a 14 day rest every 6 weeks [one cycle] for up to four cycles) in 54 patients, and gemcitabine plus S-1 [gemcitabine (800 mg/m^2 on day 1) plus S-1 (65 mg/m^2/day on days 1–7) every 2 weeks for six months] in three patients.

2.2. IPWC methods

IPWC was performed according to the Japanese General Rules for the Study of Pancreatic Cancer [19]. Briefly, after opening the abdominal cavity, we introduced 100 ml of physiological saline solution into the Douglas fossa before any manipulation of the tumor and carefully washed the cavity with gentle stirring. The wash fluids were collected from the Douglas fossa using a catheter and a syringe. The fluids were immediately transported to the laboratory and centrifuged at 2500 rpm for 3 min. The cell pellet was aspirated and smeared onto glass slides. Slides were subjected to Giemsa and Papanicolaou staining using a routine procedure. IPWC was graded by experienced cytoscreeners and pathologists. Based on the IPWC results, the patients were classified into the positive cytology group (CY+) or the negative cytology group (CY−). For confirmation, periodic acid–Schiff (PAS) and Alcian blue staining were subsequently performed in all CY+ samples. Patients with equivocal results were classified as CY−.

2.3. Statistical analysis

All data were analyzed using SPSS software, version 23. The chi-squared or Fisher's exact test was used to analyze the categorical variables. The cut-off values for the age and tumor size were defined as 65 years and 40 mm because the mean and median values for each factor were 65.8 and 66.5 years and 43.1 and 38.0 mm, respectively. A multivariate analysis of factors related to CY status was performed using the logistic regression model. Survival curves were constructed according to the Kaplan-Meier method. The log-rank test was used to compare the survival curves. The overall survival (OS) was calculated as the time from the date of surgery to either the date of death or the last follow-up, whichever occurred first. The disease-free survival (DFS) was defined as the time from the date of surgery to the date of recurrence, the last follow-up or the date of death, whichever occurred first. Patients without recurrence at the last follow-up date were censored. Cox proportional hazards models were constructed to evaluate the prognostic significance of CY status with clinical outcomes while adjusting for clinical factors. P values less than 0.05 were considered statistically significant.

3. Results

The clinical characteristics of the 166 patients are outlined in Table 1. Overall, 17 patients (10%) had positive IPWC and were classified into the CY+ group. The remaining 149 patients (90%) included 144 patients with negative cytology and five patients with equivocal results, and these patients were classified into the CY− group. A significant positive correlation was observed between a CY+ status and tumor location in the pancreatic body and/or tail ($P = 0.007$) and the presence of pancreatic anterior capsular invasion ($P = 0.007$) (Table 2). The age, gender, tumor size, serum tumor markers including carbohydrate antigen (CA) 19-9, carcinoembryonic antigen (CEA), and duke pancreatic monoclonal antigen type 2 (DUPAN-2), the presence of retroperitoneal invasion, extrapancreatic nerve plexus invasion, lymph node metastasis, UICC tumor stage, and resection status were not associated with the CY status. Tumor location in the pancreatic body and/or tail and the presence of pancreatic anterior capsular invasion were significant factors in the multivariate analysis (OR = 0.184, 95% CI, 0.050–0.687, P = 0.012 and OR = 0.115, 95% CI, 0.015–0.911, P = 0.041, respectively). At a median follow-up of 17.5 months, 116 patients experienced recurrence and 115 patients had died. Among the 116 patients who experienced recurrence, the initial recurrence was mainly observed at the following sites: the liver (n = 55, 47%), a local site (n = 34, 29%), the peritoneum (n = 19, 16%), and the lymph nodes (n = 19, 16%). Only six patients (5%) displayed lung metastasis. The initial recurrence occurred at the peritoneum with a significantly higher frequency in CY+ patients (7 of 14 patients; 50%) than in CY− patients (11 of 93 patients; 12%) (P = 0.003).

