—Report on Experiments and Clinical Cases—

Left Posterior Approach Pancreaticoduodenectomy with Total Mesopancreas Excision and Circumferential Lymphadenectomy Around the Superior Mesenteric Artery for Pancreatic Head Carcinoma

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Abstract

Background: In most cases of pancreatic head cancer, surgery often results in noncurative resection, which is frequently related to inadequate clearance of the mesopancreas.

Purpose: The aim of this report is to introduce the surgical technique of left posterior approach pancreaticoduodenectomy (PD) with total mesopancreas excision and circumferential lymphadenectomy around the superior mesenteric artery (SMA) (LPA-PD) and to examine whether this procedure increases the rate of true curative resection and decreases the rate of locoregional recurrence.

Patients and Methods: Nineteen patients underwent standard PD, and 19 patients underwent LPA-PD. The demographic characteristics, intraoperative outcomes (mean operative time and mean blood loss), postoperative outcomes (complications, type of recurrence and survival), and pathological findings (R number, number of removed regional lymph nodes and positive resection margins) were evaluated.

Results: The patient characteristics did not differ significantly between the groups. The mean blood loss in the LPA-PD group was significantly less than that in the standard PD group ($p<0.05$). The incidence rate of postoperative complications did not differ between the groups. No surgery-related deaths occurred in either group. The number of removed regional lymph nodes around the superior mesenteric artery in the LPA-PD group was significantly greater than that in the standard PD group ($p<0.01$). The R0 resection rate in the LPA-PD group was higher, although not significantly so, than that in the standard PD group. The resection margin of the mesopancreas was negative in all patients of the LPA-PD group. The rate of locoregional recurrence in the LPA-PD group was significantly lower than that in the standard PD group ($p<0.01$). The postoperative survival rate did not differ significantly between the groups.

Conclusion: Our method of LPA-PD helps secure the negative margin of the mesopancreas and enables complete circumferential lymphadenectomy around the SMA. Therefore, LPA-PD may increase the true curative resection rate and decrease the locoregional recurrence rate compared with standard PD.

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Key words: mesopancreas, pancreaticoduodenectomy, curative resection, left posterior approach

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Introduction

Pancreatic cancer continues to be the gastrointestinal malignancy with the worst prognosis[1]. Complete resection offers the only possible chance of cure, although only one-third of patients with pancreatic cancer are candidates for surgical resection[1]. However, the prognosis in patients undergoing surgical resection remains poor because of locoregional recurrence and liver metastasis soon after the procedure[2]. Recently, it has been reported that surgical resection in most cases is noncurative[3].

The mesopancreas is defined as the retroperipancreatic soft tissue between the superior mesenteric artery (SMA) and the region from the pancreas head to the uncus. It contains lymphogenic structures along the neuronal plexus posterior to the pancreas, which may play a key role in metastatic spread[4]. Inadequate posterior clearance of the mesopancreas results in locoregional recurrence soon after surgery, such that the mesopancreas represents the primary site for positive resection margins[4,5]. In addition, standard pancreaticoduodenectomy (PD) often leads to incomplete lymphadenectomy on the left side of the SMA, despite pancreatic cancer frequently metastasizing to lymph nodes in this area[6]. Therefore, total excision of the mesopancreas and complete circumferential lymphadenectomy have recently been considered key points in curative surgery for pancreatic head adenocarcinoma.

At our institution we have recently established a left posterior approach PD with total mesopancreas excision and complete circumferential lymphadenectomy around the SMA (LPA-PD). The purpose of this paper is to introduce our surgical techniques and to evaluate clinicopathological outcomes to examine whether this procedure increases the rate of true curative resection and decreases the rate of locoregional recurrence.

