CT was also alternately performed every 2–3 months as the imaging follow-up. If a recurrence was suspected by ultrasonography, contrast enhancement dynamic CT was performed at that time to reconfirm the lesion.

The image findings were reported by blinded radiologists and the presence of an intrahepatic recurrence was determined by the existence of a hypervascular nodule in early phase with a perfusion defect in the portal phase under contrast enhancement dynamic CT. If an extrahepatic recurrence was suspected, lung CT or bone scintigraphy was performed. An extrahepatic recurrence was determined by the existence of a tumor. After detecting any recurrence, appropriate therapeutic modalities were administered, and the same surveillance was performed.

The primary outcome in this study was defined as the recurrence-free survival especially within 2 years after hepatectomy and the secondary outcome in this study was defined as the overall survival.

Data Collection

The following 16 variables were collected for each patient as potent risk factors for recurrence and survival: age, gender, etiology of underlying liver disease (hepatitis C virus [HCV], hepatitis B virus [HBV], and daily alcohol intake), Child-Pugh score (A or B), indocyanine green retention rate at 15 min (ICG R_{15}), The Cancer of the Liver Italian Program (CLIP) score (0, 1, 2, or 3), primary tumor size, number of tumors (single or multiple), vascular involvement (negative or positive), serum AFP levels, liver resection procedure (major or minor), resection margin (R0 or R1), tumor differentiation (well, moderate, or poor) and blood loss during the operation.

Tumor size, number and vascular involvement were measured by the resection specimen. Resection margin and tumor differentiation were pathologically defined. More than sectionectomy and lobectomy were defined as major liver resection and the others were defined as minor liver resection.

Additionally continuous variables of age, ICG R_{15}, main tumor size, serum AFP levels, blood loss were also categorized by cutoff values of 69 years old, 15%, 5 cm, 400 IU/ml, and 880 ml, respectively.

Statistical Analyses

Continuous variables were expressed as the medians with interquartile ranges and compared by the Mann–Whitney *U*-test. Dichotomous variables were compared by the Chi-square test or Fisher's exact test. Recurrence-free survival and the overall survival rate were analyzed by the Kaplan–Meier method and log rank test.

In order to adjust for confounding variables, chemolipiodolization and 16 collected variables were analyzed univariately by a Cox proportional hazard model for recurrence-free survival and overall survival and then potent significant variables were entered into multivariate analyses. *P* values of <0.05 were considered statistically significant.

RESULTS

The patient backgrounds between those treated with and without adjuvant chemolipiodolization therapy are

TABLE 1 Patients backgrounds between those treated with or without chemolipiodolization

Variable	Chemolipiodolization		*P* value
	(−) (n = 64)	(+) (n = 63)	
Age (year)	67 (63, 73)	70 (65, 76)	0.08
Gender (male/female)	44/20	53/10	0.04
HCV antibody (+/−)	41/23	31/32	0.09
HBs antigen (+/−)	8/56	7/56	0.81
Daily alcohol intake (+/−)	19/45	25/38	0.24
Child-Pugh score (A/B)	58/6	60/3	0.31
ICG R_{15} (%)	9.9 (7.6, 14.4)	15.0 (10.0, 20.0)	<0.001
CLIP score (0/1/2/3)	30/20/12/2	30/19/13/1	0.94
Primary tumor size (cm)	4.1 (2.8, 6.6)	4.5 (2.9, 6.4)	0.96
No. of tumors (single/multiple)	48/16	46/17	0.79
Vascular involvement (+/−)	11/53	12/51	0.78
Serum AFP levels (ng/ml)	28.6 (6.0, 136.0)	14.3 (6.1, 162.8)	0.75
Liver resection (major/minor)	36/28	32/31	0.54
Resection margin (R1/R0)	4/60	5/58	0.74
Tumor differentiation (well/moderate/poor)	13/48/3	14/38/11	0.06
Blood loss (ml)	978 (513, 1850)	740 (420, 1335)	0.09

Continuous variables are expressed as the medians (25th, 75th percentile)

HBs hepatitis B surface, *CLIP* cancer of the liver Italian program

summarized in Table 1. The distributions of gender and ICG R_{15} were different between the two groups. However, the Child-Pugh score was similar between the two groups. The tumor status, such as tumor size, number of tumors, presence of vascular involvement, serum AFP levels, and tumor pathological differentiation were not statistically significantly different between the two groups. Therefore, the distributions of the CLIP scores were similar between the two groups. The surgical parameters such as operation procedure, resection margin, and blood loss were not different between the two groups.

There were no complications higher than grade 3 in Common Terminology Criteria for Adverse Event among the patients who received adjuvant chemolipiodolization.

The recurrence-free survival curves after surgery for each group are shown in Fig. 1. At 2 years after surgery, recurrences were observed in 40 patients (63%) without chemolipiodolization. On the other hand, 27 patients (43%) with chemolipiodolization experienced recurrence ($P = 0.02$). However, at 5 years after hepatectomy, these curves were no longer significantly different ($P = 0.09$).

The overall survival curves after hepatectomy for each group are shown in Fig. 2. Although the duration of observation was different between the two groups (the median follow-up period was 35 months in the chemolipiodolization-positive group and 53 months in the chemolipiodolization-negative group), the overall survival rates of the chemolipiodolization-positive and -negative groups were 92.1 and 82.8% at 2 years after surgery ($P = 0.12$) and were 82.4 and 55.7% at 5 years after surgery ($P = 0.04$).

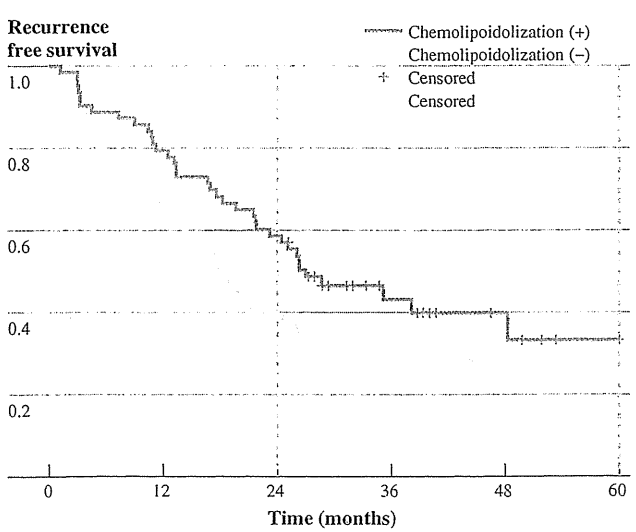

FIG. 1 Kaplan–Meier recurrence-free survival curves of patients with adjuvant chemolipiodolization and those without. The log rank test was performed at 2 and 5 years after the surgery ($P = 0.02$ and 0.09, respectively)

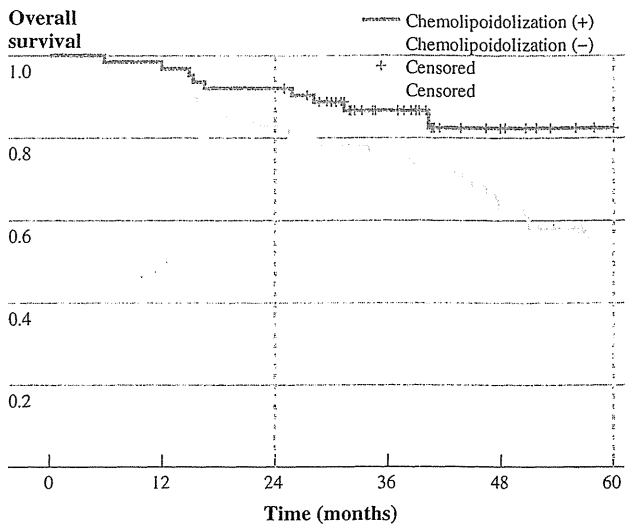

FIG. 2 Kaplan–Meier overall survival curves of patients with adjuvant chemolipiodolization and those without. The log rank test was performed at 2 and 5 years after the surgery ($P = 0.12$ and 0.04, respectively)

In order to evaluate the independent prognostic factors for 2-year recurrence-free survival after hepatectomy, a Cox proportional hazard model was used (Table 2). In univariate analysis, the number of tumors, blood loss and chemolipiodolization were recognized as potent prognostic factors. The odds ratios [95% confidential interval (CI)] were 2.16 [1.31–3.57], 1.67 [1.03–2.71] and 0.51 [0.29–0.87], respectively. To adjust for confounding factors, these three variables were entered into multivariate analysis. The number of tumors and chemolipiodolization were recognized to be independent factors, and the odds ratios [95% CI] were 1.57 [1.35–3.73] and 0.55 [0.34–0.90], respectively.

A Cox proportional hazard model was also used in order to evaluate the independent prognostic factors for overall survival after hepatectomy (Table 3). In univariate analysis, gender, primary tumor size, number of tumors, poor differentiation, blood loss and chemolipiodolization were recognized as potent prognostic factors. The odds ratios [95% CI] for these factors were 2.22 [1.12–4.40], 2.67 [1.35–5.26], 2.65 [1.31–5.17], 4.14 [1.11–15.5], 2.15 [1.07–4.32] and 0.46 [0.21–0.98], respectively. In this study, there were 35 survival events. In multivariate analysis there need to be 10–15 events per variable; therefore, the top three variables (primary tumor size, number of tumors and blood loss) were entered into multivariate analysis. Only the number of tumors was found to be an independent factor for overall survival, with an odds ratio [95% CI] of 2.18 [1.08–4.37].

The patient outcome in terms of recurrence data at 2 years after surgery is shown in Table 4. The recurrence

TABLE 2 Univariate and multivariate analyses of prognostic factors for recurrence within 2 years after hepatectomy

Variable	*N*	Univariate analysis			Multivariate analysis		
		Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age							
<69 (year)	64	1					
≥69 (year)	63	0.88	0.55–1.42	0.61			
Gender							
Male	97	1					
Female	30	1.49	0.87–2.56	0.15			
HCV antibody							
(−)	55	1					
(+)	72	1.61	0.98–2.65	0.06			
HBs antigen							
(−)	112	1					
(+)	15	0.54	0.22–1.35	0.19			
Daily alcohol intake							
(−)	83	1					
(+)	44	1.03	0.63–1.69	0.90			
Child-Pugh score							
A	118	1					
B	9	1.06	0.39–2.93	0.90			
ICG R_{15}							
<15%	78	1					
≥15%	49	0.93	0.57–1.53	0.78			
Primary tumor size							
≤5 cm	75	1					
>5 cm	52	1.43	0.89–2.32	0.14			
Number of tumors							
Single	94	1			1		
Multiple	33	2.16	1.31–3.57	0.003	1.57	1.35–3.73	0.002
Vascular involvement							
(−)	104	1					
(+)	23	1.37	0.76–2.48	0.29			
Serum AFP levels							
<400 ng/ml	105	1					
≥400 ng/ml	22	1.60	0.89–2.88	0.12			
Liver resection							
Minor	59	1					
Major	68	1.13	0.70–1.83	0.62			
Resection margin							
R0	118	1					
R1	9	1.10	0.45–2.43	0.91			
Tumor differentiation							
Well	27	1					
Moderate	86	1.26	0.68–2.32	0.46			
Poor	14	1.35	0.54–3.38	0.52			
Blood loss							
<880 ml	65	1			1		
≥880 ml	62	1.67	1.03–2.71	0.04	1.57	0.96–2.56	0.07
Chemolipiodolization							
(−)	64	1			1		
(+)	63	0.51	0.29–0.87	0.01	0.55	0.34–0.90	0.02

