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Prognostic Value of Peritoneal Lavage Cytology in Potentially Resectable Pancreatic Cancer Stratified by Cytologic Status

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Abstract. *Background/Aim: Patients with pancreatic ductal adenocarcinoma (PDAC) with positive peritoneal lavage cytology (CY) reportedly have poor prognoses. However, the value of diagnosis of suspicious for malignancy on CY is unknown. This study aimed to elucidate the prognostic impact of CY by focusing on CY subgroups. Patients and Methods: Data were collected from 231 resectable PDAC patients who underwent curative-intent resection. Patients were divided into three CY-based groups: negative (CY0), suspicious for malignancy (CY-S), and positive (CY1). Clinicopathological characteristics and prognostic factors were analyzed. Results: CY1 and CY-S were diagnosed in 7.8% and 3.9% of the patients, respectively. The CY1 group had significantly larger tumors and higher frequencies of distal tumors, anterior pancreatic tissue invasion, retropancreatic tissue invasion, and R1 resection than the CY0 group. Patient characteristics did not differ between the CY0 and CY-S groups. The CY1 group exhibited worse survival than the CY0 and CY-S groups (median survival time: 18.8 vs. 39.6 months, p=0.0021 and vs. 62.2 months, p=0.018). Multivariate analysis for survival indicated that a tumor size >2 cm, preoperative CA19-9 value >100 U/ml, CY1, lymph node metastasis, R1 resection, and lack of adjuvant chemotherapy were associated with poor prognosis. Both the CY1 and CY-S groups had higher frequencies of peritoneal recurrence than the CY0 group (50% vs. 11.8%, p<0.001 and 44.4% vs. 11.8%, p=0.019). Conclusion: The prognosis of the CY1 group was poor. Although CY-S was associated with a higher frequency of peritoneal recurrence than CY0, the long-term outcomes of patients with surgical treatment were acceptable.*

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Key Words: Pancreatic cancer, peritoneal lavage cytology, suspicious for malignancy.

Pancreatic cancer is one of the most lethal diseases and the fourth leading cause of cancer-related deaths in the United States (1). In 2023, an estimated 64,050 people will be diagnosed with pancreatic cancer, and approximately 50,550 will die from the disease in the United States (1). Although surgery is the only curative treatment for this disease, most patients develop recurrence after resection, including peritoneal dissemination.

Peritoneal lavage cytology (CY) can be performed to explore microscopically disseminated cancer cells. The clinical implications of CY in pancreatic cancer have been debated over the past few decades. Although some studies suggest that a positive CY result is not associated with adverse outcomes and that resection is still recommended (2, 3), many others have indicated that a positive CY result is associated with a poor prognosis for patients who undergo surgery (4-12). According to the American Joint Committee on Cancer and the National Comprehensive Cancer Network (NCCN) guidelines, a positive CY result is defined as M1 disease (13, 14). Although the Japan Pancreas Society has not included CY in tumor staging (15), the latest clinical practice guidelines for pancreatic ductal adenocarcinoma (PDAC) with peritoneal dissemination in Japan state that upfront surgery is not recommended for patients with a positive CY result (16).

In our institution, we used to perform surgery for patients with potentially resectable PDAC regardless of CY status because of the lack of strong evidence to preclude surgery for patients with positive CY results. However, based on the latest guidelines, as mentioned above, we changed the treatment

strategy starting July 2022, and patients with positive CY results are no longer indicated for surgery without preoperative therapy. Nevertheless, whether surgery should be abandoned when atypical cells suspected but not confirmed to be malignant are observed in patients with resectable PDAC remains unclear. That is, whether the diagnosis of suspicious for malignancy should be considered a negative or positive CY result, is an important question for surgeons when making intraoperative decisions in clinical practice. Therefore, we conducted a single-center, retrospective cohort study with the aim of clarifying the prognostic value of CY in patients with resectable PDAC by focusing on CY status, including the diagnosis of suspicious for malignancy.