Patients and Methods

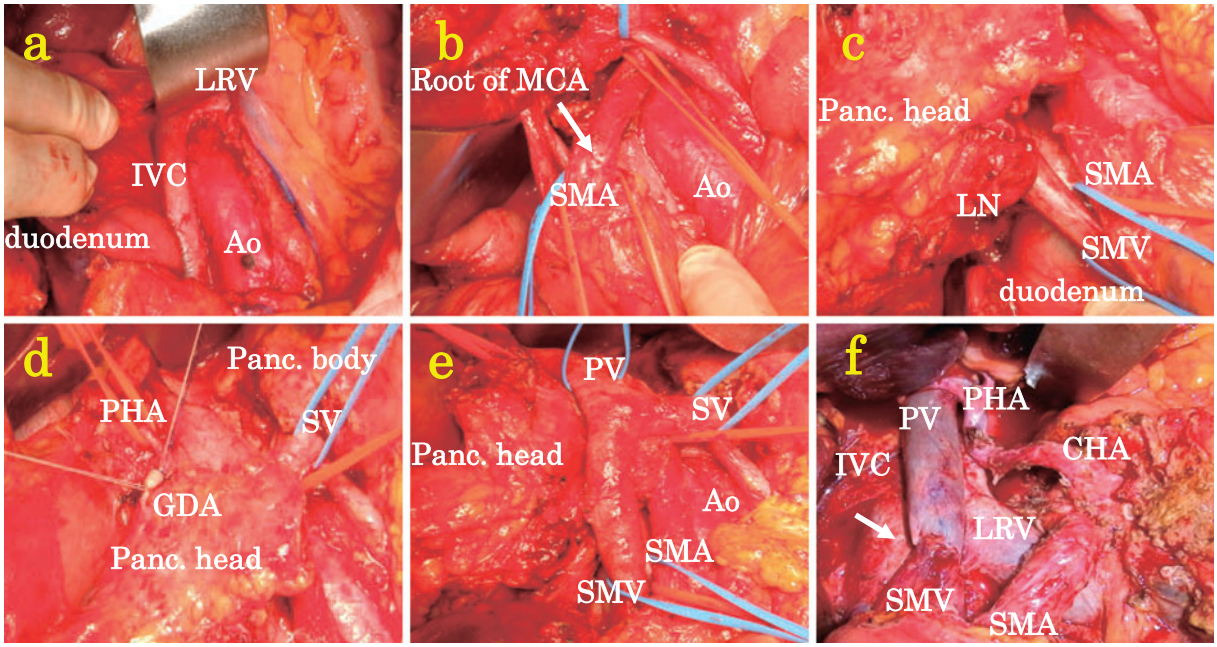
Patients

From February 2009 through December 2012, 38 consecutive patients underwent PD for pancreatic cancer at our institution. Nineteen patients underwent standard PD, and nineteen patients underwent LPA-PD. No patients underwent neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy. All patients underwent adjuvant chemotherapy with gemcitabine or S-1 or both for 6 months after surgical resection.

Surgical Technique

The greater omentum is separated from the transverse colon, and the anterior surface of the pancreas is identified. The stomach is transected after the lesser omentum is divided. With the transverse colon lifted upward, the peritoneum of the left duodenomesocolic fold is incised longitudinally. The anterior surface of the aorta, the left renal vein, and the inferior vena cava are exposed (**Fig. 1a**). The transverse mesocolon is opened from the right side of the second part of the duodenum to the left border of the aorta. The middle colic artery and the middle colic vein should be ligated.

The jejunum is transected and its mesentery is divided sequentially along the first jejunal artery. The SMA is isolated above the anterior aspect of the second part of the duodenum and slung with a vessel loop. The SMA is skeletonized in a longitudinal direction from the origin of the middle colic artery up to the confluence with the aorta (**Fig. 1b**). When circumferential lymphadenectomy is performed around the SMA, the PL sma should be preserved, if there is no evidence of tumor invasion, to prevent severe postoperative diarrhea. In this process, all the branches from the SMA, including the first jejunal artery, inferior pancreaticoduodenal artery, and replaced hepatic artery, can be easily secured. The superior mesenteric vein (SMV) can be identified on the right lateral aspect of the SMA and then completely skeletonized in accordance with the extent of invasion. The regional lymphatic tissues



