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Prognostic importance of peritoneal washing cytology in patients with otherwise resectable pancreatic ductal adenocarcinoma who underwent pancreatectomy: A nationwide, cancer registry–based study from the Japan Pancreas Society

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ABSTRACT

Background: The importance of peritoneal washing cytology status both as a sign of irresectability and as a prognostic factor for pancreatic ductal adenocarcinoma remains controversial. The purpose of this nationwide, cancer registry–based study was to clarify the clinical implications of operative resection in patients who had positive cytology status.

Methods: Clinical data from 1,970 patients who underwent tumor resection were collected from the Pancreatic Cancer Registry in Japan. Clinicopathologic factors and overall survival curves were analyzed, and multivariate Cox proportional hazard models were evaluated.

Results: Among the 1,970 patients analyzed, positive cytology status was found in 106 patients and negative cytology status was found in 1,864 patients. The positive cytology status group had a greater

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frequency of pancreatic body and tail cancer and greater preoperative serum carbohydrate antigen 19-9 levels than the negative cytology status group ($P < .001$ each). The ratio of peritoneal recurrence tended to be greater in the positive cytology status group (14% *vs* 43%; $P < .001$). Overall median survival times were less in the positive cytology status group (17.5 months vs 29.4 months; $P < .001$). The 5-year survival rates were 13.7% and 31.1% in the positive cytology status and negative cytology status groups, respectively. Multivariate analysis of positive cytology status patients revealed that adjuvant chemotherapy was an independent prognostic factor.

Conclusion: Positive cytology status was an adverse prognostic factor in patients who underwent resection for pancreatic ductal adenocarcinoma but did not preclude attempted curative resection. Curative resection followed by adjuvant chemotherapy may contribute to long-term prognosis in patients with positive cytology status.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the third and fourth leading cause of cancer-related mortality in the United States and Japan, respectively, and is associated with a poor prognosis even after curative resection.[1,2] With insufficient improvements in early detection and options for curative treatment, PDAC is projected to become the second leading cause of cancer-related death by the year 2030.[3,4]

Peritoneal washing cytology (CY) has been included in the guidelines for the staging of several cancers, such as ovarian and gastric cancers,[5-8] because of the adverse effect on survival. To date, positive CY status (CY+) in patients with resectable PDAC is defined as M1 and stage IV disease according to the criteria of the American Joint Committee on Cancer (AJCC) and the National Comprehensive Cancer Network (NCCN).[6-9] However, the importance of CY status both as a sign of irresectability and as a prognostic factor for PDAC remains controversial. The incidence of CY+ was reported to be 5% to 30% in otherwise resectable cases[10-23] and 20% to 57% in unresectable cases.[12-15,23] Several previous studies have reported that the overall survival (OS) of patients who were CY+ was less than patients who were CY−.[10,14,17-19,21-25] In contrast, other studies have reported that CY status was not associated with patient prognosis after curative resection for pancreatic cancer.[11-13,15,16,20] The problem is that the number of patients who were CY+ was too small, with most studies having fewer than 20 of these patients and most studies being conducted within a single institution. Satoi et al[18] reported on a multi-institutional study with 69 CY+ patients, the largest sample in previous studies. Because no prospective studies or randomized controlled trials have investigated this issue, the validity of operative resection in patients who are CY+ has not been clarified. Thus, the Japanese General Rules for the Study of Pancreatic Cancer have not yet included CY status for tumor staging.[8,26]

In this study, we used a well-maintained, nationwide database of patients with PDAC to evaluate the relationship among CY status, clinical factors, and overall survival and to clarify the clinical implications for operative resection in patients who are CY+ status. No other previous studies have analyzed such a large-scale database.

Methods

Study design

We analyzed retrospectively a large database from the Pancreatic Cancer Registry, a nationwide registry hosted by the Japan Pancreas Society. Since 1981, >350 medical institutions in Japan have contributed voluntarily to this registry.[4] This study is a project of the Committee of Clinical Research and is conducted with the cooperation of the Committee for Pancreatic Cancer Registry of Japan Pancreas Society. This study conforms to the ethical guidelines of the World Medical Association Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects. The institutional internal review board approved this study.

