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Pancreaticojejunostomy using duct-to-mucosa anastomosis without a stenting tube

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Abstract
Background Purpose. There is a high risk of anastomotic leakage after pancreaticojejunostomy following pancreaticoduodenectomy in patients with a normal soft pancreas because of the high degree of exocrine function. Therefore, pancreaticojejunostomy is generally performed using a stenting tube (stented method). However, pancreaticojejunostomy with a certain duct-to-mucosa anastomosis does not always require a stenting tube, even in patients with a normal soft pancreas. Recently, we have performed pancreaticojejunostomy with duct-to-mucosa anastomosis without a stenting tube (nonstented method) and obtained good results.
Methods. The point of this technique is to maintain adequate patency of the anastomosis using a fine atraumatic needle and monofilament thread. The results of end-to-side pancreaticojejunostomy of the normal soft pancreas using the nonstented method ($n = 123$) were compared with those using the stented method ($n = 45$).
Results. There were no differences in background characteristics between the groups, including age, gender, and disease. The mean times to complete pancreaticojejunostomy were around 30min in the two groups and the rates of morbidity and leakage of pancreaticojejunostomy were 26.8% and 5.7% in the nonstented group and 22.2% and 6.7% in the stented group, respectively. These differences were not statistically significant. One patient in the stented group died of sepsis following leakage of pancreaticojejunostomy. There were also no significant differences in the mean time to initiation of solid food intake or postoperative hospital stay.
Conclusions. In conclusion, complete pancreaticojejunostomy using duct-to-mucosa anastomosis for a normal soft pancreas does not require a stenting tube. This nonstented method can be considered one of the basic procedures for pancreaticojejunostomy because of its safety and certainty.

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Key words Duct-to-mucosa pancreaticojejunostomy · Nonstented pancreaticojejunostomy · Pancreaticoduodenectomy · Reconstruction of the normal soft pancreas

Introduction

Pancreatoduodenectomy was introduced by Kausch[1] in 1912 and by Whipple et al.[2] in 1935. In recent years, marked progress in imaging modalities has lead to early diagnosis of many pancreatobiliary diseases and pancreatoduodenectomy, including pylorus-preserving pancreatoduodenectomy (PPPD), has been performed increasingly as a standard operation for patients with periampullary lesions. The operative techniques have also become safer, and postoperative morbidity and mortality have been reduced markedly in many large specialized centers.[3–9] However, the postoperative complication rates in patients with a normal soft pancreas are still high because a soft normal pancreas has a nondilated pancreatic duct and a high degree of exocrine function. In particular, anastomotic leakage of the pancreaticojejunostomy, which is the most serious early complication after pancreatoduodenectomy, induces severe complications, such as intra-abdominal abscess or subsequent hemorrhage from the pseudoaneurysm of the artery. Therefore, pancreaticojejunostomy is generally carried out using a stenting tube for the normal soft pancreas.[5,10,11] However, no consensus has been obtained on which pancreaticojejunostomy procedure is the safest,[12,13] and there are some problems with stenting tubes such as twisting, bending, and occlusion of the tube. We have seen several complications associated with the stenting tube: acute pancreatitis resulting from subsequent occlusion or bending of the stenting tube or late anastomotic stenosis following iatrogenic injury sustained when withdrawing the external stenting tube. Since 1992, we have, therefore, performed pancreaticojejunostomy by duct-to-mucosa anastomosis without a stenting tube using thin monofilament stitches even in patients with a normal soft pancreas. The aim of this study was to evaluate the usefulness of nonstented duct-to-mucosa anastomosis in pancreaticojejunostomy for a normal soft pancreas with a nondilated pancreatic duct compared with stented duct-to-mucosa anastomosis.