IVC: inferior vena cava, Ao: aorta, LRV: left renal vein, MCA: middle colonic artery
SMA: superior mesenteric artery, SMV: superior mesenteric vein, LN: lymph node
PHA: proper hepatic artery, GDA: gastroduodenal artery, SV: splenic vein, PV: portal vein
CHA: common hepatic artery

Fig. 1 Intraoperative views during LPA-PD

a. The anterior surface of the aorta, the left renal vein, and the inferior vena cava are exposed.
b. The superior mesenteric artery is skeletonized in a longitudinal direction from the origin of the middle colonic artery up to the confluence with the aorta.
c. The regional lymphatic tissues around the superior mesenteric artery and superior mesenteric are completely dissected en bloc at the level of the anterior aspect of the second portion of the duodenum.
d. The gastroduodenal artery is dissected and ligated after the celiac axis, the common hepatic artery and the proper hepatic artery are exposed.
e. All tributaries into the superior mesenteric vein and the portal vein are ligated, allowing the portal vein, the superior mesenteric vein and the splenic vein to be controlled individually.
f. In cases of venous invasion, segmental resection with end-to-end anastomosis is conducted.

around the SMA and SMV are completely dissected en bloc at the level of the anterior aspect of the second part of the duodenum **(Fig. 1c)**.

The body of the pancreas is divided after the splenic artery and splenic vein have been carefully dissected and secured. The gastroduodenal artery is dissected and ligated after the celiac axis, the common hepatic artery, and the proper hepatic artery are exposed **(Fig. 1d)**. After the gallbladder is removed and the upper common bile duct is transected, the proper hepatic artery and the portal vein (PV) in the hepatoduodenal ligament are skeletonized. At this stage, the proximal jejunum can be easily delivered to the right upper quadrant by passing it behind the SMA and SMV. The pancreatic head and the duodenum are completely mobilized from the anterior surface of the inferior vena cava. The thick nerve bundle, running down from the head of the pancreas to the right celiac ganglion, remains at the right lateral aspect of the aorta and should be dissected along the ganglion. All tributaries into the SMV and the PV are ligated to allow the PV, the SMV, and the SV to be controlled individually **(Fig. 1e)**. In cases of venous invasion, segmental resection with end-to-end anastomosis is performed **(Fig. 1f)**. The digestive system is reconstructed with a modified Child's procedure.

Assessment

The demographic characteristics, intraoperative outcomes (mean operation time and mean blood loss), postoperative outcomes (complications,

Table 1 Patient characteristics

		LPA-PD (n=19)	standard PD (n=19)	
Age	mean	70.14	67.00	
	range	56-83	37-77	NS
Gender	Male	12	10	
	Female	7	9	NS
Type of operation				
PD : SSPPD		1 : 18	0 : 19	NS
Vascular resection		9	9	NS
Stage Ⅱ		1	1	
Ⅲ		6	2	
Ⅳa		11	12	
Ⅳb		1	4	NS

NS: not significant

adjuvant chemotherapy, type of recurrence and survival), and pathological findings (R number, number of removed regional lymph nodes and positive resection margins) were evaluated. A microscopic positive margin (R1) was defined as a tumor cell within 1 mm of a circumferential or transection margin independent of the mode of tumor spread[7,8]. According to the intensified histopathological workup reported by Gaedcke et al[5], the resection margins are classified into the following sites: the anterior or posterior surface, the mesopancreas, the groove of the SMV, and the pancreatic transection margin. Regional lymph nodes were classified into groups according to the General Rules for the Study of Pancreatic Cancer (6th edition) by the Japan Pancreas Society[9].

The study was approved by the ethics committee of Nippon Medical School and performed according to the Ethical Guidelines for Human Genome/Gene Research enacted by the Japanese Government and the principles embodied in the Declaration of Helsinki.