Samples

Peritoneal washing samples were collected during operations for PDAC according to the Japanese General Rules for the Study of Pancreatic Cancer.[26] Immediately after laparotomy, 100 mL of isotonic heparinized 0.9% NaCl was introduced into the pelvis. After gentle agitation, as much fluid as possible was collected using a syringe. Smears were made from the centrifuged deposit and examined by at least 2 experienced pathologists after conventional Papanicolaou and Giemsa staining. All surgical specimens were examined histopathologically after fixing and staining with hematoxylin and eosin. Patients who had liver metastases or peritoneal dissemination at laparotomy were excluded from this analysis. Postoperative adjuvant chemotherapy was applied unless contraindicated by the patient's condition. In short, the patients received gemcitabine or S-1 for 6 months according to the protocol that was available at the time of treatment. Measurement of serum tumor markers and computed tomography (CT) were performed every 3 to 6 months.

Factors evaluated

The primary endpoint of this study was OS. The secondary endpoints were the presence or absence of recurrence, classification of the primary site of recurrence classification, operative outcomes, such as duration of hospital stay, mortality within 30 days after resection, and pathologic data (histological type, T and N status according to the eighth Union for International Cancer Control [UICC] TNM classification).[8]

The records for PDAC that were registered in the Pancreatic Cancer Registry from January 2008 to December 2012 were used. The data included age, sex, comorbidities, family history of cancer, smoking history, tumor diameter, serum carbohydrate antigen (CA) 19-9 level, CY results, operative procedure, the existence of the combined resection of other organs, the residual tumor (R) classification,[8] pathologic diagnosis, duration of hospital stay, in-hospital death within 30 days after resection, and postoperative adjuvant chemotherapy. Patients who did not undergo peritoneal washing cytology and those who underwent neoadjuvant treatment were excluded from our analysis.

Table I
Clinical characteristics of the enrolled patients

	CY− (n = 1,864)	CY+ (n = 106)	P value
Age (years)*	67.9 ± 9.5	68.5 ± 9.6	.694
Sex (male/female)	1,033/827	66/40	.175
Family history of cancer	486	27	.977
Family history of PDAC	90	4	.646
No smoking history	990	55	.383
Comorbidity			
Diabetes mellitus	518	32	
Acute pancreatitis	72	3	
Chronic pancreatitis	48	3	
Cholelithiasis	112	2	
Chronic alcoholism	16	1	
Peptic ulcer	90	6	
Multiple primary malignancy	354 (19%)	24 (23%)	.374
Preoperative biliary drainage	633 (34%)	18 (17%)	<.001
Tumor location			<.001
Head	1,228 (66%)	36 (34%)	
Body-tail	614 (33%)	68 (64%)	
Entire	16 (1%)	1 (1%)	
Tumor diameter (mm)*	31.8 ± 14.4	42.5 ± 22.9	<.001
Preoperative CA19-9 level (U/mL)*	875 ± 3,601	3,854 ± 21,921	<.001

* Values are mean ± standard deviation.

Statistical analysis

Categorical variables were compared by a χ^2 test. Continuous variables were expressed as medians ± standard deviations and were compared using Student t test or the Mann-Whitney U test if the distribution was abnormal. Goodness of fit was assessed by calculating the area under the curve of the receiver operating characteristic curve, and the optimal cut-off value was determined using the Youden index. Univariate and multivariable logistic regression models were used to determine the factors associated with survival. Relative risks were expressed as hazard ratios and 95% confidence intervals. Survival time was defined as the interval between the day of operation and patient death or the last visit to the hospital. Survival was censored if the patient was still alive at the time of follow-up or had died of other causes. The median follow-up time was 22.8 months (range, 0.3–77.1 months). Survival probability was calculated using the Kaplan-Meier method, and differences in survival curves were compared with a log-rank test. Statistical analyses were performed using JMP Pro 14.1.0 (SAS Institute Inc., Cary, NC) and GraphPad Prism version 5.02 (GraphPad Software, San Diego, CA).

Additional analysis of neoadjuvant chemotherapy

To assess the effect of neoadjuvant chemotherapy in the CY+ group, 14 CY+ patients who underwent neoadjuvant chemotherapy were added. Neoadjuvant chemotherapy including gemcitabine or S-1 was administered according to the physician's discretion.