HBs hepatitis B virus surface

TABLE 3 Univariate and multivariate analyses of prognostic factors for overall survival

Variable	*N*	Univariate analysis			Multivariate analysis		
		Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age							
<69 (year)	64	1					
≥69 (year)	63	1.37	0.70–2.67	0.36			
Gender							
Male	97	1					
Female	30	2.22	1.12–4.40	0.02			
HCV antibody							
(−)	55	1					
(+)	72	1.86	0.91–3.80	0.09			
HBs antigen							
(−)	112	1					
(+)	15	0.37	0.09–1.55	0.17			
Daily alcohol intake							
(−)	83	1					
(+)	44	0.64	0.30–1.37	0.25			
Child-Pugh score							
A	118	1					
B	9	1.27	0.39–4.15	0.70			
ICG R_{15}							
<15%	78	1					
≥15%	49	0.74	0.35–1.54	0.42			
Primary tumor size							
≤5 cm	75	1			1		
>5 cm	52	2.67	1.35–5.26	0.005	2.00	0.98–4.01	0.06
Number of tumors							
Single	94	1			1		
Multiple	33	2.65	1.31–5.17	0.006	2.18	1.08–4.37	0.03
Vascular involvement							
(−)	104	1					
(+)	23	1.96	0.94–4.10	0.07			
Serum AFP levels							
<400 ng/ml	105	1					
≥400 ng/ml	22	1.66	0.76–3.67	0.21			
Liver resection							
Minor	59	1					
Major	68	1.21	0.62–2.37	0.57			
Resection margin							
R0	118	1					
R1	9	1.13	0.35–3.69	0.84			
Tumor differentiation							
Well	27	1					
Moderate	86	2.42	0.84–6.95	0.10			
Poor	14	4.14	1.11–15.5	0.04			
Blood loss							
<880 ml	65	1			1		
≥880 ml	62	2.15	1.07–4.32	0.03	1.72	0.84–3.54	0.14
Chemolipiodolization							
(−)	64	1					
(+)	63	0.46	0.21–0.98	0.04			

HBs hepatitis B virus surface

TABLE 4 Patterns of recurrence at 2 years after hepatectomy

Pattern of recurrence	Chemolipiodolization	
	(−)	(+)
Intrahepatic metastasis		
≤3 nodules	21	14
>3 nodules	17	9
Extrahepatic metastasis	2	4

patterns were not statistically significantly different between the two groups.

DISCUSSION

This study revealed that adjuvant chemolipiodolization could reduce recurrences at 2 years after surgery, which implies that it can prevent intrahepatic metastasis (IM). Moreover, a multivariate Cox proportional hazard model revealed that adjuvant chemolipiodolization was an independent favorable factor for reducing recurrences at 2 years after hepatectomy. However, this effect disappeared at 5 years after surgery, which suggests that the technique does not effectively prevent MC.

Concerning the survival outcome, chemolipiodolization appeared to improve the overall survival at 5 years after surgery. The patients with earlier recurrence tend to have a less favorable outcome.[3,6,25] Therefore, reducing IM recurrences by adjuvant chemolipiodolization would affect the overall survival at 5 years after surgery. However, adjuvant chemolipiodolization was not an independent favorable prognostic factor for overall survival in this study. This might be because the duration of follow-up observation in the chemolipiodolization-positive group was relatively short, and did not provide sufficient statistical power for the multivariate Cox proportional hazard model.

Previously ^{131}I-lipiodol was reported in various countries as an adjuvant therapy after curative liver resection for HCC that provided a favorable survival benefit.[14,21,22,26] In studies performed in China and France, ^{131}I-lipiodol provided prolonged survival benefit on recurrence-free and overall survival, and the effect was sustained for 5–7 or 8 years after surgery.[26,27] However, in contrast to these studies, a study from Italy which evaluated the prognostic impact of ^{131}I-lipiodol on HCV-associated HCC revealed that the improvement of disease-free survival rate was only over the short term, up to 15 months, and that the advantage had faded at 36 months after surgery.[22] In the previous Chinese study, more than 80% of the patient population had HBV infection. In the French study, although the prevalence of viral hepatitis was not described in the report, alcoholic hepatitis was the leading cause of HCC and was responsible for 60% of all HCC cases in France.[28] Contrary to the previous studies, the underlying liver disease in the present study was HCV hepatitis in 56.7% of patients (72 of 127), HBV hepatitis in 11.8% of patients (15 of 127) and other nonviral etiology in 33.1% of patients (42 of 127). As Japanese HCC was primarily the result of HCV hepatitis, the beneficial effect of adjuvant lipiodolization would be predicted to be similar to the Italian study, because it appears that the efficacy of chemolipiodolization is influenced by the underlying liver disease.

Adjuvant interferon (IFN) therapy is also a candidate for preventing HCC recurrences. Although IFN was reported to have direct antitumor effects, most previous studies administered IFN expecting an additional effect on hepatitis C, and reported favorable results.[29–31] From one randomized, controlled study for HCV-associated HCC, adjuvant IFN therapy could not prevent recurrences within 2 years from surgery, but could greatly reduce late recurrences that occurred more than 2 years after surgery.[32] This would indicate that treatment of the underlying viral hepatitis is more important for reducing late or MC recurrences. Therefore, a combination of therapeutic strategies targeted for reducing IM recurrences by using our approach and for MC recurrences by using IFN should be examined in order to determine whether the incidence of intrahepatic recurrences can be further reduced.

This study has some limitations. The most problematic limitation is that this study is not a randomized prospective study. Therefore, some confounders might affect our results. However, multivariate analysis revealed that adjuvant chemolipiodolization was an independent favorable factor for reducing early recurrences. Second, the patient occurred recurrence within 3 months after surgery was administered TACE instead of adjuvant chemolipiodolization in this study and which might bias our results. However, excluding these patients from analysis would bring another selection bias. Therefore, this study was performed by intention-to-treat fashion. Third, in survival analysis, the duration of follow-up observation was not very long in the chemolipiodolization group. Therefore, further follow-up will be needed for a more definitive survival analysis and a prospective study also will be needed to verify our retrospective result.

In conclusion, adjuvant chemolipiodolization could reduce the incidence of recurrences for 2 years after curative resection, and resulted in a favorable overall survival at 5 years after the surgery. However, this effect was limited to reducing IM (early) recurrences. In order to further prevent recurrences, a strategy for reducing MC (late) recurrences will be needed. A combination of chemolipiodolization with antiviral therapy could provide additional survival benefit in cases where virus-associated HCC is dominant.

REFERENCES

1. Imamura H, Matsuyama Y, Tanaka E, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol.* 2003;38:200–7.
2. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology.* 1999;30:1434–40.
3. Poon RT, Fan ST, Ng IO, Lo CM, Liu CL, Wong J. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. *Cancer.* 2000;89: 500–7.
4. Takenaka K, Adachi E, Nishizaki T, et al. Possible multicentric occurrence of hepatocellular carcinoma: a clinicopathological study. *Hepatology.* 1994;19:889–94.
5. Chen PJ, Chen DS, Lai MY, et al. Clonal origin of recurrent hepatocellular carcinomas. *Gastroenterology.* 1989;96:527–9.
6. Portolani N, Coniglio A, Ghidoni S, et al. Early and late recurrence after liver resection for hepatocellular carcinoma: prognostic and therapeutic implications. *Ann Surg.* 2006;243: 229–35.
7. Sakon M, Umeshita K, Nagano H, et al. Clinical significance of hepatic resection in hepatocellular carcinoma: analysis by disease-free survival curves. *Arch Surg.* 2000;135:1456–9.
8. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. *Hepatology.* 1998;28:751–5.
9. Tateishi R, Yoshida H, Shiina S, et al. Proposal of a new prognostic model for hepatocellular carcinoma: an analysis of 403 patients. *Gut.* 2005;54:419–25.
10. Yamamoto J, Kosuge T, Takayama T, et al. Perioperative blood transfusion promotes recurrence of hepatocellular carcinoma after hepatectomy. *Surgery.* 1994;115:303–9.
11. Eguchi S, Kanematsu T, Arii S, et al. Comparison of the outcomes between an anatomical subsegmentectomy and a non-anatomical minor hepatectomy for single hepatocellular carcinomas based on a japanese nationwide survey. *Surgery.* 2008;143:469–75.
12. Katz SC, Shia J, Liau KH, et al. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. *Ann Surg.* 2009;249:617–23.
13. Yamamoto M, Arii S, Sugahara K, Tobe T. Adjuvant oral chemotherapy to prevent recurrence after curative resection for hepatocellular carcinoma. *Br J Surg.* 1996;83:336–40.
14. Lau WY, Leung TW, Ho SK, et al. Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomised trial. *Lancet.* 1999;353:797–801.
15. Izumi R, Shimizu K, Iyobe T, et al. Postoperative adjuvant hepatic arterial infusion of lipiodol containing anticancer drugs in patients with hepatocellular carcinoma. *Hepatology.* 1994;20: 295–301.
16. Takenaka K, Yoshida K, Nishizaki T, et al. Postoperative prophylactic lipiodolization reduces the intrahepatic recurrence of hepatocellular carcinoma. *Am J Surg.* 1995;169:400–4.
17. Li JQ, Zhang YQ, Zhang WZ, Yuan YF, Li GH. Randomized study of chemoembolization as an adjuvant therapy for primary liver carcinoma after hepatectomy. *J Cancer Res Clin Oncol.* 1995;121:364–6.
18. Takayama T, Sekine T, Makuuchi M, et al. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. *Lancet.* 2000;356:802–7.
19. Mathurin P, Raynard B, Dharancy S, et al. Meta-analysis: evaluation of adjuvant therapy after curative liver resection for hepatocellular carcinoma. *Aliment Pharmacol Ther.* 2003;17: 1247–61.
20. Samuel M, Chow PK, Chan Shih-Yen E, Machin D, Soo KC. Neoadjuvant and adjuvant therapy for surgical resection of hepatocellular carcinoma. *Cochrane Database Syst Rev.* 2009;1: CD001199.
21. Boucher E, Corbinais S, Rolland Y, et al. Adjuvant intra-arterial injection of iodine-131-labeled lipiodol after resection of hepatocellular carcinoma. *Hepatology.* 2003;38:1237–41.
22. Tabone M, Vigano L, Ferrero A, Pellerito R, Carbonatto P, Capussotti L. Prevention of intrahepatic recurrence by adjuvant (131)iodine-labeled lipiodol after resection for hepatocellular carcinoma in HCV-related cirrhosis. *Eur J Surg Oncol.* 2007;33:61–6.
23. Shimoda M, Bando T, Nagata T, Shirosaki I, Sakamoto T, Tsukada K. Prophylactic chemolipiodolization for postoperative hepatoma patients. *Hepatogastroenterology.* 2001;48:493–7.
24. Tanaka K, Shimada H, Togo S, et al. Use of transcatheter arterial infusion of anticancer agents with lipiodol to prevent recurrence of hepatocellular carcinoma after hepatic resection. *Hepatogastroenterology.* 1999;46:1083–8.
25. Shimada M, Takenaka K, Gion T, et al. Prognosis of recurrent hepatocellular carcinoma: a 10-year surgical experience in Japan. *Gastroenterology.* 1996;111:720–6.
26. Lau WY, Lai EC, Leung TW, Yu SC. Adjuvant intra-arterial iodine-131-labeled lipiodol for resectable hepatocellular carcinoma: a prospective randomized trial-update on 5-year and 10-year survival. *Ann Surg.* 2008;247:43–8.
27. Boucher E, Bouguen G, Garin E, Guillygomarch A, Boudjema K, Raoul JL. Adjuvant intraarterial injection of 131i-labeled lipiodol after resection of hepatocellular carcinoma: progress report of a case-control study with a 5-year minimal follow-up. *J Nucl Med.* 2008;49:362–6.
28. Chevret S, Trinchet JC, Mathieu D, Rached AA, Beaugrand M, Chastang C. A new prognostic classification for predicting survival in patients with hepatocellular carcinoma. Groupe d'etude et de traitement du carcinome hepatocellulaire. *J Hepatol.* 1999;31:133–41.
29. Damdinsuren B, Nagano H, Sakon M, et al. Interferon-beta is more potent than interferon-alpha in inhibition of human hepatocellular carcinoma cell growth when used alone and in combination with anticancer drugs. *Ann Surg Oncol.* 2003;10: 1184–90.
30. Ikeda K, Arase Y, Saitoh S, et al. Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor—a prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology.* 2000;32:228–32.
31. Kubo S, Nishiguchi S, Hirohashi K, et al. Effects of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma. A randomized, controlled trial. *Ann Intern Med.* 2001;134:963–7.
32. Mazzaferro V, Romito R, Schiavo M, et al. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. *Hepatology.* 2006;44:1543–54.

