In conclusion, the combination of safe R0 surgical resection and adjuvant therapies, including preoperative and postoperative chemo(radiation) therapy, is essential to improve the survival of the BR pancreatic cancer patients. The development of safer and more effective multimodality treatments is necessary for the BR pancreatic cancer patients.

Conflict of interest None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Video S1 Mesenteric approach for BR pancreatic cancer located in the pancreatic head.
Video S2 Modified DP-CAR procedure for BR pancreatic cancer located in the pancreatic body and/or tail.

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Postoperative prognosis of pancreatic cancer with para-aortic lymph node metastasis: a multicenter study on 822 patients

Masayuki Sho · Yoshiaki Murakami · Fuyuhiko Motoi · Sohei Satoi · Ippei Matsumoto · Manabu Kawai · Goro Honda · Kenichiro Uemura · Hiroaki Yanagimoto · Masanao Kurata · Takumi Fukumoto · Takahiro Akahori · Shoichi Kinoshita · Minako Nagai · Satoshi Nishiwada · Michiaki Unno · Hiroki Yamaue · Yoshiyuki Nakajima

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Abstract
Background The prognosis of pancreatic cancer patients with metastatic para-aortic lymph node (PALN) has been reported to be extremely poor. In general, PALN metastasis has been considered as a contraindication for pancreatic resection. The aim of this study was to reevaluate the postoperative prognostic value of PALN metastasis in pancreatic cancer and to determine the validity of pancreatic surgery.
Methods Retrospective multicenter analysis of 882 patients who have undergone curative-intent pancreatic resection with pathological evaluation of PALNs for pancreatic ductal adenocarcinoma between 2001 and 2012 was conducted. Clinicopathological data and outcomes were evaluated with univariate and multivariate analysis.
Results In total, 102 (12.4 %) patients had positive metastasis in PALN. Patients with metastatic PALN had significantly poorer survival than those without (17 vs. 23 months; $p < 0.001$). Multivariable analysis of 822 patients identified adjuvant chemotherapy, primary tumor status, regional lymph node metastasis, portal vein invasion, pre- and post-operative serum CA19-9 levels, and tumor grade as independent prognostic factors. In contrast, PALN metastasis did not have a significant prognostic value. Furthermore, the multivariate prognostic analysis in patients with PALN metastasis revealed that adjuvant chemotherapy and the number of metastatic PALN were significantly associated with long-term survival. Lung metastasis as initial recurrence was observed more often in patients with PALN metastasis in comparison with those without.
Conclusions Some pancreatic cancer patients with metastatic PALN may survive for longer than expected after pancreatectomy. Adjuvant chemotherapy and the number of metastatic PALN were critical factors for long-term survival of those patients.

Keywords Pancreatic cancer · Para-aortic lymph node metastasis · Postoperative prognosis

M. Sho (✉) · T. Akahori · S. Kinoshita · M. Nagai · S. Nishiwada · Y. Nakajima
Department of Surgery, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan
e-mail: m-sho@naramed-u.ac.jp

Y. Murakami · K. Uemura
Department of Surgery, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

F. Motoi · M. Unno
Division of Gastroenterological Surgery, Department of Surgery, Tohoku University, Sendai, Japan

S. Satoi · H. Yanagimoto
Department of Surgery, Kansai Medical University, Osaka, Japan

I. Matsumoto · T. Fukumoto
Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Japan

M. Kawai · H. Yamaue
Second Department of Surgery, Wakayama Medical University, Wakayama, Japan

G. Honda · M. Kurata
Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

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Introduction

Pancreatic cancer has been increasing in incidence, and it is one of leading causes of cancer-related deaths worldwide [1, 2]. Despite significant progress in the treatment, the overall survival of patients remains extremely poor [3, 4]. Although surgery offers the only chance for cure or long-term survival, the majority of patients were found to be unresectable at diagnosis [5–7]. Common reasons for unresectability include vascular invasion excluding limited portal vein invasion that can be reconstructed, distant lymph node metastases, hepatic metastases, peritoneal metastases, and extra-abdominal metastases including pulmonary metastases. These surgical indications have not been much changed for many years [5, 8].

According to the TNM classification for pancreatic cancer, para-aortic lymph node (PALN) is regarded as distant lymph node and PALN metastasis is classified as distant metastasis [9, 10]. Therefore, if PALN metastasis in pancreatic cancer is suspected by preoperative images or defined by intraoperative pathological examination, pancreatic surgery is generally contraindicated. In fact, several previous studies have emphasized that the patients with metastatic PALN often had early recurrence after surgery and had extremely poor survival [11–16]. Therefore, they concluded that surgical resection did not provide survival benefit in such patients. They also discussed the need for adjuvant treatment or alternative therapeutic strategies for longer survival. However, the number of clinical studies on this issue is limited and the number of patients evaluated in each study is relatively small. Thus, there is limited clinical evidence that PALN metastasis without other distant metastasis is an absolute contraindication to pancreatic resection. In addition, due to treatment advancement including the introduction of new chemotherapeutic agents for pancreatic cancer, we occasionally see unexpected favorable outcome in daily clinical practice [17–20]. Therefore, pancreatic surgery may provide survival benefits to patients with PALN metastasis in some cases.

To address various clinical questions in the surgical treatment for pancreatic cancer including surgical indication, postoperative complications, as well as predictions of recurrence and prognosis, we have recently established a common database of seven high-volume surgical centers in Japan (Multicenter Study Group of Pancreatobiliary Surgery: MSG-PBS). By using this large-scale database, we reevaluate the postoperative prognosis of pancreatic cancer patients with PALN metastasis as a collaborative study. We further investigated risk factors for PALN metastasis and also analyzed the possibility of long-term survival in patients with metastatic PALN.

Patients and methods

Study design and data collection

This study was approved by the institutional review board of each center. We collected and registered consecutive patients who had undergone R0 or R1 pancreatic resection between 2001 and 2012 for pancreatic ductal adenocarcinoma in the database. Patients with R2 resection were not included in the database. Furthermore, patients with distant metastasis such as liver or peritoneal metastasis were also excluded from the database, even if the combined resection of metastatic sites with the primary lesion was performed. From 1,414 patients registered in the database, 592 whose PALNs had not been sampled for pathological examination were excluded. The data of a total of 822 patients with pathological proof of PALN status were collected from the database.

Para-aortic lymph nodes were sampled by harvesting the lymphocellular aortocaval tissue from the upper part of the celiac trunk to the upper part of the origin of the inferior mesenteric artery [11–13]. These lymph nodes were classified as No. 16, according to the Japanese classification [21].

Clinical data included gender, age, body mass index (BMI), neoadjuvant treatment, adjuvant chemotherapy, pre- and post-operative serum CA19-9 level, tumor location, and operation type. For tumors, pathological data included T and N status according to the 7th AJCC/UICC TNM classification, tumor size, histological type, surgical margin status, and portal vein invasion [9, 10]. Some patients received neoadjuvant treatment using chemotherapy or chemoradiotherapy depending on each institution's decision with informed consent. Postoperative adjuvant treatment of gemcitabine- or S-1-based chemotherapy was employed depending on the physicians' choice or the patients' condition.

The primary endpoint of this study was to evaluate the postoperative prognosis of pancreatic cancer patients with PALN metastasis in comparison with those without. Secondary endpoints included the assessment of risk factors for PALN metastasis and the analysis of prognostic factors in patients with PALN metastasis.

Statistical analysis

The clinicopathological parameters were compared between patients with and without PALM metastasis using Student's *t* test, the Chi-square test, or Fisher's exact test as appropriate. Continuous variables were expressed as mean values ± standard deviation. The median survival was estimated using the Kaplan–Meier method, and the difference was tested using the log-rank test. Patients alive at the time of follow-up point were censored. Date of last

follow-up was June 2013. Univariate and multivariate analyses were performed by the Cox proportional hazards model to evaluate significant prognostic predictors and their relative role. Statistical analyses were performed using JMP statistical discovery software (JMP version 11.0, SAS Institute, Cary, NC, USA). A p value < 0.05 was considered statistically significant.

Results

Correlations of clinicopathological factors with para-aortic lymph node metastasis

Among a total of 822 patients, pancreatoduodenectomies were performed in 617 patients (75.1 %), distal pancreatectomies in 161 patients (19.6 %), and total pancreatectomies in 44 patients (5.3 %). The 30-day and 90-day mortality rates were 0.7 and 2.9 %, respectively. The mean and median numbers of PALNs sampled for pathological examination were 4.3 (standard deviation, 4.2) and 3 (range, 1–27), respectively. As a result, while PALNs were negative for metastasis in 720 patients, they were positive in 102 patients (12.4 %). The mean and median numbers of metastatic PALNs were 1.9 (standard deviation, 1.6) and 1 (range, 1–11), respectively. Sixty patients (58.8 %) had single metastasis in PALNs, while 42 (41.2 %) had multiple metastasis.

