postoperative mortality. Today, the surgical procedure can be performed safely, and the postoperative mortality in some specialized pancreatic centers is reported to be less than 5% [15-17]. In the many previous reports, the follow-up period was within five years, but precise data on the long-term survival and prognostic factors can be obtained by analysis not only of actuarial data, but also of data of patients who achieve actual long-term survival of five years or more.

The aim of this study was to identify the clinical and pathological features of five-year survivors after surgical resection of pancreatic ductal carcinoma. This study could aid oncologists and surgeons in determining which characteristics or clinicopathological factors suggest an increased possibility of five-year survival after pancreatic resection for pancreatic carcinoma.

Methods

Patients

A total of 195 patients who underwent pancreatectomy for pancreatic ductal carcinoma at our institution between January 1988 and October 2012 were studied. Informed consent was obtained from all patients to use the specimens for this study according to the institutional rules of the hospital. All patients were histologically confirmed to have the common type of invasive ductal carcinoma of the pancreas. Any patients with neuroendocrine carcinoma, mucinous cystic carcinomas, or intraductal papillary mucinous carcinomas were excluded. Of the 195 patients, 48 patients were excluded for the following reasons: 42 censored cases, composed of four patients who were lost to follow-up during the observation period and 38 patients who were alive within five years after the operation; four due to postoperative mortality within 30 days; and two were five-year survivors with recurrence disease. The data from the remaining 147 patients, who were five-year survivors without disease recurrence (five-year survivors) and died within five years after surgery (short-term survivors), was retrospectively analyzed. The demographic and clinical variables included age, sex, preoperative serum CA19-9 level, and tumor location. In patients with preoperative jaundice, the data after the jaundice was reduced was used as the preoperative serum CA19-9 values. In patients with jaundice at our medical center, endoscopic or percutaneous bile duct drainage is usually performed. The CA19-9 value in all patients was the value after total bilirubin was reduced to under 5 mg/dL. All patients had presented with resectable localized disease without distant metastasis. None of the patients received neoadjuvant therapy before surgery. Fourteen patients had intraoperative radiation therapy (IORT), and 20 patients received adjuvant chemotherapy with gemcitabine. All patients were followed up on for survival, and the median follow-up period was 14.5 (2.1 to 170.2) months.

Surgery and pathology

Surgery involved standard or subtotal stomach-preserving pancreaticoduodenectomy in 90 patients (61.2%), distal pancreatectomy in 49 (33.3%), and total pancreatectomy in eight (5.4%). Regional lymph node dissection was performed in all patients and the median number of resected lymph nodes was 24 (range: 2 to 100). The resected specimens were fixed in 10% formalin at room temperature, and the size and gross appearance of the tumor were recorded. The pathologic stage of all tumor specimens was determined using the American Joint Committee on Cancer (Sixth edition) staging system [18]. Tumor differentiation was classified according to the World Health Organization's classification of either well-differentiated (Grade 1), moderately differentiated (Grade 2), poorly differentiated (Grade 3), or undifferentiated (Grade 4) [19]. A positive margin was defined as the presence of at least one cancer cell within 1 mm of one or more resection margins on a macroscopic examination. The pathological features that might affect prognosis were histologically assessed tumor size, serosal invasion (S), retroperitoneal tissue invasion (RP), intrapancreatic common bile duct invasion (CH), portal vein invasion (PV), lymph node metastasis, lymphatic invasion (LY), venous invasion (V), and intrapancreatic nerve invasion (NE), on the basis of the Japan Pancreas Society classification (Sixth edition) [20].

Statistical analysis

The clinicopathological features were compared between five-year survivors and short-term survivors. The risk factors related to survival were examined in long-term survivors. Categorical variables were compared using the χ^2 test or Fisher's exact test. A receiver operating characteristics (ROC) curve was constructed to estimate the optimal cutoff value of preoperative serum CA19-9. The cutoff value was determined as the point closest to the upper left-hand corner of the graph. Variables with a significance of $P < 0.05$ on a univariate analysis were included in a multivariate regression analysis to identify factors associated with long-term survival. Survival was calculated using the Kaplan-Meier method and compared between groups by the log-rank test. P values <0.05 were considered significant. Statistical analyses were performed using SAS version 9.0 software (SAS Institute, Inc., Cary, North Carolina, United States).

Results

Characteristics of patient and tumor-related data of these 147 patients are given in Table 1. The median overall survival of all cases was 14.4 months; short-term and five-year survivors were 12 months and 125.6 months, respectively. The actuarial three- and five-year survival rates were 18.4% and 12.2%, respectively. The median

Table 1 Patient characteristics

Characteristics	Number
Gender	
Male	85
Female	62
Age (years)	
Median (range)	67 (33 to 85)
Tumor location	
Head	97
Body/tail	50
Tumor size (cm)	
Median (range)	3.4 (1.2 to 18)
Surgery	
Pancreatoduodenectomy	90
Distal pancreatectomy	49
Total pancreatectomy	8
Histologic differentiation	
Grade 1	33
Grade 2	80
Grade 3	24
Grade 4	10
UICC stage **Union for International Cancer Control**	
IA	1
IB	7
IIA	46
IIB	71
III	3
IV	19
Positive lymph node	
N0	59
N1	88
Resection status	
R0	72
R1	34
R2	41

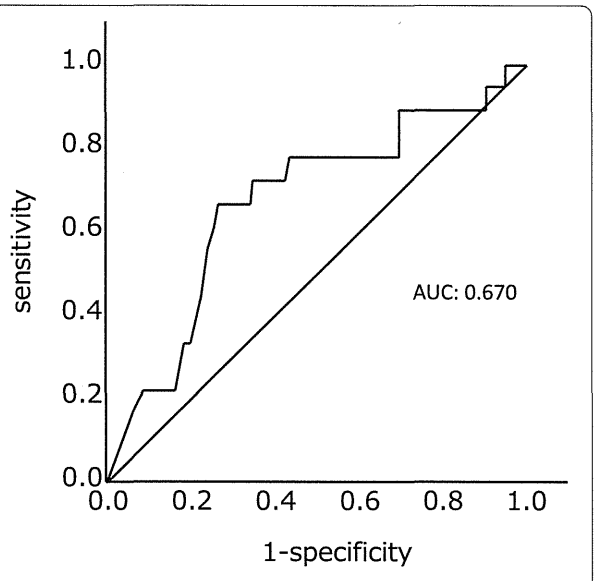

Figure 1 Receiver operating characteristic (ROC) curve analysis of preoperative CA19-9 for prediction of five-year survival of patients with pancreatic carcinoma. An ROC curve demonstrated that a preoperative serum CA19-9 level of 40 U/mL was the optimal cutoff point. The area under the curve (AUC) was 0.670.

overall survival times of early cases (who were operated on between 19888 and 2000) and late cases (2001 to 2012) were 13.5 and 14.7 months, respectively. There are no statistical differences in survival ($P = 0.65$).

The median preoperative serum CA19-9 level of the 147 patients was 122 U/mL. An ROC curve demonstrated that a preoperative serum CA19-9 level of 40 U/mL was the optimal cutoff point for five-year survival, with a sensitivity of 66.7% and a specificity of 73.6%. The area under the curve (AUC) was 0.670 (Figure 1).

Of the 147 patients, 18 patients (12.2%) survived more than five years after surgery without disease recurrence. The median age of five-year survivors (13 men, five women) was 65 years (range: 46 to 76). The distribution of the tumor stages according to The UICC TNM Classification (UICC (Union for International Cancer Control) Sixth) was: stage IA (n = 1; 5.6%); IB (n = 2; 11.1%); IIA (n = 6; 33.3%); IIB (n = 9; 50%); and stage III or IV (none). The pancreatic resections were standard pancreaticoduodenectomy in 12 patients and distal pancreatectomy in six patients. The median tumor size was 32 mm (range: 12 to 55), including five patients (27.8%) with tumor diameters of 20 mm or less. Eight patients were positive for lymph node metastasis, and all patients with positive lymph nodes had within two positive lymph nodes. Portal vein resection was performed in two patients, and R0 surgery was performed in 14 (77.8%) patients. Tumor recurrences beyond five years after surgery were observed in four patients. The longest time for recurrence was 8.4 years after surgery (Table 2).