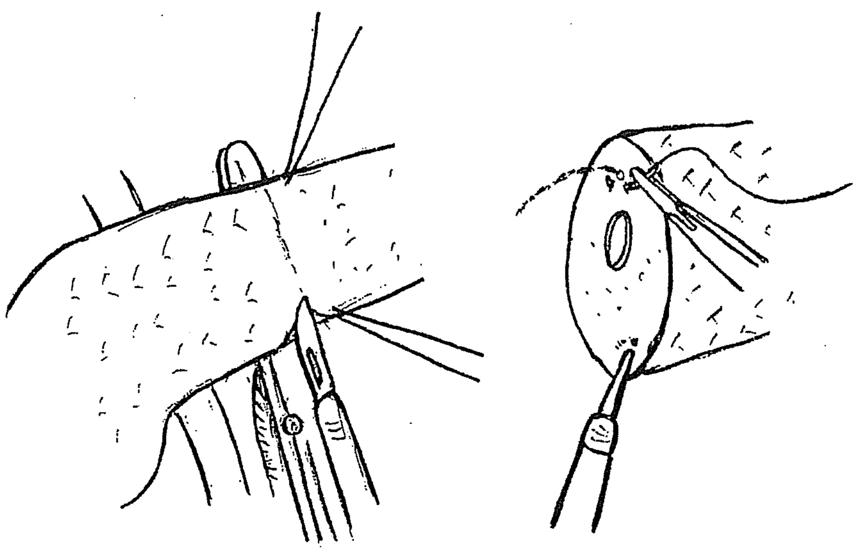
Patients and methods

A consecutive series of 168 patients who underwent pancreatoduodenectomy and pancreaticojejunostomy with duct-to-mucosa anastomosis for a normal soft pancreas with a nondilated pancreatic duct between September 1992 and March 2003 at Tokyo Women's Medical University Hospital was included in the study. Of these, 123 patients underwent pancreaticojejunostomy without stenting tube [nonstented group: pancreatic head cancer, 44; cancer of the papilla of Vater, 22; bile duct cancer, 16; intraductal papillary-mucinous neoplasm (IPMN), 11; endocrine tumor, 5; gastric cancer, 4; duodenal cancer, 4; serous cystadenoma, 3; others, 14] and the remaining 45 patients underwent pancreaticojejunostomy with an internal or external stenting tube (stented group: pancreatic head cancer, 12; cancer of the papilla of Vater, 7; bile duct cancer, 11; IPMN, 1; endocrine tumor, 1; gastric cancer, 5; duodenal cancer, 0; serous cystadenoma, 0; others, 8). Among the 123 patients in the nonstented group, 106 patients underwent PPPD and 17 patients underwent pancreatoduodenectomy with distal gastrectomy (PD). Among the 45 patients in the stented group, 31 patients underwent PPPD and 14 patients underwent PD. The choice of anastomosis with or without a stenting tube was the surgeon's decision. The only difference between the two groups was whether a stenting tube was used, and pancreaticojejunostomy by duct-to-mucosa and end-to-side anastomosis was performed using the same methods described below in both groups.

The normal soft pancreas with a nondilated pancreatic duct was defined as follows: the results of the preoperative pancreatic function test was within normal limits, intraoperative assessment showed a soft pancreatic parenchyma without fibrosis, and the diameter of the main pancreatic duct measured after pancreatic resection was less than 3 mm. The operative results including operating time, time to complete pancreaticojejunostomy, intraoperative blood loss, morbidity rate, mortality rate, time to initiation of solid food intake, and postoperative hospital stay were compared between the two groups. Statistical evaluation between the two groups was carried out using Student's t test and the χ^2 text. Significance was defined as a P value of less than or equal to 0.05. Numeric data are expressed as the means ± SD.

Operative techniques

The operative techniques of the nonstented method are illustrated in Figs. 1–6. The pancreas, including the pancreatic duct, is sharply transected with a scalpel. Leaving only the pancreatic duct should be avoided at this time. Any arterial bleeding points on the pancreatic cut end are repaired with 4-0 or 5-0 nonabsorbable sutures and any oozing points are coagulated by electrocautery. No other treatment of the stump such as mattress or fish-mouth suturing is performed. A small hole compatible with the caliber of the pancreatic duct is made in the jejunal wall using electrocautery. No other treatment such as excision or scarification of the jejunum wall is



a b

Fig. 1a,b. Transection of the pancreas and treatment of the pancreatic cut end. **a** The pancreas is sharply transected with a scalpel. **b** Any arterial bleeding points on the pancreatic cut end are repaired with 4-0 or 5-0 nonabsorbable sutures and any oozing points are coagulated by electrocautery. No other treatment of the stump such as mattress or fish-mouth suturing is performed

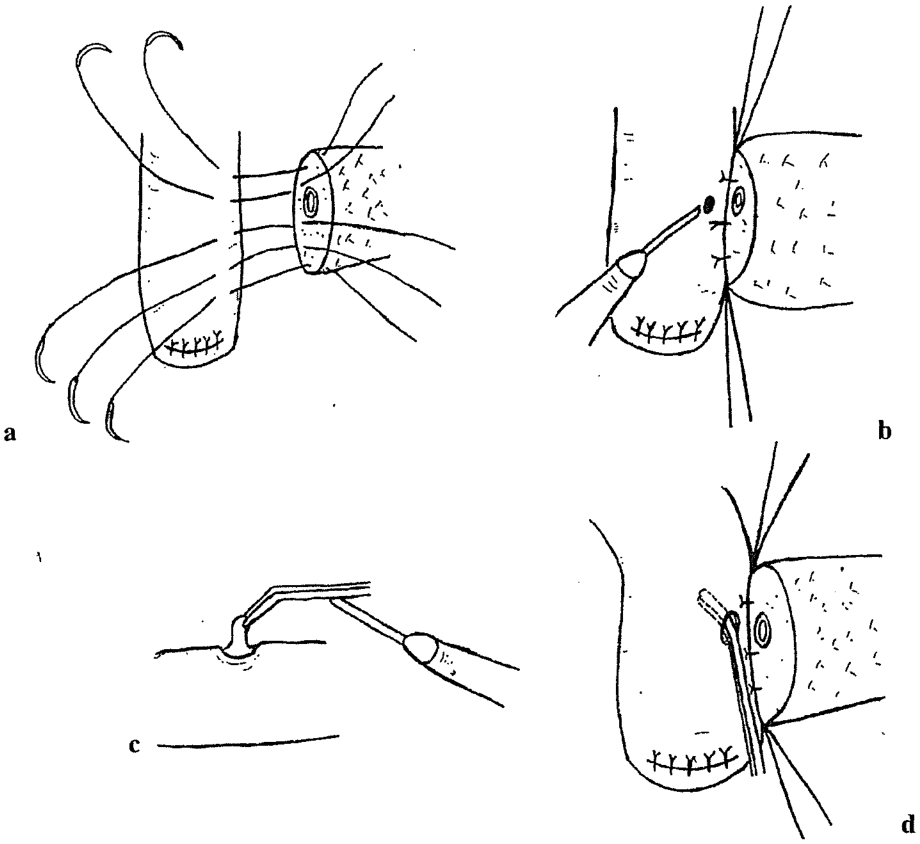


Fig. 2a–d. Anastomosis of the outer layer (posterior row) and procedure for making a small hole in the jejunal wall. **a** Interrupted sutures between the pancreatic parenchyma and the jejunal seromuscularis are placed in the outer layer (posterior row) using 4-0 or 5-0 nonabsorbable sutures. **b–d** A small hole compatible with the caliber of the pancreatic duct is made in the jejunal wall using electrocautery