The OS rates at 1 and 3 years were significantly higher for patients with a CY− status (75.1% and 35.3%, respectively) than for patients with a CY+ status (47.1% and 17.6%, respectively; P = 0.012)

Table 1
Patient characteristics.

	n (%)
Age, mean (range), year	65.8 (41–84)
Sex	
Male	91 (55%)
Female	75 (45%)
Tumor location	
Ph	85 (51%)
Pb and/or Pt	75 (45%)
Ph and Pb and/or Pt	6 (4%)
Tumor size, mean (range), mm	43.2 (10–200)
CA19-9 (≤ 37 U/mL)	
Normal	49 (30%)
High	115 (70%)
CEA (≤ 5 ng/mL)	
Normal	115 (70%)
High	50 (30%)
DUPAN-2 (≤ 150 mAU/mL)	
Normal	79 (57%)
High	59 (43%)
Lymph node metastasis	
Negative	47 (28%)
Positive	119 (72%)
Stage	
IA	4 (2%)
IB	2 (1%)
IIA	39 (24%)
IIB	107 (65%)
III	4 (2%)
IV	10 (6%)
Surgical procedure	
PD	86 (52%)
DP	72 (43%)
DP-CAR	2 (1%)
TP	6 (4%)
Resection status	
R0	142 (86%)
R1	24 (14%)

Ph: pancreatic head; Pb: pancreatic body; Pt: pancreatic tail; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; DUPAN-2: duke pancreatic monoclonal antigen type 2; PD: pancreatoduodenectomy (PD) including pylorus-preserving PD and subtotal stomach-preserving PD; DP: distal pancreatectomy; DP-CAR: DP with en bloc celiac axis resection; TP: total pancreatectomy.

(Fig. 1A). Among the 17 CY+ patients, 13 died of their disease and one died of other causes (median OS: 12 months, range: 3–66 months). Of the patients who died, eight died within 1 year after surgery. However, one CY+ patient who had para-aortic lymph node metastasis at surgery (T3N1M1) and received adjuvant chemotherapy using gemcitabine displayed lymph node metastasis four years after surgery and survived 66 months after surgery without evidence of peritoneal metastasis. Additionally, another two CY+ patients have survived for more than three years after surgery without evidence of peritoneal metastasis. The first patient (T3N0M0) experienced recurrence at the para-aortic lymph node 9 months after surgery despite receiving adjuvant chemotherapy using S-1 and benefited from the administration of the FOLFIRINOX regimen with a partial prolonged radiological response but experienced recurrence in the lymph nodes and brain at the last follow-up. The second patient (T3N0M0) has not received adjuvant chemotherapy due to old age and has survived three years after surgery without evidence of recurrence.

In the univariate analysis of survival, several clinicopathological variables were associated with OS, including the CY+ status (P = 0.012), serum CA19-9 level (P = 0.020), combined major vascular resection (P = 0.042), lymph node metastasis (P = 0.011), and adjuvant chemotherapy (P = 0.002) (Table 3). In contrast, OS was not associated with gender, tumor location, tumor size, CEA, DUPAN-2, extrapancreatic nerve plexus invasion or resection status. In the multivariate analysis, the independent predictors of OS included the CY+ status (HR = 2.107, 95% CI, 1.208–3.676, P = 0.009), lymph node metastasis (HR = 1.831, 95% CI, 1.138–2.946, P = 0.013), and adjuvant chemotherapy (HR = 0.590, 95% CI, 0.402–0.866, P = 0.007) (Table 4). Patients with a CY+ status had significantly shorter DFS than patients with a CY− status (P = 0.009) (Fig. 1B). For other clinicopathological parameters, the serum CA19-9 level (P = 0.002), the presence of extrapancreatic nerve plexus invasion (P = 0.024), and lymph node metastasis (P = 0.003) were significantly associated with a shorter DFS (Table 3). In the multivariate analysis, the CY+ status (HR = 1.897, 95% CI, 1.009–3.273, P = 0.021), serum CA19-9 level (HR = 1.690, 95% CI, 1.094–2.613, P = 0.018) and lymph node metastasis (HR = 1.707, 95% CI, 1.063–2.740, P = 0.027) were variables independently associated with DFS.