Results

Patient characteristics

A total of 1,970 patients in the Pancreatic Cancer Registry in Japan who underwent tumor resection from January 2008 to December 2012 were enrolled in this study. The clinical characteristics are shown in Table I. CY+ status was present in 106 patients, and CY− status in 1,864 patients. Preoperative biliary drainage was performed more frequently in the CY− group (P < .001). Patients with CY+ had a greater frequency of pancreatic body and tail cancer, had greater tumor diameters, and greater preoperative CA19-9 levels than did patients in the CY− group (P < .001 each). The existence of comorbidities and multiple primary malignancies did not differ between the 2 groups. No differences were observed in several other parameters, including age, sex, family history, or smoking history, between the 2 groups.

Operative results and recurrence

Table II shows the operative and pathologic outcomes in each group. The ratio of the type of operation differed between the 2 groups; pancreatoduodenectomy was performed more frequently in patients who were CY−, whereas the ratio of patients who underwent distal pancreatectomy was greater in the CY+ group (P < .001), resulting from a high frequency of CY+ in patients with pancreatic body and tail cancer. The percentage of patients who had concomitant arterial resection was also greater in the CY+ group (P < .001), whereas concomitant portal vein resection was not. Patients in the CY+ group were more frequently classified as T3 and T4 in the UICC T category than were those in the CY− group (P < .001). The percentage of pathologic positive lymph nodes tended to be less in the CY− group (P = .069). R0 resection was more frequent in the CY− group (P < .001). The percentage of recurrence was greater in the CY+ group than in the CY− group (75% vs 56%; P < .001). Regarding the recurrence pattern, the ratio of peritoneal recurrence was greater in the CY+ group (P < .001); however, the ratio of local, liver, and lung recurrence was not. No differences were observed between the 2 groups in terms of postoperative hospital stay, mortality, or use of adjuvant chemotherapy.

Peritoneal recurrence

Peritoneal recurrence was considerably greater in the CY+ group (43% vs 14%; P < .001, Table II). Peritoneal recurrence also tended to appear earlier in the CY+ group than in the CY− group (P = .097), with median recurrence times of 6.2 and 7.5 months, respectively. The 1-, 2-, 3-, and 5-year appearance rates of peritoneal recurrences in the patients in whom peritoneal recurrence occurred were 73%, 93%, 98%, and 100%, respectively, in the CY− group and 83%, 98%, 100%, and 100%, respectively, in the CY+ group.

Table II
Operative and pathologic results

	CY− (n = 1,864)	CY+ (n = 106)	P value
Type of operation			<.001
Pancreatoduodenectomy	1,168	30	
Distal pancreatectomy	595	65	
Total pancreatectomy	75	9	
Other	6	0	
Concomitant portal vein resection	505 (27%)	34 (32%)	.230
Concomitant arterial resection	83 (4%)	14 (13%)	<.001
Postoperative hospital stay (days)*	33 ± 47	29 ± 18	.701
In-hospital death within 30 days	8	0	.499
UICC T (Tis/T1/T2/T3/T4)	22/324/1,118/286/108	0/6/47/38/15	<.001
Pathologic positive lymph nodes	1,227 (66%)	78 (74%)	.069
Differentiation (well/moderate/poor)	356/1,055/215	17/68/11	.487
Residual tumor (R0/R1/R2)	1,535/276/35	62/33/9	<.001
Adjuvant chemotherapy	1,367 (73%)	77 (73%)	.602
Recurrence	1,040 (56%)	79 (75%)	<.001
Recurrence pattern†			
Local	405	24	
Liver	463	28	
Peritoneum	269	46	
Lung	186	12	

* Values are mean ± standard deviation.
† Some patients had multiple recurrences.