The Carcinoembryonic Antigen Level in Pancreatic Juice and Mural Nodule Size Are Predictors of Malignancy for Branch Duct Type Intraductal Papillary Mucinous Neoplasms of the Pancreas

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

Objective: Identification of predictors of malignancy for branch duct type intraductal papillary mucinous neoplasms (IPMN).

Background: Main duct type IPMN has been recommended for resection. However, the indications for resection of the branch duct type IPMN have been controversial.

Methods: We retrospectively analyzed the clinicopathological factors of 134 patients undergoing resection for branch duct type IPMN, excluding main duct type IPMN, to identify predictors of the malignant behavior of this neoplasm. The cutoff values of tumor size, main pancreatic duct (MPD) size, mural nodule size, and carcinoembryonic antigen (CEA) level in the pancreatic juice obtained during preoperative endoscopic retrograde pancreatography (ERP) were analyzed using receiver–operator characteristic curves.

Results: We found 7 significant predictors for malignancy in the branch duct type IPMN in a univariate analysis; jaundice, tumor occupying the pancreatic head, MPD size >5 mm, mural nodule size >5 mm, serum carbohydrate antigen (CA)19–9 level, positive cytology in the pancreatic juice, and CEA level in the pancreatic juice >30 ng/mL. In a multivariate analysis, a mural nodule size >5 mm and a CEA level in the pancreatic juice >30 ng/mL were independent factors associated with malignancy. The positive predictive value of a mural nodule size >5 mm and a CEA level in the pancreatic juice >30 ng/mL was 100%, and the negative predictive value was 96.3%.

Conclusions: We identified 2 useful predictive factors for malignancy in branch duct type IPMN; a mural nodule size >5 mm and a CEA level in the pancreatic juice obtained by preoperative ERP >30 ng/mL.

(*Ann Surg* 2012;255:517–522)

As a result of improvements of radiological imaging and increased clinician awareness, intraductal papillary mucinous neoplasm (IPMN) of the pancreas has been recognized with increasing frequency because it was formally defined in 1996 by the World Health Organization.[1] It has been established that IPMN has malignant potential and that it first transforms from an adenoma to a borderline neoplasm, then develops into carcinoma, including carcinoma in situ (CIS), and ultimately becomes an invasive carcinoma [invasive IPMC (intraductal papillary mucinous carcinoma)].[1] In general, IPMN has a favorable prognosis, because of its indolent biological behavior; therefore, excellent survival outcomes have been reported after complete resection in the patients with noninvasive IPMN, including adenoma, borderline neoplasm, and CIS.[2–6] However, once IPMN progresses to invasive carcinoma, it becomes aggressive and is associated with a poor prognosis, with the 5-year survival in patients with invasive IPMC reportedly ranging from 22% to 67%.[7–9] Therefore, the timing of resection is important for the successful treatment of IPMN, and it is necessary to establish a treatment protocol and surgical indications for patients with IPMN.

Depending on the morphology of the changes of the ductal system, IPMNs have been classified into the 3 variations—main duct type, branch duct type, and mixed type by radiological imaging. Many recent clinicopathological studies have shown that IPMNs arising in the main pancreatic duct (MPD) are more aggressive than those arising in the branch pancreatic duct (BPD), and the malignancy rate of main duct type IPMN has been reported to be 57% to 92%,[4–6,10] whereas that of branch duct type IPMN has been reported to be 6% to 58%.[10–14] Therefore, although most clinicians agree that surgical resection is required for all main duct type IPMNs, the management of branch duct type IPMNs remains controversial, because branch duct type IPMN generally has a low risk of malignancy.

We previously suggested that measurement of the carcinoembryonic antigen (CEA) level in the pancreatic juice obtained during preoperative endoscopic retrograde pancreatography (ERP) was useful for distinguishing malignant from benign IPMNs,[2,3]; however, our previous studies had 2 problems: (1) a small number of patients analyzed (n = 54), and (2) the subjects in the study were patients with all types of IPMNs, including the main duct type. Therefore, in the present study, we examined 134 patients with IPMNs, other than the main duct type, and reanalyzed the cutoff values for predicting malignancy of the tumor size, MPD size, mural nodule size, and the CEA level in the pancreatic juice, using receiver–operator characteristic (ROC) curves. We retrospectively analyzed the clinical and imaging findings and laboratory data to identify the predictors of malignancy and determined the optimal indications for the patients with branch duct type IPMN.

MATERIALS AND METHODS

Patient Enrollment

From July 1999 to February 2011, 196 consecutive patients with IPMN underwent a pancreatectomy at Wakayama Medical University Hospital. We classified the patients into 2 groups on the basis of their type of IPMN as determined by preoperative imaging studies; main duct type IPMN and branch duct type IPMN. We defined the main duct type IPMN as that found to have diffuse or segmental MPD dilation, but not cyst formation caused by BPD dilation. Next, we defined the branch duct type IPMN as that with cyst formation caused by BPD dilation with or without MPD dilation. In this study, we excluded 23 patients who had IPMN concomitant with common pancreatic cancer. Among the remaining 173 consecutive patients with resected IPMNs, 134 patients were classified as having branch duct type IPMN, and all were enrolled in this study. The study protocol was approved by the Human Ethics Review Committee of Wakayama Medical University Hospital, and a signed consent form was obtained from each subject.

From the Second Department of Surgery, Wakayama Medical University, School of Medicine, Kimiidera, Wakayama, Japan.

Disclosure: The authors declare that they have nothing to disclose.

Reprints: Hiroki Yamaue, MD, Second Department of Surgery, Wakayama Medical, University, School of Medicine, 811–1 Kimiidera, Wakayama 641–8510, Japan. E-mail: yamaue-h@wakayama-med.ac.jp.

ISSN: 0003-4932/12/25503-0517
DOI: 10.1097/SLA.0b013e3182444231

Preoperative Examination and Indications for Surgery

Before surgery, all patients underwent a clinical evaluation, routine laboratory tests including the assessment of tumor markers, abdominal ultrasonography (US), and computed tomography (CT). Magnetic resonance imaging cholangiopancreatography and endoscopic US (EUS) were performed in 131 and 125 patients, respectively. Endoscopic retrograde pancreatography was performed in all patients with branch duct type IPMN, excluding the 4 patients undergoing Billroth II reconstruction after distal gastrectomy. Preoperative pancreatic juice cytology (n = 104) and measurement of CEA levels in pancreatic juice (n = 91) were performed using the samples obtained during preoperative ERP, using the previously reported method.[2,3] Briefly, the pancreatic juice in the MPD was collected by preoperative ERP, and immediately centrifuged, and the precipitate was used for cytological examination, and the CEA levels in the supernatant were measured by means of a CEA immunometric chemiluminescent assay kit (Bayer Medical Co, Tokyo, Japan). The tumor size was measured by CT, and the mural nodule size was determined by EUS in 125 patients who underwent preoperative EUS, and by CT in other 9 patients without performing EUS.

Surgery was performed in the patients with IPMN who met at least one of the following criteria: (1) the presence of symptoms, (2) main duct type IPMN, (3) the presence of mural nodules, (4) an MPD larger than 7 mm in diameter, or gradual dilation of the MPD observed during follow-up, (5) tumor size larger than 30 mm, or a gradual increase in the tumor size during follow-up, (6) class IV or V in cytology of the pancreatic juice, or (7) a CEA level higher than 110 ng/mL in the pancreatic juice, which was the cutoff level identified by analyzing the difference between benign and malignant IPMNs in all patients with all types of IPMN, using ROC curves, as previously reported.[2,3]

All resected specimens were examined pathologically and classified into adenoma, borderline, CIS, and invasive IPMC, according to the classification established by the World Health Organization by 2 independent pathologists (A.Y. and Y.N.). *Invasive IPMC* was defined as that presenting the pathological findings of continuance of an invasive component from CIS, to distinguish it from common pancreatic ductal cancer concomitant with IPMN.

Statistical Analysis

For the purpose of the analyses, we classified IPMN with adenoma and borderline neoplasm as a benign IPMN group, whereas CIS and invasive IPMC were classified as a malignant IPMN group. The cutoff levels for the tumor size, MPD size, mural nodule size, and CEA level in the pancreatic juice were determined to maximize the difference between benign and malignant IPMNs by ROC curves (SPSS, Release 17.0; SPSS Inc, Chicago, IL). The 16 preoperative potential risk factors were assessed by a univariate analysis with the χ^2 and included the patient age, sex, symptoms, jaundice, body weight loss, abdominal pain, back pain, diabetes mellitus, the tumor location, tumor size, MPD size, mural nodule size, serum CEA level, serum carbohydrate antigen (CA) 19–9 level, cytology in the pancreatic juice, and CEA levels in the pancreatic juice (SPSS, Release 17.0). The $P < 0.1$ predictors of malignant IPMN in the univariate analysis were then included in a forward stepwise multiple logistic regression model (SPSS, Release 17.0). Statistical significance was defined as $P < 0.05$.

RESULTS

Patient Characteristics and Histopathological Findings

Table 1 shows the characteristics of the enrolled patients. This study included 74 men and 60 women, with a mean age ± standard deviation of 68.9 ± 9.7 years. The mean tumor size, mean MPD size, and the mean mural nodule size were 30.4 ± 12.3, 6.5 ± 4.2, and 5.5 ± 5.0, respectively. A total pancreatectomy was performed in 3 patients (2.2%); a pancreatoduodenectomy (PD), including a pylorus-preserving PD and a pylorus-resecting PD, was performed in 101 patients (75.4%); a distal pancreatectomy was performed in 14 patients (10.5%); and a central pancreatectomy was performed in 16 patients (11.9%). Combined venous resection (portal vein or superior mesenteric vein) was performed in 10 patients (7.4%), and combined celiac artery resection was performed in 1 patient (0.8%).