done. The end-to-side anastomosis between the pancreas and jejunum consists of two layers of sutures. The outer layer encompasses the capsular parenchyma of the pancreas and the jejunal seromuscularis, and the inner layer encompasses the pancreatic duct with a little pancreatic parenchyma and the whole jejunal wall. A posterior row of interrupted sutures and an anterior row of continuous suture are placed in the outer layer using 4-0 or 5-0 nonabsorbable sutures. In contrast, interrupted sutures are placed in the inner layer using 6-0 absorbable sutures. The important aim of this technique is to preserve adequate patency of the anastomosis between the pancreatic duct and jejunum. Therefore, fine atraumatic needles and monofilament sutures should be used, carefully picking up the pancreatic duct wall to avoid injury of the pancreatic tissues or constriction of the anastomosis. Placing a fine stay suture in the middle of the anterior wall of the pancreatic duct is very useful when the inner-layer anastomosis is started because pulling it to the left or upward expands the pancreatic duct enough to allow easy needle suturing. Usually four or five stitches can be placed in the posterior wall and two or three stitches in the anterior wall. Although this technique without a stenting tube can preserve adequate patency of the anastomosis, one should not persist with the nonstented method if any injury of the pancreatic tissues occurs during the inner layer of suturing. In this series, the decision on whether to use a stenting tube was left to the staff surgeon's discretion.

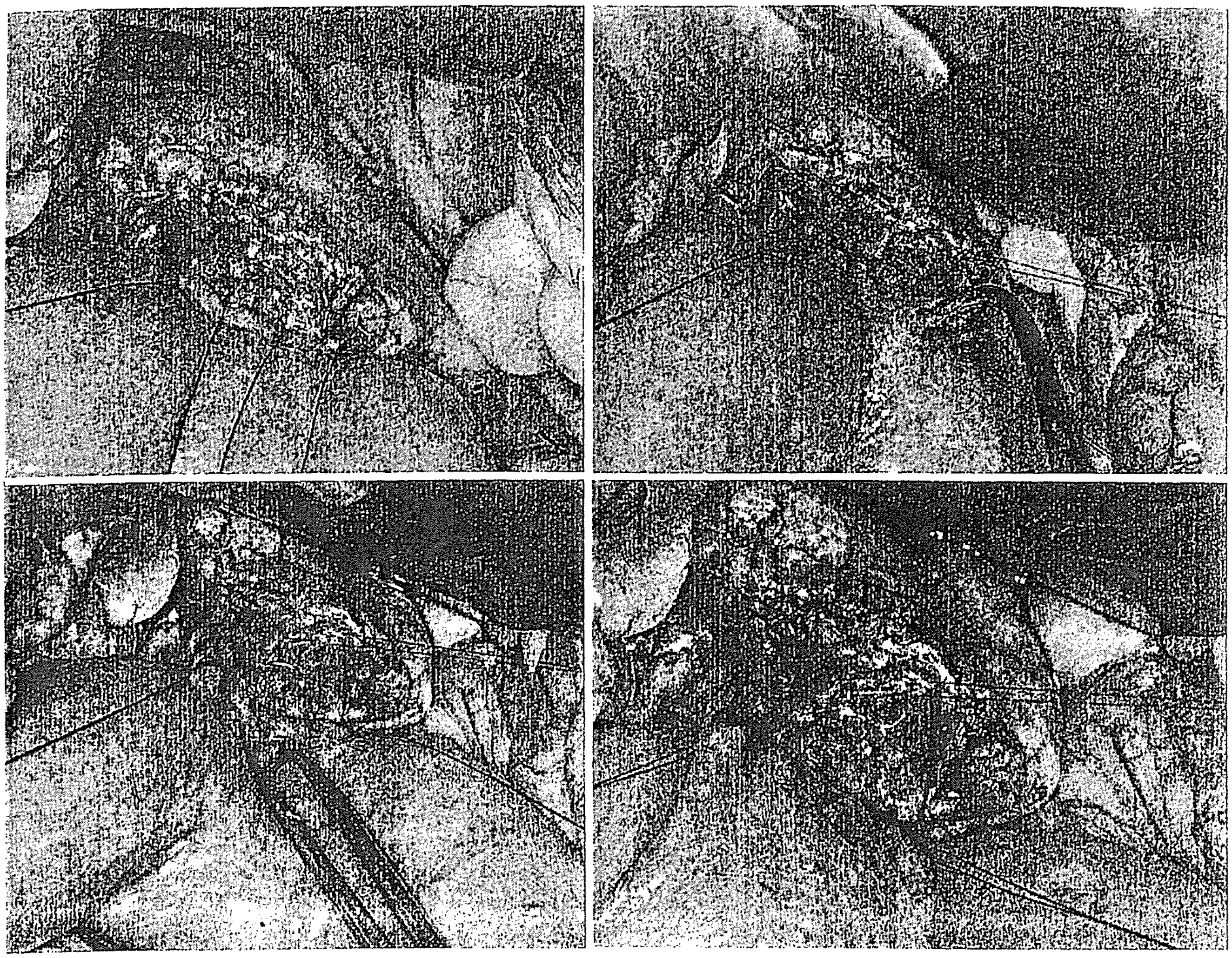
Results

Patient backgrounds

There were no significant differences in patient backgrounds, including age, sex, or disease distribution between the two groups. However, about one-third of patients in the stented group underwent PD and there was a significant difference in the operative procedure between the two groups (Table 1).