Statistical Analysis

The statistical analysis was performed with IBM SPSS® Statistics version 20.0 (IBM Corp., Armonk, NY, USA), following the instructions of medical statistical articles[10–12]. Fisher's exact test or the $\chi 2$ test was used for comparisons between groups, as appropriate. The nonparametric Mann-Whitney U test was used for data of continuous variables. Survival curves were calculated with the Kaplan-Meier method, and survival rates were compared by means of the log-rank test. Statistical significance was indicated by $p<0.05$.

Results

Patient Characteristics

The patients were 10 men and 9 women with a median age of 67 years in the standard PD group and 12 men and 7 women with a median age of 70 years in the LPA-PD group (**Table 1**). Whipple's procedure was performed for only 1 patient in the LPA-PD group; all other patients underwent subtotal stomach-preserving PD. Vascular resection was performed in 9 patients in the LPA-PD group and in 9 patients in the standard PD group. The final stage did not differ significantly between the groups.

Intraoperative Outcomes

The mean operation time was 489.84 minutes for the LPA-PD group and 481.16 minutes for the standard PD group (**Table 2**). The mean blood loss in the LPA-PD group was significantly less than that in the standard PD group ($p<0.05$). Moreover, the mean operative time and mean blood loss in the LPA-PD group were less than those in the standard PD group, even in cases requiring venous resection.

Table 2 Intra-operative outcomes

	LPA-PD (n=19)	standard PD (n=19)	
Mean operation time (min)	489.84	481.16	NS
Mean blood loss (mL)	973.16	1,568.05	P<0.05
In cases with vascular resection			
Mean operation time (min)	483.78	544.67	NS
Mean blood loss (mL)	1,195.00	1,878.44	P<0.05

NS: not significant

Table 3 Post-operative complications

	LPA-PD (n=19)	standard PD (n=19)	
Pancreatic fistula	2 (11%)	0 (0%)	NS
Delayed gastric emptying	1 (5%)	2 (11%)	NS
Peritonitis due to colonic perforation	1 (5%)	0 (0%)	NS
Respiratory failure	1 (5%)	0 (0%)	NS
Diarrhea (over 4 times per day)	9 (47%)	6 (32%)	NS
Re-operation	1 (5%)	0 (0%)	NS
In-hospital death	0 (0%)	0 (0%)	NS

NS: not significant

Table 4 Pathological findings

	LPA-PD (n=19)	standard PD (n=19)	
Histological type			
Well differentiated tubular	5 (26%)	5 (26%)	
Moderately differentiated tubular	11 (58%)	13 (68%)	
Poorly differentiated tubular	2 (11%)	1 (5%)	
Mucinous	1 (5%)	0 (0%)	NS
Extrapancreatic plexus invasion	8 (42%)	11 (58%)	NS
Mean number of removed regional LN	7.9	3.4	p<0.01
R0 resection	14 (74%)	13 (68%)	NS
Positive resection margin in cases with R1			
Posterior surface	4 (21%)	2 (10%)	NS
Pancreatic transection margin	1 (5%)	2 (10%)	NS
mesopancreas	0 (0%)	2 (10%)	NS

NS: not significant

Postoperative Complications

Severe complications occurred in 4 cases in the LPA-PD group and in 2 in the standard PD group (**Table 3**). Grade B pancreatic fistulas developed in 2 cases in the LPA-PD group. Delayed gastric emptying was found in 1 case in the LPA-PD group and in 2 cases in the standard PD group. Postoperative diarrhea (more than 4 times per day) occurred in 9 cases in the LPA-PD group and in 6 cases in the standard PD group but could be managed with antidiarrheal agents in all cases. There were no surgery-related deaths in either group.