Between patients with and without PALN metastasis, there were no significant differences in various clinicopathological factors including gender, age, BMI, neoadjuvant treatment, adjuvant chemotherapy, tumor size, tumor location, tumor differentiation, and portal vein invasion (Table 1). In contrast, PALN metastasis significantly correlated with R1 resection, advanced primary tumor status, regional lymph node metastasis, and elevated pre- and post-operative serum CA19-9 levels. In patients with metastatic PALN, only three patients had T1 tumor and/or no regional lymph node metastasis. While approximately two-thirds (72.3 %) of the patients without PALN metastasis had normal CA19-9 levels after surgery, more than half (55.0 %) of patients with PALN metastasis still had elevated CA19-9 levels.

Table 1 Clinicopathological characteristics for patients with pancreatic adenocarcinoma

Variables	Para-aortic lymph node metastasis		p value
	Absent ($n = 720$)	Present ($n = 102$)	
Gender, male, n (%)	401 (56 %)	46 (45 %)	0.056
Age, mean ± SD (years)	66.5 ± 9.5	65.6 ± 9.3	0.422
Body mass index (BMI), mean ± SD (kg/m^2)	21.6 ± 3.2	21.1 ± 2.8	0.098
Neoadjuvant treatment			0.061
Yes	214 (30 %)	21 (21 %)	
No	506 (70 %)	81 (79 %)	
Adjuvant chemotherapy			0.113
Yes	373 (52 %)	44 (43 %)	
No	347 (48 %)	58 (57 %)	
Tumor size, mean ± SD (cm)	2.9 ± 1.2	3.0 ± 1.3	0.241
R status			<0.001
R0	566 (79 %)	44 (43 %)	
R1	154 (21 %)	58 (57 %)	
T status			0.016
T1-2	61 (9 %)	2 (2 %)	
T3-4	659 (91 %)	100 (98 %)	
N status			<0.001
Negative	279 (39 %)	2 (2 %)	
Positive	441 (61 %)	100 (98 %)	
Portal vein invasion			0.911
No	474 (66 %)	67 (66 %)	
Yes	242 (34 %)	35 (34 %)	
Preoperative CA19-9 (units/ml)			<0.001
<100	368 (51 %)	32 (31 %)	
>100	352 (49 %)	70 (69 %)	
Postoperative CA19-9 (units/ml)			<0.001
<37	485 (72 %)	45 (45 %)	
>37	186 (28 %)	55 (55 %)	
Tumor location			0.598
Head/whole	574 (80 %)	84 (82 %)	
Body/tail	146 (20 %)	18 (18 %)	
Tumor differentiation			0.248
G1	185 (27 %)	19 (19 %)	
G2	447 (65 %)	70 (71 %)	
G3/4	59 (8 %)	10 (10 %)	

Survival of patients according to para-aortic lymph node metastasis status

There was a significant difference in overall survival between patients with and without PALN metastasis ($p < 0.001$; Fig. 1a). The median survival time (MST) for patients with and without PALN metastasis were 16.9 and 22.6 months, respectively. The 1-, 2-, 3-, and 5-year survival rates were for patients with PALN metastasis were 63.8, 30.0, 16.7, and 6.8 %, respectively, compared with 74.6, 48.4, 35.6, and 25.4 % for patients without PALN metastasis.

To evaluate the change and improvement of treatment outcome during the study period, we compared the prognosis of patients with PALN metastasis treated in the first 5 years of 2001–2005 with that in the latter 5 years of

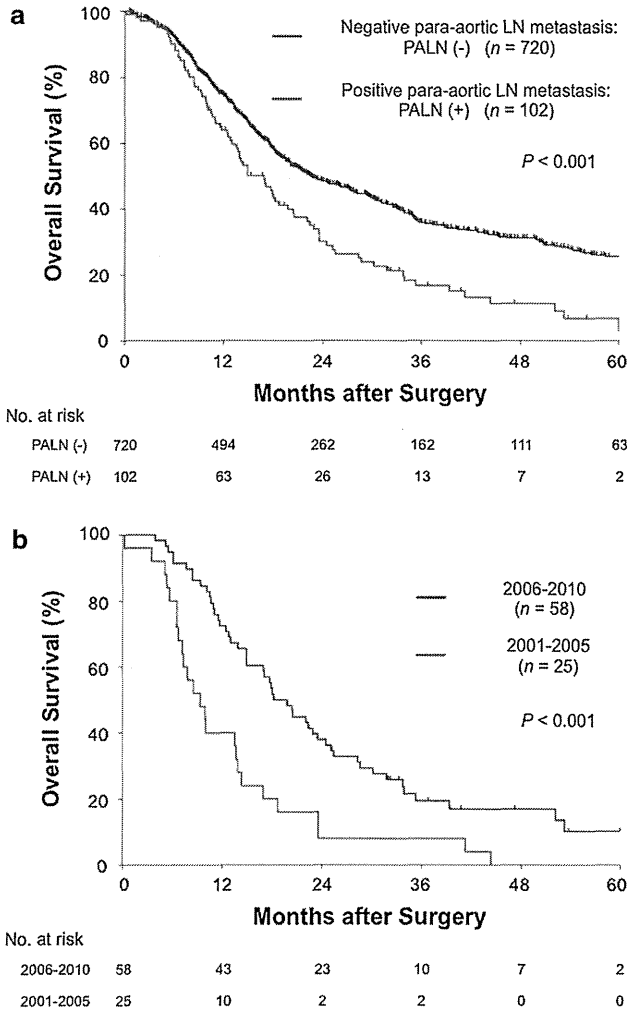

Fig. 1 Kaplan–Meier analysis of overall survival. **a** Patients with para-aortic lymph node (PALN) metastasis ($n = 102$) had worse survival compared to those without ($n = 720$). **b** Postoperative survival of patients with PALN metastasis operated in the year of 2006–2010 ($n = 58$) was better than that in 2001–2005 ($n = 25$)

2006–2010. For data accuracy, we excluded patients operated on between 2011 and 2012 with a follow-up of less than 30 months from this analysis. The survival of patients with PALN metastasis treated in the latter period was significantly better than that of patients in the first half period ($p < 0.001$; Fig. 1b). The MST for patients treated in the first and latter half period were 9.3 and 18.2 months, respectively.

Univariate and multivariate survival analyses

Using the Cox proportional hazards model, we examined prognostic factors in 822 patients with pancreatic adenocarcinoma. In univariate analysis, factors associated with better patient survival included the administration of adjuvant chemotherapy, R0 resection, T1-2 tumor, negative regional lymph node metastasis, no portal vein invasion, a preoperative value of CA19-9 $\leq$100 units/ml, normal level of postoperative CA19-9, high-grade differentiation of tumor, and negative PALN metastasis (Table 2). On the other hand, gender, age, neoadjuvant treatment, and tumor location did not correlate with prognosis. Multivariable analysis indicated that adjuvant chemotherapy, T status, N status, portal vein invasion, and pre- and post-operative CA19-9 level, and tumor grade had significant prognostic value (Table 2). In contrast, not only *R* status but also PALN metastasis did not have prognostic value.

Factors for long-term survival in patients with para-aortic lymph node metastasis

Among 102 patients with PALN metastasis, 39 (38.2 %) died within 1 year after surgery. On the other hand, 63 patients (61.8 %) survived for over 1 year, 26 (25.5 %) for over 2 years, 13 (12.7 %) for over 3 years, and two (2.0 %) for over 5 years. To investigate predictive factors for long-term survival in patients with PALN metastasis, we further performed survival analysis in these patients. As a result, adjuvant chemotherapy and the number of metastatic PALN were found to be significant independent predictors of long-term survival (Table 3). In contrast, the total number of metastatic regional lymph nodes and postoperative CA19-9 level did not have significant prognostic value in patients with PALN metastasis. The MST of patients with adjuvant chemotherapy was 23.6 months, while that without adjuvant chemotherapy was 10.6 months (Fig. 2a). In addition, the MST of patients with single PALN metastasis was 22.1 months, while that with multiple PALN metastasis was 12.8 months. Furthermore, MST of patients with two metastatic PALNs was 11.7 months, and that with more than two metastatic PALNs was 16.9 months. Although the difference between these two groups was not significant, both were significantly worse that that of patients with single PALN metastasis (Fig. 2b).

Postoperative recurrence pattern according to para-aortic lymph node metastasis status

At the time of analysis, 516 patients (71.7 %) without PALN metastasis had recurrence. On the other hand, there were significantly more recurrences in patients with PALN metastasis ($n = 91$, 89.2 %, $p < 0.001$). Finally, we compared the initial recurrence pattern between patients with PALN metastasis and those without (Table 4). There were no significant differences in the frequency of hepatic, local, and peritoneal recurrence as initial recurrence. In contrast, lung metastasis was observed more often in patients with PALN metastasis than those without ($p = 0.012$).