Patients and Methods

Study design and data collection. We retrospectively reviewed clinical data that had been prospectively collected from 245 consecutive Japanese patients who underwent curative-intent surgery for resectable PDAC from January 2007 to June 2022 at Saitama Cancer Center. Five patients who underwent simultaneous treatment for other malignancies, four with PDAC in the remnant pancreas, and five without recurrence data were excluded. Finally, 231 patients were enrolled in this study, which was approved by the Institutional Ethics Committee of Saitama Cancer Center (approval number: SCC-1420).

Surgery and perioperative therapy. Resectability was assessed using computed tomography, according to the NCCN guidelines (14). Upfront surgery was performed in patients with resectable PDAC from 2007 to 2018. Since 2019, neoadjuvant gemcitabine and S-1 therapy was administered to patients <80 years of age, based on the results of the Prep-02/JSAP-05 study (17). We performed surgery regardless of CY status during the study period. Macroscopic peritoneal dissemination and liver metastasis were deemed contraindications for surgery. Adjuvant chemotherapy (AC) was included as a part of the standard treatment strategy, when applicable. Gemcitabine was administered from 2007 to 2011 (18), whereas S-1 was primarily administered from 2012 to the end of the study period, based on the results of the JASPAC-01 study (19).

CY. In the beginning of surgery, CY was performed using 50 ml of normal saline in the pouch of Douglas for all patients. The peritoneal lavage fluid was examined using conventional Papanicolaou and Giemsa staining in our Pathology Department and evaluated by experienced pathologists. Patients were divided into three groups based on their CY status: negative (CY0), suspicious for malignancy (CY-S), and positive (CY1). In terms of Papanicolaou classification, class II was deemed the same as CY0, class III as CY-S, and classes IV and V as CY1.

Pathological evaluation. Pathological evaluation was performed to detect tumor invasion of the serosal tissue on the anterior surface of the pancreas (S); retropancreatic tissue (RP); portal vein and splenic vein (PV); arterial system, including the superior mesenteric artery, celiac axis, common hepatic artery, and splenic artery (A); extrapancreatic nerve plexus (PL); and other organs (OO), as well as to detect lymph node metastasis. The resection margin status was directly determined. R1 was defined as cancer infiltration at the pancreatic cut-end margin or at the dissected peripancreatic tissue margins, whereas R0 was defined as the absence of cancer infiltration along all margins.

Statistical analyses. The data are presented as totals, medians (ranges), or percentages (95% confidence intervals). Continuous variables are expressed as medians with ranges and were compared using the Mann–Whitney *U*-test. Fisher's exact test was used to compare categorical variables. The Kaplan–Meier method was used to estimate overall survival (OS) and recurrence-free survival (RFS). OS was calculated from the date of the start of the initial treatment to the date of the last follow-up or death from any cause. RFS was calculated from the date of the surgery in which peritoneal lavage CY was performed to the date of the last follow-up or diagnosis of recurrence. The log-rank test was used to analyze differences in survival. The Cox proportional-hazards model was used to evaluate prognostic variables for multivariate analysis. Statistical significance was defined as a p-value <0.05. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Specifically, the interface is a modified version of R Commander, designed to add statistical functions frequently used in biostatistics (20).

Results

Comparison of characteristics according to CY status. Among the 231 patients enrolled in this study, 18 (7.8%) and 9 (3.9%) were classified as CY1 and CY-S, respectively. We compared the patients' characteristics according to their CY status (Table I). The CY1 group had larger tumors (40 *vs*. 30 mm, p=0.012) and higher frequencies of distal tumors (66.7% *vs*. 34.8%, p=0.01), anterior pancreatic tissue invasion (83.3% *vs*. 53.4%, p=0.023), retropancreatic tissue invasion (94.4% *vs*. 69.1%, p=0.027), and R1 resection (44.4% *vs*. 18.1%, p=0.014) than the CY0 group. No significant differences were observed between the CY0 and CY-S groups.