Table 3 shows the results of the univariate analysis of the factors affecting five-year survival after pancreatectomy in the 147 patients. Sex, age, tumor location, tumor size, histologic differentiation, T classification, N classification, adjuvant therapy, S, RP, CH, LY, V, portal vein resection, and IORT were evaluated, but were not significant on univariate analysis. Significant associations with five-year survival were observed for number of lymph node metastases being two or less ($P = 0.014$), a preoperative serum CA19-9 level cutoff of 40 U/mL ($P = 0.0018$), the absence of NE (P = 0.028), and undergoing an R0 resection ($P = 0.011$).

A logistic regression model adjusted for two or fewer lymph node metastases, a preoperative serum CA19-9

Table 2 Characteristics of five-year survivors without disease recurrence

Age/gender	CA19-9 (U/mL)	Tumor location	Tumor size (mm)	UICC stage	TNM-N	Number of lymph node metastasis	Surgery	R	Outcome (month)	Recurrence
71/F	2	Pb	16	IA	0	0	DP	0	68/A	None
76/F	65	Ph	30	IIB	1	2	PD	0	69/D	None
72/M	597	Pt	40	IIB	1	2	DP	1	73/D	Dissemination
57/M	611	Ph	42	IIB	0	0	PD with PV	0	74/A	None
73/F	3221	Pbt	32	IIB	1	2	DP	0	78/A	None
76/M	21	Ph	20	IIA	0	0	PD	0	79/D	None
62/M	103	Ph	40	IIB	1	2	PD	0	85/D	Lymph node
61/M	29	Ph	12	IIA	0	0	PD	1	86/A	None
46/M	31	Ph	40	IIA	0	0	PD	0	89/D	Liver/local
68/F	2381	Ph	55	IIA	0	0	PD	0	92/A	None
73/M	39	Pb	38	IIB	1	1	DP	0	100/A	None
60/F	34	Ph	50	IIB	1	2	PD	0	108/A	None
70/M	29	Ph	32	IB	0	0	PD	0	111/A	None
57/M	20	Ph	30	IIB	1	2	PD with PV	1	122/D	Lung/skin
56/M	4.1	Ph	20	IIA	0	0	PD	0	129/D	None
57/M	30	Pb	30	IB	0	0	DP	0	144/A	None
57/M	7	Pb	35	IIA	0	0	DP	0	145/A	None
70/M	2	Ph	15	IIB	1	1	PD	1	170/A	None

A, alive; D, dead; DP, distal pancreatectomy; Pb, body of the pancreas; Pbt, body and tail of the pancreas; PD, pancreaticoduodenectomy; Ph, head of the pancreas; Pt, tail of the pancreas; PV, portal vein resection; R, resection status.

level cutoff of 40 U/mL, resection margin status, and the absence of NE identified the following independent cancer-related predictors of five-year survivors: two or fewer lymph node metastases, (OR: 6.02, 95% CI: 1.08 to 112.98; $P = 0.0385$), CA19-9 ≤ 40 U/mL (OR: 5.02; 95% CI: 1.68 to 16.48; $P = 0.036$), and R0 resection (OR: 3.63; 95% CI: 1.12 to 14.28; $P = 0.0316$) (Table 4).

On the basis of the multivariate analysis results, a combined analysis of the preoperative serum CA19-9 level, R0 resection, and number of lymph node metastases being two or less was performed. When each of the three predictors was counted as one point and the points were calculated for all 147 cases, a good stratified survival curve was obtained, showing the longer survival in the higher points: median survival times of three, two, one, and zero points were 39.0, 17.0, 8.2, and 8.6 months, respectively (P <0.0001) (Figure 2).

Discussion

The present study identified three factors (number of lymph node metastases being two or less, preoperative serum CA19-9 level of ≤40 U/mL, and R0 resection), as being related to five-year survival after surgical resection of pancreatic ductal carcinoma. Moreover, the longest survival time was observed in patients who had all of these three factors (Figure 2). To date, prognostic factors for pancreatic carcinoma have been vigorously investigated [4-11]. However, the present study did not simply examine prognostic factors; instead, by analyzing patients who actually achieved five-year survival, factors for five-year survival were more accurately identified.

Tumor size has been considered an important prognostic factor for pancreatic cancer. Large surgical series showed that five-year survival rate (20 to 41%) and median survival time (23 to 38 months) of small pancreatic cancer were better than the five-year survival rate (1 to 20%) and median survival time (10 to 17 months) of large pancreatic cancer [5,21-24]. In the present study, small pancreatic cancer (≤2 cm) was not a factor related to five-year survival after surgical resection for pancreatic cancer on univariate analysis. About a quarter of patients surviving for more than five years had tumors 2 cm or smaller, suggesting that even patients with a larger tumor can achieve five-year survival.

There are many reports that lymph node metastases are a prognostic factor [4-6]. In addition, the number of positive lymph nodes divided by the total number of lymph nodes evaluated (LNR) has also been reported as a prognostic factor [8]. However, there are few reports limited to the number of lymph nodes. Huebner *et al.* reported new findings on predictive factors for five-year survival when dividing patients into groups with ≤1 versus ≥2 lymph node metastases [25]. In the present study, actual five-year survivors were limited to patients with two or few lymph node metastases. This result suggested that three or more lymph node metastases may mean that lymph node metastases exist outside the area of dissection, or that distal metastases may be present.

Table 3 Univariate analysis of factors affecting five-year survival after pancreatectomy for pancreatic adenocarcinoma

Characteristics	Short-term survivors (n = 129)	Five-year survivors (n = 18)	*P* value
Gender			
Male	72	13	0.21
Female	57	5	
Age (years)			
Median (range)	67 (33-85)	65 (46-76)	0.28
Tumor location			
Head	85	12	1
Body/tail	44	6	
Tumor size (cm)			
Median (range)	3.5 (1.2-18)	3.2 (1.2-5.5)	0.52
≤2 cm	14	5	0.06
>2 cm	115	13	
Histologic differentiation			
Grade 1-2	102	11	0.13
Grade 3-4	27	7	
T classification			
T1-T2	14	3	0.44
T3-T4	115	15	
N classification			
N0	49	10	0.2
N1	80	8	
Number of resected lymph nodes			
Median (range)	25 (2100)	17 (258)	0.51
Number of lymph node metastasis			
≤2	95	18	0.01
≥3	34	0	
CA19-9 level (U/mL)			
Median (range)	172 (223009)	30.5 (23221)	0.02
≤40	34	12	0
>40	94	6	
Resection margin			
R0	58	14	0.01
R1-R2	71	4	
Adjuvant therapy			
Yes	19	1	0.47
No	110	17	
Serosal invasion			
Present	81	10	0.61
Absent	48	8	
Retroperitoneal invasion			
Present	91	11	0.58
Absent	36	6	
Intrapancreatic common bile duct invasion			
Present	61	7	0.62
Absent	68	11	
Lymphatic permeation			
Present	113	16	1
Absent	16	2	
Vascular permeation			
Present	63	8	0.8
Absent	66	10	
Intrapancreatic nerve invasion			
Present	118	13	0.03
Absent	13	5	
Portal vein resection			
Present	31	2	0.37
Absent	98	16	
Intraoperative radiation therapy			
Present	11	3	0.38
Absent	118	15	