Table 2 Univariate and multivariate analysis of prognostic factors in 822 patients with pancreatic adenocarcinoma

Variable	No. of patients (%)	Univariable analysis		Multivariable analysis		
		Hazard ratio	*P* value	Hazard ratio	95 % CI	*P* value
Gender			0.817			
Male	447 (54)	1.000				
Female	375 (46)	0.980				
Age (years)			0.085			
<70	499 (61)	1.000				
>70	323 (40)	1.166				
Neoadjuvant treatment			0.783			
Yes	235 (29)	1.000				
No	587 (71)	1.028				
Adjuvant chemotherapy			<0.001			<0.001
Yes	417 (51)	1.000		1.000	–	
No	405 (49)	3.047		2.730	2.253–3.313	
R status			<0.001			0.968
R0	610 (74)	1.000		1.000	–	
R1	212 (26)	1.620		1.005	0.811–1.250	
T status			<0.001			0.002
T1-2	63 (8)	1.000		1.000	–	
T3-4	759 (92)	3.030		1.925	1.264–3.085	
N status			<0.001			<0.001
Negative	281 (34)	1.000		1.000	–	
Positive	541 (66)	2.003		1.854	1.483–2.330	
Portal vein invasion			<0.001			0.002
No	541 (66)	1.000		1.000	–	
Yes	277 (34)	1.649		1.360	1.116–1.654	
Preoperative CA19-9, units/ml			<0.001			0.046
<100	400 (49)	1.000		1.000	–	
>100	422 (51)	1.767		1.250	1.004–1.556	
Postoperative CA19-9, units/ml			<0.001			0.006
<37	530 (69)	1.000		1.000	–	
>37	241 (31)	2.140		1.376	1.097–1.724	
Tumor location			0.269			
Head/whole	658 (80)	1.000				
Body/tail	164 (20)	0.889				
Tumor differentiation			<0.001			0.047
G1	204 (26)	1.000		1.000	–	
G2	517 (65)	1.488		1.181	0.944–1.490	
G3/4	69 (9)	1.774		1.565	1.095–2.207	
Para-aortic lymph node metastasis			<0.001			0.335
Positive	102 (12)	1.000		1.145	0.867–1.496	
Negative	720 (88)	0.592		1.000	–	

Discussion

In the past several years, some progress has been made in the treatment for pancreatic cancer [5]. However, patient prognosis remains extremely poor and surgical indication has not been greatly changed. In general, pancreatic cancer with distant metastasis such as liver, lung, and peritoneal metastasis is thought to be systemic and incurable disease. Therefore, even if clinically apparent distant metastasis is a single lesion, surgery has usually been contraindicated. Para-aortic lymph nodes have been classified as non-regional lymph nodes and cancer cells existing in PALN are recognized as distant metastasis [9, 10]. To date, there are only a limited number of studies on the postoperative

Table 3 Univariate and multivariate analysis of prognostic factors in 102 patients with para-aortic lymph node metastasis

		Univariate Analysis		Multivariate analysis		
	No. of patients (%)	Hazard ratio	*p* value	Hazard ratio	95 % CI	*p* value
Gender			0.488			
Male	46 (45)	1.000				
Female	56 (55)	0.855				
Age			0.901			
<70	65 (64)	1.000				
>70	37 (36)	1.029				
Neoadjuvant treatment			0.306			
Yes	21 (21)	1.000				
No	81 (79)	1.361				
Adjuvant chemotherapy			<0.001			0.003
Ye s	44 (43)	1.000		1.000	–	
No	58 (57)	2.405		2.060	1.270–3.384	
Number of metastatic regional LN			0.013			0.161
<3	28 (27)	1.000		1.000	–	
>4	74 (73)	1.864		1.474	0.860–2.619	
R status			0.083			
R0	44 (43)	1.000				
R1	58 (57)	1.481				
Preoperative CA19-9			0.057			
<100	32 (31)	1.000				
>100	70 (69)	1.578				
Postoperative CA19-9			0.005			0.307
<37	45 (45)	1.000		1.000	–	
>37	55 (55)	1.918		1.288	0.794–2.113	
Tumor location			0.065			
Head/Whole	84 (82)	1.000				
Body/Tail	18 (18)	0.586				
Tumor differentiation			0.218			
G1	19 (19)	1.000				
G2	70 (71)	1.605				
G3/4	10 (10)	1.176				
Number of metastatic PALN			<0.001			0.017
Single	60 (59)	1.000		1.000	–	
Multiple	42 (41)	2.200		1.840	1.115–3.062	

prognosis in patients with PALN metastasis [11–16]. These previous studies reported that the median survival time of patients with metastatic PALN was only between 5.1 and 15.7 months. Furthermore, early recurrence and little benefit of surgery have been described [11, 13]. These clinical data have supported that PALN metastasis is a common reason for unresectability in pancreatic cancer. However, this large-scale collaborative study has demonstrated that the prognosis of pancreatic cancer patients with PALN metastasis in the current study seems to be better than that in previous studies (Table 5). Furthermore, this study also clarified that the prognosis of those patients has been improved during the study period. The median overall survival was approximately 9 months in patients treated between the years 2001 and 2005. This is comparable to that shown in previous reports. In contrast, the median overall survival is up to 18 months in patients treated in the most recent 5 years. In fact, whereas Doi et al. reported that PALN metastasis was the only independent prognostic factor for resectable pancreatic cancer, multivariable analysis of this study demonstrates that it no longer has an independent prognostic value [13]. Recent clinical trials to evaluate new chemotherapeutic regimens including FOLFILINOX or nab-paclitaxel plus gemcitabine have demonstrated significantly improved survival for metastatic pancreatic cancer with the median survival times of 11.1

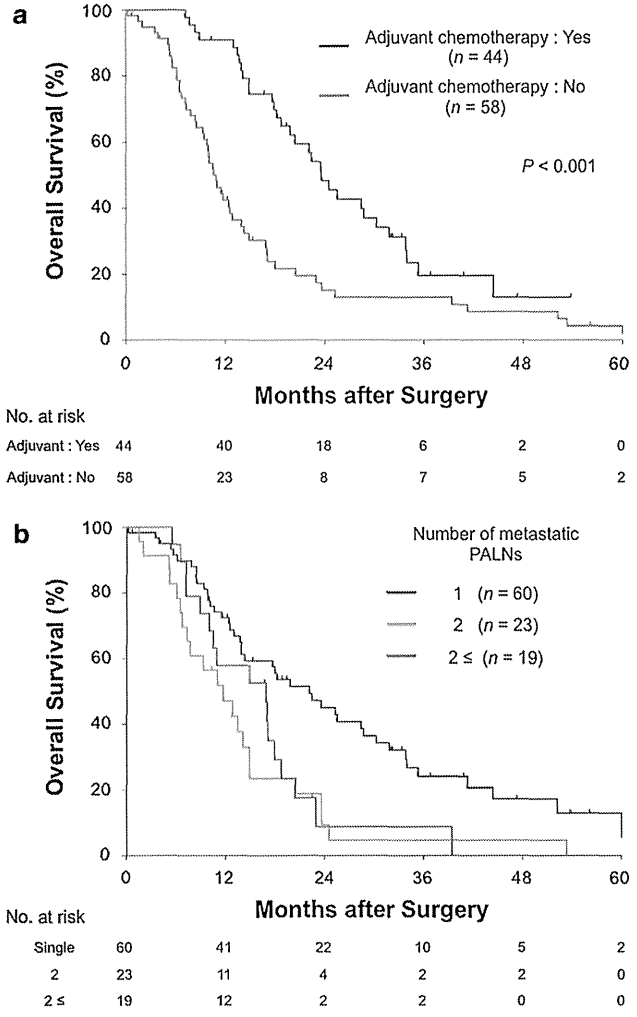

Fig. 2 Kaplan–Meier analysis of overall survival in patients with para-aortic lymph node (PALN) metastasis. **a** Patients with adjuvant chemotherapy ($n = 44$) had better survival than those without ($n = 58$) ($p < 0.001$). **b** Patients with single PALN metastasis ($n = 60$) had better survival than those with two metastatic PALNs ($p = 0.001$, $n = 23$) or more than two metastatic PALNs ($p = 0.018$, $n = 19$)

and 8.5 months, respectively [22, 23]. Even in comparison with these latest data for metastatic pancreatic cancer, the median overall survival of about 18 months is likely to be better, suggesting that there may be some differences in the tumor behavior of pancreatic cancer between PALN metastasis and other types of distant metastasis.

The precise reasons for the improved survival of patients with PALN metastasis are not fully elucidated. One of the major reasons is most likely to perform adjuvant chemotherapy. In Japan, gemcitabine was approved in 2001 and S-1 in 2006 for the treatment of pancreatic cancer. These chemotherapeutic reagents occasionally bring unexpectedly favorable clinical outcomes. In addition, recent randomized clinical trials indicating the efficacy of gemcitabine in adjuvant settings encourage surgeons and

Table 4 Recurrence pattern according to para-aortic lymph node metastasis status

	Para-aortic lymph node metastasis		p value
	Absent ($n = 516$)	Present ($n = 91$)	
Liver	194 (38 %)	29 (32 %)	0.346
Local	180 (35 %)	26 (29 %)	0.280
Peritoneum	112 (22 %)	19 (21 %)	1.000
Lung	73 (14 %)	23 (25 %)	0.012

Table 5 Comparison of other series with prognosis of patients with para-aortic lymph node metastasis

Author	Year	Study period	No. of total patients	No. of patients with para-aortic lymph node metastasis (%)	MST (months)
Present	2014	2001–2012	822	102 (12)	16.9
Schwarz et al.	2014	2000–2010	111	17 (15)	15.7
Kanda et al.	2011	1981–2009	429	49 (11)	8.3
Murakami et al.	2010	1992–2008	103	18 (17)	12.4
Doi et al.	2007	1980–2000	133	19 (14)	5.1
Shimada et al.	2006	1999–2003	133	29 (22)	13

MST median survival time

oncologists to employ adjuvant chemotherapy more actively than before [24, 25]. In this study, approximately 20 % of patients with PALN metastasis received neoadjuvant treatment and 43 % received adjuvant chemotherapy. Other various efforts in an adjuvant setting and after postoperative recurrence might have contributed to improve patient survival [20, 26, 27].