Survival analyses. The median follow-up period after initial treatment was 25.3 months (range=2.0-150.0 months). During the study period, 135 patients (58.4%) died, and recurrence was observed in 158 patients (68.4%). The OS and RFS were compared according to patients' CY status. Figure 1 shows the Kaplan–Meier curves for the included patients. The CY1 group exhibited worse survival than the CY0 and CY-S groups [median survival time (MST): 18.8 *vs*. 39.6 months, p=0.0021 and 18.8 *vs*. 62.2 months, p=0.018]. The median RFS of the CY0, CY-S, and CY1 groups was 15.2, 12.0, and 8.6 months, respectively. The CY1 group exhibited a significantly worse RFS than the CY0 group (p<0.001). The difference in RFS between the CY-S and CY0 groups and that between the CY-S and CY1 groups were not statistically significant. AC was associated with a better prognosis of patients for each CY status (Figure 2). The CY1 group with AC exhibited better survival than that without AC (MST: 20.5 *vs*. 8.6 months, p<0.001). Multivariate analysis for survival indicated that a

Table I. *Clinicopathological characteristics according to the peritoneal lavage cytology (CY) status.*

Factor		CY0 n=204	CY-S n=9	CY1 n=18	*p*-Value CY0 *vs.* CY-S	*p*-Value CY0 *vs.* CY1
Age, median (range), year		72 (47, 87)	70 (50, 83)	73 (55, 89)	0.89	0.49
Sex, n(%)	Male	96 (47.1)	4 (44.4)	11 (61.1)	1	0.33
	Female	108 (52.9)	5 (55.6)	7 (38.9)		
Tumor location, n(%)	Head	133 (65.2)	5 (55.6)	6 (33.3)	0.72	0.01
	Body/Tail	71 (34.8)	4 (44.4)	12 (66.7)		
Preoperative CA19-9, median (range), U/ml		166 (2-61,406)	288 (21-2,554)	667 (2-2,423)	0.41	0.32
Preoperative chemotherapy, n(%)	Yes	32 (15.7)	3 (33.3)	4 (22.2)	0.17	0.5
	No	172 (84.3)	6 (66.7)	14 (77.8)		
Operation, n(%)	PD	132 (64.7)	5 (55.6)	6 (33.3)	0.74	0.02
	DP	71 (34.8)	4 (44.4)	12 (66.7)		
	TP	1 (0.5)	0	0		
Vascular resection, n(%)		53 (26)	3 (33.3)	7 (38.9)	0.7	0.27
Approach	Open	193 (94.6)	9 (100)	18 (100)	1	0.61
	Laparoscopic	11 (5.4)	0	0		
Operation time, median (range), min		405 (135-790)	370 (186-763)	353 (181-659)	0.34	0.39
Blood loss, median (range), ml		698 (26-5729)	458 (143-2,468)	465 (101-5,322)	0.082	0.36
Postoperative hospital stay, median (range), days		22 (9-125)	16 (12-40)	23 (11, 32)	0.27	0.64
Complication ≥ CD grade 3, n(%)		40 (24.5)	2 (22.2)	7 (43.8)	1	0.13
Adjuvant therapy	Yes	150 (73.5)	8 (88.9)	14 (77.8)	0.45	0.79
	No	54 (26.5)	1 (11.1)	4 (22.2)		
S invasion, n(%)	Negative	95 (46.6)	3 (33.3)	3 (16.7)	0.51	0.023
	Positive	109 (53.4)	6 (66.7)	15 (83.3)		
RP invasion, n(%)	Negative	63 (30.9)	2 (22.2)	1 (5.6)	0.73	0.027
	Positive	141 (69.1)	7 (77.8)	17 (94.4)		
Artery invasion, n(%)	Negative	191 (93.6)	7 (77.8)	16 (88.9)	0.13	0.35
	Positive	13 (6.4)	2 (22.2)	2 (11.1)		
PV invasion, n(%)	Negative	150 (73.5)	7 (77.8)	9 (50)	1	0.053
	Positive	54 (26.5)	2 (22.2)	9 (50)		
PL invasion, n(%)	Negative	171 (83.8)	9 (100)	16 (88.9)	0.36	0.75
	Positive	33 (16.2)	0	2 (11.1)		
OO invasion, n(%)	Negative	195 (95.6)	9 (100)	16 (88.9)	1	0.22
	Positive	9 (4.4)	0	2 (11.1)		
Tumor size, median (range), mm		30 (3-125)	30 (20-42)	40 (18-75)	0.97	0.012
Pathological type	Well	69 (33.8)	4 (44.4)	3 (16.7)	0.62	0.17
	Moderate	111 (54.4)	5 (55.6)	14 (77.8)		
	Poor	24 (11.8)	0	1 (5.6)		
Retrieved LN, median (range)		30 (4-86)	30 (13-63)	42 (14-63)	0.51	0.083
Metastatic LN, median (range)		1 (0-15)	1 (0-8)	2 (0-5)	0.53	0.77
LN status, n(%)	Negative	79 (38.7)	2 (22.2)	6 (33.3)	0.49	0.8
	Positive	125 (61.3)	7 (77.8)	12 (66.7)		
pT, UICC8th, n(%)	1	49 (24)	3 (33.3)	1 (5.6)	0.61	0.12
	2	106 (52)	5 (55.6)	10 (55.6)		
	3	49 (24)	1 (11.1)	7 (38.9)		
pN, UICC8th, n(%)	0	79 (38.7)	2 (22.2)	6 (33.3)	0.43	0.58
	1	75 (36.8)	5 (55.6)	12 (66.7)		
	2	50 (24.5)	2 (22.2)	0		
Resection margin, n(%)	R0	167 (81.9)	8 (88.9)	10 (55.6)	1	0.014
	R1	37 (18.1)	1 (11.1)	8 (44.4)		