In the present study, a CA19-9 cutoff value of 40 U/mL was established using ROC curve analysis as described in the statistical section. The AUC of 0.67 at the cutoff value may be statistically insufficient for sensitivity and specificity, however, it was optimal in our data. Abnormally elevated CA19-9 levels have been reported as a prognostic factor in previous studies, but the cutoff values have ranged widely from 30 to 1,000 U/mL. The normal value for CA19-9 is ≤37 U/mL, and interestingly, a CA19-9 of ≤40 U/mL (near the normal value) was associated with

Table 4 Multivariate analysis of factors affecting five-year survival after pancreatectomy with invasive carcinoma of the pancreas

Predictors	Odds ratio	95% confidence interval	*P* value
Number of lymph node metastasis			
≤2	6.02	1.08-112.98	0.0385
≥3	1		
CA-19-9 level (U/mL)			
≤40	5.02	1.68-16.48	0.0036
>40	1		
Resection margin			
R0	3.63	1.12-14.28	0.0316
R1-R2	1		
Intrapancreatic perineural invasion			
Absent	2.72	0.645-10.86	0.1664
Present	1		

Number of predictors	n	MST (month)	5-year survival rate(%)
0	16	8.6	0
1	53	8.2	2.3
2	59	17.0	11.9
3	19	39.0	42.1

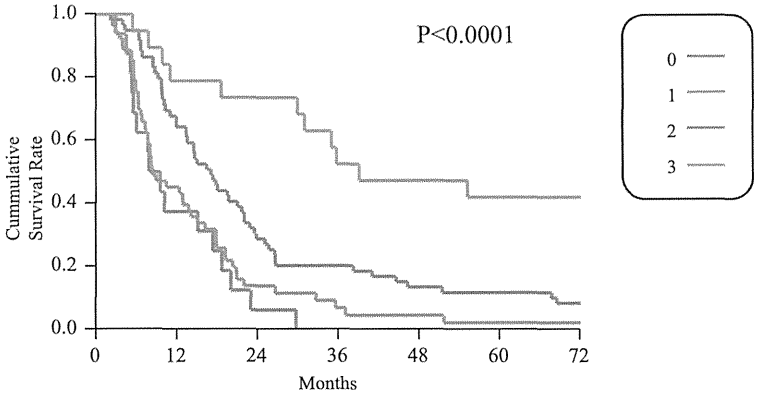

Figure 2 A combined analysis of the preoperative serum CA19-9 level, R0 resection, and number of lymph node metastases being two or less. The subgroup of preoperative serum CA19-9 ≤ 40 U/mL and R0 resection, together with number of lymph node metastases ≤2, is associated with a probability of five-year survival of 42.1%. MST, median survival time.

five-year survival in the present study. Waraya *et al.* reported cutoff values of 28 U/mL or 30 U/mL in terms of prognosis, which supports the current results [9]. These results might suggest that long-term survival after surgical resection for pancreatic ductal carcinoma requires that the preoperative CA19-9 level be around the normal range. No other tumor markers, including CEA (Carcinoembryonic antigen) and DUPAN-2, were useful as prognostic indicators (data not shown).

Resection status has also been often reported as a prognostic factor. The present study also found residual tumor status to be an independent predictive factor related to five-year survival. On the other hand, retroperitoneal invasion was not a predictive factor for five-year survival. This important finding means that, even in cases with retroperitoneal invasion, R0 resection is important and hopeful for five-year survival.

In addition, four patients had tumor recurrence beyond five years of follow-up. The longest interval to recurrence was 8.7 years, with lung and skin metastases. Therefore, it should be kept in mind during the follow-up period that recurrences may occur even after five years. Schnelldorfer *et al.* reported that none of the 30 patients who survived beyond 7.8 years had recurrence of disease, and all survived beyond 10 years [6]. Katz *et al.* also reported that late recurrence after five years occurred in seven patients and the latest cancer-related death occurred at 7.6 years [26]. In consideration of our report and the previous reports, survival beyond 10 years might suggest a potential cure.

The CONKO-001 trial [27] reported gemcitabine to be effective as a postoperative adjuvant therapy. This trial reported that treatment with adjuvant gemcitabine led to a 24% improvement in overall survival, with a significant 10.3 percentage point absolute improvement in the five-year overall survival rate (20.7 versus 10.4%), compared with observation alone. Moreover, a recent phase three study compared S-1 and gemcitabine as postoperative adjuvant therapy and reported S-1 to be superior. In this study, in the S-1 therapy group, median relapse-free survival time was 23.2 months, and the two-year relapse-free survival rate was 49% [28]. These results strongly suggest that adjuvant chemotherapy achieved long-term survival after surgical resection. However, in the present study a small number of 20 patients received gemcitabine as adjuvant therapy, resulting in no impact of adjuvant therapy on the survival time (Table 3). Since gemcitabine and S-1 have been recently recognized as standard adjuvant therapies after pancreatectomy for pancreatic cancer with the above mentioned evidences [27,28], the rate of adjuvant therapy using either of the two drugs has gradually increased in Japan. Nowadays more than 80% of the

patients with pancreatic cancer are given gemcitabine or S-1 after pancreatectomy in our institution. With increasing use of adjuvant therapy for pancreatic cancer in the future, five-year survivors would be expected to increase. Although neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy for pancreatic cancer have been investigated for last two decades, their survival benefit has still not been proven [29,30]. At our institution, neoadjuvant chemoradiotherapy with gemcitabine and S-1 have been used since 2013 for unresectable and borderline resectable pancreatic adenocarcinoma. In our series, some initially unresectable cases have been resectable. But several years are needed to evaluate whether neoadjuvant chemoradiotherapy will become a prognostic factor or not.

Using the predictive model, the subgroup of preoperative serum CA19-9 level cutoff of 40 U/mL and R0 resection, together with number of lymph node metastases being two or less, is associated with a probability of five-year survival of 42.1% (Figure 2). Although long-term survival in this subgroup can be strongly expected, R0 resection and two or fewer lymph node metastases were post-resection parameters. This result suggests that patients not expected to have these factors at the time of preoperative diagnosis should have neoadjuvant treatment or stronger adjuvant chemotherapy.

The limitations of the present study are as follows. This was a retrospective study conducted at a single institution. Approximately 5 to 10% of the general population is Lewis antigen A and B-negative, which means that they do not synthesize the CA19-9 antigen and will not have elevated levels, even with pancreatic cancer or other malignancies. In the present series, the data related to Lewis antigens A and B could not be included because of the retrospective nature of the study.

Conclusions

In conclusion, the present study showed that two or fewer lymph node metastases, a preoperative serum CA19-9 level of 40 U/mL or less, and R0 resection were associated with five-year disease-free survival of patients with pancreatic cancer who underwent surgical resection. Patients with these three factors are expected to have a high five-year survival rate after surgical resection of pancreatic carcinoma.

Abbreviations

AUC: Area under the curve; CA19-9: Carbohydrate antigen 19-9; CH: Intrapancreatic common bile duct invasion; CI: Confidence interval; IORT: Intraoperative radiation therapy; LY: Lymphatic invasion; NE: Intrapancreatic nerve invasion; OR: Odds ratio; PV: Portal vein invasion; ROC: Receiver operating characteristics; RP: Retroperitoneal tissue invasion; S: Serosal invasion; V: Venous invasion.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KK designed the studies and performed the manuscript. RA and BN supported with design and interpretation of this study. Statistical analysis was performed by MO and SY. KH and AM helped to draft the manuscript. KM, KN and TH carried out the catamnestic followup. Overall supervision of the manuscript was completed by KH. All authors read and approved the final manuscript.

Author details

[1]Department of Surgical Oncology, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan. [2]Department of Surgery, Kashiwara Municipal Hospital, 1-7-9 Hozenji, Kashiwara City, Osaka 582-0005, Japan.