Survival analysis

The OS rates were considerably better in the CY− group than in the CY+ group, with median survival times (MSTs) of 29.4 and 17.5 months, respectively ($P < .001$; Supplementary Fig 1). The 1-, 2-, 3-, and 5-year survival rates were 81%, 57%, 43%, and 31% in the CY− group and 73%, 33%, 18%, and 14%, respectively, in the CY+ group. Moreover, the OS rates were examined by the UICC T stage (Fig 1). Among patients with T1, T2, and T3 stage tumors, patients who were CY− exhibited markedly greater survival times than the patients who were CY+ (T1; MST: 56 vs 16 months; T2; MST: 28 vs 19 months; and T3; MST: 21 vs 15 months; $P \leq .044$ each). In contrast, no differences were found in the OS between the CY− group and the CY+ group among patients with T4 stage tumors (MST: 20 vs 18 months; $P = .910$).

Multivariate analysis

We also determined the optimal cut-off value of the preoperative serum CA19-9 level to predict CY+ status. Receiver operating characteristic curve analysis revealed that the area under the curve value for the serum CA19-9 level was 0.607 for CY+ and that the optimal cut-off value was 167 U/mL (sensitivity 66%; specificity 58%). The factors predicting survival are shown in Table III. Multivariate analysis showed that positive cytology was an independent prognostic factor (hazard ratio, 1.51; 95% confidence interval, 1.14–2.00; $P = .004$) as were the preoperative CA19-9 level, tumor location, tumor diameter, portal vein resection, pathologic lymph node metastasis, residual tumor, tumor differentiation, and adjuvant chemotherapy. In multivariate analysis of only the patients who were CY+, preoperative CA 19-9 level, tumor differentiation, and adjuvant chemotherapy independently predicted OS (Supplementary Table I).

Association between OS and adjuvant chemotherapy or neoadjuvant chemotherapy

The OS rates were statistically significantly better in patients who underwent adjuvant chemotherapy than in patients who did not (Fig 2). Notably, in the CY+ group, the OS of patients who underwent adjuvant were greater than that of patients who did not, with MSTs of 18.2 and 12.6 months ($P < .04$).

Figure 3 shows the comparison of overall survival between patients who underwent upfront resection and those who underwent neoadjuvant chemotherapy followed by resection in the CY+ group. There was no survival benefit of patients who were CY+ who underwent neoadjuvant chemotherapy.

Discussion

The clinical implications of attempted curative resection in patients with PDAC who are CY+ are still controversial. CY+ is classified as M1 disease by the American Joint Committee on Cancer staging system and NCCN guidelines, whereas the Japanese General Rules for Pancreatic Cancer have not yet included the CY status for staging.[6,8,9,26] In this study, we demonstrated that OS in patients who underwent resection was markedly worse in patients who were CY+ than in patients who were CY− who underwent resection and that peritoneal recurrence appeared earlier in patients who were CY+. When peritoneal recurrence was present in the CY− group, the median recurrence time was only 8 months, and there was no considerable difference compared with the median recurrence time of 6 months in the CY+ group. There is a possibility that the CY results of the peritoneal washing were false negatives or that dissemination of cancer cells occurred during operation.

Several previous studies have reported that CY+ status was associated with a poorer prognosis,[10,14,17-19,21-25] whereas other studies have reported no difference in prognosis between CY+ and CY− patients.[11-13,15,16,20] The weakness of previous studies is that the number of patients who were CY+ was relatively small, approximately 5 to 30, and moreover, most of them were single-institutional studies. The present study analyzed 106 CY+ patients in a nationwide, cancer registry–based study which arguably yield the most realistic results.

In a systematic review, Steen et al[24] reported a probable negative prognostic relationship between CY+ status and survival in patients with PDAC who underwent curative resection. Cao et al[25] also concluded that CY+ was associated with a poor prognosis in their systematic review and meta-analysis; moreover, they suggested that radical resection should not be performed. Yamada et al[17] and Abe et al[22] reported that among the CY+ patients, the