CA19-9: Carbohydrate antigen 19-9; CY: peritoneal lavage cytology; CY0: negative; CY-S: suspicious for malignancy; CY1: positive; S: serosal side of the anterior pancreatic tissue; RP: retropancreatic tissue; PL: extrapancreatic nerve plexus; OO: other organs; LN: lymph node.

tumor size >2 cm [hazard ratio (HR)=2.40, p=0.0038], preoperative CA19-9 value >100 U/ml (HR=1.64, p=0.015), CY1 (HR=2.17, p=0.015), lymph node metastasis (HR=1.77, p=0.0034), R1 resection (HR=1.96, p=0.0044), and lack of AC (HR=3.91, p<0.001) were associated with a poor prognosis (Table II).

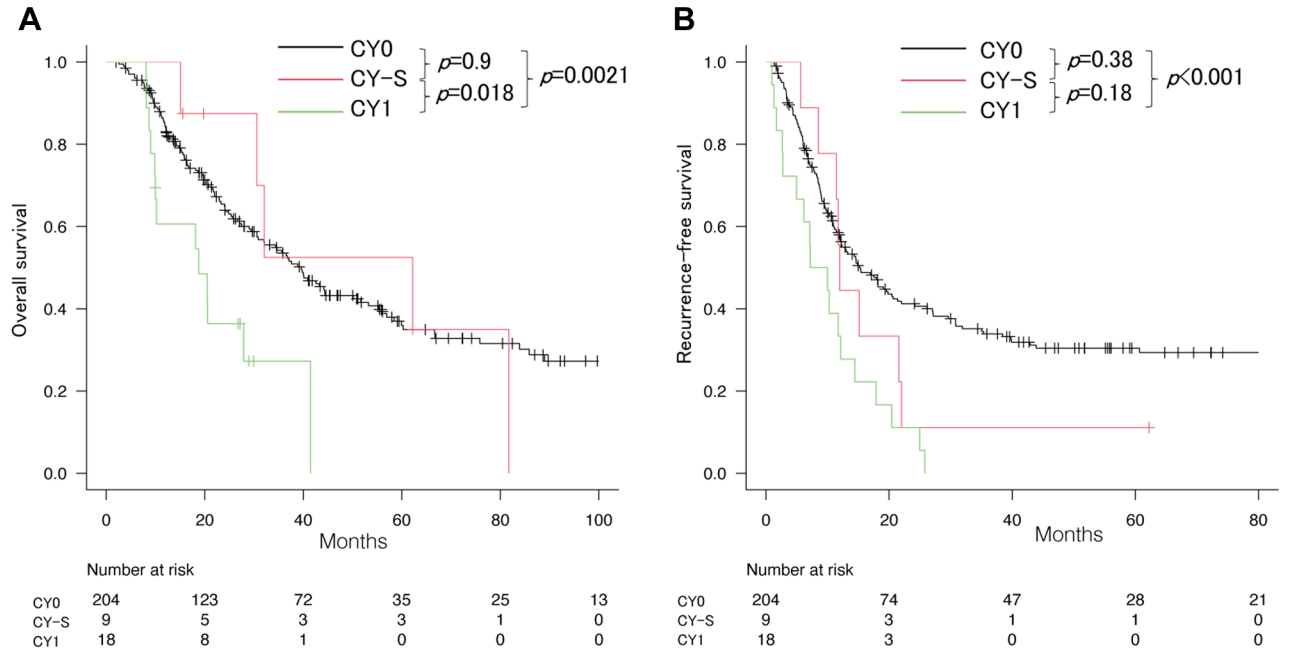


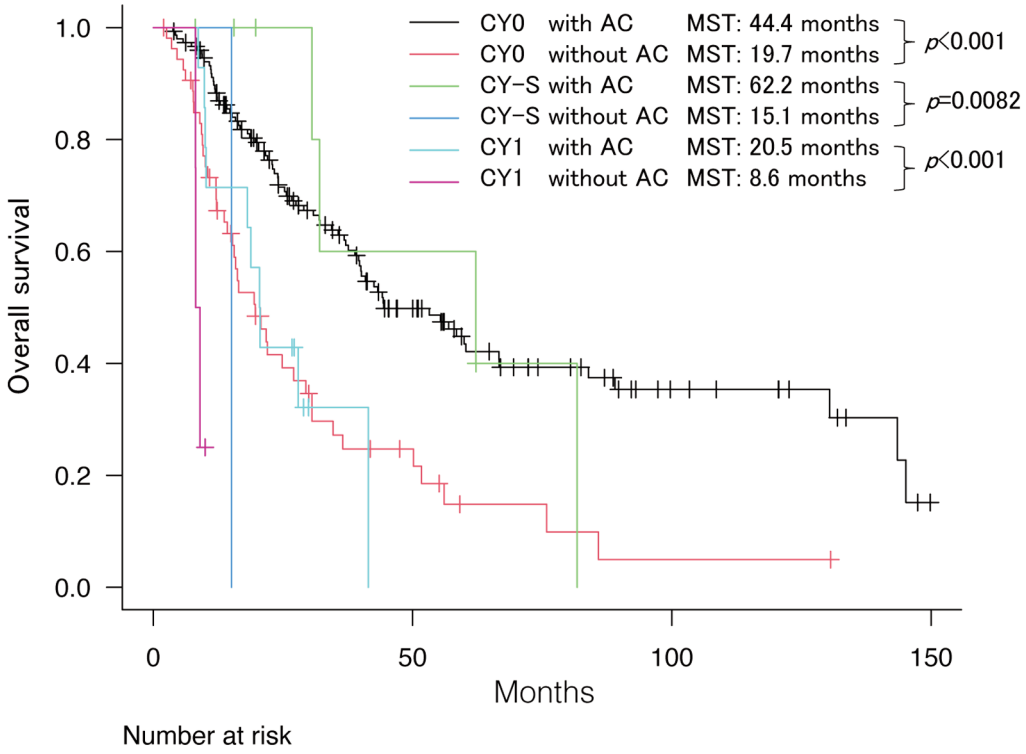
Figure 1. *Comparison of overall survival (A) and recurrence-free survival (B) rates according to the subgroup of peritoneal lavage cytology (CY): negative (CY0), suspicious for malignancy (CY-S), and positive (CY1).*