Received: 9 February 2014 Accepted: 6 November 2014
Published: 27 November 2014

References

1. Siegel R, Naishadham D, Jemal A: **Cancer statistics, 2012.** *CA Cancer J Clin* 2012, **62**:10–29.
2. Matsuno S, Egawa S, Fukuyama S, Motoi F, Sunamura M, Isaji S, Imaizumi T, Okada S, Kato H, Suda K, Nakao A, Hiraoka T, Hosotani R, Takeda K: **Pancreatic Cancer Registry in Japan: 20 years of experience.** *Pancreas* 2004, **28**:219–230.
3. Zuckerman DS, Ryan DP: **Adjuvant therapy for pancreatic cancer: a review.** *Cancer* 2008, **112**:243–249.
4. Zacharias T, Jaeck D, Oussoultzoglou E, Neuville A, Bachellier P: **Impact of lymph node involvement on long-term survival after R0 pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas.** *J Gastrointest Surg* 2007, **11**:350–356.
5. Lim JE, Chien MW, Earle CC: **Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients.** *Ann Surg* 2003, **237**:74–85.
6. Schnelldorfer T, Ware AL, Sarr MG, Smyrk TC, Zhang L, Qin R, Gullerud RE, Donohue JH, Nagorney DM, Farnell MB: **Long-term survival after pancreatoduodenectomy for pancreatic adenocarcinoma: is cure possible?** *Ann Surg* 2008, **247**:456–462.
7. Ferrone CR, Brennan MF, Gonen M, Coit DG, Fong Y, Chung S, Tang L, Klimstra D, Allen PJ: **Pancreatic adenocarcinoma: the actual 5-year survivors.** *J Gastrointest Surg* 2008, **12**:701–706.
8. Hartwig W, Hackert T, Hinz U, Gluth A, Bergmann F, Strobel O, Buchler MW, Werner J: **Pancreatic cancer surgery in the new millennium: better prediction of outcome.** *Ann Surg* 2011, **254**:311–319.
9. Waraya M, Yamashita K, Katagiri H, Ishii K, Takahashi Y, Furuta K, Watanabe M: **Preoperative serum CA19-9 and dissected peripancreatic tissue margin as determiners of long-term survival in pancreatic cancer.** *Ann Surg Oncol* 2009, **16**:1231–1240.
10. Ferrone CR, Finkelstein DM, Thayer SP, Muzikansky A, Fernandez-delCastillo C, Warshaw AL: **Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma.** *J Clin Oncol* 2006, **24**:2897–2902.
11. Hallemeier CL, Botros M, Corsini MM, Haddock MG, Gunderson LL, Miller RC: **Preoperative CA 19–9 level is an important prognostic factor in patients with pancreatic adenocarcinoma treated with surgical resection and adjuvant concurrent chemoradiotherapy.** *Am J Clin Oncol* 2011, **34**:567–572.
12. Adham M, Jaeck D, Le Borgne J, Oussoultzouglou E, Chenard-Neu MP, Mosnier JF, Scoazec JY, Mornex F, Partensky C: **Long-term survival (5–20 years) after pancreatectomy for pancreatic ductal adenocarcinoma: a series of 30 patients collected from 3 institutions.** *Pancreas* 2008, **37**:352–357.
13. Cleary SP, Gryfe R, Guindi M, Greig P, Smith L, Mackenzie R, Strasberg S, Hanna S, Taylor B, Langer B, Gallinger S: **Prognostic factors in resected pancreatic adenocarcinoma: analysis of actual 5-year survivors.** *J Am Coll Surg* 2004, **198**:722–731.
14. Shimada K, Sakamoto Y, Nara S, Esaki M, Kosuge T, Hiraoka N: **Analysis of 5-year survivors after a macroscopic curative pancreatectomy for invasive ductal adenocarcinoma.** *World J Surg* 2010, **34**:1908–1915.
15. Gordon TA, Burleyson GP, Tielsch JM, Cameron JL: **The effects of regionalization on cost and outcome for one general high-risk surgical procedure.** *Ann Surg* 1995, **221**:43–49.

16. Ho V, Heslin MJ: **Effect of hospital volume and experience on in-hospital mortality for pancreaticoduodenectomy.** *Ann Surg* 2003, **237**:509–514.
17. Sosa JA, Bowman HM, Gordon TA, Bass EB, Yeo CJ, Lillemoe KD, Pitt HA, Tielsch JM, Cameron JL: **Importance of hospital volume in the overall management of pancreatic cancer.** *Ann Surg* 1998, **228**:429–438.
18. SLaW C: *TMN Classification of Malignant Tumours.* 6th edition. New Jersey: John Wiley and Sons Ltd; 2002.
19. Bosman ESJ FT, Lakhani SR, Hiroko O: *WHO Classification of Tumours of the Digestive System.* Lyon: International Agency for Research on Cancer; 2010.
20. Japanese Pancreas Society: *General Rules for the Study of Pancreatic Cancer.* 6th edition. Tokyo: Kanehara-syuppan; 2009.
21. Meyer W, Jurowich C, Reichel M, Steinhauser B, Wunsch PH, Gebhardt C: **Pathomorphological and histological prognostic factors in curatively resected ductal adenocarcinoma of the pancreas.** *Surg Today* 2000, **30**:582–587.
22. Pantalone D, Ragionieri I, Nesi G: **Improved survival in small pancreatic cancer.** *Dig Surg* 2001, **18**:41–46.
23. Pongprasobchai S, Pannala R, Smyrk TC, Bamlet W, Pitchumoni S, Ougolkov A, de Andrade M, Petersen GM, Chari ST: **Long-term survival and prognostic indicators in small (<or = 2 cm) pancreatic cancer.** *Pancreatology* 2008, **8**:587–592.
24. Yeo CJ, Cameron JL, Lillemoe KD, Sitzmann JV, Hruban RH, Goodman SN, Dooley WC, Coleman J, Pitt HA: **Pancreaticoduodenectomy for cancer of the head of the pancreas: 201 patients.** *Ann Surg* 1995, **221**:721–731. discussion 731–723.
25. Huebner M, Kendrick M, Reid-Lombardo KM, Que F, Therneau T, Qin R, Donohue J, Nagorney D, Farnell M, Sarr M: **Number of lymph nodes evaluated: prognostic value in pancreatic adenocarcinoma.** *J Gastrointest Surg* 2012, **16**:920–926.
26. Katz MH, Wang H, Fleming JB, Sun CC, Hwang RF, Wolff RA, Varadhachary G, Abbruzzese JL, Crane CH, Krishnan S, Vauthey JN, Abdalla EK, Lee JE, Pisters PW, Evans DB: **Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma.** *Ann Surg Oncol* 2009, **16**:836–847.
27. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, Niedergethmann M, Zulke C, Fahlke J, Arning MB, Sinn M, Hinke A, Riess H: **Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial.** *JAMA* 2013, **310**:1473–1481.
28. Uesaka K, Fukutomi A, Boku N, Kanemoto M, Konishi I, Matsumoto Y, Shimizu S: **Randomized phase 3 trial of adjuvant chemotherapy with gemcitabine vs. S-1 for resected pancreatic cancer (JASPAC-01 study).** *J Clin Oncol* 2013, **31**(4s):abst145.
29. Reni M: **Neoadjuvant treatment for resectable pancreatic cancer: time for phase III testing?** *World J Gastroenterol* 2010, **16**:4883–4887.
30. Festa V, Andriulli A, Valvano MR, Uomo G, Perri F, Andriulli N, Corrao S, Koch M: **Neoadjuvant chemo-radiotherapy for patients with borderline resectable pancreatic cancer: a meta-analytical evaluation of prospective studies.** *JOP* 2013, **14**:618–625.

doi:10.1186/1477-7819-12-360
Cite this article as: Kimura *et al.*: Clinical and pathological features of five-year survivors after pancreatectomy for pancreatic adenocarcinoma. *World Journal of Surgical Oncology* 2014 **12**:360.