Pathological Findings

Neither the histological diagnoses nor the rate of

Table 5 Adjuvant chemotherapy and recurrence

	LPA-PD (n=19)	standard PD (n=19)	
Adjuvant chemotherapy			
gemcitabine	9 (47%)	13 (68%)	
S-1	5 (26%)	0 (0%)	
gemcitabine+S-1	3 (16%)	5 (26%)	
no treatment	2 (11%)	1 (5%)	NS
Recurrence			
liver	6 (32%)	9 (47%)	NS
peritoneum	8 (42%)	10 (45%)	NS
local	0 (0%)	7 (37%)	p<0.01
para-aortic LN	4 (21%)	7 (37%)	NS

NS: not significant

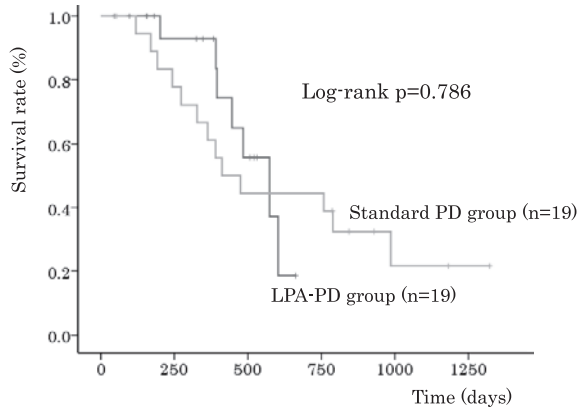


Fig. 2 Postoperative survival curves
No significant difference in postoperative survival was found between the groups.

extrapancreatic plexus invasion differed significantly between the groups (**Table 4**). The number of removed regional lymph nodes around the SMA in the LPA-PD group was significantly greater than that in the standard PD group ($p<0.01$). The R0 resection rate in the LPA-PD group was higher, although not significantly so, than that in the standard PD group. In all cases with R1 resection, tumor cells were detected not at the resection margin but at the distance of 1 mm from the resection margin. The posterior surface (n=4) and pancreatic transection margin (n=1) were infiltrated in the LPA-PD group, and the mesopancreas (n=2), posterior surface (n=2), and pancreatic transection margin (n=2) had positive resection margins in the standard PD group.

Postoperative Outcomes and Survival

In both groups, most patients could receive adjuvant chemotherapy with gemcitabine or S-1 chemotherapy or both (**Table 5**). The rate of locoregional recurrence in the LPA-PD group was significantly lower than that in the standard PD group ($p<0.01$). Postoperative survival did not differ significantly between the groups (**Fig. 2**).

Discussion

The present study found that LPA-PD increased the rate of true R0 resection compared with standard PD, because a negative resection margin of the mesopancreas could be secured, and that LPA-PD improved the rate of locoregional recurrence by achieving complete lymphadenectomy of the regional lymph nodes around the SMA.

LPA-PD may increase the true curative resection rate compared with standard PD because it helps secure the negative margin of the mesopancreas. The mesopancreas is the primary site for a positive resection margin[4,5] because standard PD does not completely remove the mesopancreas, where cancer of the pancreatic head frequently infiltrates from an early stage[6]. Therefore, total mesopancreas excision with LPA-PD can achieve complete clearance of the mesopancreas, which may increase the rate of curative resection compared with standard PD. In the present study, the rate of curative resection in the LPA-PD group was higher (74%), although not significantly so, than that in the standard PD group

(68%). Furthermore, the resection margin of the mesopancreas was negative in all patients of the LPA-PD group. Kurosaki et al[13] have also found no significant difference in the R0 resection rate between PD with the left posterior approach (72.5%) and standard PD (71.4%). On the other hand, Adham et al.[14] introduced a surgical technique of standardized total mesopancreas excision and concluded that this procedure could achieve a high rate of R0 resection (80%) with optimized posterior clearance. Moreover, Kawabata et al[15] have demonstrated that total mesopancreatoduodenal excision with PD achieved a significantly higher rate of R0 resection (93%) than did standard PD.