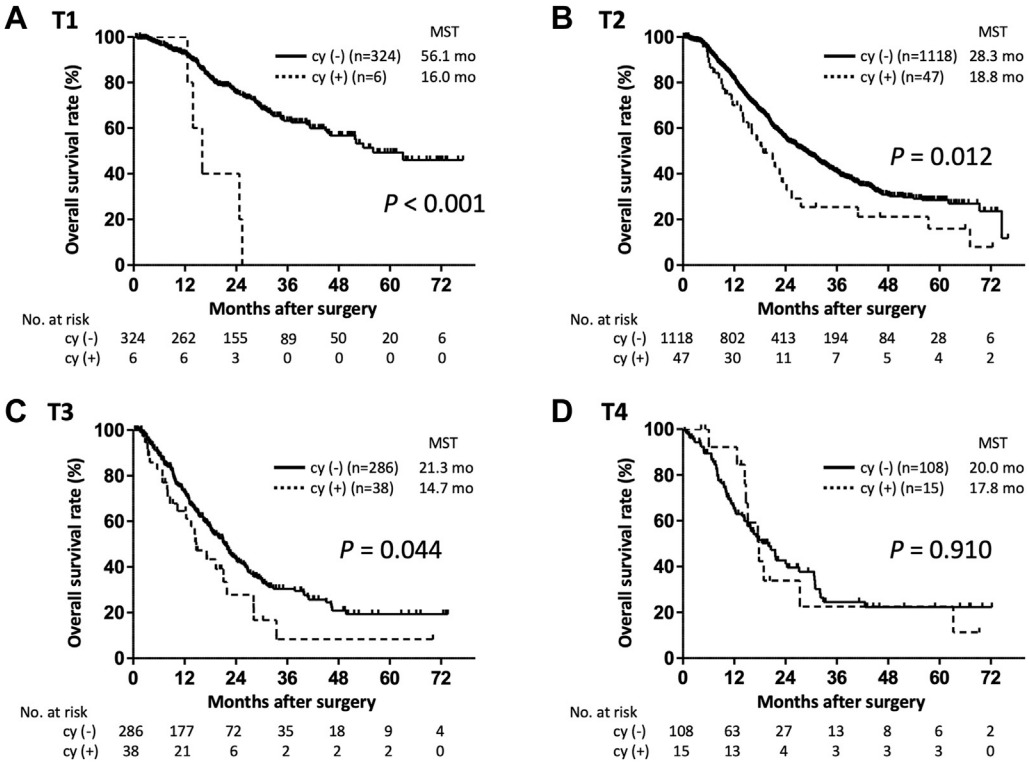

Fig 1. OS of the patients who underwent resection for pancreatic ductal cancer (PDAC) stratified by the cytology status of peritoneal washing and the UICC T stage.

Table III
Predictive factors for survival in patients with PDAC who underwent pancreatectomy

		n		MST (mo)		Univariate			Multivariate		
		CY−	CY+	CY−	CY+	HR	95% CI	P value	HR	95% CI	*P* value
Cytologic status of periotoneal washings	CY+		106		17.5	1.88	1.46–2.38	<.001	1.51	1.14–2.00	.004
	CY−	1,864		29.4							
Preoperative serum CA19-9 level	≥167 U/mL	769	69	22.5	15.2	1.71	1.50–1.94	<.001	1.36	1.17–1.57	<.001
	<167 U/mL	1,047	36	36.1	22.7						
Tumor location	Head	1,228	36	25.6	18.9	1.47	1.28–1.70	<.001	1.32	1.13–1.56	<.001
	Body/tail	614	68	41.3	17.1						
Tumor diameter	≥30 mm	950	69	22.5	17.2	1.75	1.53–2.01	<.001	1.41	1.20–1.65	<.001
	<30 mm	825	38	39.6	17.5						
Portal vein resection	Yes	505	34	21.0	17.8	1.68	1.47–1.93	<.001	1.32	1.12–1.54	<.001
	No	1,328	69	33.6	17.2						
Pathologic LN metastasis	Yes	1,227	78	23.3	19.3	2.00	1.72–2.32	<.001	1.52	1.28–1.81	<.001
	No	622	26	51.8	14.1						
Residual tumor	R0	1,535	62	31.8	17.1	0.52	0.45–0.60	<.001	0.66	0.56–0.79	<.001
	R1, R2	311	42	18.3	17.2						
Tumor differentiation	Well	356	17	34.2	23.1	0.75	0.63–0.89	<.001	0.72	0.60–0.86	<.001
	Moderate/poor	1,270	79	26.8	16.1						
Adjuvant chemotherapy	Yes	1,367	77	30.8	18.2	0.77	0.67–0.89	<.001	0.66	0.56–0.79	<.001
	No	458	29	24.4	12.6						