Preoperative diagnosis of PALN metastasis is not always easy, even when using the latest imaging technology [28, 29]. In daily clinical practice, enlarged PALNs suspicious of metastasis or inflammation are sometimes encountered. The enlarged PALN may be thought to be a distant metastasis and the reason for unresectability in some institutions, even if it is not pathologically proven. In the United States and Europe, the sampling of PALNs does not seem a routine procedure during surgery. Therefore, the actual rate of metastatic PALN in pancreatic cancer is unknown. However, even with the small number of PALN sampling of 4.3, the metastatic rate in PALN of 12 % in this analysis is not low and cannot be ignored. Previous studies have demonstrated that several factors including tumor size, surgical margin, postoperative CA19-9 level, extrapancreatic nerve invasion, age, and portal vein

invasion were associated with PALN metastasis [11, 12, 30]. Our data, including R status, pre- and post-operative CA19-9 levels, corroborate some of the previous reports. On the other hand, Nagai et al. have reported that even T1 and T2 primary tumors of pancreatic cancer had a relatively high rate of PALN metastasis [31]. In this series, two T1 primary tumors had PALN metastasis. Furthermore, Hirono et al. have reported that there is a direct lymphatic drainage pathway from the pancreatic head to the PALN area [32]. Taken together, although PALN metastasis is a common feature of pancreatic cancer, it may occur at a relatively early stage before metastasizing to other distant organs.

Previous studies have shown that there were no or very few long-term survivors after pancreatic resection for the patients with PALN metastasis [11–13]. In contrast, 26 out of 102 patients with metastatic PALN survived for over 2 years and 13 for over 3 years. We then analyzed the conditions for long-term survival after pancreatic resection for patients with PALN metastasis. As a result, adjuvant chemotherapy and the number of metastatic PALNs were independent prognostic factors in patients with PALN metastasis. Data suggested that multimodal treatment including surgery and chemotherapy might lead to long-term survival in some patients, especially with single PALN metastasis. To consider future strategy, we analyzed the initial recurrence pattern. The pattern did not differ much between patients with PALN metastasis and those without. However, only lung metastasis was observed more often in patients with PALN metastasis, although the underlying mechanism is unclear at present. Data suggested that a more effective systemic anticancer treatment was needed. As demonstrated in recent clinical trials, several promising chemotherapy regimens may further improve postoperative prognosis of PALN-positive patients [22, 23].

There are several limitations in this study. Firstly, the sampling of PALNs was performed based on the surgeon's decision at each institution. Furthermore, massive PALN metastases even in patients without any other distant metastases might be considered to be contraindications in most cases. Therefore, actual status of PALN remained unknown in all patients. Secondly, this study is retrospective and the true significance of pancreatic resection remains unknown. Thirdly, since this is multi-institutional study, each institution has different treatment strategies including neoadjuvant and adjuvant treatment. Such inter-institutional differences can affect the analyzed data. Therefore, in order to obtain medical evidence and to evaluate surgical indications precisely, prospective clinical studies, especially under current circumstances, need to be done. However, since this study is the largest as well as the first multicenter investigation to explore the postoperative prognosis of patients with PALN metastasis, our data may provide useful information on surgical indications and multimodal treatment for advanced pancreatic cancer.

In conclusion, some pancreatic cancer patients with PALN metastasis may survive for longer than expected after pancreatectomy. To expect long-term survival in those patients, adjuvant chemotherapy and single PALN metastasis are critical factors.

Conflict of interest The authors declare no conflicts of interest.

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2014 SSAT PLENARY PRESENTATION

Reappraisal of Peritoneal Washing Cytology in 984 Patients with Pancreatic Ductal Adenocarcinoma Who Underwent Margin-Negative Resection

Sohei Satoi · Yoshiaki Murakami · Fuyuhiko Motoi · Kenichiro Uemura · Manabu Kawai · Masanao Kurata · Masayuki Sho · Ippei Matsumoto · Hiroaki Yanagimoto · Tomohisa Yamamoto · Masamichi Mizuma · Michiaki Unno · Yasushi Hashimoto · Seiko Hirono · Hiroki Yamaue · Goro Honda · Minako Nagai · Yoshiyuki Nakajima · Makoto Shinzeki · Takumi Fukumoto · A-Hon Kwon

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Abstract

Objective The objective of the present study was to reappraise the clinical value of peritoneal washing cytology (CY) in 984 pancreatic ductal adenocarcinoma patients who underwent margin-negative resection.

Methods In a 2001–2011 database from seven high-volume surgical institutions in Japan, 69 patients (7 %) had positive CY (CY+ group) indicative of M1 disease and 915 patients had negative CY (CY− group). Clinicopathological data and survival were compared between groups.

Results Significant correlations between CY+ and high CA19-9 level, pancreatic body and tail cancer, lymph node metastasis, and a lower frequency of R0 resection were observed. Overall survival (OS) of CY+ patients was significantly worse than that of CY− patients (median survival time [MST], 16 vs. 25 months; 3-year OS rate, 6 vs. 37 %; $p<0.001$). CY+ patients had a significantly higher rate of post-operative peritoneal carcinomatosis than CY− patients (48 vs. 21 %; $p<0.001$). Administration of adjuvant chemotherapy did not provide a favorable survival outcome to CY+ patients. The current study showed that patients with M1 disease had acceptable MST after margin-negative resection and a high incidence of peritoneal carcinomatosis within 3 years after surgery, resulting in decreased long-term survival. The development of a new strategy to control peritoneal carcinomatosis when surgical resection is performed in such patients is required.

S. Satoi · H. Yanagimoto · T. Yamamoto · A.-H. Kwon
Department of Surgery, Kansai Medical University, Osaka, Japan

Y. Murakami (✉) · K. Uemura · Y. Hashimoto
Department of Surgery, Institute of Biomedical and Health Sciences, Hiroshima University, 1-2-4, Kasumi, Minami-ku, Hiroshima 734-8551, Japan
e-mail: mura777@hiroshima-u.ac.jp

F. Motoi · M. Mizuma · M. Unno
Division of Gastroenterological Surgery, Department of Surgery, Tohoku University, Sendai, Japan

M. Kawai · S. Hirono · H. Yamaue
Second Department of Surgery, Wakayama Medical University, Wakayama, Japan

M. Kurata · G. Honda
Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

M. Sho · M. Nagai · Y. Nakajima
Department of Surgery, Nara Medical University, Nara, Japan

I. Matsumoto · M. Shinzeki · T. Fukumoto
Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Japan

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is associated with a poor prognosis, even in patients who have undergone margin-negative resection. The results of surgery alone for ductal pancreatic adenocarcinoma are disappointing, and the 5-year actual survival rate ranges from 3 to 17 %, even after surgical resection.[1–5] Positive peritoneal washing cytology (CY) status in patients with resectable PDAC is defined as M1 disease in the American Joint Committee on Cancer (AJCC) guidelines.[6] Ferrone et al. reported that positive cytology in patients who have undergone surgical resection was associated with poor survival (median survival time [MST], 8 vs. 16 months in patients with negative cytology; $p<0.001$); their survival time did not significantly differ from that of patients with metastatic (7 months) or locally advanced disease (6 months).[7] Although some studies have reported no significant difference in overall survival (OS) between patients with positive (CY+) and negative (CY−) peritoneal washing cytology who underwent surgical resection, only a small number of CY+ patients (10–20) were evaluated.[8–10] Thus, the clinical role of surgical resection in PDAC patients with CY+ is still being debated.

In Japan, many institutions routinely perform curative surgical resection in patients with CY+ when PDAC is diagnosed as resectable or borderline resectable. We have recently established a common database by collecting data from patients who underwent margin-negative resection for pancreatic ductal adenocarcinoma from seven high-volume centers in Japan (Multicenter Study Group of Pancreatobiliary Surgery [MSG-PBS]). The objective of the present study was to retrospectively reappraise the clinical role of surgical resection in patients with CY+ PDAC based on this large-scale database.

Methods

Study Design and Patient Selection

This was a case-control study that compared the surgical results of PDAC patients with CY+ and CY− who underwent surgical resection. The primary endpoint was OS rate, and secondary endpoints included disease-free survival (DFS) rate and primary site of recurrence. After several discussions, the MSG-PBS collected the data from 1,389 patients who had undergone R0 or R1 pancreatic resection from 2001 to June 2011 for pancreatic ductal adenocarcinoma according to our guidelines for correct registration of patients into the database. Among these patients, 37 patients with initially unresectable PDAC who underwent curative surgical resection after long-term favorable responses to chemotherapy or chemoradiotherapy, 13 patients with anaplastic carcinoma, and 12 patients with mucinous carcinoma were excluded. In addition, 343 patients whose CY had not been sampled for pathological examination were also excluded. A total of 984 patients were included in the present study.