J Gastrointest Surg (2014) 18:1597–1603
DOI 10.1007/s11605-014-2521-5

ORIGINAL ARTICLE

Predictive Factors for Change of Diabetes Mellitus Status After Pancreatectomy in Preoperative Diabetic and Nondiabetic Patients

Keiichiro Hirata · Bunzo Nakata · Ryosuke Amano · Sadaaki Yamazoe · Kenjiro Kimura · Kosei Hirakawa

Received: 20 February 2014 / Accepted: 31 March 2014 / Published online: 8 July 2014

Abstract
Introduction This study aimed to determine risk factors for exacerbation of diabetes mellitus (DM) after pancreatectomy.
Methods Medical records of 167 patients with benign and malignant pancreaticobiliary diseases who underwent pancreaticoduodenectomy or distal pancreatectomy were retrospectively analyzed. DM was diagnosed by diabetic history or American Diabetes Association criteria. Worsened and improved DM after pancreatectomy was defined when treatment intensity or insulin/oral antidiabetic drug dosage increased or decreased, respectively, postoperatively. Long-standing DM was defined as a duration of >2 years.
Results In 76 preoperative diabetic patients, worsened and improved DM was observed postoperatively in 46 (60.5 %) and 9 (11.8 %) patients, respectively. In 91 preoperative nondiabetic patients, 22 (24.2 %) developed new-onset DM after pancreatectomy. Multivariate logistic analysis of the preoperative diabetic patients demonstrated long-standing DM and malignancy as independent predictors for postoperative worsened DM. No patients with long-standing DM or insulin treatment experienced improved DM after pancreatectomy. Multivariate logistic analysis of the preoperative nondiabetic patients showed body mass index of ≥25 and hard pancreatic texture as independent risk factors for new-onset postoperative DM.
Conclusions These results may enable preoperative evaluation of risk factors for worsened or new-onset DM after pancreatectomy and may help plan intensive care for patients at a high risk of postoperative worsened DM.

Keywords Diabetes mellitus · Pancreaticoduodenectomy · Distal pancreatectomy · Body mass index · Pancreatic texture

Introduction

Pancreatectomy usually causes deterioration of glucose tolerance because the pancreas is the organ responsible for the hormonal regulation of glucose metabolism by secreting insulin and glucagon.[1] The American Diabetes Association (ADA) categorizes diabetes mellitus (DM) after pancreatectomy as "type 3C DM." Type 3 is "other specific type" DM in ADA category, meaning features are distinct from type 1 or type 2 DM. Type 1 DM commonly begins in childhood and is caused mainly by a T cell-mediated autoimmune attack on the beta cells. Type 2 DM is caused by a defect in the responsiveness of body tissue to insulin as a result of an unknown mechanism and is a lifestyle-related disease. Code "C" is one of eight pathophysiological entities (A to H) of type 3. Type 3C DM is caused by "disease of the exocrine pancreas" including pancreatitis, trauma, pancreatectomy, neoplasm, and cystic fibrosis.[2] Type 3C DM, or generally called "pancreatogenic diabetes," after pancreatectomy has the following clinical characteristics:[3,4] (1) rarely developing ketoacidosis, (2) mild hyperglycemia, (3) high sensitivity to insulin administration, (4) common iatrogenic hypoglycemia, and (5) hepatic resistance to insulin and unsuppressed glucose production. The serum levels of insulin, glucagon, and pancreatic polypeptide decrease after pancreatectomy because the insulin-secreting beta cells, glucagon-secreting alpha cells,

K. Hirata · B. Nakata (✉) · R. Amano · S. Yamazoe · K. Kimura · K. Hirakawa
Department of Surgical Oncology, Graduate School of Medicine, Osaka City University, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan
e-mail: bunzo@med.osaka-cu.ac.jp

B. Nakata
Department of Surgery, Kashiwara Municipal Hospital, Kashiwara City, Osaka, Japan

and pancreatic polypeptide-secreting PP cells in pancreatic tissue have been reduced. The association of glucose intolerance and hepatic insulin resistance with deficiency of pancreatic polypeptide has been demonstrated.[3] Low insulin, normal/high glucagon, and high pancreatic polypeptide levels are characteristic of type 1 DM, whereas high insulin, normal/high glucagon, and high pancreatic polypeptide levels are distinctive of type 2 DM.[3,4] Although hormonal status differs among the DM types, hyperglycemia of patients with type 3C DM is treated with dietary management, an oral antidiabetic drug (OAD), or insulin according to the intensity of the glucose regulation disturbance.[3] Principally, the goal of glucose control is the reduction of hemoglobin (Hb)A1c levels below 6.5 % for Japanese[5] and 7.0 % for Americans and Europeans[6] with type 1 or 2 DM. The target HbA1c level is the same for type 3C DM.[3]

It has been recognized that the change in glucose metabolism after pancreatectomy is usually small, unless more than 50 % of the parenchyma is excised in patients with diffuse parenchymal disease or more than 80 % in patients with normal pancreatic function.[4] As approximately half the volume of the pancreatic tissue, including endocrine cells, is removed by pancreaticoduodenectomy (PD)[7] or distal pancreatectomy (DP),[8] some patients who undergo resection develop type 3C DM. There may be different reduced ratios in the individual kinds of islet cells between PD and DP, because beta cells are located evenly throughout the pancreas, and alpha cells are localized selectively in pancreatic tail, and PP cells are localized mainly in the pancreatic head.[4] However, it is difficult to predict exactly how glucose metabolic derangement will occur after pancreatectomy in individual patients. The present study investigated the impact of clinicopathological factors on the change in postoperative diabetic status in patients with benign and malignant tumors who underwent PD or DP.

Materials and Methods

Patients

Data were collected retrospectively on 167 patients who underwent PD (n=100) or DP (n=67) between June 2007 and April 2012 at Osaka City University Hospital and who survived more than 1 year. The patients reviewed consisted of 86 males and 81 females, and their mean age was 66.0± 12.2 years. PD included subtotal stomach-preserving PD[9] (n=70) and pylorus-preserving PD (n=7). Most of the PD procedures included reconstruction by Child's method (n= 83). Operative duration was 375±150 min. Intraoperative blood loss volume was 719±688 ml. The pathological diagnoses of the lesions are shown separately in the preoperative diabetic and nondiabetic patients in Table 1. Comprehensive written informed consent was acquired from all patients.

Definition of DM

Diabetes in the preoperative diabetic patients was defined as history of diabetes as treated by dietary management, OAD, or insulin, which were listed according to treatment intensity. Worsened DM in the preoperative diabetic patients was defined as an increase in the intensity of the treatment or amount of insulin/OAD after pancreatectomy compared with preoperative treatment. Improved DM was defined as a decrease in the intensity of the treatment or amount of insulin/OAD compared with the preoperative treatment. New-onset DM in the nondiabetic patients after operation was defined according to the ADA diagnostic criteria for DM. For instance, in patients with classic symptoms of hyperglycemia or with hyperglycemic crisis, a random plasma glucose level of ≥200 mg/dl was sufficient for the diagnosis of DM. In patients with unequivocal hyperglycemia, the following criteria were required to be confirmed on more than one occasion: (a) HbA1c of ≥6.5 %, (b) fasting plasma glucose of ≥126 mg/dl