4. Discussion

Currently, the UICC TNM classification system and the Japanese General Rules for Pancreatic Cancer do not include peritoneal cytology for tumor staging [10,19], whereas the NCCN guidelines for pancreatic adenocarcinoma and the AJCC staging system for pancreatic cancer classify positive peritoneal cytology as M1 or stage IV disease [8,18]. In the present study, we demonstrated that CY+ patients initially experienced recurrence at the peritoneum with a higher frequency than CY− patients, and a CY+ status was an independent predictor of OS and DFS in patients with curatively resected PDAC. In the survival analysis, lymph node metastasis was also an independent prognostic factor for OS and DFS in PDAC patients who underwent curative surgery. The serum CA19-9 level was an independent prognostic factor for DFS. Adjuvant chemotherapy was the strongest prognostic factors for OS but was not significant for DFS. One possible explanation for the discrepancy between OS and DFS in adjuvant chemotherapy was that patients administered at least one cycle were assigned to the adjuvant chemotherapy group. Our data support the usefulness of IPWC for tumor staging in patients with PDAC.

The rate of IPWC positivity in patients with potentially resectable pancreatic cancer ranges from 5 to 14% in different studies [11–17], whereas the rate ranges from 38 to 45% in patients with visible metastatic disease [11,14,20]. The rate of IPWC positivity in the present study is similar to rates in previous studies of potentially resectable pancreatic cancers [12,13,15,17]. We adopted the IPWC procedure according to the Japanese General Rules for the Study of Pancreatic Cancer; however, the reported procedures varied by institution according to the sites used for washing or the volume of the instilled saline solution [12,17,21], which might affect the positivity rates. Therefore, thorough standardization is needed to integrate IPWC into routine clinical practice for future application in tumor staging.

Conventional IPWC is currently the gold standard for the detection of free cancer cells in the peritoneal cavity with high specificity; however, the reported sensitivity ranges between 28 and 60% [22]. Therefore, more sensitive molecular techniques have been introduced to identify free cancer cells in the peritoneal cavity. Earlier studies have demonstrated that immunocytochemical staining for adenocarcinoma markers, such as Ber-EP4, carcinoembryonic antigen (CEA), and carbohydrate antigen (CA)19-9, was a useful procedure to differentiate adenocarcinoma cells from reactive mesothelial cells [22,23]. In addition, reverse transcription polymerase chain reaction has been used to detect CEA mRNA in the washing fluid to increase the sensitivity of conventional peritoneal cytology. These techniques have demonstrated a higher sensitivity than conventional cytology and may predict early peritoneal recurrence [24,25]. However, the limitations of these

Table 2
Correlation of intra-operative peritoneal washing cytology status with clinicopathological variables.

		CY− (n = 149)	CY+ (n = 17)	P
Age				
	≤65 (n = 79)	71	8	1.000
	>65 (n = 87)	78	9	
Sex	M:F	81:68	10:7	0.801
Tumor location				
	Ph (n = 85)	82	3	0.007
	Pb and/or Pt (n = 75)	62	13	
Tumor size				
	<40 mm (n = 101)	93	8	0.294
	≥40 mm (n = 65)	56	9	
CA19-9 (≤37 U/mL)				
	Normal (n = 49)	44	5	1.000
	High (n = 115)	103	12	
CEA (≤5 ng/mL)				
	Normal (n = 115)	106	9	0.101
	High (n = 50)	42	8	
DUPAN-2 (≤150 AU/mL)				
	Normal (n = 79)	73	6	0.557
	High (n = 59)	52	7	
Pancreatic anterior capsular invasion				
	Yes (n = 109)	93	16	0.007
	No (n = 57)	56	1	
Retroperitoneal invasion				
	Yes (n = 146)	129	17	0.229
	No (n = 20)	20	0	
Extrapancreatic nerve plexus invasion				
	Yes (n = 94)	85	9	0.800
	No (n = 72)	64	8	
Lymph node metastasis				
	Negative (n = 47)	42	5	1.000
	Positive (n = 119)	107	12	
UICC tumor stage				
	IA/IB/IIA (n = 45)	40	5	0.780
	IIB/III/IV (n = 121)	109	12	
Resection status				
	R0 (n = 142)	130	12	0.076
	R1 (n = 24)	19	5	