Clinical data included gender, age, body mass index (BMI), neoadjuvant treatment, adjuvant chemotherapy, pre- and post-operative serum CA19-9 level, tumor location, resectability status defined by the National Cancer Comprehensive Network (NCCN),[11] status of post-operative CA19-9 normalization,[12] and operation type. For tumors, pathological data included T and N status according to the seventh AJCC/International Union Against Cancer (UICC) TNM classification, tumor size, histological type, surgical margin status, and CY.[13,14] Typically, post-operative peritoneal carcinomatosis was defined when patients had significant ascites and/or multiple peritoneal tumors found on the planned high-quality CE-CT during the post-operative follow-up period (every 3 months for 2 years after surgical resection and every 6 months over 2 years after surgical resection).

Surgical indications at the seven institutions were based on resectable and borderline resectable PDAC as defined by NCCN resectability status.[11] As an exception, patients who underwent distal pancreatectomy with celiac axis resection (6 %) despite having unresectable disease as defined by the NCCN were also included in this analysis. Directly after opening the abdominal cavity for a planned margin-negative resection, it was washed with physiologic saline solution (40–100 mL) into the pelvis and/or subhepatic space, and subsequently, cytologic washings (20–50 mL) were obtained for pathological examination. Smears were made from the centrifuged deposit and examined by experienced pathologists following conventional Papanicolaou and/or Giemsa staining. The CY results were given to the surgeons before resection (pancreatectomy) in some centers and post-operatively in the other centers. Surgical resection was routinely performed even in CY+ patients due to the policy at the seven institutions. Neoadjuvant or adjuvant therapy was performed based on each institution's policies. Neoadjuvant therapy regimens included gemcitabine chemotherapy, gemcitabine plus S-1 chemotherapy, gemcitabine chemotherapy with concurrent radiation, S-1 chemotherapy with concurrent radiation, and gemcitabine plus S-1 chemotherapy with concurrent radiation. Chemotherapeutic agents used in adjuvant therapy included gemcitabine alone, S-1 alone, gemcitabine plus S-1, and gemcitabine plus 5-fluorouracil. This study was approved by the institutional review board of each center.

Statistical Analysis

The database from seven institutions was carefully checked for clerical errors by YM and SS for 1 month before the

statistical analyses started in each institution. A total of 13 continuous variables and 45 categorical variables from the database were required for the statistical analyses conducted in this study. Missing values were observed in only 0.32 % of cases in the database. Data are expressed as median values and ranges. The clinicopathological parameters were compared between CY+ and CY− patients. Continuous or categorical variables were compared by Mann-Whitney *U* test, chi-squared test, or Fisher's exact test as appropriate. OS was defined as the time from the date of surgery or neoadjuvant treatment to death or the last follow-up date (June 30, 2013); OS and DFS were compared using the log-rank test. All patients were followed up for at least 1 year. In addition, factors identified by univariate analysis were further examined by multivariate Cox proportional hazards models to identify independent significant factors for survival. Hazard ratios and 95 % confidence intervals were calculated for all estimates. A two-tailed p value of <0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS Version 18.0 for Windows (Chicago, IL, USA).

Results

Among 984 patients who underwent tumor resection, 69 patients (7 %) had a positive CY status (CY+ group), and 915 patients had a negative CY status (CY− group). Overall, 38 % of patients underwent portal or superior mesenteric vein resection. Morbidity was observed in 39.5 % of patients and in-hospital mortality was noted in 2.1 % of this population. With respect to therapy, 27 % of patients underwent neoadjuvant treatment, and 82 % received post-operative adjuvant chemotherapy consisting of gemcitabine- or S-1-based regimens depending on the physicians' or patients' choice.

Comparison of Clinicopathological Factors Between the CY+ and CY− Groups

As shown in Table 1, patients in the CY+ group had a significantly higher frequency of pancreatic body and tail cancer, higher pre- and post-operative CA19-9 levels, a lower incidence of post-operative CA19-9 normalization, and greater tumor diameter on CT scan relative to patients in the CY− group ($p<0.05$). Biliary drainage was more frequently performed in patients in the CY− group compared to patients in the CY+ group ($p<0.001$). No significant differences in several other parameters, including age, gender, BMI, diabetes mellitus, albumin and C-reactive protein levels, NCCN resectability status, neoadjuvant therapy, or adjuvant therapy, were observed between groups.

Comparisons of surgical parameters (Table 2) revealed that pathologically, patients in the CY+ group had a significantly higher frequency of lymph node metastasis and higher lymph node ratios and R1 rates relative to patients in the CY− group ($p<0.05$). Significant differences in tumor differentiation and pathological tumor stage were also observed between the two groups. No significant differences in type of surgery, operative time, extent of blood loss, frequency of concomitant resection of the portal/superior mesenteric vein, or overall morbidity or mortality were observed between groups.

Table 1 Comparison of pre- and post-operative parameters

Parameter	CY− n=915	CY+ n=69	p value
Age, years (range)	68 (27–91)	65 (41–85)	0.19
Gender, male: female (%)	490 (54):425 (46)	35 (51):34 (49)	0.865
Body mass index, ≥25:<25 (%)	118 (13):761 (87)	6 (9):62 (91)	0.352
Diabetes mellitus, +:− (%)	382 (42):525 (58)	28 (41):41 (59)	0.899
Biliary drainage, +:− (%)	430 (47):485 (53)	15 (22):54 (78)	<0.001
Albumin, g/dL (range)	3.8 (1.8–5.5)	3.9 (2.2–4.7)	0.739
CRP, mg/dL (range)	0.2 (0–16.7)	0.1 (0–14.3)	0.066
Pre-op CA19-9, U/L (range)	109 (0–42,060)	171 (1.0–47,470)	0.023
Post-op CA19-9, U/L (range)	17 (0–10,061)	52 (1–2,339)	0.001
Rate of post-op CA19-9 normalization	69 %	46 %	<0.001
Location of cancer, Ph:Pbt (%)	664 (73):251 (27)	27 (39):42 (61)	<0.001
Tumor diameter, mm (range)	27 (5–86)	33 (14–200)	<0.001
NCCN resectability status R:BR/UR (%)	613 (67):302 (33)	41 (59):28 (41)	0.234
Neoadjuvant therapy, +:− (%)	247 (27):668 (73)	20 (29):49 (71)	0.779
Adjuvant therapy, +:− (%)	746 (82):167 (18)	59 (86):10 (14)	0.517

CY peritoneal washing cytology, *CRP* C-reactive protein, *CA19-9* carbohydrate antigen 19-9, *Ph* pancreatic head, *Pbt* pancreatic body and tail, *NCCN* National Comprehensive Cancer Network, *R* resectable, *BR* borderline resectable, *UR* unresectable

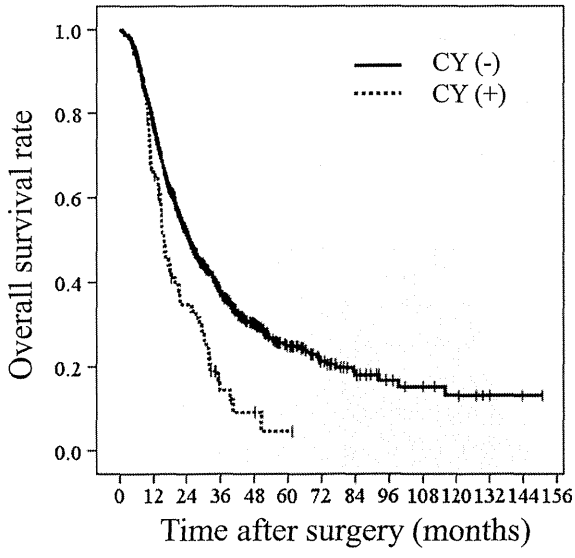
Table 2 Comparison of surgical and pathological parameters

Parameter	CY (−) n=915	CY (+) n=69	p value
Type of procedure, PpPD/PD:DP:TP (%)	300/330 (69):256 (28):29 (3)	8/15 (34):42 (60):4 (6)	<0.001
Operative time, minutes (range)	423 (101–1,160)	395 (137–727)	0.095
Extent of blood loss, mL (range)	1,000 (52–9,639)	1,160 (110–9,163)	0.146
Blood transfusion, +:− (%)	328 (36):584 (64)	25 (37):43 (63)	0.896
Concomitant resection of the artery, +:− (%)	76 (8):839 (92)	13 (19):56 (81)	0.007
Concomitant resection of the PV/SMV, +:− (%)	345 (38):570 (62)	26 (38):43 (62)	1.000
Overall complication, +:− (%)	357 (39):558 (61)	32 (46):37 (54)	0.251
In-hospital death, +:− (%)	18 (2.0):897	3 (4.3):66	0.178
Clavien score, 0-IIIA:IIIB-V (%)	868 (95):47 (5)	65 (94):4 (6)	0.777
Tumor differentiation, well:mod/por (%)	238 (26):677 (74)	12 (17):57 (83)	0.150
Lymph node metastasis, +:− (%)	593 (65):321 (35)	60 (87):9 (13)	<0.001
Lymph node ratio (range)	0.05 (0–0.88)	0.1 (0–0.67)	<0.001
R0:R1 (%)	706 (77):209 (23)	40 (58):29 (42)	0.001
T1/2:3/4 (%)	91 (10):824 (90)	3 (4):66 (96)	0.198
Stage 1:2:3:4 (%)	59 (7):786 (85):10 (1):60 (7)	0:0:0:69 (100)	<0.001