With regards to the resection margins, we should note that LPA-PD also has limitations in securing a cancer-free margin against all resection margins. Regardless of the type of procedure, securing a completely negative margin against other margins, such as the anterior surface, the posterior surface or the pancreatic transaction margin, is extremely challenging, if cancer cells have infiltrated beneath these margins. In the present study, the posterior surface or the pancreatic transection margin was infiltrated within 1 mm of the resection margin, without apparent tumor exposure, in 4 patients and 1 patient, respectively, in the LPA-PD group and 2 patients and 2 patients, respectively in the standard PD group.

From the viewpoint of local disease control, LPA-PD may be an excellent procedure because it can decrease the rate of locoregional recurrence. In the present study, no locoregional recurrence occurred in the LPA-PD group, and the rate of locoregional recurrence differed significantly between the groups. First, one reason the rate of locoregional recurrence was decreased in the LPA-PD group is that the left posterior approach enables complete circumferential lymphadenectomy around the SMA by the "SMA first" procedure. Metastasis to lymph nodes around the SMA has often been detected as locoregional recurrence in pancreatic head cancer[6] because standard PD does not include lymphadenectomy on the left side of the SMA[5,16]. Indeed, the number of removed regional lymph nodes in the LPA-PD group was significantly greater than that in the standard PD group. Kawabata et al.[15] have described surgical techniques for total mesopancreatoduodenal excision with PD using a left posterior approach for pancreatic cancer and have also found that the total number of regional lymph nodes around the SMA with this technique was greater than with standard PD and that no locoregional recurrence was found around the SMA. Second, total mesopancreas excision may help decrease the rate of locoregional recurrence because the mesopancreas is the primary site for the positive margin that causes locoregional relapse.

Further investigation is needed regarding a possible survival benefit conferred by LPA-PD because there have been few studies of survival after PD with the left posterior approach[13,17]. The short-term survival time after LPA-PD seems to be similar to that after standard PD because LPA-PD does not greatly inhibit recurrence, including liver metastasis, peritoneal dissemination, or metastasis to para-aortic lymph nodes. In the present study, no significant difference was found in postoperative survival time between patients undergoing LPA-PD and those undergoing standard PD. Moreover, the rate of distant metastasis, which caused death soon after surgery, did not differ between the groups. Dumitrascu et al.[17] have reported no significant difference in overall survival between PD with the posterior approach and standard PD. Kurosaki et al.[13] have concluded that the left posterior approach does not impair short-term survival, although the rate of long-term survival was greater in patients with positive regional lymph nodes, and emphasized that the 3-year survival rate in patients undergoing this procedure was high (52.8%).

LPA-PD appears to offer several benefits over standard PD. First, early detection of tumor involvement of the SMA or SMV and optimal exposure of the replaced or aberrant hepatic artery are advantages of the "SMA first" approach[13–17]. Therefore, we can avoid useless R2 resections and secure the replaced artery safely from the beginning of the operation. Second, the "SMA first" approach reduces blood loss and enables a rapid and safe resection and reconstruction of the PV or SMV because all the branches from the SMA to the

pancreatic head are ligated early[13–18]. Indeed, the mean blood loss in the LPA-PD group was significantly less than that in the standard PD group. Moreover, the mean operative time and mean blood loss in the LPA-PD group were less than those in the standard PD group, even in cases requiring venous resection. Third, LPA-PD is as feasible and safe, in terms of postoperative complications, as standard PD. There were no significant differences in the rates of postoperative complications, and no surgery-related deaths occurred. Finally, the left posterior approach can provide the technical advantages of dissection of the SMA pedicle without prior extensive kochelization and full mobilization of the right colon, as discussed by Pessaux et al[19] and Dumitrascu et al[17].

In conclusion, LPA-PD is a feasible and safe procedure that helps secure the negative margin of the mesopancreas and enables complete circumferential lymphadenectomy around the SMA. Therefore, LPA-PD may increase the true curative resection rate and can decrease the locoregional recurrence rate compared with standard PD.