Table 1 Pathology of 167 patients who underwent pancreatectomy

Feature	Preoperative diabetic patients	Preoperative nondiabetic patients
No. of patients	76	91
Malignant		
Pancreatic cancer	38	31
Intraductal papillary mucinous carcinoma	4	2
Acinar cell carcinoma	1	0
Pancreatic metastatic tumor from renal cell carcinoma	1	1
Ampullary cancer	7	9
Distal bile duct cancer	3	11
Duodenal cancer	3	3
Gallbladder cancer	0	1
Benign or low-grade malignancy		
Intraductal papillary mucinous adenoma	11	12
Nonfunctioning islet cell tumor	2	7
Gastrinoma	0	1
Solid pseudopapillary tumor	1	4
Mucinous cystadenoma	0	4
Schwannoma	0	1
Serous cystadenoma	1	0
Simple cyst	1	0
Ectopic spleen	1	0
Chronic pancreatitis	2	5

after fasting for ≥8 h, or (c) 2-h value of plasma glucose of ≥200 mg/dl during an oral glucose tolerance test.[2] DM status was observed for 1 year after operation both in the preoperative diabetic and nondiabetic patients. Outcome-based physical and blood examinations were conducted at least every 12 weeks. The data were collected until 1 year after operation to avoid the effect of recurrent disease on DM status. Duration of DM more than 2 years before operation was defined as long-standing DM.[10]

Statistical Analysis

Statistical analysis was performed using JMP® 10 statistical software (SAS Institute, Inc., Cary, NC, USA). All subjects were classified into two groups: preoperative diabetic and nondiabetic patients, and analyses were performed for each group. We examined the clinicopathological risk factors for worsened or new-onset DM using univariate logistic regression analysis. We also utilized the stepwise forward selection method in multivariate logistic analysis to identify the covariate most strongly associated with worsened or new-onset DM. The cutoff value of body mass index (BMI) was 25, above of which is defined as overweight by the World Health Organization.[11] Mean values were recorded with plus or minus of the standard deviation. Significance for all studies was accepted at two-tailed P values of <0.05.

Results

Change of DM Status and Treatment Alteration

In the 76 preoperative diabetic patients, worsened DM after pancreatectomy was found in 46 (60.5 %) patients within 1 year (Fig. 1a, Table 2). Nine (11.8 %) patients experienced improved DM and are characterized in Table 3. Of the 91 preoperative nondiabetic patients, 22 (24.2 %) developed new-onset DM after pancreatectomy within 1 year (Fig. 1b, Table 2).

Of the 76 preoperative diabetic patients, 33 were controlled preoperatively by dietary management, 36 by OAD, and 7 by insulin injection. An itemization of the treatment alteration for the patients with changed DM status is shown in Table 2.

Univariate and Multivariate Analysis

With regard to risk factors for worsened DM in the preoperative diabetic patients, univariate logistic analysis showed that long-standing DM and preoperative treatment for DM with insulin or OAD were significant factors for worsening of DM after pancreatectomy (Table 4). Multivariate logistic analysis revealed that long-standing DM (odds ratio, 11.4221; 95 % confidence interval (CI), 3.2732–51.1931; $P<0.0001$) and malignant disease (odds ratio, 5.9241; 95 % CI, 1.6165–25.6499; $P=0.0066$) were significant independent factors for worsening of DM following pancreatectomy. With regard to risk factors for new-onset DM in preoperative nondiabetic patients, BMI≥25 and hard pancreatic texture were shown as factors by univariate logistic analysis (Table 5) and were shown as significant independent factors by multivariate logistic analysis (odds ratio, 3.5264 and 2.8522; 95 % CI, 1.0648–11.7383 and 1.0038–8.2644; $P=0.0394$ and 0.0492, respectively).

Discussion

The number of patients with diabetes before undergoing pancreatectomy accounted for 45.5 % (76/167) of the subjects in the present study (Table 1). The prevalence of preoperative DM in patients undergoing pancreatectomy has been scarcely reported except with respect to pancreatic cancer and chronic pancreatitis. In the present study, the incidence of preoperative diabetic patients with pancreatic cancer was 55.7 % (38/69) (Table 1); this proportion is concordant with the proportions of patients with pancreatic cancer reported in previous studies as 30.9–54.9 %.[10,12–16] These data also demonstrate the apparently high rates of preoperative diabetic patients with various diseases requiring treatment by pancreatectomy, although the patient numbers were small for the individual diseases (Table 1).

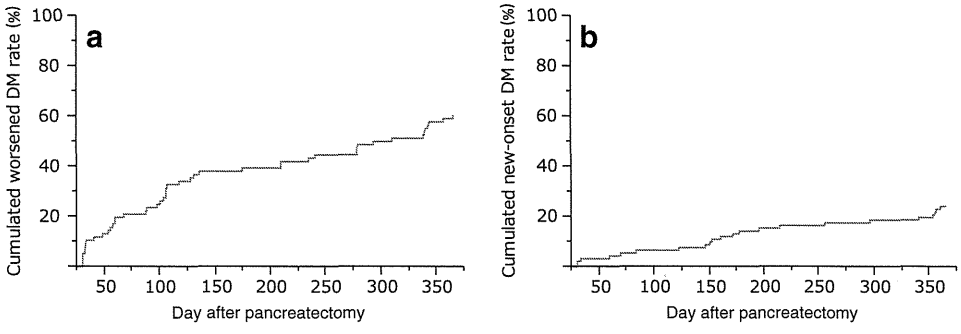

Fig. 1 Time-dependent cumulated curves. (**a**) Rate of worsened diabetes mellitus (*DM*) in preoperative diabetic patients after pancreatectomy. (**b**) Rate of new-onset DM in preoperative nondiabetic patients after pancreatectomy

Table 2 Change of diabetes mellitus status and treatment alteration after pancreatectomy

Change	Treatment alteration	No. of preoperative diabetic patients	No. of preoperative nondiabetic patients
Worsened DM		46	
	Diet[a]→OAD	9	–
	Diet→insulin	3	–
	OAD→insulin	9	–
	Increased OAD	20	–
	Increased insulin	5	–
Improved DM		9	
	Insulin→diet	0	–
	Insulin→OAD	0	–
	OAD→diet	2	–
	Decreased OAD	1	–
	Decreased insulin	0	–
	Diet→no treatment	6	–
New-onset DM			22
	No treatment→diet	–	14
	No treatment→OAD	–	7
	No treatment→insulin	–	1

DM diabetes mellitus, *OAD* oral antidiabetic drug

[a] Dietary management

The cause of worsened DM after pancreatectomy in preoperative diabetic patients is probably due to glucose-regulating disturbance caused by a reduction of hormone-secreting cells. Previous studies have found rates of worsened DM in preoperative diabetic patients after pancreatectomy in a wide range of 18–83.3 %.[7,15,17] The present study found that 60.5 % (46/76) of the preoperative diabetic patients experienced worsened DM after pancreatectomy. The definitions of worsened DM in the previous reports were almost uniform, defining worsened DM as a postoperative escalation of medication for blood sugar control, which is the same definition used in the current study (Table 2).

One possible explanation for the different rates of worsened DM observed in various individual studies might be different observation periods after pancreatectomy. An advantage of the present investigation was that the study design allowed the ability to indicate a gradually increasing rate of worsened DM according to time progression (Fig. 1a); such time-dependent data have not been demonstrated previously. However, the weakness of the data in the present study is that the observation period was limited to 1 year after pancreatectomy, which is the same duration as that of the data from several previous investigations.[15,18–20] The purpose of the 1-year postoperative observation period was to diminish the effects on DM status by pancreatic disease recurrence. The investigations to find predictors for change in DM status caused by pancreatectomy have been very limited. White et al.[15] retrospectively analyzed the impact of several variables on worsened DM, together with new-onset DM, in 101 patients with pancreatic malignant neoplasms who underwent pancreatectomy. They showed that the duration of hospital

Table 3 Characteristics of patients who experienced improvement in preoperative diabetes mellitus after pancreatectomy