Comparison of recurrence pattern. The primary site of recurrence according to the CY status is summarized in Table III. Both the CY1 and the CY-S groups exhibited a higher frequency of peritoneal recurrence than the CY0 group (50% *vs*. 11.8%, $p<0.001$ and 44.4% *vs*. 11.8%, $p=0.019$, respectively).

Discussion

The prognostic impact of CY1 in PDAC and the surgical indications for such patients have been controversial for decades. Several studies suggested that CY1 is not a prognostic factor, and that surgical resection is recommended even for CY1 patients (2, 3, 21). However, many other studies have revealed that CY1 is associated with a poorer prognosis (4-12, 22). Among them, two studies suggested that the prognosis of patients with CY1 who undergo surgical resection is better than that of patients with CY1 who do not undergo resection, and, thus, that surgery should not be precluded (5, 7). In a recent, large-scale, nationwide, retrospective study in Japan, Tsuchida *et al*. (9) reported that prognosis was significantly worse in the CY1 group than in the CY0 group, with MSTs of 17.5 and 29.4 months, respectively ($p<0.001$), and that CY1 was an independent, negative prognostic factor. They also reported that curative resection followed by adjuvant therapy may improve the long-term prognosis of patients with CY1, as the prognosis of patients who underwent adjuvant therapy was better than those who did not (MST: 18.2 *vs*. 12.6 months; $p<0.04$). However, a meta-analysis by Cao *et al*. (23) revealed that CY1 was associated with an advanced tumor stage and a poor prognosis, and that radical resection should not be performed in such patients with PDAC. In this study, patients with CY1 had a significantly worse survival than those with CY0, and AC was associated with a longer survival in both groups, which was compatible with the results in recent studies (9, 11).

Adjuvant therapy is considered an important factor in prolonging the survival of patients with PDAC and CY1. In Japan, S-1 has been the standard regimen of adjuvant therapy in recent years, following the results of the JASPAC-01 study (19). As the two large-scale, nationwide studies to investigate the prognostic outcomes of patients with CY1 in Japan included patients who were treated until 2012, the outcomes following the change in the standard regimen of adjuvant therapy were unknown (6, 9). Todaka *et al*. (24) investigated the survival outcomes of patients with CY1 who received gemcitabine or S-1 after resection, and revealed that the MSTs of the S-1 and gemcitabine groups were 21.0 and 19.2 months ($p=0.23$), respectively. Therefore, S-1 is considered insufficient to prolong the survival of patients with CY1 in clinical practice in Japan. As the standard AC is considered insufficient, further development of intensive adjuvant therapy after resection is required. Although the PRODIGE 24/CCTG PA.6 trial revealed that adjuvant



Number at risk

CY0 with AC	150	46	12	0
CY0 without AC	54	8	1	0
CY−S with AC	8	3	0	0
CY−S without AC	1	0	0	0
CY1 with AC	14	0	0	0
CY1 without AC	4	0	0	0

Figure 2. *Comparison of overall survival rate according to the subgroup of peritoneal lavage cytology [negative (CY0), suspicious for malignancy (CY-S), and positive (CY1)] and adjuvant chemotherapy (AC). MST: Median survival time.*

therapy with a modified FOLFIRINOX regimen (leucovorin calcium, fluorouracil, irinotecan hydrochloride, and oxaliplatin) led to a significantly longer survival than gemcitabine in patients with resected pancreatic cancer (25), this regimen has not been approved as adjuvant chemotherapy in Japan, and no reports of promising results in the patients with resected PDAC with CY1 who received this modern regimen as adjuvant therapy have been made.