Conflict of Interest: All authors have no conflicts of interest or financial ties to disclose.

References

1. Beger HG, Rau B, Gansauge F, Poch B, Link KH: Treatment of pancreatic cancer: challenge of the facts. World J Surg 2003; 27: 1075–1084.
2. Heye T, Zausig N, Klauss M, et al.: CT diagnosis of recurrence after pancreatic cancer: is there a pattern? World J Gastroenterol 2011; 17: 1126–1134.
3. Mu DQ, Peng SY, Wang GF: Risk factors influencing recurrence following resection of pancreatic head cancer. World J Gastroenterol 2004; 10: 906–909.
4. Gockel I, Domeyer M, Wolloscheck T, Konerding MA, Junginger T: Resection of the mesopancreas (RMP): a new surgical classification of a known anatomical space. World J Surg Oncol 2007; 5: 44.
5. Gaedcke J, Gunawan B, Grade M, et al.: The mesopancreas is the primary site for R1 resection in pancreatic head cancer: relevance for clinical trials. Langenbecks Arch Surg 2010; 395: 451–458.
6. Noto M, Miwa K, Kitagawa H, et al.: Pancreas head carcinoma: frequency of invasion to soft tissue adherent to the superior mesenteric artery. Am J Surg Pathol 2005; 29: 1056–1061.
7. Khalifa MA, Maksymov V, Rowsell C: Retroperitoneal margin of the pancreaticoduodenectomy specimen: anatomic mapping for the surgical pathologist. Virchows Arch 2009; 454: 125–131.
8. Esposito I, Kleeff J, Bergmann F, et al.: Most pancreatic cancer resections are R1 resections. Ann Surg Oncol 2008; 15: 1651–1660.
9. Japan Pancreas Society: General Rules for the Study of Pancreatic cancer, The 6th Edition. 2006; pp 7–10, Kanehara, Tokyo, Japan.
10. Watanabe H: Applications of statistics to medical science, II overview of statistical procedures for general use. J Nippon Med Sch 2012; 79: 31–36.
11. Watanabe H: Applications of statistics to medical science, III. Correlation and regression. J Nippon Med Sch 2012; 79: 115–120.
12. Watanabe H: Applications of statistics to medical science, IV survival analysis. J Nippon Med Sch 2012; 79: 176–181.
13. Kurosaki I, Minagawa M, Takano K, Takizawa K, Hatakeyama K: Left posterior approach to the superior mesenteric vascular pedicle in pancreaticoduodenectomy for cancer of the pancreatic head. JOP 2011; 12: 220–229.
14. Adham M, Singhirunnusorn J: Surgical technique and results of total mesopancreas excision (TMpE) in pancreatic tumors. Eur J Surg Oncol 2012; 38: 340–345.
15. Kawabata Y, Tanaka T, Nishi T, Monma H, Yano S, Tajima Y: Appraisal of a total meso-pancreatoduodenum excision with pancreaticoduodenectomy for pancreatic head carcinoma. Eur J Surg Oncol 2012; 38: 574–579.
16. Popescu I, Dumitrascu T: Total meso-pancreas excision: key point of resection in pancreatic head adenocarcinoma. Hepatogastroenterology 2011; 58: 202–207.
17. Dumitrascu T, David L, Popescu I: Posterior versus standard approach in pancreatoduodenectomy: a case-match study. Langenbecks Arch Surg 2010; 395: 677–684.
18. Moldovan SC, Moldovan AM, Dumitraaecu T, Andrei S, Popescu I: The advantages of retropancreatic vascular dissection for pancreatic head cancer with portal/superior mesenteric vein invasion: posterior approach pancreatico-duodenectomy technique and the mesopancreas theory. Chirurgia (Bucur) 2012; 107: 571–578.
19. Pessaux P, Varma D, Arnaud JP: Pancreaticoduodenectomy: superior mesenteric artery first approach. J Gastrointest Surg 2006; 10: 607–611.

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