CY−: negative intra-operative peritoneal washing cytology; CY+: positive intra-operative peritoneal washing cytology; Ph: pancreatic head; Pb: pancreatic body; Pt: pancreatic tail; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; DUPAN-2: duke pancreatic monoclonal antigen type 2.

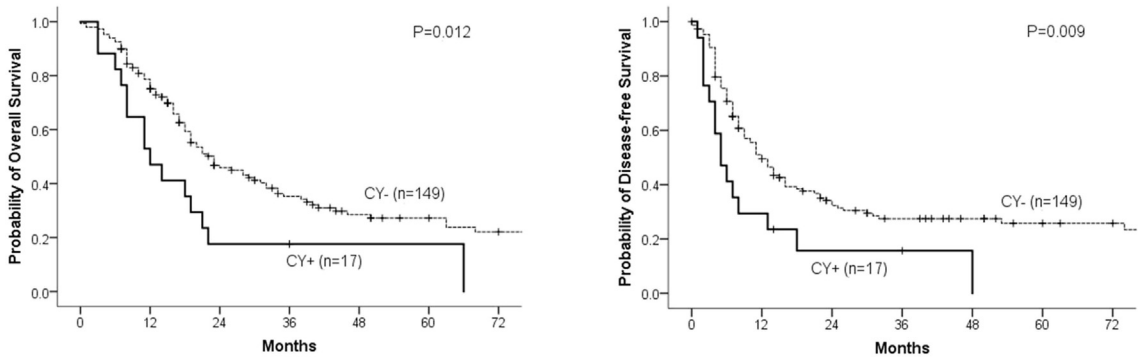

Fig. 1. Kaplan–Meier survival curves based on intraoperative peritoneal washing cytology. **A**, The overall survival (OS) for patients with positive cytology (CY+) was significantly worse than that for patients with negative cytology (CY−) (P = 0.012). **B**, The disease-free survival (DFS) for CY+ patients was significantly worse than that for CY− patients (P = 0.009).

techniques include the cost, the time required for their use, and their lack of reproducibility. RT-PCR is also limited by its exquisite sensitivity, which can lead to false-positive results [26,27]. Therefore, none of these methods have become part of standard diagnostic protocols.

Peritoneal metastases occur through an invasive process in which cancer cells are exposed from the pancreatic anterior capsule and exfoliate into the peritoneal cavity. Several factors, such as tumor size, tumor location in the pancreatic body and/or tail, pancreatic anterior capsular invasion, retroperitoneal invasion, and serum CA19-9 levels have been correlated with positive peritoneal washing cytology [11–13,15–17]. The present study demonstrated that tumor location in the pancreatic body and/or tail and pancreatic anterior capsular invasion were independent predictors of positive cytology. In our series, the tumor size was significantly larger in tumors in the pancreatic body and/or tail than in the pancreatic head (mean, 48.9 vs. 37.2 mm, P = 0.005), and the presence of pancreatic anterior capsular invasion tended to be higher in tumors located at the pancreatic body and/or tail (69.3% vs. 61.2%). The most likely reason is that pancreatic cancers in the

Table 3
Univariate analysis of survival and clinicopathological parameters.