Operative results

There were no significant differences in the mean operating time, mean time to complete pancreaticojejunostomy, or mean intraoperative blood loss between the two groups. The overall morbidity rates were 26.8% in the nonstented group and 22.2% in the stented group. Major leakage of the pancreaticojejunostomy occurred in 7 of 123 patients (5.7%) with the nonstented method and in 3 of 45 patients (6.7%) with the stented method. There were no significant differences between the two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d

Fig. 3a–d. Anastomosis of the outer layer (posterior row) to make a small hole on the jejunal wall. **a** View after finishing anastomosis of the outer layer (posterior row). **b–d** Making a small hole in the jejunal wall. A fine stay suture in the middle of the anterior wall of the pancreatic duct has already been placed

Table 1. Background characteristics and operative procedure of patients with a normal soft pancreas undergoing pancreaticojejunostomy (September 1992 to March 2003)

	Nonstented (n = 123)	Stented (n = 45)	P value
Age (years)	59.7 ± 12.9	61.4 ± 13.5	N.S.
Male/female	74/49	27/18	N.S.
Disease			N.S.
Pancreatic head cancer	44	12	
Cancer of the papilla of Vater	22	7	
Bile duct cancer	16	11	
Intraductal papillary-mucinous neoplasm	11	1	
Endocrine tumor	5	1	
Gastric cancer	4	5	
Duodenal cancer	4	0	
Serous cystadenoma	3	0	
Others	14	8	
Operative procedure			$P < 0.05$
PPPD	106	31	
PD	17	14	

PPPD, pylorus-preserving pancreaticoduodenectomy; PD, pancreaticoduodenectomy with distal gastrectomy; N.S., not significant

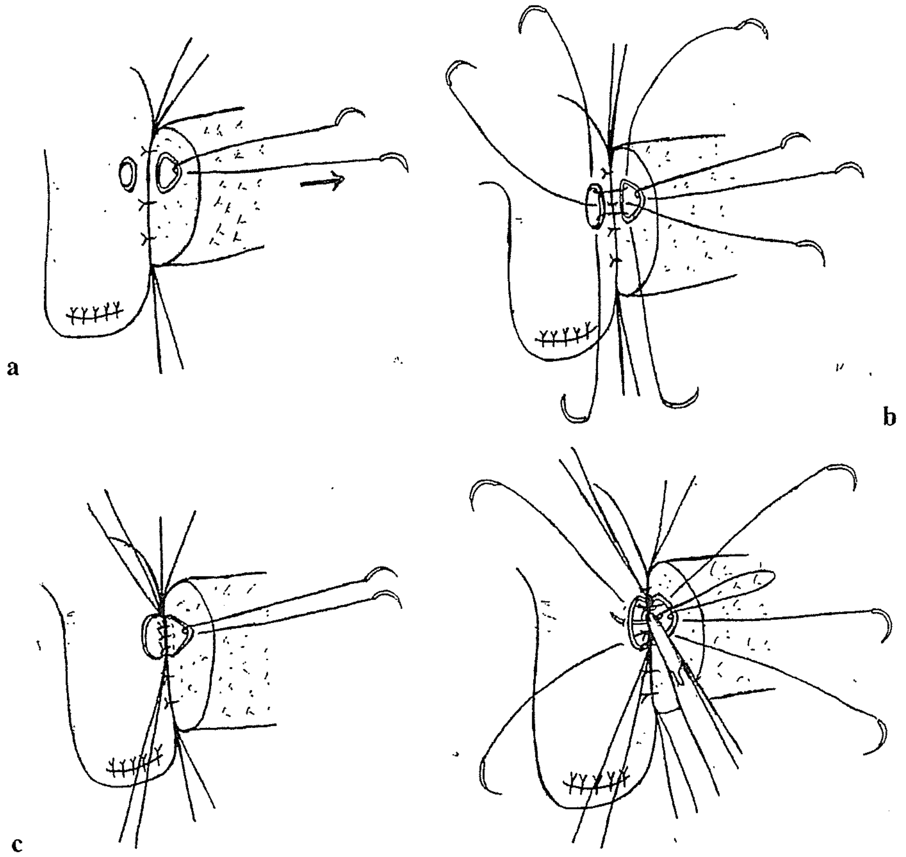

Fig. 4a–d. Duct-to-mucosa anastomosis of the pancreaticojejunostomy. **a** A fine stay suture in the middle of the anterior wall of the pancreatic duct can expand the pancreatic duct by pulling it to the left or upward. **b–d** Interrupted sutures in the inner layer between the pancreatic duct, including the pancreatic parenchyma, and the whole wall of the jejunum. Usually four or five stitches can be placed in the posterior wall and two or three stitches in the anterior wall at an equal distance using 6-0 absorbable sutures