CI, confidence interval; *HR*, hazard ratio; *LN*, lymph node.

median OS was worse in unresectable patients than in patients who underwent resection, reporting 6.8 vs 14.3 months and 6.9 vs 16.0 months, respectively. In contrast, Ferrone et al[14] reported no difference in the median OS between CY+ patients who did and those who did not undergo resection (8 vs 7 months); however, Ferrone et al[14] reported a lesser median OS for CY+ patients who underwent resection than that reported in recent studies (8 vs 14–23.8 months). In the present study, the MST and 5-year survival rates were 17.5 months and 13.7% in patients who were CY+. The MST and 5-year survival rates in patients with nonresected pancreatic cancer were 4 to 12 months and almost 0% in previous reports.[27,28] In fact, the multivariate analysis revealed that CY+ status was an independent prognostic factor; however, the hazard ratio was not stronger than that of the other parameters. It is noteworthy that CY+ status was an adverse factor but importantly did not preclude attempted curative resection.

In the present study, the incidence of CY+ status was found frequently in patients with clinically curative body-tail tumors without other gross distant metastases or larger tumor diameters, patients with a greater serum CA19-9 levels, and in patients who underwent preoperative biliary drainage or concomitant arterial resection. These findings suggest that the incidence of CY+ status

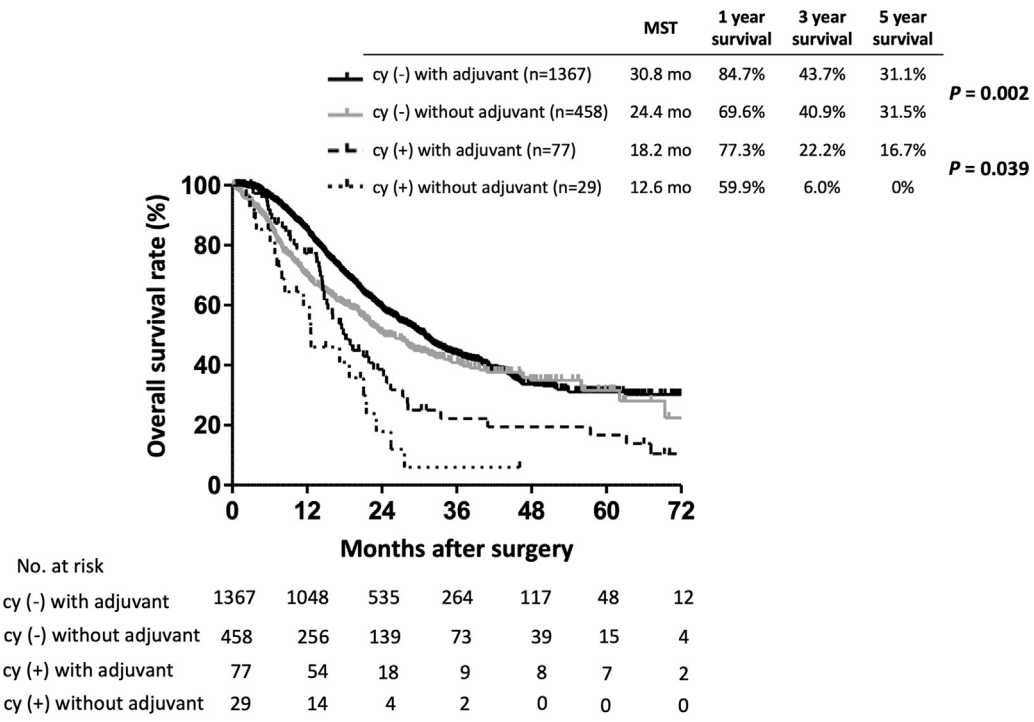

Fig 2. OS of the patients who underwent resection for PDAC stratified by the cytologic status of peritoneal washings and adjuvant chemotherapy.