CY peritoneal washing cytology, *PpPD* pylorus preserving pancreaticoduodenectomy, *PD* pancreaticoduodenectomy, *DP* distal pancreatectomy, *TP* total pancreatectomy, *PV* portal vein, *SMV* superior mesenteric vein, *mod* moderate, *por* poor

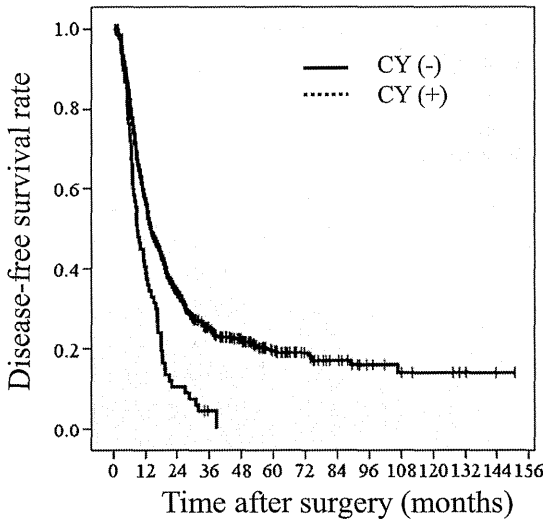
Comparisons of OS and DFS Between the CY+ and CY− Groups

The median duration of follow-up was 19.7 months. All patients were followed up for at least 1 year. OS in the CY+ group was significantly worse than that of the CY− group (MST, 16 vs. 25 months; p<0.001) (Fig. 1). OS rates at 1, 3, and 5 years were 77, 37, and 25 %, respectively, in the CY− group, and 45, 6, and 1 %, respectively, in the CY+ group. Overall, 59 of 69 patients in the CY+ group and 572 of 915 patients in the CY− group died. Similar results were observed upon comparison of DFS in the CY− and CY+ groups (8.8 vs. 13.8 months; p<0.001) (Fig. 2). DFS rates at 1, 3, and 5 years were 57, 25, and 19 %, respectively, in the CY− group, and



Patients at risk	1y	2y	3y	4y	5y	7.5y	10y	12.5y
CY (-) 915	697	355	204	120	64	16	6	1
CY (+) 69	65	35	14	9	5	0		

Fig. 1 Comparison of OS between patients with positive (n=69) and negative (n=915) cytology. OS in patients with CY+ (*dotted black line*) was significantly worse than that in patients with CY− (*solid black line*) (MST, 16 vs. 25 months; p<0.001). OS rates at 1, 3, and 5 years were 77, 37, and 25 %, respectively, in the CY− group, and 45, 6, and 1 %, respectively, in the CY+ group



Patients at risk	1y	2y	3y	4y	5y	7.5y	10y	12.5y
CY (-) 915	489	228	137	91	49	14	4	1
CY (+) 69	27	7	1	0				

Fig. 2 Comparison of DFS between patients with positive (n=69) and negative (n=915) cytology. DFS in patients with CY+ (*dotted black line*) was significantly worse than that in patients with CY− (*solid black line*) (median DFS, 8.8 vs. 13.8 months; p<0.001). DFS rates at 1, 3, and 5 years were 57, 25, and 19 %, respectively, in the CY− group, and 27, 1, and 0 %, respectively, in the CY+ group

27, 1, and 0 %, respectively, in the CY+ group. Overall, 65 of 69 patients in the CY+ group and 648 of 915 patients in the CY− group experienced disease recurrence.

Identification of Prognostic Factors in All Patients

As shown in Table 3, significant prognostic factors identified using univariate analysis included cytology status, pre-operative CA19-9 levels, tumor location, NCCN resectability status, arterial resection, portal/superior mesenteric vein resection, residual tumor grading, tumor differentiation, lymph node metastasis, and adjuvant therapy. In addition, multivariate analysis revealed CY− status, CA19-9 <115 U/L, resectable disease, R0 resection, negative lymph node metastasis, well-differentiated pathology, and use of post-operative adjuvant therapy to be significantly independent prognostic factors for better survival.

Primary Site of Recurrence

Patients in the CY+ group had a significantly higher frequency of post-operative peritoneal carcinomatosis as the primary site of recurrence compared to patients in the CY− group (49 vs. 21 %, $p<0.001$; Table 4). No differences in the rates of local recurrence or recurrence in the liver, lung, or other sites were observed between the two groups.

Identification of Prognostic Factors in the CY+ Group

Cox proportional hazards analysis in the CY+ subgroup revealed that the only independent significant factor for survival

Table 3 Univariate and multivariate cox proportional hazards analysis for overall survival: association with overall survival and patient, tumor, and treatment characteristics

Variable	No. (%)	MST (months)	Univariate analysis		Multivariate analysis			
	CY− vs. +	CY− vs. +	*p* value	Hazard ratio (95 % CI)	Estimate	SE	*p* value	Hazard ratio (95 % CI)
Group, CY− vs. +	915 vs. 69	24.9 vs. 16.0	<0.001	0.57 (0.44–0.75)	−0.31	0.15	0.035	0.74 (0.55–0.98)
Pre-op CA19-9, IU/L			<0.001	1.83 (1.56–2.15)	0.52	0.08	<0.001	1.68 (1.43–1.98)
≥115	447 vs. 41	18 vs. 16						
<115	464 vs. 28	34 vs. 15						
Tumor location			0.013	0.80 (0.67–0.96	−0.15	0.11	0.16	0.86 (0.70–1.06)
Pancreas body and tail	251 vs. 42	34 vs. 19						
Pancreas head	664 vs. 27	24 vs. 13						
NCCN resectability status			<0.001	0.56 (0.48–0.66)	−0.37	0.11	0.001	0.69 (0.56–0.86)
Resectable	613 vs. 41	32 vs. 19						
BR/UR	302 vs. 28	18 vs. 15						
Arterial resection			0.025	0.74 (0.58–0.96	−0.05	0.16	0.74	0.95 (0.70–1.30)
No	839 vs. 56	25 vs. 16						
Yes	76 vs. 13	21 vs. 14						
Portal vein resection			<0.001	0.64 (0.55–0.75)	−0.02	0.11	0.82	0.98 (0.79–1.21)
No	570 vs. 43	31 vs. 16						
Yes	345 vs. 26	18 vs. 16						
Residual tumor grading			<0.001	0.77 (0.71–0.84)	−0.25	0.09	0.006	0.78 (0.65–0.93)
R0	706 vs. 40	28 vs. 17						
R1	209 vs. 29	18 vs. 15						
Tumor differentiation			<0.001	0.65 (0.54–0.79)	−0.38	0.10	<0.001	0.69 (0.57–0.83)
Well	238 vs. 12	34 vs. 22						
Mod/por	677 vs. 57	22 vs. 16						
Lymph node metastasis			<0.001	0.72 (0.66–0.79)	−0.50	0.10	<0.001	0.61 (0.50–0.73)
No	321 vs. 9	40 vs. 29						
Yes	593 vs. 60	21 vs. 15						
Adjuvant therapy			<0.001	1.25 (1.14–1.38)	0.57	0.10	<0.001	1.77 (1.46–2.16)
No	167 vs. 10	14 vs. 10						
Yes	746 vs. 59	27 vs. 16						

MST median survival time, *CY* peritoneal washing cytology, *CA19-9* carbohydrate antigen 19-9, *NCCN* National Comprehensive Cancer Network, *BR* borderline resectable, *UR* unresectable, *mod* moderate, *por* poor, *CI* confidential interval, *SE* standard error

Table 4 Primary site of recurrence and median survival time according to metastatic site between the two groups

	Number of events	Primary site of recurrence				
		Peritoneum	Liver	Local	Lung	Others
CY+, n=69 (%)	65	31 (49 %)*	13 (20 %)	13 (20 %)	7 (11 %)	0
MST, month		11	17	26	30	-
CY−, n=915 (%)	648	132 (21 %)	210 (33 %)	180 (28 %)	86 (14 %)	26 (4 %)
MST, month		13	17	25	37	22

Data of the primary site of recurrence were missing in 1 patient in the CY+ group and 14 patients in the CY− group

CY peritoneal washing cytology, *MST* median survival time

*CY+ vs. CY−, p<0.001

was the presence of post-operative peritoneal carcinomatosis (hazard ratio, 2.65; 95 % confidential interval, 1.52–4.60; p=0.001). OS in patients with post-operative peritoneal carcinomatosis (n=31; MST, 11 months) was significantly worse than that in patients with other sites of recurrence (n=33; MST, 22 months; p<0.001, Fig. 3a). Data for the primary site of recurrence were missing for one patient. Adjuvant chemotherapy was administered to 86 % of patients in the CY+ group and 82 % of patients in the CY− group. No significant differences in OS were observed between patients who did (n=59; MST, 16 months) and did not (n=10; MST, 10 months) receive adjuvant therapy in the CY+ group (p=0.21) (Fig. 3b, Table 3). However, OS was significantly longer in patients who received adjuvant chemotherapy in the CY− group compared to patients who did not (MST, 27 vs. 14 months; p<0.001) (Table 3).