A different approach for patients with CY1 is preceding systemic therapy combined with resection. The latest guidelines from Japan state that upfront surgery is not recommended for patients with PDAC and CY1 (16). Ariake *et al*. (26) reported promising results of a treatment strategy in which patients with CY1 were scheduled for surgical resection after the introduction of gemcitabine plus nab-paclitaxel therapy and confirmation of negative conversion of CY status. The MST of their entire cohort was 31.4 months, and the prognosis of patients who underwent conversion surgery was significantly better than that of those who did not. The authors suggested that avoiding upfront surgery but instituting preceding systemic chemotherapy may improve the prognosis of patients with CY1, especially those with potentially resectable PDAC. In our study, CY1 was an independent, negative prognostic factor, and the prognosis of patients who did not receive adjuvant therapy was poor. As the tolerability of aggressive therapy in PDAC patients with CY1 after resection is unknown, we consider CY1 as M1 disease, deeming systemic chemotherapy necessary before radical resection is planned for such patients. Further evaluation of indications and timing of surgery for initially resectable PDAC with CY1 after systemic therapy is required in future studies.

The intraoperative diagnosis of CY1 is challenging to interpret. In certain previous studies, patients were divided

Table II. *Univariate and multivariate analyses of risk factors for survival*.

		Univariate		Multivariate	
Factor	n	Hazard ratio (95%CI)	*p*-Value	Hazard ratio (95%CI)	*p*-Value
Age					
≤70 yr	109	1			
>70 yr	122	1.3 (0.92-1.82)	0.135		
Sex					
Female	120	1		1	
Male	111	1.43 (1.02-2.01)	0.041	1.32 (0.94-1.87)	0.11
Tumor location					
Ph	144	1			
Pb/Pt	87	1.34 (0.94-1.91)	0.1		
Pathological type					
Well/mod	206	1			
Poor	25	1.45 (0.89-2.35)	0.14		
Preoperative CA19-9					
≤100 U/ml	95	1		1	
>100 U/ml	136	1.67 (1.17-2.39)	0.0046	1.64 (1.10-2.43)	0.015
Preoperative therapy					
No	192	1			
Yes	39	0.57 (0.3-1.1)	0.094		
Tumor size					
≤20 mm	55	1		1	
>20 mm	176	2.49 (1.45-4.26)	<0.001	2.40 (1.33-4.34)	0.0038
CY					
CY0	204	1		1	
CY-S	9	0.95 (0.39-2.3)	0.91	1.28 (0.51-3.18)	0.6
CY1	18	2.5 (1.39-4.49)	0.0023	2.17 (1.16-4.07)	0.015
S invasion					
Negative	101	1		1	
Positive	130	1.64 (1.15-2.33)	0.0065	1.36 (0.91-2.01)	0.13
RP invasion					
Negative	66	1		1	
Positive	165	1.51 (1.03-2.21)	0.036	0.90 (0.57-1.41)	0.63
Artery invasion					
Negative	214	1			
Positive	17	1.4 (0.75-2.6)	0.29		
PV invasion					
Negative	166	1		1	
Positive	65	1.54 (1.07-2.22)	0.019	0.95 (0.64-1.43)	0.82
PL invasion					
Negative	196	1			
Positive	35	1.52 (0.99-2.36)	0.059		
LN metastasis					
Negative	92	1		1	
Positive	139	1.68 (1.17-2.42)	0.005	1.77 (1.21-2.60)	0.0034
Resection margin					
R0	185	1		1	
R1	46	2.03 (1.37-3.02)	<0.001	1.96 (1.23-3.11)	0.0044
Adjuvant therapy					
Yes	122	1		1	
No	49	2.58 (1.79-3.71)	<0.001	3.91 (2.59-5.89)	<0.001

CA19-9: Carbohydrate antigen 19-9; CY: peritoneal lavage cytology; CY0: negative; CY-S: suspicious for malignancy; CY1: positive; S: serosal side of the anterior pancreatic tissue; RP: retropancreatic tissue; PL: extrapancreatic nerve plexus; LN: lymph node.