	Overall survaival rate (%)			Disease-free survival (%)		
	1-year OS	3-year OS	P	1-year DFS	3-year DFS	P
IPWC status						
CY− (n = 149)	75.1	35.3	0.012	49.5	27.5	0.009
CY+ (n = 17)	47.1	17.6		29.4	15.7	
Age						
≤ 65 (n = 79)	77.6	39.3	0.126	55.8	23.8	0.410
> 65 (n = 87)	67.4	28.1		39.6	29.3	
Sex						
Male (n = 91)	69.2	33.1	0.496	45.3	27.2	0.850
Female (n = 75)	75.0	33.9		49.8	25.5	
Tumor location						
Ph (n = 85)	67.5	32.N8	0.137	42.8	22.7	0.328
Pb and/or Pt (n = 75)	78.1	33.4		50.8	29.6	
Tumor size						
< 40 mm (n = 101)	74.8	36.8	0.360	46.8	28.9	0.850
≥40 mm (n = 65)	68.3	27.8		49.1	22.8	
CA19-9 (≤37 U/mL)						
Normal (n = 49)	81.6	44.6	0.020	61.2	43.7	0.002
High (n = 115)	68.4	28.0		41.3	18.2	
CEA (≤5 ng/mL)						
Normal (n = 115)	71.1	35.4	0.679	48.0	26.6	0.779
High (n = 50)	73.8	27.3		45.4	23.8	
DUPAN-2 (≤150 AU/mL)						
Normal (n = 79)	76.7	33.1	0.152	49.7	28.1	0.350
High (n = 59)	65.4	30.1		40.8	23.9	
Combined major vascular resection						
Yes (n = 76)	63.7	28.1	0.042	38.3	15.4	0.075
No (n = 90)	79.3	38.4		55.0	35.4	
Extrapancreatic nerve plexus invasion						
Yes (n = 94)	68.5	26.6	0.075	40.7	18.3	0.024
No (n = 72)	76.9	42.4		56.3	37.1	
Lymph node metastasis						
Negative (n = 47)	79.9	44.4	0.011	57.0	45.2	0.003
Positive (n = 119)	69.1	29.1		43.5	19.5	
Resection status						
R0 (n = 142)	74.7	32.8	0.766	49.2	26.1	0.526
R1 (n = 24)	57.4	36.5		36.4	26.6	
Adjuvant chemotherapy						
Yes (n = 94)	78.9	44.0	0.002	52.5	30.7	0.239
No (n = 72)	63.4	20.7		40.5	19.9	

IPWC: intra-operative peritoneal washing cytology; CY−: negative intra-operative peritoneal washing cytology; CY+: positive intra-operative peritoneal washing cytology; Ph: pancreatic head; Pb: pancreatic body; Pt: pancreatic tail; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; DUPAN-2: duke pancreatic monoclonal antigen type 2.

Table 4
Multivariate analysis of survival and clinicopathological parameters.

	Overall survaival		Disease-free survival	
	HR (95% CI)	P	HR (95% CI)	P
CY− vs. CY+	2.107 (1.208–3.676)	0.009	1.897 (1.099–3.273)	0.021
CA19-9	1.480 (0.953–2.296)	0.081	1.690 (1.094–2.613)	0.018
Combined major vascular resection	1.464 (0.999–2.147)	0.051		
Extrapancreatic nerve plexus invasion			1.418 (0.964–2.087)	0.076
Lymph node metastasis	1.831 (1.138–2.946)	0.013	1.707 (1.063–2.740)	0.027
Adjuvant chemotherapy	0.590 (0.402–0.866)	0.007		

CY−: negative intra-operative peritoneal washing cytology; CY+: positive intra-operative peritoneal washing cytology; CA19-9: carbohydrate antigen 19-9.

pancreatic body and/or tail display symptoms at later stages than cancers in the pancreatic head, resulting in higher positivity of peritoneal cytology. In contrast, the tumor size itself was not significantly associated with the CY status. Using the cut-off value of 40 mm, the tumor size was not associated with the presence of pancreatic anterior capsular invasion in our series (data not shown), which might have been a reason for our conflicting data.