Discussion

PDAC is still associated with a dismal prognosis, and potential cure can only be achieved when the primary tumor is completely resected. However, the 5-year survival rate in patients who undergo resection is <20 %. Surgical resection is not usually indicated for PDAC with M1 disease, because the MST in patients with metastatic disease is only 6–8 months.[15,16] The AJCC/TNM staging system classifies positive cytology in the washing peritoneal fluid (CY+) as M1 disease,[13,14] and the NCCN pancreatic adenocarcinoma guidelines[11] state that positive cytology from washings (CY+) obtained at laparoscopy or laparotomy is equivalent to M1 disease. Even if resection has been performed in such patients, they should be treated as having M1 disease.

To date, only a limited number of studies on the post-operative prognosis of patients with CY+ have been

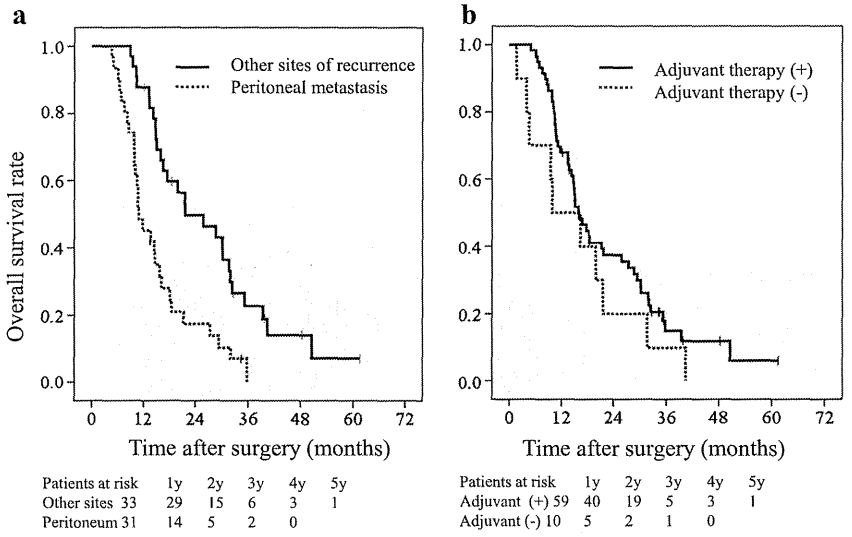


Fig. 3 Comparisons of OS by primary site of recurrence and adjuvant therapy in patients with positive cytology (n=69). **a** OS in patients with post-operative peritoneal carcinomatosis (n=31, *dotted black line*) was significantly worse than that in patients with recurrence in other sites (n=33, *solid black line*) (p<0.001). Data regarding the primary site of recurrence were missing for one patient in the CY+ group; the remaining four patients were free of disease. **b** No significant difference in survival was observed between patients who did (n=59, *solid black line*) and did not (n=10, *dotted black line*) receive adjuvant chemotherapy

conducted, as shown in Table 5. CY+ in patients with resectable[7] and unresectable[17] PDAC has been reported to negatively influence their prognosis. Some studies from Japan reported no significant difference in survival between CY+ and CY− patients.[8–10] The investigators in these studies concluded that CY status in the absence of other distant metastasis was not a contraindication for radical surgery, as surgical resection remained the only modality that offers a chance for long-term survival. However, as only approximately 10–20 patients with CY+ were statistically evaluated in these previous studies,[8–10] their statistical power was not sufficiently strong. Very recently, Yamada et al. re-evaluated the clinical impact of CY+ in patients who underwent surgical resection from 1991 to 2012.[18] The OS of patients with resected CY+ tumors (n=51) was worse than that of patients with resected CY− tumors (n=339). The current study also showed that from 2001 to 2011, survival in the 69 patients with CY+ was significantly worse than that of the 915 patients with CY−. Moreover, the present multivariate analysis revealed that cytology status was an independent prognostic factor. Thus, this large-scale study clearly demonstrated the negative impact of surgical resection in patients with CY+ on their prognosis. However, Yamada et al.[18] stated that the survival of 51 resected patients with CY+ (MST, 14 months) was significantly better than that of 133 unresected patients regardless of CY status (MST, 7 months). The MST of the CY+ group in the present study was 16 months, which appears to be better than the 6–12 months reported for modern chemotherapy regimens in patients with unresectable PDAC.[15,16,19–21] However, the MST in locally advanced PDAC patients who underwent chemoradiation was reported to be approximately 16 months in recent phase II studies.[22,23] Thus, the current study showed that the MST in patients with M1 disease with CY+ who underwent margin-negative resection was acceptable compared to MSTs achieved with other treatment modalities.

Although margin-negative resection provides the only chance for long-term survival in patients with pancreatic ductal adenocarcinoma, the 5-year survival rates range from 3 to 17 %.[1–5] In the present study, the 3- and 5-year OS rates were 37 and 25 %, respectively, in the CY− group, and 6 and 1 %, respectively, in the CY+ group. Patients in the CY+ group were less likely to be alive >3 years after surgical resection, as evidenced by 3- and 5-year DFS rates of only 1 and 0 %, respectively. With a median follow-up duration of 19.7 months, only 4 of 69 patients (5.8 %) in the CY+ group were free of disease, compared to 267 of 915 patients (29.2 %) in the CY− group. Similar 3-year OS and DFS rates of <10 % in CY+ patients have also been observed in other studies.[7,8,18] Thus, CY+ patients appear to have a high incidence of recurrent disease at 3 years after surgical resection, resulting in fewer long-term survivors. Moreover, patients in the CY+ group were significantly more likely to develop peritoneal carcinomatosis as the primary site of recurrence compared to patients in the CY− group (49 vs. 21 %). Among patients in the CY+ group, no pre-operative, surgical, or pathological factors were identified as prognostic factors; development of peritoneal carcinomatosis as the primary site of recurrence was the only prognostic factor identified. Moreover, survival in patients with peritoneal carcinomatosis was significantly worse than that in patients with other sites of recurrence. Motoi et al.[12] reported that even in patients who underwent R0 resection, sustained elevation of post-operative CA19-9 levels was accompanied by poor prognosis which was associated with distant metastases. In the present study, the significantly lower incidence of post-operative CA19-9 normalization in the CY+ group may reflect the potential micrometastasis that occurs during margin-negative resection and may therefore be associated with the higher incidence of disease recurrence relative to that of the CY− group. Thus, CY+ status should be considered as a specific subgroup in future survival analyses of PDAC patients.

The introduction of advanced adjuvant chemotherapy regimens may prevent potential microscopic residual disease and micrometastasis during or immediately after surgical resection. A potentially beneficial effect of adjuvant therapy in CY+ patients has been observed in previous studies.[8,18] The authors of these studies concluded that as surgical resection remains the only treatment modality that offers a chance for long-term survival, and considering the efficacy of modern chemotherapy regimens in eliminating micrometastases, margin-negative resection should be offered to patients with

Table 5 Recent reports on pancreatic cancer patients with positive peritoneal washing cytology who underwent surgical resection

First author	Publication year	Study period	CY(+)/surgical resection	MST (CY+ vs. CY−, months)	p value
Yachida[10]	2002	1990–1999	16/130 (12.3 %)	18 vs. 15	0.347
Ferrone[7]	2006	1995–2005	10/217 (4.6 %)	8 vs. 16	<0.0001
Yamada[9]	2007	1991–2006	21/157 (13.4 %)	14 vs. 14	0.269
Yoshioka[8]	2012	2003–2010	20/254 (7.9 %)	24 vs. 27	0.302
Yamada[18]	2013	1991–2012	51/390 (13.1 %)	14 vs. 18	0.009
Current study	2014	2001–2012	69/984 (7.0 %)	16 vs. 25	<0.001

CY peritoneal washing cytology, *MST* median survival time

PDAC, regardless of CY status. However, in the present study, administration of gemcitabine- or S-1-based adjuvant chemotherapy did not provide a favorable survival outcome in CY+ patients. This result may be indicative of the limitations of current adjuvant chemotherapy regimens. Recent progress in chemotherapy regimens has been closely associated with the improved prognosis of patients with unresectable PDAC.[15,16,19–21] However, no studies regarding the clinical efficacy of chemotherapy in patients with peritoneal carcinomatosis of pancreatic origin have been published. Thomassen et al.[24] stated that the biological response to systemic chemotherapy may differ between patients with peritoneal carcinomatosis and patients with liver metastasis due to the different blood supplies to the metastatic sites and/or different biological responses to cytotoxic agents. A CY+ finding indicates a risk of development of peritoneal carcinomatosis; thus, controlling the development of peritoneal carcinomatosis in patients with CY+ is an important issue. There are two approaches for treating such patients in the clinical setting. In some centers, the use of diagnostic laparoscopy is limited and intraoperative cytology is not available. In such a situation, we advocate surgical resection followed by effective adjuvant chemotherapy using extensive intraoperative peritoneal lavage,[25] heated intraperitoneal chemotherapy (HIPEC),[26,27] or systemic and intraperitoneal chemotherapy[28] in patients with CY+ in a clinical trial setting. We also advocate the selective use of diagnostic laparoscopy in patients at risk for occult distant organ metastasis. Chemotherapy for controlling peritoneal carcinomatosis should be first administered in such patients, and surgical resection should be selectively performed in patients with long-term favorable responses to chemotherapy. These approaches should be appropriately used according to the availability of staging laparoscopy and intraoperative cytology in each institution. This issue must be addressed in future randomized control trials.