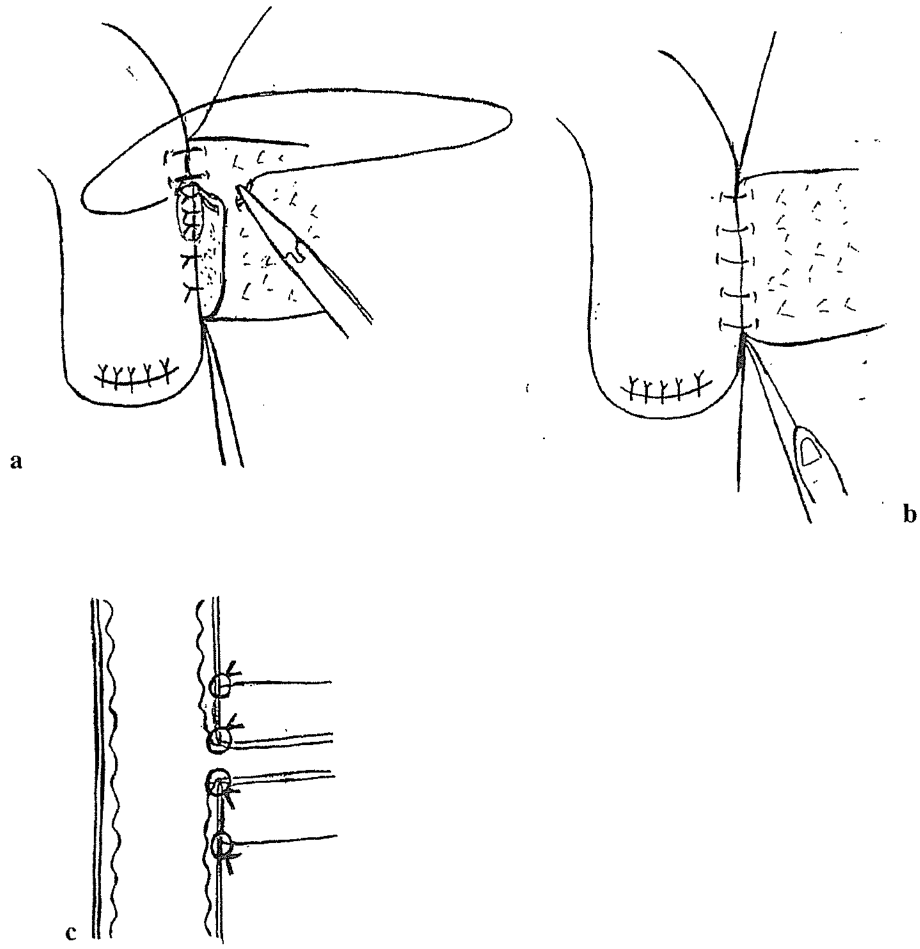

Fig. 5a–c. Anastomosis of the outer layer (anterior row) and scheme of a cross section of the pancreaticojejunostomy. **a,b** A continuous suture is placed in the outer layer (anterior row) using 4-0 or 5-0 nonabsorbable sutures. **c** The outer layer of anastomosis consists of the capsular parenchyma of the pancreas and the seromuscular layer of the jejunum. The inner layer, a duct-to-mucosa anastomosis, consists of the pancreatic duct (including the pancreatic parenchyma) and the whole jejunal wall. Two-layer anastomosis is completed without stenting

Fig. 6a–d. Anastomosis of the inner layer to the outer layer (anterior row). **a, b** Interrupted sutures of the posterior wall in the inner layer. **c** interrupted sutures of the anterior wall in the inner layer. **d** View after a continuous suture in the outer layer (anterior row). Nonstented pancreaticojejunostomy has been completed

groups. The mortality rates were 0% in the nonstented group and 2.2% in the stented group. One patient in the stented group died of sepsis as a result of leakage of the pancreaticojejunostomy. There were no significant differences in the mean time to initiation of food intake and mean postoperative hospital stay between the two groups (Table 2).

Discussion

Pancreatoduodenectomy is one of the most complicated operations in abdominal surgery and includes various surgical procedures such as dissection and reconstruction of the pancreatic duct, bile duct, portal vein, and digestive tract. Since pancreatoduodenectomy was established by Whipple[2], various innovations have been made and the procedure has been improved by many modifications. These improvements have made pancreatoduodenectomy a widely used low-risk operation for diseases of the pancreatic head region. However, it is still a fact that there are some serious complications such as intra-abdominal hemorrhage or abscesses associated with anastomotic leakage of the pancreaticojejunostomy. If such complications occur after pancreatoduodenectomy, they directly affect the patient's life. In general, the morbidity rate as a result of complications after pancreatoduodenectomy ranges from 18% to 52%. A pancreatic fistula has been reported in 8%–19% of patients and the associated

Table 2. Operative results of pancreaticojejunostomy on patients with a normal soft pancreas (September 1992 to March 2003)

	Nonstented (n = 123)	Stented (n = 45)	P value
Mean operating time (min)	311 ± 79	347 ± 96	N.S.
Mean time to complete pancreaticojejunostomy (min)	31 ± 12	32 ± 14	N.S.
Mean intraoperative blood loss (g)	1219 ± 1437	1315 + 1225	N.S.
Morbidity rate (%)	26.8	22.2	N.S.
Leakage of pancreaticojejunostomy (%)	5.7	6.7	N.S.
Mortality rate (%)	0	2.2	N.S.
Mean time to initiate food intake (days)	14 ± 8	16 ± 9	N.S.
Mean postoperative hospital stay (days)	31 ± 17	34 ± 21	N.S.