In the 134 patients with branch duct type IPMN, there were 56 patients (41.8%) with benign IPMN, including 51 with adenomas and 5 with borderline neoplasms, and there were 41 patients (30.6%) with CIS, and 37 patients (27.6%) with invasive IPMC, including 5 with minimally invasive IPMC (Table 1).

Complications of ERP and Pancreatic Duct Irrigation

The definition of post-ERP acute pancreatitis and the grading of its severity were based on consensus criteria.[15] Seven patients (5.4%) developed pancreatitis in 130 patients who underwent preoperative ERP. Among them, 5 patients (4.8%) developed pancreatitis (moderate in 1 patient and mild in 4 patients) in 104 patients whose pancreatic juice obtained by ERP.

Diagnostic Cutoff Levels for the Tumor Size, MPD Size, Mural Nodule Size, and CEA Levels in the Pancreatic Juice for the Prediction of Malignant IPMN

In this study, ROC curves were used to determine the cutoff levels for the tumor size, MPD size, mural nodule size, and CEA level in the pancreatic juice (Fig. 1) to differentiate between benign and malignant IPMN in the patients with the branch duct type IPMN. Mathematically, the cutoff values were defined as those corresponding to points on the ROC curve situated furthest away from the reference line. The areas under curve for the tumor size, MPD size, mural nodule size, and CEA level in the pancreatic juice were 0.612, 0.711, 0.819, and 0.920, respectively, and the determined cutoff levels for the differentiation between benign and malignant IPMNs were 30 mm, 5 mm, 5 mm, and 30 ng/mL, respectively (Table 2).

TABLE 1. The Demographics and Clinical Characteristics of 134 Patients With Branch Duct Type IPMN

Characteristics	Value
Age, mean ± SD (range), yr	68.9 ± 9.7 (32–84)
Sex, male/female	74/60
Tumor size, mean ± SD (range), mm	30.4 ± 12.3 (5–88)
Main pancreatic duct size, mean ± SD (range), mm	6.5 ± 4.2 (1–20)
Mural nodule size, mean ± SD (range), mm	5.5 ± 5.0 (0–20)
Operation	
Total pancreatectomy	3 (2.2%)
Pancreatoduodenectomy (PD/PpPD/PrPD)	101(17/43/41) (75.4%)
Distal pancreatectomy	14 (10.5%)
Central pancreatectomy	16 (11.9%)
Histopathology	
Adenoma	51 (38.1%)
Borderline	5 (3.7%)
Carcinoma in situ	41 (30.6%)
Invasive IPMC	37 (27.6%)

PpPD indicates pylorus-preserving PD; PrPD, pylorus-resecting PD

Predictors of Malignancy for Branch Duct Type IPMN

In the univariate analysis, we found 7 significant factors predicting the malignancy of branch duct type IPMNs: the presence of jaundice ($P < 0.001$), a tumor occupying the pancreatic head ($P = 0.006$), a MPD size larger than 5 mm ($P < 0.001$), mural nodule size larger than 5 mm ($P < 0.001$), elevated serum CA19–9 ($P = 0.002$), positive cytology (class IV or V) in the pancreatic juice ($P = 0.023$), and a CEA level in the pancreatic juice >30 ng/mL ($P < 0.001$) (Table 3). Furthermore, a mural nodule size larger than 5 mm ($P = 0.003$; odds ratio = 12.9) and a CEA level in the pancreatic juice higher than 30 ng/mL ($P < 0.001$; odds ratio = 299) were independent malignant predictors in the subsequent multivariate analysis (Table 4).

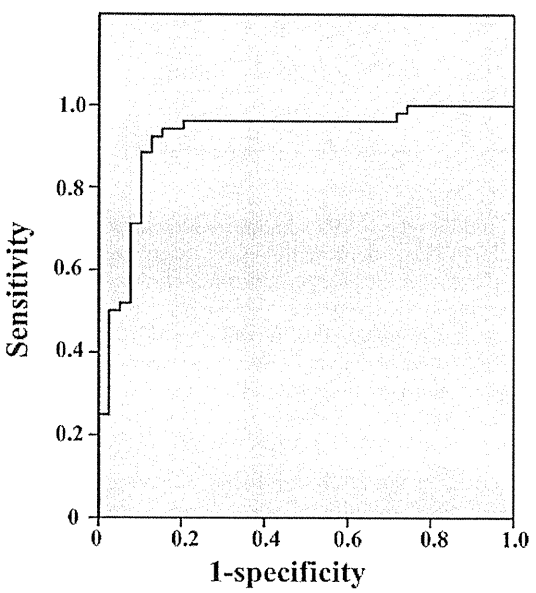

FIGURE 1. The receiver operating characteristic curve used to determine the optimal CEA cutoff levels in the pancreatic juice obtained by preoperative endoscopic retrograde pancreatography for the prediction of the malignancy of branch duct type IPMN. The area under the curve for the CEA levels in the pancreatic juice was 0.92, and the determined cutoff level for differentiation between benign and malignant IPMNs was 30 ng/mL.

TABLE 2. The Diagnostic Cutoff Levels of the Tumor Size, Main Duct Size, Mural Nodule Size, and CEA Levels in the Pancreatic Juice for Differentiating Between Benign and Malignant IPMN Based on the Receiver Operating Characteristic Curves

	Area Under Curve	Cutoff Value
Tumor size	0.612	30 mm
Main pancreatic duct size	0.711	5 mm
Mural nodule size	0.819	5 mm
CEA levels in the pancreatic juice*	0.920	30 ng/mL

*The CEA in the pancreatic juice could be measured in 91 patients who received preoperative ERP.

With regard to the mural nodule size, the sensitivity, specificity, and accuracy of the cutoff (5 mm) for differentiating between benign and malignant IPMN were 74.4%, 80.4%, and 76.9%, respectively and those for the CEA cutoff level in the pancreatic juice (30 ng/mL) were 94.2%, 84.6%, and 90.1%, respectively.

We found that mural nodule size determined by EUS and CEA levels in the pancreatic juice were significantly correlated ($P < 0.001$; Table 5). There were 5 patients with just 5 mm of mural nodule with a CEA level in the pancreatic juice higher than 30 ng/mL, and they included 4 patients with adenoma and 1 patient with CIS.

Combination Analysis of the Mural Nodule Size and CEA Level in the Pancreatic Juice

If the analyses of the mural nodule size and CEA level in the pancreatic juice were combined, all patients with a mural nodule size larger than 5 mm who also had a CEA level in the pancreatic juice higher than 30 ng/mL had malignancy, indicating that the positive predictive value of both a mural nodule larger than 5 mm and a CEA level in the pancreatic juice higher than 30 ng/mL was 100%. Moreover, 26 patients of the 27 patients with a mural nodule size larger than 5 mm and a CEA level in the pancreatic juice higher than 30 ng/mL had benign IPMN, indicating that the negative predictive value of both a mural nodule size larger than 5 mm or a CEA level in the pancreatic juice higher than 30 ng/mL was 96.3% (Fig. 2).

DISCUSSION

Surgical resection offers the best chance for a cure for the patients with IPMN; however, observation may be a better management strategy for the patients with a low risk of malignancy, because a pancreatectomy is an invasive procedure, especially in elderly patients.[16] Therefore, many investigators have performed studies to identify factors that can be used to predict the likelihood of malignancy in the patients with IPMNs. Most clinicians have agreed that the main duct type IPMN has high malignant potential, and surgical resection is recommended for all patients with main duct type IPMN.[4–6,10] However, there is still no definite management consensus, including the surgical indications, for patients with branch duct type IPMN, because the malignant potential of branch duct type IPMN is relatively low.[10–14] Thus, it is necessary to identify more accurate factors that can predict the malignancy and determine the indications for surgical resection for the patients with the branch duct type IPMN.

The International Consensus Guidelines have put forward an algorithm for the surgical management of branch duct type IPMN, which is based on the tumor size, patient symptoms, and "high risk stigmata" (mural nodule and positive cytology in the pancreatic juice).[17] Several recent studies reported that the size of mural nodules was a more significant malignant factor than the tumor size for predicting the malignancy of branch duct type IPMN.[6,10,12,14] In addition, the MPD size, positive EUS fine-needle aspiration (FNA) cytology, and high CEA or carbohydrate antigen (CA)72.4 levels in the cystic fluid have been reported to be factors that can be used to predict the malignancy of branch duct type IPMN.[5,18–21] However, the accuracies of these factors were not high enough to distinguish between benign and malignant IPMNs. Moreover, the cytology of the pancreatic juice should be a criterion standard for the preoperative pathological diagnosis. However, the sensitivity of preoperative cytology was only 11.1% in this series. Therefore, we tried to identify more accurate predictors of the malignant potential of branch duct IPMN to determine an optimal management consensus. If CIS could be determined for the patients with branch duct type IPMN by several parameters, that would be powerful. However, in this study, the number of CIS was small; only 41 patients. Therefore, we could not analyze separately in each group. In the future, we would like to try

TABLE 3. The Results of the Univariate Analysis of the Malignant Predictive Factors for Branch Duct Type IPMN

	Benign (n = 56), n (%)	Malignant (n = 78), n (%)	*P*
Age, >70 yr	25/56 (44.6%)	44/78 (56.4%)	0.179
Sex, male	30/56 (53.6%)	44/78 (56.4%)	0.745
Symptom	27/56 (48.2%)	46/78 (59%)	0.217
Jaundice	0 (0%)	14 (18%)	<0.001
Body weight loss	5 (8.9%)	11 (14.1%)	0.362
Abdominal pain	14 (25%)	23 (29.5%)	0.567
Back pain	9 (16.1%)	9 (11.5%)	0.448
Onset or worsening of diabetes mellitus	13/56 (23.2%)	26/78 (33.3%)	0.203
Tumor occupied location, head	35/56 (62.5%)	65/78 (83.3%)	0.006
Tumor size, >30 mm	20/56 (35.7%)	37/78 (47.4%)	0.176
Main pancreatic duct size, >5 mm	16/56 (28.6%)	52/78 (66.7%)	<0.001
Mural nodule size, >5 mm	11/56 (19.6%)	57/78 (73.1%)	<0.001
Serum CEA, elevated	3/56 (5.4%)	9/78 (11.5%)	0.217
Serum CA19–9, elevated	6/56 (10.7%)	27/78 (34.6%)	0.002
Cytology in the pancreatic juice,* class IV or V	0/44 (0%)	6/54 (11.1%)	0.023
CEA levels in the pancreatic juice,† >30 ng/m	6/39 (15.4%)	49/52 (94.2%)	<0.001

*Cytological examination of the pancreatic juice was possible in 98 patients.
†The CEA in the pancreatic juice could be measured in 91 patients.