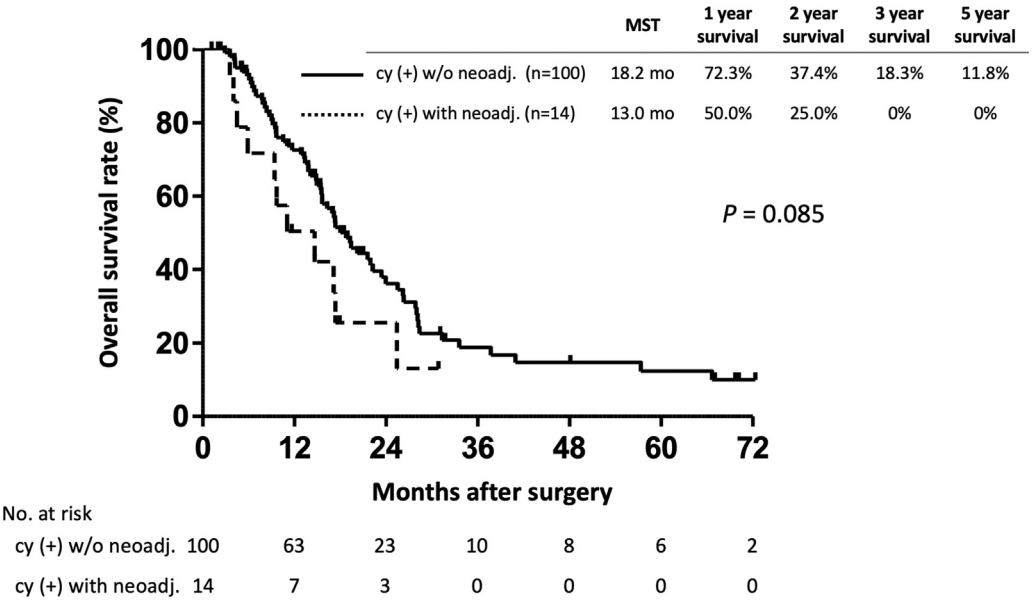

Fig 3. OS of the CY+ patients who underwent resection for PDAC as stratified by neoadjuvant chemotherapy.

increases as the tumor progresses. Based on these results, staging laparoscopy including peritoneal washing cytology may be useful if these findings are identified preoperatively. If CY+ is observed during staging laparoscopy, one option may be to aim for adjuvant resection after neoadjuvant chemotherapy without resection of the primary lesion. We also found that adjuvant chemotherapy was an independent prognostic factor in CY+ patients who underwent resection. Therefore, it may be necessary to perform the best adjuvant chemotherapy such as FOLFIRINOX in patients who are found to be CY+.[29] Moreover, an additional analysis demonstrated that no difference was found in OS between patients who underwent upfront surgery and those who underwent neoadjuvant chemotherapy among the CY+ patients; however, the number of cases was few, and a robust suggestions is not possible. These results were only based on neoadjuvant chemotherapy with gemcitabine or S-1, and recent state-of-the-art regimens such as FOLFIRINOX or nab-paclitaxel may have a better prognosis. We also demonstrated that patients who were CY− exhibited OS than patients who were CY+ among patients, but only with T1, T2, and T3 tumors; no differences were found among patients with T4 stage tumors. These results suggest that other areas of metastasis, such as lymph nodal or neural invasion, may determine the

prognosis of the underlying malignancy of CY+ in patients with T4 stage tumors.

The present study has some limitations. This analysis was a retrospective, multicenter database study, and unknown sources of bias related to patient selection, concordance, sensitivity of the cytologic examination, and inaccuracies in postoperative follow-up cannot be excluded completely. Moreover, because registry data were submitted from >350 institutions, some data are likely missing. There are some difficulties in ethical aspects in the setting prospective studies and randomized controlled trials. In the present study, we used a well-maintained, nationwide database; thus, this study could most likely address this issue. Resectability status was also one of the limitations. In this registry, data on the degree of portal vein invasion had not been accumulated originally. There is a possibility that borderline resectable disease was mixed in with resectable disease; however, it was difficult to show the exact resectability status because NCCN criteria have also been changing each year.

In conclusion, in patients who underwent resection for PDAC who were CY+ predicts an earlier peritoneal recurrence and a poorer prognosis than does CY− status. Curative resection followed by adjuvant chemotherapy may contribute to a more long-term prognosis in CY+ patients.

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Conflict of interest/Disclosure

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Supplementary materials

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