Table III. *Recurrence pattern according to the peritoneal lavage cytology (CY) status.*

Primary site of recurrence	CY0 n=204	CY-S n=9	CY1 n=18	*p*-Value CY0 *vs*. CY-S	*p*-Value CY0 *vs*. CY1
Peritoneum	24 (11.8)	4 (44.4)	9 (50)	0.019	<0.001
Liver	43 (21.1)	3 (33.3)	5 (27.8)	0.41	0.551
Local	35 (17.2)	1 (11.1)	4 (22.2)	1	0.53
Lymph node	21 (10.3)	0	3 (16.7)	0.6	0.422
Lung	25 (12.3)	1 (11.1)	2 (11.1)	1	1

CY0: Negative; CY-S: suspicious for malignancy; CY1: positive.

into two groups based on CY status: negative and positive, whereas other researchers added a third group, comprising patients with only atypical cells, but excluded such patients from their survival analyses (21, 22). Additionally, the frequency and clinical value of CY-S have not been reported. However, a diagnosis of suspicious for malignancy is not rare. In fact, the frequency of CY-S was half that of CY1 in this study. Furthermore, considering the recent reports support the preclusion of upfront surgery for PDAC patients with CY1 (16), the prognostic impact of CY-S in patients with potentially resectable PDAC is an important issue for surgical decision-making. Therefore, in contrast to previous studies, we investigated the clinical value of CY, including patients with CY-S as an independent group. In this study, the CY-S and CY0 groups did not differ in terms of clinicopathological factors. Although the prognosis of the CY-S group was comparable to that of the CY-0 group, the frequency of peritoneal recurrence was significantly higher in the CY-S group than that in the CY-0 group. Based on our results, patients with CY-S may be reasonably viewed as candidates for surgery. However, surgeons should keep in mind that R0 resection and smooth introduction of adjuvant therapy, with careful monitoring for peritoneal recurrence, are important when intraoperative CY is diagnosed as CY-S.

This study has several limitations, including its single-center, retrospective design, relatively small sample, and inclusion of patients with heterogeneous characteristics. However, considering the low prevalence of PDAC patients with CY-S and CY1, our results may provide surgeons with valuable information for decision-making. Additionally, the diagnosis of CY in this study was somewhat subjective because no routine immunohistochemical evaluation was performed. Nevertheless, the single-center design of this study is also one of its strengths, as evaluations were performed by the same board-certified pathologists, reducing variation in diagnoses. A prospective study with a large sample and expert central review for CY diagnosis is required to determine whether CY-S should be classified as CY0 or CY1 or as an independent subgroup.

In conclusion, the prognosis of patients with potentially resectable PDAC with CY1 who underwent surgery was poor, and the development of other treatment strategies combined with more aggressive systemic therapy may be required. Although patients with CY-S had a higher frequency of peritoneal recurrence than patients with CY0, surgery for CY-S was acceptable as the long-term outcome was comparable with that of patients with CY0. Therefore, patients with CY-S should be treated with the same treatment strategy as those with CY0.

Conflicts of Interest

The Authors declare that they have no conflicts of interest that are directly relevant to the content of this study.

Authors' Contributions

Conception and design of the work: Hiroyuki Ishida, Toshiro Ogura. Data analysis and interpretation: Hiroyuki Ishida, Toshiro Ogura, Amane Takahashi, Kei Kitamura, Ryoichi Miyamoto, Shinichi Matsudaira, Hiroaki Kanda. Writing - original draft: Hiroyuki Ishida. Writing – review and editing: Toshiro Ogura, Amane Takahashi, Hiroaki Kanda. Supervision: Minoru Tanabe, Yoshiyuki Kawashima. All Authors reviewed the results and approved the final version of the manuscript.

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