TABLE 4. The Results of the Multivariate Analysis of the Malignant Predictive Factors for Branch Duct Type IPMN

	P	Odds Ratio	95% Confidence Interval
Jaundice	0.989		
Tumor occupied location, head	0.136		
Main pancreatic duct size, >5 mm	0.082		
Mural nodule size, >5 mm	0.003	12.9	2.38–70.3
Serum CA19–9, elevated	0.803		
Cytology in the pancreatic, class IV or V	0.983		
CEA levels in the pancreatic juice, >30 ng/mL	<0.001	299	17.7–5067

TABLE 5. Correlation Between Findings of EUS and CEA in the Pancreatic Juice Obtained by ERP for the Patients With Branch Duct Type IPMN

EUS Findings (Mural Nodule Size)	CEA Levels in the Pancreatic Juice Obtained by ERP		
	≤30 ng/mL (n = 36)	>30 ng/mL (n = 55)	*P*
≤5 mm (n = 45)	27	18	<0.001
>5 mm (n = 46)	9	37	

to analyze by clustering the patients with branch duct type IPMN into 3 groups—adenoma, CIS, and invasive IPMC.

In this study, we defined branch duct type IPMN as that with cyst formation caused by BPD dilation with or without MPD dilation. The reasons that we included mixed type IPMN into the branch duct type IPMN are as follows:

1. It is difficult to distinguish branch duct type IPMN with MPD dilatation caused by outflow of copious mucin from a side branch cyst from the mixed type IPMN with MPD dilatation resulting from the production of mucin in the MPD,[6] by preoperative radiological imaging.
2. Branch duct type IPMN sometimes has microscopic involvement into the MPD without radiological evidence of dilatation of the MPD; however, the preoperative prediction of this phenomenon is impossible.
3. The malignant potential of mixed type IPMN was reported to be lower than that of the main duct type,[6] although there have been a limited number of reports about the potential of mixed type IPMN.

Indeed, in this study, we found 22 patients with branch duct IPMN with MPD dilation, ie, mixed type on imaging findings (the pathological diagnosis in branch pancreatic duct is 5 adenoma, 10 CIS, and 7 invasive IPMC). In 5 mixed type IPMN patients with adenoma, only 1 patient had an adenoma in MPD. Remaining 4 patients had no atypia in MPD, which had the secondary dilation of MPD because of inflow of mucinous fluid from cystic branch duct. Thus, it is very difficult to distinguish branch duct type IPMN from mixed type IPMN by radiological imaging, because we could not predict microscopic involvement into MPD in mixed type IPMN patients.

For this study, we reanalyzed the cutoff values for the tumor size, MPD size, mural nodule size, and CEA level in the pancreatic juice to distinguish between benign and malignant IPMN exclusively in patients with branch duct type IPMN, using ROC curves. Our results suggested that a mural nodule size larger than 5 mm and a CEA level in the pancreatic juice obtained by preoperative ERP higher than 30 ng/mL were independent significant predictors of malignancy in a multivariate analysis. In several significant malignant predictors for branch duct type IPMN on univariate analysis, but not significant on multivariate analysis, we found jaundice, MPD dilation, and elevated serum CA19–9 as malignant predictive factors for IPMN.[10–14] All 8 branch duct type IPMN patients with jaundice, MPD dilation, and elevated serum CA19–9 had malignancy, whereas in 32 patients without jaundice, MPD dilation or elevated serum CA19–9, 10 patients had malignancy with a high CEA in the pancreatic juice. Therefore, the branch duct type IPMN patients with jaundice, MPD dilation, and elevated serum CA19–9 may not require ERP, because the positive predictive values for malignancy of combination of these 3 factors are high, whereas ERP may be useful procedure to distinguish between

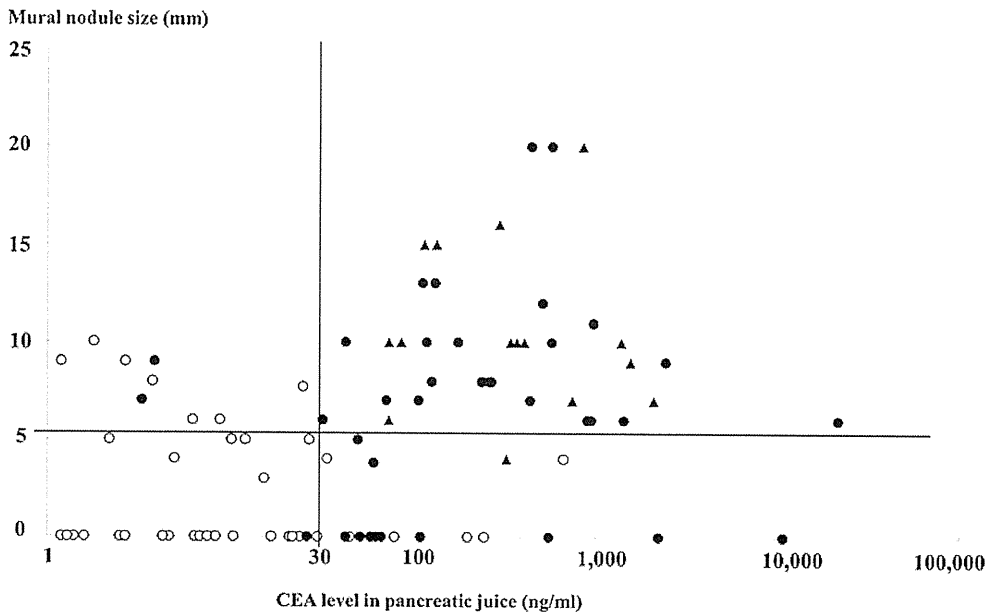

FIGURE 2. The distribution of the mural nodule size and CEA levels in the pancreatic juice in patients with branch duct type IPMN. IPMNs classified as adenoma and borderline neoplasm are indicated by white circles (○), carcinoma in situ by black circles (●), and invasive IPMC by black triangles (▲). All patients (100%) with a mural nodule size larger than 5 mm and a CEA level in the pancreatic juice higher than 30 ng/mL had malignant IPMN, whereas only 1 patient among 27 with a mural nodule size ≤5 mm and a CEA level in the pancreatic juice 30 ng/mL or lower had malignant IPMN.

benign and malignant IPMNs for patients without jaundice, MPD dilation, nor elevated serum CA19–9.

We previously reported that the cutoff value for the CEA level in the pancreatic juice to distinguish malignant from benign IPMN was 110 ng/mL for the patients with all types IPMN,[2] whereas this study suggested that the cutoff value was 30 ng/mL for the patients with branch duct type IPMN. It is considered that the CEA levels in main duct type IPMN are higher than those of other types of IPMN, because the CEA levels of the pancreatic juice obtained from the MPD reflect the direct secretion of CEA for the main duct type, whereas the CEA levels for the branch duct type IPMN reflect the outflow into the MPD from cystic side branch secretions.

Recently, measurements of CEA or/and CA72.4 in the cystic fluid obtained by EUS-FNA were reported to be useful for the differentiation of malignant from benign IPMN.[20] In our institute, we have measured the CEA levels in the pancreatic juice obtained from the MPD by preoperative ERP in the patients with all types IPMN, but not in the cyst fluid obtained by EUS-FNA, because (1) obtaining pancreatic juice by ERP is not associated with any risk of peritoneal seeding, and actually, peritoneal seeding was not found in all patients, whose pancreatic juice obtained by preoperative ERP, and (2) the branch duct type IPMNs are often consisted of multilocular cysts, and it is unknown which cyst has the most severe atypia, whereas the pancreatic juice in the MPD obtained by ERP includes secreted CEA from all of the pancreatic ducts. However, further studies of the evaluation of the correlations between the CEA levels in the pancreatic juice in the MPD and the CEA levels in the cyst fluid should be performed.

In this study, there were 29 patients with a mural nodule size 5 mm or smaller and a tumor size 30 mm or larger, who were predicted to have benign IPMN by findings of EUS and CT. Among 29 patients, we had 8 malignant IPMN patients with a CEA level in the pancreatic juice obtained by ERP more than 30 ng/mL. Furthermore, in 23 patients with branch duct type IPMN without a mural nodule and a tumor size 30 mm or smaller, 6 patients had malignancy with a CEA level in the pancreatic juice higher than 30 ng/mL. These results suggest that ERP may be a useful procedure for some branch duct type IPMN patients with a mural nodule size 5 mm or smaller and a tumor size 30 mm or smaller, whereas we cannot clarify which types of patients would be benefited from this additional invasive procedure.

When the combination of a mural nodule size larger than 5 mm and a CEA level in the pancreatic juice higher than 30 ng/mL is used, the predictive value is excellent (100%), indicating that branch duct type IPMN with a mural nodule size larger than 5 mm and a CEA level in the pancreatic juice higher than 30 ng/mL would be recommended for resection. Only 1 patient (1 of 27 patients) with a mural nodule size 5 mm or smaller and a CEA level in the pancreatic juice 30 ng/mL or lower had malignant IPMN, which suggests that the patients with branch duct type IPMN in this group might be better treated by strict observation.

In conclusion, we identified 2 useful predictive factors for malignancy in branch duct type IPMN; a mural nodule size larger than 5 mm and a CEA level in the pancreatic juice obtained by preoperative ERP more than 30 ng/mL. Additional studies in other populations will be needed to confirm the validity of our findings.

REFERENCES

1. Kloppel G, Solcia E, Longnecker DS, et al. *Histologic Typing of Tumors of the Exocrine Pancreas*. 2nd ed. Geneva, Switzerland: Springer-Verlag; 1996.
2. Kawai M, Uchiyama K, Tani M, et al. Clinicopathological features of malignant intraductal papillary mucinous tumors of the pancreas. *Arch Surg*. 2004;139:188–192.
3. Hirono S, Tani M, Kawai M, et al. Treatment strategy for intraductal papillary mucinous neoplasm of the pancreas based on malignant predictive factors. *Arch Surg*. 2009;144:345–349.
4. Jang JY, Hwang DW, Kim MA, et al. Analysis of prognostic factors and a proposed new classification for invasive papillary mucinous neoplasms. *Ann Surg Oncol*. 2011;18:644–650.