No.	Age	Sex	Preoperative BMI	Preoperative serum albumin (mg/dl)	Preoperative jaundice	Long-standing DM[a]	Preoperative treatment for DM	Operative procedure	Pancreatic texture	Pathology	Postoperative pancreatic fistula grade B/C
1	68	Male	23.5	3.8	No	No	Diet[b]	DP	Soft	Pancreatic cancer	No
2	75	Female	22.4	4.1	No	No	OAD	DP	Soft	Pancreatic cancer	No
3	67	Female	26	3.3	Yes	No	OAD	PD	Soft	Pancreatic cancer	No
4	76	Male	24.8	3.9	No	No	OAD	PD	Hard	Pancreatic cancer	No
5	74	Male	21.3	3.9	No	No	OAD	PD	Hard	Intraductal papillary mucinous carcinoma	No
6	67	Male	23.7	4.4	No	No	Diet	DP	Soft	Acinar cell carcinoma	Yes
7	63	Male	28.7	4.2	No	No	Diet	PD	Soft	Intraductal papillary mucinous adenoma	No
8	50	Male	22.9	3.8	No	No	Diet	PD	Soft	Nonfunctioning islet cell tumor	No
9	61	Male	21.3	3.8	No	No	Diet	DP	Soft	Schwannoma	Yes

Pancreatic texture was subjectively judged by the operating surgeon. Grade of pancreatic fistula was defined according to the International Study Group on Pancreatic Fistula

BMI body mass index, *DM* diabetes mellitus, *OAD* oral antidiabetic drug, *PD* pancreaticoduodenectomy, *DP* distal pancreatectomy

[a] Treatment for DM over 2 years

[b] Dietary management

Table 4 Impact of clinicopathological features on worsened diabetic mellitus after pancreatectomy in preoperative diabetic patients according to univariate analysis

Feature	No. of patients	Univariate analysis		
		Odds ratio	95 % CI	*P* value
Age (≥70:<70 years)	37:39	1.1429	0.4544–2.8947	0.7762
BMI (≥25:<25)	19:57	1.5758	0.5395–5.0230	0.4117
Preoperative serum albumin (≥3.5:<3.5 g/dl)	67:9	2.1	0.5105–9.1871	0.2990
Preoperative jaundice (yes/no)	18:58	1.4118	0.4771–4.5384	0.5388
Long-standing DM[a] (yes/no)	30:46	5.9524	2.0614–20.1269	0.0007
Preoperative treatment for DM (insulin or OAD/diet[b])	43:33	2.7026	1.0574–7.1323	0.0378
DP:PD	42:34	1.3750	0.5443–3.5452	0.5016
Pancreatic texture (hard/soft)	28:48	1.2857	0.4953–3.4428	0.6076
Malignant/benign or low-grade malignancy	57:19	2.7500	0.9584–8.2260	0.0600
Postoperative pancreatic fistula (grade B or C/none or grade A)	21:55	0.8235	0.2968–2.3307	0.7100

Pancreatic texture was subjectively judged by the operating surgeon. Grade of pancreatic fistula was defined according to the International Study Group on Pancreatic Fistula

CI confidence interval, *BMI* body mass index, *DM* diabetes mellitus, *OAD* oral antidiabetic drug, *PD* pancreaticoduodenectomy, *DP* distal pancreatectomy

[a] Treatment for DM over 2 years

[b] Dietary management

stay alone predicted worsened/new-onset DM after pancreatectomy according to univariate logistic regression analysis; however, the odds ratio was only 1.05. You et al.[7] compared clinicopathological features between 36 patients with unchanged glucose metabolism and 19 patients with worsened/new-onset DM who underwent PD for various periampullary cancers and benign diseases. They concluded that none of the clinicopathological features showed any statistical differences between the two patient groups. In the present study, multivariate logistic analysis showed that long-standing DM and malignant disease were independent predictors for worsened DM after pancreatectomy (Table 4). We speculated that long duration of pancreatogenic DM might strongly destroy the pancreatic tissue, including the glucose regulation hormone-secreting islet cells, in patients with preoperative long-standing DM. The destruction of pancreatic parenchyma may be partly caused by a compression of the pancreatic duct by the occupying lesion. A malignant neoplasm might be more capable than benign disease in destroying pancreatic tissue by this compression mechanism to the pancreatic duct. The notable point of difference between the present study and the studies by White et al. and You et al. was that the previous investigators analyzed worsened DM and new-onset DM in the same group.

Table 5 Impact of clinicopathological features on new-onset diabetes mellitus after pancreatectomy in preoperative nondiabetic patients according to univariate analysis

Feature	No. of patients	Univariate analysis		
		Odds ratio	95 % CI	*P* value
Age (≥70:<70 years)	57:34	1.0581	0.3965–2.9665	0.9113
BMI (≥25:<25)	16:75	3.1111	0.9738–9.7737	0.0553
Preoperative serum albumin (≥3.5:<3.5 g/dl)	77:14	1.2011	0.3323–5.7155	0.7918
Preoperative jaundice (yes/no)	27:64	1.1433	0.3873–3.1590	0.8009
DP:PD	33:58	1.298	0.4743–3.4559	0.6047
Pancreatic texture (hard/soft)	27:64	2.549	0.9276–6.9999	0.0693
Malignant/benign or low-grade malignancy	57:34	1.8211	0.6592–5.5950	0.2535
Postoperative pancreatic fistula (grade B or C/none or grade A)	28:63	1.0667	0.3624–2.9341	0.9028

Pancreatic texture was subjectively judged by the operating surgeon. Grade of pancreatic fistula was defined according to the International Study Group on Pancreatic Fistula

CI confidence interval, *BMI* body mass index, *PD* pancreaticoduodenectomy, *DP* distal pancreatectomy

Several investigators have found that DM was ameliorated after pancreatectomy.[18,19,21,22] Litwin et al.[18] observed improved DM in two of four preoperative diabetic patients with pancreatic cancer. These authors speculated that one possible mechanism of improved DM after PD in pancreatic cancer might be attributed to an unknown diabetogenic factor secreted by the tumor which is removed by resection. Previous investigators have also suggested this possible mechanism.[20,23,24] Sato et al.[22] observed five of seven preoperative diabetic patients who had various periampullary neoplasms or chronic pancreatitis with dilated pancreatic duct. In these patients, their DM improved within 2 months after PD. In the present study, improved DM after pancreatectomy was observed in nine (11.8 %) patients whose indications for surgery were various malignant and benign neoplasms (Tables 2 and 3). The outstanding points of Table 3 were that long-standing DM or preoperative insulin injection, which may suggest intensive devastation of pancreatic tissue of the patients, was not included in improved DM patients after pancreatectomy.

The published rates of new-onset DM after pancreatectomy have ranged from 8 to 38 %.[7,8,15,17,25–27] In the present series, 22 (24.2 %) of 91 preoperative nondiabetic patients developed new-onset DM after pancreatectomy (Fig. 1b, Table 2). In the present study, most patients with new-onset DM after pancreatectomy were treated with dietary management. Only one patient needed insulin injections (Table 3), coinciding with clinical characteristics of mild hyperglycemia in pancreatogenic DM after pancreatectomy. King et al.[25] found no significant predictors for the development of new-onset DM after DP among 125 patients with various pancreatic neoplasms or chronic pancreatitis by retrospective analysis. Bock et al.[26] showed that the age of the 18 patients who experienced new-onset DM was significantly younger than the age of the 59 patients who did not develop DM after PD performed for various malignant and benign diseases. Shirakawa et al.[8] identified HbA1c of ≥5.7 % and percent resected volume of >44 % as independent risk factors for new-onset DM after DP by multivariate logistic regression analysis in 61 nondiabetic patients who underwent DP for malignant and benign pancreatic diseases. The current study indicated that BMI≥25 and hard pancreatic texture were independent predictive factors for new-onset DM according to multivariate logistic analysis. It has been reported that the odds of developing DM in Asians increases significantly according to increasing BMI.[28] We speculate that the higher incidence of new-onset DM after pancreatectomy in patients with BMI≥25 compared to patients with BMI<25 may be attributed to increasing insulin resistance of peripheral tissue and/or the liver in patients with BMI≥25. We also conjecture that a change to hard pancreatic texture (meaning strong fibrosis) in pancreatic tissue may cause decreased secretion of glucose-regulating hormones prior pancreatectomy; therefore, stronger glucose regulation disturbance after pancreatectomy may occur in the patients with hard pancreatic texture. The different results between the previous reports and our investigation might be due to different statistical methods and the number of patients investigated.