The current study has some limitations. The first limitation is that it was conducted in a retrospective fashion with a hidden bias; however, it should be noted that prospective data collection is difficult in patients with CY+ who undergo surgical resection. The second limitation is that this study included only a small number of patients with CY+ (n=69); however, this is the largest database of such patients to date. It is particularly notable that our database had a relatively small amount of missing data. Other limitations include a lack of central review of cytologic results, a lack of quantification of the degree of cytologic abnormalities, and the varieties of neoadjuvant and adjuvant chemotherapy regimens that were used, which can influence survival in patients.

In conclusion, the results of the current study showed that PDAC patients with CY+ who underwent margin-negative resection had an acceptable MST. However, a high rate of peritoneal carcinomatosis was observed within 3 years after margin-negative resection, resulting in decreased long-term survival. Therefore, the development of a new strategy to control post-operative peritoneal carcinomatosis is required to obtain long-term survival when surgical resection is performed.

Conflict of Interest The authors have no conflicts of interest to disclose.

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Discussant

Dr. Steven J Hughes (Gainesville, FL):

The peritoneum is a rich soil for cancerous seeds, and carcinomatosis is a devastating development for pancreatic cancer patients. The authors' findings that CY+ is a profound indicator of poor prognosis are intuitive, and I rise to applaud your thoughtful study design and careful analysis of data from a truly impressive series of pancreas cancer patients. I would also like to thank the authors for providing me with a copy of the manuscript well in advance of the meeting. I have two questions.

Question #1: I am inclined to think that positive cytology should be indicative of subsequent carcinomatosis. I can understand why carcinomatosis was not subsequently identified in approximately half of the CY+ patients; cross-sectional imaging struggles to accurately diagnose this condition. Nonetheless, your data would suggest that current methods of cytology are not particularly specific for the development of clinically relevant carcinomatosis. More importantly in my mind, 21 % of CY− patients did subsequently develop carcinomatosis. Thus, this data suggests this particular assay may lack sensitivity. What are the authors' opinions regarding the sensitivity and specificity of peritoneal washings and how should that impact our interpretation of the data.

Question #2: For pancreatic adenocarcinoma, the NCCN guidelines characterize positive cytology as M1 disease, yet some authors have advocated proceeding with curative resection in this setting based upon data that your study would suggest suffered from Type II error. In your series, 7 % of patients proved to have positive cytology. How would you suggest we apply your findings to current clinical practice? Specifically, do you advocate diagnostic laparoscopy with peritoneal washings as a separate procedure? Are there barriers to intraoperative cytology?

Closing Discussant

Dr. Satoi:

Answer #1. I greatly appreciate your very important suggestions. The current study was retrospectively performed in a multi-center setting, and cytology analysis was conducted using Papanicolou and May-Giemsa staining, not with molecular techniques. As Dr. Hughes indicated, I agree that current cytology methods may not be particularly specific. The current method of cytology for predicting subsequent peritoneal carcinomatosis as the primary site of recurrence showed sensitivity of 15 %, specificity of 95 %, a positive predictive value of 49 %, and a negative predictive value of 21 %. However, it is difficult to accurately evaluate the sensitivity and specificity of peritoneal washing because the second site of recurrence was not recorded in this database. Therefore, we could not evaluate the overall rate of peritoneal recurrence. We should conduct a prospective study to evaluate this issue.

We would like to share the data from a Korean multi-center randomized control trial that showed that extended lymph node dissection was significantly associated with a high rate (25 %) of peritoneal carcinomatosis relative to the 9 % rate in patients who underwent standard lymphadenectomy. In the current study, extended lymph node dissection had been routinely performed at the seven institutions. I therefore think that patients with CY− may have had a high frequency of peritoneal carcinomatosis due to extended lymph node dissection.

Answer #2. First, we strongly suggest that peritoneal washing cytology should be done in pancreatic cancer patients who undergo planned surgical resection in all centers to select patients with CY+. Although we recognize that CY+ can be a prognostic factor and a risk factor for the development of peritoneal carcinomatosis after surgical resection, margin-negative resection might not be a good surgical indication in patients with CY+ but should not be a contraindication. The important issue for such patients is to control the development of peritoneal carcinomatosis and malignant ascites. There are two potential approaches for treating such patients. The availability of diagnostic laparoscopy is limited and intraoperative cytology is not available in some centers. In such a situation, we advocate surgical resection followed by effective adjuvant chemotherapy such as hyperthermic intraperitoneal chemotherapy or intravenous and intraperitoneal chemotherapy in patients with CY+ in a clinical trial setting. We also advocate the selective use of diagnostic laparoscopy in patients at risk for occult distant organ metastasis. Chemotherapy for controlling the development of peritoneal carcinomatosis should be first administered in such patients, and surgical resection should be selectively performed in patients with long-term favorable responses to chemotherapy. These approaches should be appropriately used according to the availability of staging laparoscopy and intraoperative cytology in each institution.

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ORIGINAL SCIENTIFIC REPORT

Preservation of the Left Gastric Artery on the Basis of Anatomical Features in Patients Undergoing Distal Pancreatectomy with Celiac Axis En-bloc Resection (DP-CAR)

Ken-ichi Okada · Manabu Kawai · Masaji Tani · Seiko Hirono · Motoki Miyazawa · Atsushi Shimizu · Yuji Kitahata · Hiroki Yamaue

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Abstract

Background The incidence of delayed gastric emptying (DGE) is high in patients undergoing distal pancreatectomy with celiac axis en-bloc resection (DP-CAR).

Methods The medical records of 37 consecutive patients who underwent DP-CAR were evaluated for the incidence of DGE in 23 patients (62 %) with left gastric artery (LGA)-resecting DP-CAR (conventional DP-CAR) compared with 14 patients (38 %) who underwent distal pancreatectomy with resection of the common hepatic artery and splenic artery, with preservation of the LGA (modified DP-CAR) for pancreatic carcinoma. The patients with tumors situated more than 10 mm away from the antecedent branching LGA underwent modified DP-CAR.

Results Antecedent branching of the LGA was found in 19 patients (51 %) in this series. In the conventional DP-CAR group, the LGA was involved in 20 patients (87.0 %). The International Study Group of Pancreatic Surgery (ISGPS) grades for the conventional DP-CAR group were as follows: no DGE = 43 %, grade A = 26 %, B = 13 %, and C = 17 %. In the modified DP-CAR group, they were as follows: no DGE = 93 %, grade A = 7 %, and grade B/C = 0 %. The R0 rate was higher in the modified DP-CAR group (79 %) than in the conventional DP-CAR group (43 %) ($p = 0.048$). Univariate analyses revealed resection of LGA, residual tumor status (R1), and clinically relevant (Grade B, C) pancreatic fistula increased the risk of DGE. On multivariate analysis, resection of the LGA was an independent risk factor for increased incidence of DGE.

Conclusion Modified DP-CAR, when it is feasible, significantly reduces the incidence of DGE in comparison with conventional DP-CAR.

Introduction

Excellent results have recently been reported for distal pancreatectomy with celiac axis en-bloc resection (DP-CAR), with an R0 resection rate of 91 % (21/23), a mortality rate of 0 %, and an estimated 5-year survival probability of 42 % [1]. However, delayed gastric emptying (DGE) or ischemic gastropathy after DP-CAR is a persistent and frustrating complication [1, 2]. DGE induced by ischemic gastropathy, with an incidence varying from 13.0 to 30.8 % in previous series [1, 3], is not a life-threatening complication, but results in a prolonged hospital stay and leads to a decreased quality of life (QOL), poorer nutritional status, and delayed administration of postoperative adjuvant chemotherapy. In a recent study, seven of 13 patients underwent combined total gastrectomy to prevent gastric ischemic complications during DP-CAR [3].

The left gastric artery (LGA) develops as the first branch of the celiac trunk embryologically, and it has been reported to branch antecedently in 68–72 % of cases as a first branch of trifurcation in previous studies [4–10].

K. Okada · M. Kawai · M. Tani · S. Hirono · M. Miyazawa · A. Shimizu · Y. Kitahata · H. Yamaue (✉)
Second Department of Surgery, Wakayama Medical University, 811-1 Kimiidera, Wakayama, Japan
e-mail: yamaue-h@wakayama-med.ac.jp