5. Murakami Y, Uemura K, Hayashidani Y, et al. Predictive factors of malignant or invasive intraductal papillary-mucinous neoplasms of the pancreas. *J Gastroitest Surg*. 2007;11:338–344.
6. Hwang DW, Jang JY, Lee SE, et al. Clinicopathologic analysis of surgically proven intraductal papillary mucinous neoplasms of the pancreas in SNUH: a 15-year experience at a single academic institution. *Langenbecks Arch Surg*. 2012;397:93–102.
7. Wasif N, Bentrem DJ, Farrell JJ, et al. Invasive intraductal papillary mucinous neoplasm versus sporadic pancreatic adenocarcinoma. *Cancer*. 2010;116:3369–3377.
8. Poultsides GA, Reddy S, Cameron JL, et al. Histopathologic basis for the favorable survival after resection of intraductal papillary mucinous neoplasm-associated invasive adenocarcinoma of the pancreas. *Ann Surg*. 2010;251:470–476.
9. Yopp AC, Katabi N, Janakos M, et al. Invasive carcinoma arising in intraductal papillary mucinous neoplasms of the pancreas. A matched control study with conventional pancreatic ductal adenocarcinoma. *Ann Surg*. 2011;253:968–974.
10. Schmidt CM, White PB, Waters JA, et al. Intraductal papillary mucinous neoplasms. Predictors of malignant and invasive pathology. *Ann Surg*. 2007;246:644–654.
11. Jang JY, Kim SW, Lee SE, et al. Treatment guidelines for branch duct type intraductal papillary mucinous neoplasms of the pancreas: when can we operate or observe? *Ann Surg Oncol*. 2007;15:199–205.
12. Akita H, Takeda Y, Hoshino H, et al. Mural nodule in branch duct-type intraductal papillary mucinous neoplasms of the pancreas is a marker of malignant transformation and indication for surgery. *Am J Surg*. 2011;202:214–219.
13. Shimizu Y, Kanemitsu Y, Sano T, et al. A nomogram for predicting the probability of carcinoma in patients with intraductal papillary mucinous neoplasm. *World J Surg*. 2010;34:2932–2938.
14. Salvia R, Crippa S, Falconi M, et al. Branch-duct intraductal papillary mucinous neoplasms of the pancreas: to operate or not to operate? *Gut*. 2007;56:1086–1090.
15. Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc*. 1991;37:383–393.
16. Weinberg BM, Spiegel BMR, Tomlinson JS, et al. Asymptomatic pancreatic cyst neoplasms: maximizing survival and quality of life using Markov-based clinical nomograms. *Gastroenterology*. 2010;138:531–540.
17. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology*. 2006;6:17–32.
18. Maker AV, Lee LS, Raut CP, et al. Cytology from pancreatic cysts has marginal utility in surgical decision-making. *Ann Surg Oncol*. 2008;15:3187–3192.
19. Paris SA, Attasaranya S, Leblanc JK, et al. Role of endoscopic ultrasound in the diagnosis of intraductal papillary mucinous neoplasms: correlation with surgical histopathology. *Clin Gastroenterol Hepatol*. 2007;5:489–495.
20. Maire F, Voitot H, Aubert A, et al. Intraductal papillary mucinous neoplasms of the pancreas: performance of pancreatic fluid analysis for positive diagnosis and the prediction of malignancy. *Am J Gasetroenterol*. 2008;103:2871–2877.
21. Jong K, Poley JW, Hooft JE, et al. Endoscopic ultrasound-guided fine-needle aspiration of pancreatic cyst lesions provides inadequate material for cytology and laboratory analysis: initial results from a prospective study. *Endoscopy*. 2011;43:585–590.

Use of omentum or falciform ligament does not decrease complications after pancreaticoduodenectomy: Nationwide survey of the Japanese Society of Pancreatic Surgery

Masaji Tani, MD,[a] Manabu Kawai, MD,[a] Seiko Hirono, MD,[a] Takashi Hatori, MD,[b] Toshihide Imaizumi, MD,[c] Akimasa Nakao, MD,[d] Shinichi Egawa, MD,[e] Takehide Asano, MD,[f] Takukazu Nagakawa, MD,[g] *and* Hiroki Yamaue, MD,[a] *Wakayama, Tokyo, Isehara, Nagoya, and Sendai, Japan*

Background. *Wrapping is thought to prevent pancreatic fistula and postoperative hemorrhage for pancreaticoduodenectomy (PD), and we analyzed whether omentum/falciform ligament wrapping decreases postoperative complications after PD.*

Methods. *This is a retrospective study of wrapping using the omentum/falciform ligament in patients that underwent PD between January 2006 and June 2008 in 139 institutions that were members of the Japanese Society of Pancreatic Surgery.*

Results. *Ninety-one institutions responded to the questionnaires, and data were accumulated from 3,288 patients. The data from 2,597 patients were acceptable for analysis; 918 (35.3%) patients underwent wrapping and 1,679 patients did not. A pancreatic fistula occurred in 623 patients (37.3%) in the nonwrapping group, in comparison to 393 patients (42.8%) in the wrapping group (P = .006). The incidence of a grade B/C pancreatic fistula was lower in the nonwrapping group than the wrapping group (16.7% vs 21.5%; P = .002). An intra-abdominal hemorrhage occurred in 54 patients (3.2%) in the nonwrapping group, which was similar to the incidence in the wrapping group (32 patients; 3.5%). The mortality was 1.3% and 1.0% in nonwrapping and wrapping groups, respectively. A multivariate analysis revealed 7 independent risk factors for pancreatic fistula; male, hypoalbuminemia, soft pancreas, long operation time, extended resection, pylorus preservation, and omentum wrapping. There were 4 independent risk factors for early intra-abdominal hemorrhage and 2 independent risk factors for late intra-abdominal hemorrhage.*

Conclusion. *This retrospective study revealed that omentum wrapping did not decrease the incidence of pancreatic fistula. An additional validation study is necessary to evaluate the efficacy of wrapping for PD. (Surgery 2012;151:183-91.)*

From the Second Department of Surgery,[a] Wakayama Medical University School of Medicine, Wakayama; Department of Surgery,[b] Institute of Gastroenterology, Tokyo Women's Medical University, Tokyo; Department of Gastroenterological Surgery,[c] Tokai University School of Medicine, Tokyo; Department of Surgery II,[d] Nagoya University Graduate School of Medicine, Isehara, Nagoya; Division of Hepato-Biliary-Pancreatic Surgery,[e] Department of Surgery, Tohoku University Graduate School of Medicine, Sendai; Department of Surgery,[f] Teikyo University School of Medicine, Tokyo; and the Japanese Society of Pancreatic Surgery,[g] Wakayama, Japan

PANCREATICODUODENECTOMY (PD) is a major operation associated with a high incidence of mortality and morbidity, and numerous trials have been attempted to decrease the mortality and morbidity after PD.[1-4] The incidence of mortality has decreased at high-volume centers because of the progression of surgical techniques and perioperative treatment[5-7]; however, the incidence of morbidity still remains high.[1-4,8-10] Pancreatic fistula, delayed gastric emptying,[11,12] and postoperative hemorrhage after PD are the most frequent postoperative complications. Although delayed gastric emptying is not a lethal complication, both pancreatic fistula and postoperative intra-abdominal hemorrhage can lead to

Accepted for publication July 7, 2011.

Reprint requests: Hiroki Yamaue, MD, Second Department of Surgery, Wakayama Medical University, School of Medicine, 811-1 Kimiidera, Wakayama 641-8510, Japan. E-mail: yamaue-h@wakayama-med.ac.jp.

0039-6060/$ - see front matter

doi:10.1016/j.surg.2011.07.023

operation-related death.[13,14] In addition, a low incidence of complications is required in pancreatic surgery in order to administer postoperative adjuvant therapy quicker to improve the survival of patients with pancreatic cancer.[15] The International Study Group of Pancreatic Fistula (ISGPF) has proposed a consensus definition and clinical grading of postoperative pancreatic fistula, which made it possible to compare the incidence of pancreatic fistula associated with various surgical techniques.[16]

Wrapping with omentum/falciform ligament is one of the procedures to protect the surrounding organs against the pancreatic juice having autolytic activity, and this surgical technique is simple and easy for surgeons to perform. Several reports have so far shown the usefulness of wrapping after PD at individual institutions.[6,17-20] However, such wrapping may disturb the drainage of amylase-rich fluid, which might cause intra-abdominal adipose tissue inflammation like panniculitis, which could result in the occurrence of an intra-abdominal abscess.

The Japanese Society of Pancreatic Surgery (JSPS) decided to perform a nationwide survey to evaluate whether wrapping using the omentum/falciform ligament can help to prevent postoperative complications after PD.

MATERIAL AND METHODS

Patients. A nationwide survey of omental wrapping in patients who underwent PD between January 2006 and June 2008 was conducted at the initiative of JSPS to compare the patients' characteristics, preoperative status, preoperative treatment, surgical factors, perioperative status, and postoperative outcomes.

Postoperative complications. Pancreatic fistula was defined according to the ISGPF guidelines as an amylase level in the drainage fluid on postoperative day (POD) 3 that was >3 times the normal serum amylase level.[16] Postoperative intra-abdominal hemorrhage was defined as bleeding requiring a blood transfusion, reoperation, or interventional radiology. Early intra-abdominal hemorrhage indicates incomplete hemostasis and a failure of carrying out sufficient intra-operative management. It was defined as occurring within 3 days after PD, and it was not associated with any other postoperative complications. Late intra-abdominal hemorrhage is associated with other postoperative complications, including pancreatic fistula and intra-abdominal abscess. A biliary fistula was defined as the presence of bile in the drainage fluid that persisted to POD 4. An intra-abdominal abscess was defined as intra-abdominal fluid collection with positive cultures identified by ultrasonography or computed tomography associated with persistent fever and elevated white blood cells. Delayed gastric emptying is defined as output from a nasogastric tube of >500 mL per day that persists beyond POD 10, the failure to maintain oral intake by POD 14, or the reinsertion of a nasogastric tube. Vascular complications were defined as cerebral infarction, cerebral hemorrhage, and deep vascular embolization. Cardiac complications were defined as myocardial infarctions and heart failure. Respiratory complications were defined as pneumonia, pulmonary embolism, and respiratory distress requiring mechanical ventilation. Renal failure was defined as acute onset of hemodialysis. Mortality was defined as death within POD 30.

Statistical analyses. Comparisons between the 2 groups were carried out using unpaired t test for continuous data and the 2-tailed Chi-square or the Fisher exact test, where appropriate, for categorical data. The Tukey significant difference test was performed to evaluate the differences in postoperative drain amylase level among 3 groups. All factors with $P < .1$ in a univariate analysis were analyzed by a multivariate analysis. The analyses were performed with SPSS software for Windows (version 15.0; SPSS Inc., Chicago, IL). All statistical tests were 2-sided, and significance was defined as $P < .05$. The results are reported as the mean ± standard deviation.

RESULTS

Patients. Ninety-one institutions (65.5%) responded to the questionnaires, and the data from 2,597 patients were able to evaluate the occurrence of pancreatic fistula using the ISGPF criteria and postoperative hemorrhage and were acceptable for analysis in this study. The patients' characteristics are shown in **Table I**. The average number of PDs was 10.5 ± 11.5 and 7.5 ± 7.0 per year at the institutions with and without wrapping, respectively. There was no difference between the 2 groups ($P = .141$).