Conclusion

In conclusion, worsened DM and new-onset DM after pancreatectomy should be considered separately because different predictors were detected by the present study. The use of these predictors to identify patients who might be at risk for worsened or new-onset DM after pancreatectomy may facilitate an early diagnosis of DM and intensive care for appropriate patients, possibly contributing to prolonged survival in patients who undergo pancreatectomy.

Acknowledgments This investigation has no financial support.

Conflict of Interest All authors have no conflict of interests.

References

1. Andersen DK, Brunicardi FC. Pancreatic anatomy and physiology. In: Greenfield LJ, ed. Surgery: Scientific Principles and Practice, 2nd ed. Philadelphia, PA: Lippincott-Raven; 1997, pp 857-874.
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2012;35:S64-S71.
3. Cui Y, Andersen DK. Pancreatogenic diabetes: special considerations for management. Pancreatology 2011;11:279–294.
4. Slezak LA, Andersen DK. Pancreatic resection: Effects on glucose metabolism. World J Surg 2001;25:452–460.
5. Japan Diabetes Society. Treatment guide for diabetes. Tokyo, Japan: Bunkodo, 2007.
6. American Diabetes Association. Standards of medical care in diabetes-2008. Diabetes Care 2008;31:S12-S54.
7. You DD, Choi SH, Choi DW, Heo JS, Ho CY, Kim WS. Long-term effects of pancreaticoduodenectomy on glucose metabolism. ANZ J Surg 2012;82:447–451.
8. Shirakawa S, Matsumoto I, Toyama H, Shinzeki M, Ajiki T, Fukumoto T, Ku Y. Pancreatic volumetric assessment as a predictor of new-onset diabetes following distal pancreatectomy. J Gastrointest Surg 2012;16:2212–2219.
9. Hayashibe A, Kameyama M, Shinbo M, Makimoto S. The surgical procedure and clinical results of subtotal stomach preserving pancreaticoduodenectomy (SSPPD) in comparison with pylorus preserving pancreaticoduodenectomy (PPPD). J Surg Oncol 2007;95:106–109.
10. Chu CK, Mazo AE, Sarmiento JM, Staley CA, Adsay NV, Umpierrez GE, Kooby DA. Impacts of diabetes mellitus on perioperative outcomes after resection for pancreatic adenocarcinoma. J Am Coll Surg 2010;210:463–473.
11. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:1–253.
12. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Survival after resection for ductal adenocarcinoma of the pancreas. Br J Surg 1996;83:625–631.

13. Chagpar RB, Martin RC, Ahmad SA, Kim HJ, Rupp C, Weber S, Ebelhar A, Gilbert J, Brinkman A, Winslow E, Cho CS, Kooby D, Chu CK, Staley CA, McMasters KM, Scoggins CR. Medically managed hypercholesterolemia and insulin-dependent diabetes mellitus preoperatively predicts poor survival after surgery for pancreatic cancer. J Gastrointest Surg 2011;15:551–557.
14. Dandona M, Linehan D, Hawkins W, Strasberg S, Gao F, Wang-Gillam A. Influence of obesity and other risk factors on survival outcomes in patients undergoing pancreaticoduodenectomy for pancreatic cancer. Pancreas 2011;40:931–937.
15. White MA, Agle SC, Fuhr HM, Mehaffey JH, Waibel BH, Zervos EE. Impact of pancreatic cancer and subsequent resection on glycemic control in diabetic and nondiabetic patients. Am Surg 2011;77: 1032–1037.
16. Cannon RM, LeGrand R, Chagpar RB, Ahmad SA, McClaine R, Kim HJ, Rupp C, Cho CS, Brinkman A, Weber S, Winslow ER, Kooby DA, Chu CK, Staley CA, Glenn I, Hawkins WG, Parikh AA, Merchant NB, McMasters KM, Martin RC, Callender GG, Scoggins CR. Multi-institutional analysis of pancreatic adenocarcinoma demonstrating the effect of diabetes status on survival after resection. HPB 2012;14:228–235.
17. DiNorcia J, Ahmed L, Lee MK, Reavey PL, Yakaitis EA, Lee JA, Schrope BA, Chabot JA, Allendorf JD. Better preservation of endocrine function after central versus distal pancreatectomy for mid-grand lesions. Surgery 2010;148:1247–1254.
18. Litwin J, Dobrowolski S, Orłowska-Kunikowska E, Sledziński Z. Changes in glucose metabolism after Kausch-Whipple pancreatectomy in pancreatic cancer and chronic pancreatitis patients. Pancreas 2008;36:26–30.
19. Ohtsuka T, Kitahara K, Kohya N, Miyoshi A, Miyazaki K. Improvement of glucose metabolism after a pancreatoduodenectomy. Pancreas 2009;38:700–705.
20. Permert J, Ihse I, Jorfeldt L, von Schenck H, Arnquist HJ, Larsson J. Improved glucose metabolism after subtotal pancreatectomy for pancreatic cancer. Br J Surg 1993;80:1047–1050.
21. Ishikawa O, Ohigashi H, Eguchi H, Yokoyama S, Yamada T, Takachi K, Miyashiro I, Murata K, Doki Y, Sasaki Y, Imaoka S. Long-term follow-up of glucose tolerance function after pancreaticoduodenectomy: comparison between pancreaticogastrostomy and pancreaticojejunostomy. Surgery 2004;136:617–623.
22. Sato N, Yamaguchi K, Yokohata K, Shimizu S, Morisaki T, Chijiiwa K, Tanaka M. Short-term and long-term pancreatic exocrine and endocrine functions after pancreatectomy. Dig Dis Sci 1998;43: 2616–2621.
23. Saruc M, Pour PM. Diabetes and its relationship to pancreatic carcinoma. Pancreas 2003;26:381–387.
24. Permert J, Adrian TE, Jacobsson P, Jorfelt L, Fruin AB, Larsson J. Is profound peripheral insulin resistance in patients with pancreatic cancer caused by a tumor-associated factor? Am J Surg 1993;165: 61–67.
25. King J, Kazanjian K, Matsumoto J, Reber HA, Yeh MW, Hines OJ, Eibl G. Distal pancreatectomy: incidence of postoperative diabetes. J Gastrointest Surg 2008;12:1548–1553.
26. Bock EA, Hurtuk MG, Shoup M, Aranha GV. Late complications after pancreaticoduodenectomy with pancreaticogastrostomy. J Gastrointest Surg 2012;16:914–919.
27. Fang WL, Su CH, Shyr YM, Chen TH, Lee RC, Tai LC, Wu CW, Lui WY. Functional and morphological changes in pancreatic remnant after pancreaticoduodenectomy. Pancreas 2007;35:361–365.
28. Boffetta P, McLerran D, Chen Y, Inoue M, Sinha R, He J, Gupta PC, Tsugane S, Irie F, Tamakoshi A, Gao YT, Shu XO, Wang R, Tsuji I, Kuriyama S, Matsuo K, Satoh H, Chen CJ, Yuan JM, Yoo KY, Ahsan H, Pan WH, Gu D, Pednekar MS, Sasazuki S, Sairenchi T, Yang G, Xiang YB, Nagai M, Tanaka H, Nishino Y, You SL, Koh WP, Park SK, Shen CY, Thornquist M, Kang D, Rolland B, Feng Z, Zheng W, Potter JD. Body mass index and diabetes in Asia: a cross-sectional pooled analysis of 900,000 individuals in the Asia cohort consortium. PLoS One.2011;6:e19930.