mortality rate after pancreatoduodenectomy is high once a pancreatic fistula occurs.[3–9,14,15] Therefore, safe and certain pancreaticojejunostomy is required after pancreatoduodenectomy. In particular, since the normal soft pancreas is very vulnerable to ischemia and actively produces exocrine secretions, serious complications such as pancreatic fistula occur more easily in a normal soft pancreas than in a hard pancreas after pancreatoduodenectomy.[16] Various ideas on how to avoid pancreatic fistula and improve safety have been reported, such as abandoning one-step reconstruction involving pancraticojejunostomy,[17] preventing exocrine function by means of ligation plugging of the pancreatic duct[18] or by total pancreatectomy. However, while these methods may actually avoid leakage of the pancreaticojejunostomy, they may not successfully maintain the pancreatic function after surgery. Besides the prevention of pancreatic fistula, it is very important to preserve pancreatic function by ensuring long-term patency of the anastomosis of the pancreaticojejunostomy. Stenting tubes are generally utilized when performing pancreaticojejunostomy with a normal soft pancreas.[5,10,11] However, we have encountered several complications associated with stenting tubes. Acute pancreatitis when withdrawing the external stenting tube occurred in two patients because of injury of the wall of the pancreatic duct. A number of patients also suffered from pancreatic leakage or pancreatitis caused by bending or stenosis of the external stenting tube at the point fixed to the skin. Moreover, even in patients with an internal stenting tube, we have encountered late pancreatic insufficiency as a result of subsequent obstruction of the tube or long-term placement of the tube. It has been reported that stenting tubes are harmful for some patinets undergoing a duct-to-mucosa anastomosis during pancreaticojejunostomy, especially when the pancreatic duct is less than 3 mm in diameter.[19] Based on our experience with postoperative complications associated with stenting tubes, it was considered that no stenting tube is necessary if duct-to-mucosa anastomosis is performed completely and the patency of the anastomosis is preserved adequately.

On the other hand, it has been repoted that a stenting tube can reduce the leakage of the pancreaticojejunostomy.[12] However, more than half of those patients who underwent the nonstented method and in whom leakage of the pancreaticojejunostomy occurred had undergone the invagination technique in this study. The invagination technique without a stenting tube tends to lead to leakage or stenosis of the anastomosis in pancreaticojejunostomy. Moreover, if pancreaticojejunostomy is performed using a stenting tube, duct-to-mucosa anastomosis can be used to prevent leakage of the anastomosis and to maintain the pancreatic function.[16] To evaluate the usefulness of the stenting tube in pancreaticojejunostomy, the method of anastomosis and the degree of pancreatic fibrosis should be standardized. Our study was limited to patients with a normal soft pancreas with a nondilated pancreatic duct and the procedure of pancreaticojejunostomy was limited to duct-to-mucosa anastomosis.

In this study, the rates of overall morbidity and leakage of the pancreaticojejunostomy in the nonstented group were 26.8% and 5.7%, respectively. There were no patient deaths as a result of the operation in the nonstented group and no significant differences in the operative results were seen between the two groups. Although this procedure requires a fine technique to prevent injury of the pancreatic duct, no stenting tube is needed to maintain the patency of the anastomosis when pancreaticojejunostomy has been achieved completely. Therefore, a fine atraumatic needle and monofilament thread (6-0 or 5-0) should be used in this procedure, and if any injury of the pancreatic duct is suspected through the duct-to-mucosa anastomosis, one should not persist in the nonstented method.

In conclusion, complete pancreaticojejunostomy using duct-to-mucosa anastomosis for a normal soft pancreas does not require a stenting tube. Although these results need confirmation by further studies, this nonstented method can be considered one of the basic procedures for pancreaticojejunostomy because of its safety and certainty.

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Indications and Techniques of Extended Resection for Pancreatic Cancer

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Abstract

Introduction: The resectability rate and postoperative survival rate for pancreatic carcinoma are poor. Aggressive resection including vascular resection and extended lymphadenectomy represent one strategy for improving survival. This study was carried out to clarify the indications for extended resection, especially vascular resection, for pancreatic carcinoma.

Methods: From July 1981 to March 2005, we performed curative resection in 289 of 443 patients with pancreatic carcinoma in our department (65.2%). Vascular resection was performed in 201 (69.5%) patients and portal vein resection without arterial resection in 186 patients. Combined portal and arterial resection was performed in 14 patients and arterial resection without portal vein resection in 1. Extended lymphadenectomy including paraaortic lymph nodes was done. The postoperative survival rate was stratified according to operative and pathology findings.

Results: Operative mortality (any death within 30 days after surgery) occurred in 11 of the 289 curative resection patients (3.8%), including 1 of 88 patients without vascular resection (1.1%), 5 of 186 portal vein resection patients without arterial resection (2.7%), and 5 of 14 (35.7%) arterial resection patients undergoing portal vein arterial resection as well. Most patients who survived for 2 to 3 years had carcinoma-free surgical margins.

Conclusions: The most important indication for vascular resection in patients with pancreatic cancer is the ability to obtain cancer-free surgical margins. Otherwise, vascular resection is contraindicated. Extended lymphadenectomy may be not of benefit.

Early diagnosis of pancreatic cancer remains difficult despite progress in diagnostic imaging, identification of tumor markers, and advances in molecular biology. Surgical resection provides the only chance for cure or long-term survival, but the 5-year survival of patients with carcinoma of the pancreas after resection is only 13%.[1]

In 1973, Fortner proposed "regional pancreatectomy as a means of increasing resectability and radicality to improve the outcome for pancreatic cancer patients."[2] Our department has been performing vascular resection for pancreatic cancer since 1981, when Nakao and colleagues developed a procedure for catheter bypass of the portal vein and isolated pancreatectomy using an antithrombogenic bypass catheter.[3–6] Our surgery for pancreatic cancer consists of three components. The first is combined resection of major vessels, including the portal vein and visceral arteries if necessary. The second component is extrapancreatic nerve plexus excision, and

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Table 1.
Resectability rate and operative procedure for carcinoma of the pancreas (July 1981 to March 2005)