Postoperative outcome. The postoperative complications are shown in **Table II**. The incidence of pancreatic fistula in the wrapping group was significantly higher than that in the nonwrapping group. The intra-abdominal hemorrhagic site was identified in 24 patients in the nonwrapping group, and 22 patients (83.3%) experienced hemorrhage from an artery (9 common hepatic artery, 6 gastroduodenal artery, 4 superior mesenteric artery, 1 left gastric artery, 1 proper hepatic artery, and 1 splenic artery). The intra-abdominal hemorrhagic site was identified in 20 patients in the wrapping group, and 18 patients (90.0%) experienced hemorrhage from an artery (6 gastroduodenal artery, 5 common hepatic artery, 2 proper hepatic

Table I. Patients' characteristics

Parameter	*Nonwrapping group* (n = *1,679*)	*Wrapping group* (n = *918*)*	P *value*
Age, y (mean ± SD)	65.9 ± 10.1	66.5 ± 9.9	.100
Gender (male/female)	1,018/661	541/377	.402
Disease (carcinoma/other)	1,337/342	729/189	.895
Comorbidity			
Diabetes mellitus	466	268	.436
Respiratory disease	82	39	.463
Chronic pancreatitis	120	75	.344
Preoperative examination (mean ± SD)			
Hemoglobin (g/dL)	12.4 ± 1.7	12.4 ± 1.6	.887
Creatinine (mg/dL)	0.77 ± 0.41	0.79 ± 0.59	.490
Albumin (g/dL)	3.86 ± 0.49	3.81 ± 0.51	.017
Total bilirubin (mg/dL)	3.0 ± 4.8	2.2 ± 3.3	<.001
AST (IU/L)	70.3 ± 101.9	56.0 ± 79.3	<.001
ALT (IU/L)	100.0 ± 142.7	83.1 ± 211.6	.017
Amylase (IU/L)	123.7 ± 139.5	121.8 ± 181.6	.790
Preoperative biliary drainage	743 (44.3%)	478 (52.1%)	<.001
Duration of preoperative biliary drainage, days (mean ± SD)	25.8 ± 17.5	29.7 ± 21.4	.001
Pylorus preservation	1,016 (60.5%)	384 (41.8%)	<.001
Extended lymph node resection	1,399	773	.307
Pancreatic texture (hard/soft)	730/949	408/510	.635
Pancreaticoenterostomy			
Jejunum/stomach	1,523/156	792/126	.001
Duct-to-mucosal anastomosis	1,269 (75.6%)	778 (84.7%)	<.001
Usage of pancreatic stent tube	1,262 (75.1%)	779 (84.9%)	.001
Operative time, min (mean ± SD)	441 ± 137	534 ± 142	<.001

*Wrapping of pancreatic anastomosis or vessels, including hepatic artery, using either the omentum or falciform ligament.
ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase.

artery, 1 superior mesenteric artery, 1 right hepatic artery, 1 left hepatic artery, 1 splenic artery, and 1 dorsal pancreatic artery). Thirty patients (75%) had late intra-abdominal hemorrhage accompanied by grade B + C pancreatic fistula and/or intra-abdominal abscess, and intra-abdominal hemorrhage was accompanied by all grades of pancreatic fistula in 32 patients (80%). Mortality was 1.3% and 1.0% in the nonwrapping and wrapping groups, respectively.

The level of amylase in the drainage fluid is shown in **Table III.** The amylase level of the omentum wrapping group was significantly lower than the other groups ($P = .027$) on POD 3.

Complications according to the material used for wrapping after PD. Two materials were used to wrap (**Table IV**). The incidence of grade B + C pancreatic fistula in the omentum group (23.9%) was significantly higher than in both the nonwrapping ($P < .001$) and falciform ligament groups ($P < .001$).

Complications according to the location of wrapping after PD. Wrapping was performed at 2 locations: wrapping of vessels, including the common hepatic artery, proper hepatic artery, stump of gastroduodenal artery, and portal vein, and wrapping of the pancreaticoenterostomy (**Table V**). The incidences of grade B + C pancreatic fistula in the anastomosis wrapping group and the vessel wrapping groups were also higher than those in the nonwrapping group.

Risk factors of postoperative complications. The risk factors of grade B + C pancreatic fistula and intra-abdominal hemorrhage were predicted using categorized data by a univariate analysis (**Tables VI and VII**). A multivariate analysis predicted 7 independent risk factors for grade B + C pancreatic fistula (**Table VIII**). A multivariate analysis revealed 4 independent risk factors for early intra-abdominal hemorrhage: male gender ($P = .017$; odds ratio [OR], 2.078), long operation time (≥600 minutes; $P = .020$; OR, 2.198), blood transfusion ($P = .002$; OR, 2.747), and soft pancreas ($P < .001$; OR, 4.184), and 2 independent risk factors for late intra-abdominal hemorrhage: male gender ($P = .017$; OR, 2.591) and soft pancreas ($P = .001$; OR, 4.274).

Table II. Complications after pancreaticoduodenectomy

Parameter	*Nonwrapping group* (n = *1,679*)	*Wrapping group* (n = *918*)*	P *value*
Pancreatic fistula			
All grades	627 (37.3)	393 (42.8)	.006
Grade B + C	281 (16.7)	198 (21.6)	.002
Delayed gastric empting	182 (10.8)	117 (12.7)	.146
Bile leakage	52 (3.1)	29 (3.2)	.931
Intra-abdominal abscess	179 (10.7)	111 (12.1)	.269
Intra-abdominal hemorrhage†			
Early	32 (1.9)	14 (1.5)	.482
Late	22 (1.3)	18 (2.0)	.198
Wound infection	151 (9.0)	115 (12.5)	.005
Other organ complications			
Respiratory	76 (4.6)	43 (4.7)	.859
Cardiac	25 (1.5)	28 (3.1)	.007
Vascular	24 (1.4)	20 (2.2)	.157
Renal	17 (1.0)	4 (0.4)	.117
Mortality	22 (1.3)	9 (1.0)	.459
Postoperative hospital stay, days (mean ± SD)	38.0 ± 37.9	41.3 ± 30.1	.014

*Wrapping of pancreatic anastomosis or vessels, including hepatic artery, using omentum or falciform ligament.
†Early intra-abdominal hemorrhage indicates incomplete hemostasis and a failure of carrying out sufficient intraoperative management. It was defined as occurring within 3 days after pancreaticoduodenectomy, and it was not associated with any other postoperative complications. Late intra-abdominal hemorrhage is associated with other postoperative complications, including pancreatic fistula and intra-abdominal abscess.

Table III. Postoperative drainage after pancreaticoduodenectomy

		*Wrapping group**	
Parameter	*Nonwrapping group* (n = *1,679*)	*Falciform ligament* (n = *219*)	*Omentum* (n = *699*)
Amylase level of postoperative drainage fluid (IU/l)			
POD1	4,405 ± 14,129	4,802 ± 17,644	4,950 ± 13,324
POD3	2,924 ± 2,963	2,077 ± 10,947	1,317 ± 2,963†
POD4	1,384 ± 6,876	327 ± 639	1,395 ± 8,227

*Wrapping of pancreatic anastomosis or vessels, including hepatic artery, using omentum or falciform ligament.
†$P = .027$ (nonwrapping versus omentum).
POD, Postoperative day.

DISCUSSION

This study was a report with a large number of patients on the effect of omentum wrapping or falciform ligament after a PD by a retrospective analysis after the report of ISGPF definition.[16] Each institution had their own criteria for pancreatic fistula before the publication of the definition of pancreatic fistula by an ISGPF. Therefore, it was difficult to compare the incidence of pancreatic fistula. The members of the JSPS now share the same definition of pancreatic fistula, and we can accumulate clinical data to compare the incidence of pancreatic fistula by using this common definition. These data were collected between January 2006 and June 2008. However, only 65% of the institutions could respond to the survey, because 35% of the institutions do not have database systems that can evaluate the incidence of pancreatic fistula according to the ISGPF criteria. Seven independent risk factors were identified for grade B + C pancreatic fistula, 4 factors for early intra-abdominal hemorrhage, and 2 factors for late intra-abdominal hemorrhage. Although the evaluation of delayed gastric emptying and intra-abdominal hemorrhage should be based on grading of ISGPS,[21,22] this study was conducted as a retrospective study, and it was difficult to accumulate sufficient data based on the ISGPS criteria that were reported in 2007.

The incidence of pancreatic fistula was significantly higher in the wrapping group in comparison to the nonwrapping group; moreover, the incidence of grade B + C pancreatic fistula was also higher in the wrapping group. However, the amylase level of the drainage fluid was lower in

Table IV. Complications according to the material used by wrapping

Parameter	*Nonwrapping group* (n = *1,679*)	*Wrapping group**			
		Falciform ligament, (%) (n = *219*)	P *value*†	*Omentum, (%)* (n = *699*)	P *value*†
Pancreatic fistula					
All grades	627 (37.3)	72 (32.8)	.197	321 (45.9)	<.001
Grade B + C	281 (16.7)	31 (14.2)	.332	167 (23.9)	<.001
Delayed gastric empting	182 (10.8)	25 (11.4)	.797	92 (13.2)	.106
Bile leakage	52 (3.1)	6 (2.7)	.773	23 (3.3)	.806
Intra-abdominal abscess	179 (10.7)	33 (15.1)	.051	78 (11.2)	.722
Intra-abdominal hemorrhage					
Early	32 (1.9)	3 (1.4)	.791	11 (1.6)	.580
Late	22 (1.3)	4 (0.5)	.532	14 (2.0)	.208
Wound infection	151 (9.0)	26 (11.8)	.168	89 (12.7)	.006
Other organ complications					
Respiratory	76 (4.6)	8 (3.7)	.554	35 (5.0)	.613
Cardiac	25 (1.5)	5 (2.3)	.382	23 (3.3)	.004
Vascular	24 (1.4)	8 (3.7)	.025	12 (1.7)	.601
Renal	17 (1.0)	1 (0.5)	.712	3 (0.4)	.156
Mortality	22 (1.3)	2 (0.9)	>.999	7 (1.0)	.532

*Wrapping of pancreatic anastomosis or vessels, including hepatic artery, using omentum or falciform ligament.
†Versus nonwrapping group.

Table V. Complications according to the location of wrapping

Parameter	*Nonwrapping group, (%)* (n = *1,679*)	*Wrapping group**			
		Vessels, (%) (n = *552*)	P *value*†	*Anastomosis,*‡ *(%)* (n = *366*)	P *value*†
Pancreatic fistula					
All grades	627 (37.3)	223 (40.4)	.200	170 (46.4)	.001
Grade B + C	281 (16.7)	110 (19.9)	.087	88 (24.0)	.001
Delayed gastric empting	182 (10.8)	52 (11.2)	.798	55 (15.1)	.023
Bile leakage	52 (3.1)	18 (3.3)	.848	11 (3.0)	.927
Intra-abdominal abscess	179 (10.7)	55 (9.9)	.643	56 (15.3)	.012
Intra-abdominal hemorrhage					
Early	32 (1.9)	4 (0.7)	.056	10 (2.7)	.313
Late	22 (1.3)	8 (1.4)	.806	10 (2.7)	.047
Wound infection	151 (9.0)	61 (11.1)	.153	54 (14.8)	.001
Other organ complications					
Respiratory	76 (4.6)	22 (4.0)	.591	21 (5.7)	.323
Cardiac	25 (1.5)	12 (2.2)	.274	16 (4.4)	<.001
Vascular	24 (1.4)	10 (1.8)	.525	10 (2.7)	.077
Renal	17 (1.0)	1 (0.2)	.059	3 (0.3)	.734
Mortality	22 (1.3)	6 (1.1)	.683	3 (0.8)	.602

*Wrapping of vessels, including hepatic artery, using omentum or falciform ligament.
†Versus nonwrapping group.
‡Pancreaticojejunostomy or pancreaticogastrostomy using either the omentum or falciform ligament.

patients with omental wrapping than that with other procedures. It might be suggested that the omental wrapping would disturb the drainage of oozing pancreatic juice, and that this may cause damage of the omentum. Indeed, omental wrapping is associated with complications, such as intestinal obstruction, necrosis of the omentum, and infection.[20]

A soft pancreas is susceptible to postoperative intra-abdominal hemorrhage, and a late intra-abdominal hemorrhage is a lethal complication. Omentum wrapping influenced the occurrence of intra-abdominal hemorrhage, which might be related to omentum wrapping, which is performed to protect skeletonized vessels when the surgeon considers the vessels to be fragile during an operation.