In contrast to gastric or ovarian cancer, the clinical role of IPWC in PDAC regarding the tumor staging or indication of radical surgery is still debatable due to the diverse recurrence patterns of PDAC. Hishinuma et al. [6] reported recurrence patterns of 27 autopsied PDAC patients who underwent curative resection; a total of 7 of the 8 patients with peritoneal metastasis recurred at multiple sites, including the local site, liver, lymph node, and other distant metastases. The most promising treatment for patients with pancreatic cancer is R0 resection; however, a multi-modal approach may be needed to improve survival. Recent advances in adjuvant chemotherapy have led to remarkably longer survival times in patients with resectable pancreatic cancer [28]. However, the effect of systemic chemotherapy on peritoneal metastasis in pancreatic cancer remains unclear. Satoi et al. demonstrated that no significant difference in OS existed between patients with positive cytology who received adjuvant therapy and patients who did not [17]. These data may indicate that conventional adjuvant chemotherapy

does not offer survival advantages for PDAC patients with occult peritoneal metastasis. Therefore, intraperitoneal administration of anticancer drugs may be a reasonable method for the treatment of peritoneal metastasis. The same authors recently demonstrated the efficacy of intravenous and intraperitoneal paclitaxel with S-1 for 33 PDAC patients with peritoneal metastases, including 11 patients with positive peritoneal cytology but without peritoneal dissemination [29]. Their results may encourage a trend in which PDAC patients with positive cytology are considered for the indication of systemic and/or intraperitoneal chemotherapy. However, the appropriate surgical and chemotherapeutic interventions for PDAC patients with positive cytology and no evidence of macroscopic peritoneal metastasis has not been validated and sufficiently argued. If patients with positive cytology may not benefit or receive limited benefits from surgery, minimally invasive procedures, including diagnostic laparoscopy with IPWC, will be useful to avoid unnecessary surgical interventions. Ferrone et al. [11] reported that patients with pancreatic cancer who underwent resection in the presence of positive peritoneal cytology and the absence of other identifiable metastatic disease had survival rates similar to patients with grossly visible metastases. However, the OS for patients with positive cytology in their study was shorter than the OS reported in other studies (median 8 vs. 10–23.8 months) [11–13,15–17]. Yamada et al. demonstrated that CY+ patients had shorter OS than CY− patients, but no correlation was observed between the CY status and subsequent peritoneal carcinomatosis and curative resection was recommended regardless of the CY status [21]. In the large series of multi-institutional studies, the 1- and 3-year OS rates of CY+ patients who underwent resection were reported to be 45% and 6% [17], whereas these rates were 47.1% and 17.6% in the present series. The number of CY+ patients is relatively small and three of the 17 CY+ patients (17.6%) in our series have survived more than 3 years, resulting in a better 3-year OS rate.

Although several earlier studies have evaluated the clinical significance of positive cytology in PDAC patients, few reports have reviewed long-term survivors with positive cytology. We experienced three long-term survivors with positive cytology without peritoneal recurrence. However, no trend regarding the clinical characteristics or adjuvant chemotherapy was observed in these patients. Our data suggest that a small but not insignificant subset of PDAC patients with positive peritoneal cytology may avoid peritoneal carcinomatosis and benefit from radical surgery. Therefore, we propose that IPWC should be considered in future clinical trials of treatment strategies for patients with pancreatic cancer, such as intra-peritoneal chemotherapy followed by conventional systemic adjuvant chemotherapy, to determine the therapeutic benefit for patients with positive peritoneal washing cytology.

In conclusion, this study demonstrates that positive IPWC predicts early peritoneal recurrence and a poor prognosis for patients with PDAC. Our data suggest that IPWC may be necessary to detect free intra-peritoneal cancer cells and that this technique may be a useful procedure for staging pancreatic cancer. However, a small but not insignificant subset of PDAC patients with positive peritoneal cytology may avoid peritoneal carcinomatosis and benefit from radical surgery.

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