Tumor location	Operation	Resection	PV resection	Resectability	Operative deaths	Operative procedure					
						TP	PpTP	PD	PpPD	DP	PHRSD
Head	329	226	177	68.7%	9	49 (48)	2 (2)	137 (107)	37 (20)		1
Body, tail	92	56	17	60.9%	1	7 (7)	1 (1)	1 (0)		47 (9)	
Entire gland	22	7	6	31.8%	1	7 (6)					
Totals	443	289	200 (69.2%)	65.2%	11 (3.8%)	63 (61)	3 (3)	138 (107)	37 (20)	47 (9)	1

PV: portal vein; TP; total pancreatectomy; PD, pancreatoduodenectomy; PpPD, pylorus-preserving pancreatoduodenectomy; PHRSD, pancreatic head resection with segmental duodenectomy; DP, distal pancreatectomy.
Numbers in parentheses indicate the number of portal vein resections accompanying each type of pancreatectomy.

the third is retroperitoneal connective tissue clearance, including the paraaortic lymph nodes.

MATERIALS AND METHODS

From 1981 to March 2005, surgery was performed in our department on 443 patients with invasive ductal carcinoma of the pancreas, of whom 289 (65.2%) underwent curative resection as follows: 63 total pancreatectomies, 3 pylorus-preserving total pancreatectomies, 138 pancreatoduodenectomies, 37 pylorus-preserving pancreatoduodenectomies, 47 distal pancreatectomies, and 1 pancreatic head resection with segmental duodenectomy (Table 1). Portal vein resection was performed in 200 patients (69.2%), including 14 arterial resections and 1 arterial vessel resection without portal vein resection.

Catheter-bypass procedures of the portal vein using an antithrombogenic catheter were used to prevent portal congestion or hepatic ischemia during the resection and reconstruction of the portal vein or simultaneous resection of the portal vein and hepatic artery (Figs. 1, 2).[3–6] Paraaortic lymph node dissection (n = 16a2, b1)[7] was performed after isolated pancreatectomy and before reconstruction of the portal vein (Fig. 3).

The resected specimens were examined histopathologically according to the rules of the Japan Pancreas Society.[7] The cumulative survival rate was calculated by the Kaplan-Meier method.[8] Statistical analysis was performed using the log-rank and chi–squared tests. A value of $P < 0.05$ was considered to indicate significance.

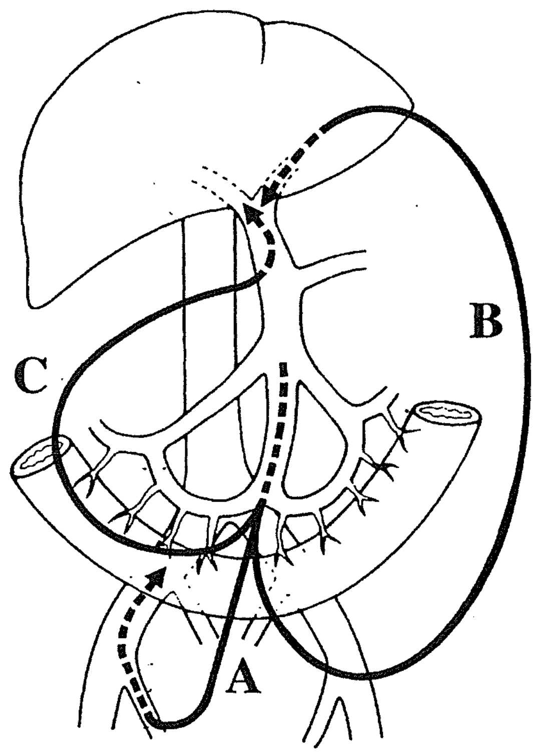


Figure 1. Catheter bypass of the portal vein. A: bypass between the mesenteric and femoral veins; B: bypass between the mesenteric and umbilical veins; C: bypass between the mesenteric and hepatic hilar portal veins.

RESULTS

Portal vein resection or superior mesenteric vein resection was performed in 200 of the 289 patients (69.2%) (Fig. 4). Reconstruction of the portal vein was performed by end-to-end anastomosis in 198 patients (99%). An autograft using the external iliac vein was performed in two patients who underwent distal pancreatectomy. Arterial resection with portal vein resection was undertaken in 14 patients (3 celiac artery, 8 hepatic artery, 3 superior mesenteric artery) (Fig. 5), and hepatic artery resection without portal vein resection was undertaken in 1 patient. Operative death (within 30 days after surgery) occurred in 11 patients among the 289

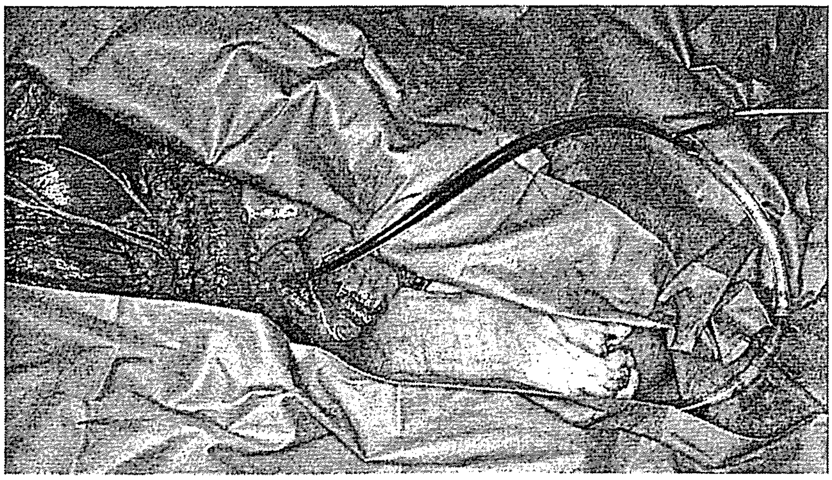


Figure 2. Operative photograph of a catheter bypass between the mesenteric and femoral veins. One end of the catheter is inserted in one of the branches of the superior mesenteric vein, and the other end of the catheter is inserted in the femoral vein via the right greater saphenous vein. Portal venous blood flows into the femoral vein owing to the pressure difference between the portal and femoral veins.