Table VI. Univariable analysis for pancreatic fistula

Parameter	*Pancreatic fistula**		P *value*
	With (n = *479*)	*Without* (n = *2,118*)	
Age, y (≥70/<70)	221/258	862/1,256	.029
Gender (male/female)	321/158	1,238/880	.010
Albumin, g/dL (≥3.5/<3.5)	354/108	1,674/383	.020
AST, IU/L (>40/<40)	211/257	807/1,261	.016
ALT, IU/L (>40/<40)	253/215	987/1,083	.013
Amylase, IU/L (>180/<180)	52/406	307/1,709	.034
Preoperative biliary drainage (yes/no)	248/231	973/1,145	.021
Pylorus preservation (yes/no)	282/197	1,118/1,000	.018
Extended resection (yes/no)	384/86	1,788/287	.013
Operation time, min (>600/<600)	116/354	378/1,693	.001
Blood loss, mL (>1,500/<1,500)	119/359	470/1,632	.233
Pancreatic texture (hard/soft)	389/90	1,070/1,048	<.001
Anastomosis (P-J/P-G)	439/40	1,876/242	.051
Duct-to-mucosal anastomosis (yes/no)	372/107	1,675/443	.491
Pancreatic stent (yes/no)	402/77	1,639/479	.002
Wrapping			<.001
Falciform ligament at pancreaticoenterostomy	5	3	
Falciform ligament at vessels	67	144	
Omentum at pancreaticoenterostomy	165	193	
Omentum at vessels	156	185	
No	627	1,052	

*Grade B + C pancreatic fistula according to the International Study Group of Pancreatic Fistula.
ALT, Alanine aminotransferase; *AST*, aspartate aminotransferase; *P-G*, pancreaticogastrostomy; *P-J*, pancreaticojejunostomy.

Table VII. Univariable analysis for intra-abdominal hemorrhage

Parameter	*Early intra-abdominal hemorrhage*			*Late intra-abdominal hemorrhage*		
	With (n = *46*)	*Without* (n = *2,551*)	P *value*	*With* (n = *40*)	*Without* (n = *2,557*)	P *value*
Age, y (≥70/<70)	25/21	1,058/1,493	.079	16/24	1,067/1,490	.826
Gender (male/female)	35/11	1,534/1,027	.025	32/8	1,527/1,030	.009
Albumin, g/dL (≥3.5/<3.5)	35/10	1,993/481	.641	29/11	1,999/480	.197
AST, IU/L (>40/<40)	20/26	998/1,492	.641	13/26	1,005/1,492	.382
ALT, IU/L (>40/<40)	25/21	1,215/1,277	.452	17/22	1,223/1,276	.507
Extended resection (yes/no)	35/10	2,137/363	.148	34/5	2,138/368	.744
Operation time, min (>600/<600)	18/30	478/2,017	.008	13/27	481/2,020	.035
Blood loss, mL (>1,500/<1,500)	15/31	574/1,960	.111	13/27	576/1,964	.142
Blood transfusion (yes/no)	27/18	776/1,642	<.001	9/27	794/1,633	.327
Pancreatic texture (hard/soft)	38/8	1,421/1,130	<.001	34/6	1,425/1,132	<.001
Anastomosis (P-J/P-G)	40/6	2,275/276	.630	35/5	2,280/277	.616
Duct-to-mucosal anastomosis (yes/no)	34/12	2,013/538	.411	31/9	2,016/541	.837
Pancreatic stent (yes/no)	38/8	2,003/548	.503	38/2	2,003/554	.011
Wrapping (yes/no)	14/32	904/1,647	<.001	22/18	1,657/900	.198
Omentum	11	688	.901	14	685	.562
At panceaticoenteric anastomosis	10	356	.109	10	356	.209

ALT, Alanine aminotransferase; *AST*, aspartate aminotransferase; *P-G*, pancreaticogastrostomy; *P-J*, pancreaticojejunostomy.

Surgeons might therefore have chosen to use wrapping for inappropriate cases or when they suspected an increased likelihood of leakage. If surgeons choose to use wrapping in worst cases, a high incidence of pancreatic fistula should be indicated in both omental wrapping and falciform ligament groups.

This study has revealed that wrapping using the omentum did not decrease the incidence of pancreatic fistula. However, this study has several

Table VIII. Risk factors for postoperative pancreatic fistula after pancreaticoduodenectomy according to a multivariable analysis

Predictor	P *value*	*Odds ratio (95% CI)*
Gender (male)	<.001	1.508 (1.200–1.896)
Albumin (<3.5 g/dL)	.035	1.332 (1.021–1.738)
Pancreas texture (soft)	<.001	4.129 (3.139–5.339)
Operation time (≥600 minutes)	.031	1.345 (1.027–1.761)
Extended resection	.013	1.461 (1.084–1.969)
Pylorus preservation	.032	1.276 (1.021–1.595)
Wrapping		
Omentum at pancreaticoenterostomy	.040	1.378 (1.104–1.871)
Omentum at vessels	.005	1.555 (1.141–2.120)

CI, Confidence interval.

limitations because it was a multicenter study using retrospective data collection, which makes it a potential source for significant bias. This study indicated that the usage of an omental flap does not reduce the occurrence of complications after PD, including the incidence of pancreatic fistula. A further validation study is therefore necessary to evaluate the efficacy of wrapping for PD.

The authors are especially grateful to the 91 leading Japanese institutions that kindly took part in the survey. These institutions are listed here:

Aichi Medical University, Department of Surgery; Division of Gastroenterological Surgery
Akita City Hospital, Department of Surgery
Asahikawa Medical College, Department of Gastroenterological Surgery
Chiba Cancer Center, Department of Gastroenterological Surgery
Chiba Rosai Hospital, Department of Surgery
Dokkyo Medical University, Department of Surgery II
Fujita Health University School of Medicine, Department of Biliary Pancreatic Surgery
Fukuoka University Faculty of Medicine, Department of Surgery
Fukui Red Cross Hospital, Department of Surgery
Fukui Saiseikai Hospital, Department of Surgery
Hachioji-Shokaki Hospital, Department of Surgery
Hamamatsu University School of Medicine, Department of Surgery II
Hino Municipal Hospital, Department of Surgery
Hirosaki University School of Medicine, Department of Surgery II
Hiroshima City Hospital, Department of Surgery
Hiroshima University Graduate School of Biomedical Sciences, Department of Surgery, Division of Clinical Medical Science
Hiroshima University Graduate School of Biomedical Sciences, Department of Surgery, Division of Frontier Medical Science
Hokkaido University Graduate School of Medicine, Department of General Surgery
Hyogo College of Medicine, Department of Surgery 1
Ise Municipal General Hospital, Department of Surgery
Itabashi Chuo Medical Center, Department of Surgery
Iwate Medical University School of Medicine, Department of Surgery
Jichi Medical University, Department of Surgery
Jikei University School of Medicine, Department of Surgery
Jikei University School of Medicine, Aoto Hospital, Department of Surgery
Jikei University, Daisan Hospital, Department of Surgery
Jikei University, Kashiwa Hospital, Department of Surgery
Kagawa University, Faculty of Medicine, Department of Gastroenterological Surgery
Kagoshima Medical Association Hospital, Department of Surgery
Kagoshima University, Department of Surgical Oncology
Kanazawa Medical University Hospital, Department of surgical Oncology
Kanazawa University Graduate School of Medical Science, Department of Gastroenterological Surgery
Keio University School of Medicine, Department of Surgery
Kitakyushu Municipal Medical Center, Department of Surgery
Kitasato University School of Medicine, Department of Surgery
Kobe University Graduate School of Medicine, Department of Hepato-Biliary-Pancreatic Surgery
Kumamoto University, Department of Gastroenterological Surgery
Kurume University School of Medicine, Department of Surgery

Kyorin University School of Medicine, Department of Surgery
Kyoto University, Department of Hepato-Biliary-Pancreatic Surgery and Transplantation
Kyushu University, Faculty of Medicine, Department of Surgery I
Matsunami General Hospital, Department of Surgery
Meiwa Hospital, Department of Surgery
Mie University Graduate School of Medicine, Department of Hepatobiliary Pancreatic Surgery
Miyagi Cancer Center, Department of Surgery
Miyazaki University School of Medicine, Department of Surgical Oncology and Regulation of Organ Function
Nagasaki Medical Center, Department of Surgery
Nagasaki University Graduate School of Medicine, Department of Gastroenterological Surgery
Nagasaki University Graduate School of Medicine, Department of Translational Medical Science
Nagoya City University Graduate School of Medical Sciences, Department of Gastroenterological Surgery
Nagoya University Graduate School of Medicine, Department of Gastroenterological Surgery
Nara Medical University, Department of Surgery
National Cancer Center Hospital East, Department of Upper Abdominal Surgery
Nihon University School of Medicine, Division of Digestive Surgery
Niigata Prefectural Central Hospital, Department of Surgery
Niigata University School of Medicine, Department of Surgery
Nippon Medical School, Department of Surgery I
Ogaki Municipal Hopital, Department of Surgery
Okayama University Medical School, Department of Surgery
Osaka City University Graduate School of Medicine, Department of Hepato-Biliary-Pancreatic Surgery
Osaka City University Graduate School of Medicine, Department of Surgical Oncology
Osaka Medical Center for Cancer and Cardiovascular Diseases, Department of Surgery
Osaka University Graduate School of Medicine, Department of Gastroentelogical Surgery
Rinku Medical Center, Department of Surgery
Saku Central Hospital, Department of Surgery
Saga University Faculty of Medicine, Department of Surgery
Sapporo Medical University, Department of Surgery I
Saitama Medical University International Medical Center, Department of Surgery
Shiga University of Medical Science, Department of Surgery
Shinshu University School of Medicine, Department of Surgery
Showa University School of Medicine, Department of Surgery
St. Marianna University School of Medicine, Department of Surgery
St. Marianna University, Yokohama City Seibu Hospital, Department of Surgery
Teikyo University, Department of Surgery
Teikyo University Chiba Medical Center, Department of Surgery
Tochigi Cancer Center, Department of Surgery
Tobata Kyoritsu Hospital, Department of Surgery
Tohoku University Graduate School of Medicine, Department of Surgery, Division of Hepato-Biliary-Pancreatic Surgery
Tokai University, School of Medicine, Department of Gastroenterological Surgery
Tokyo Medical and Dental University, Department of Hepato-Biliary-Pancreatic Surgery
Tokyo Medical and Dental University Ichikawa General Hospital, Department of Surgery
Tokyo Medical University, Department of Surgery
Tokyo Women's Medical University Medical Center East, Department of Surgery
Tokyo Women's Medical University, Institute of Gastroenterology, Department of Gastroenterological Surgery
University of Occupational and Environmental Health, Department of Surgery I
University of Yamanashi Faculty of Medicine, Department of Surgery I
Wakayama Medical University, Second Department of Surgery
Yamagata University Faculty of Medicine, Department of Gastroenterological and General Surgery
Yamaguchi University Graduate School of Medicine, Department of Digestive Surgery and Surgical Oncology
Yame General Hospital, Department of Surgery
Yokohama City University, Department of Gastroenterological Surgery.

REFERENCES

1. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997;226:248-57.
2. Neoptolemos JP, Russell RCG, Bramhall S, Theis B. Low mortality following resection for pancreatic and periampullary tumours in 1026 patients: UK survey of specialist pancreatic units. Br J Surg 1997;84:1370-6.
3. Büchler MW, Friess H, Wagner M, Kulli C, Wagener V, Z'Graggen K. Pancreatic fistula after pancreatic head resection. Br J Surg 2000;87:883-9.