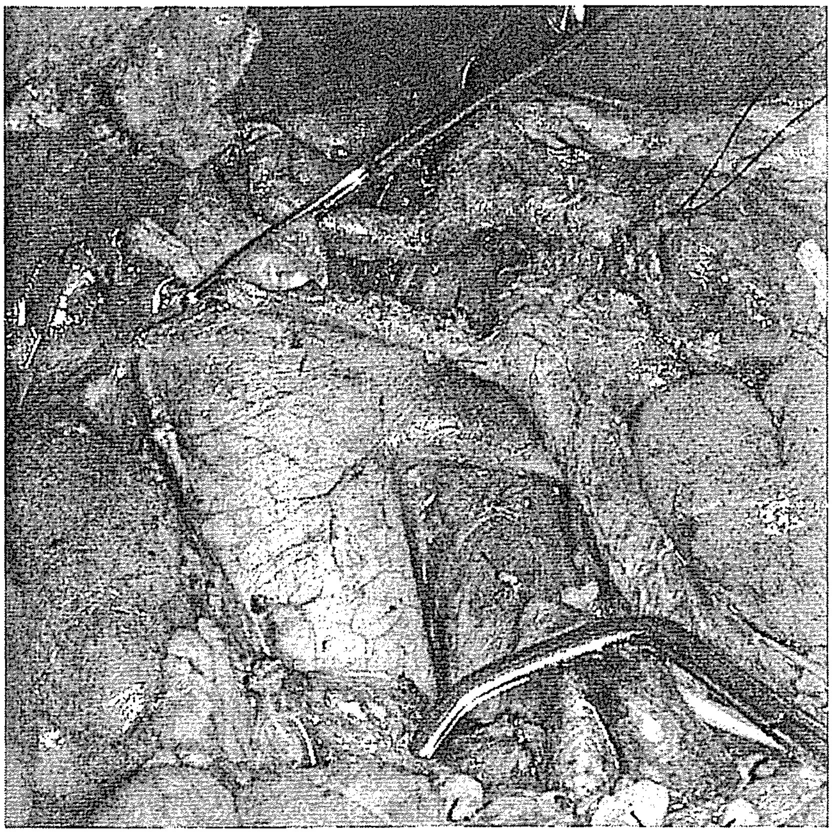
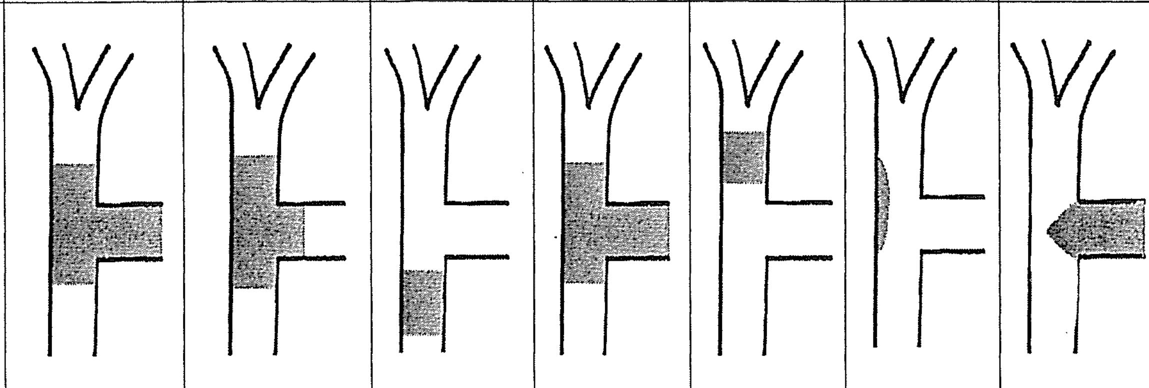


Figure 3. Pancreatoduodenectomy combined with portal and superior mesenteric veins resection is completed under catheter bypass of the portal vein. Paraaortic lymph node dissection is done before reconstruction of the portal vein.

who underwent resection (3.8%), in 1 of 89 patients without vascular resection (1.1%), in 5 of 186 portal vein resection patients without arterial resection (2.7%), and in 5 of the 14 patients undergoing portal vein plus arterial resection (35.7%).

Cumulative survival rates, including operative and hospital deaths among patients with and without portal vein preservation and those with combined portal vein and arterial resection, as well as the patients with unresectable carcinoma of the pancreatic head, are shown in Figure 6. Survival for patients with portal vein preservation was much higher than for those who underwent portal vein resection ($P < 0.0001$), and survival following portal vein resection was much higher than for those with combined portal vein and arterial resection ($P = 0.0191$) or those whose lesions were unresectable ($P < 0.0001$). This means that the combined portal vein and arterial resection group had a high operative death rate, tumors

operative procedure	TP+PV, SMV 60 PpTP+PV, SMV 3	PD+PV, SMV 78 PpPD+PV, SMV 13	PD+ SMV 25 PpPD+SMV 7 TP+SMV 1	DP+PV, SMV 8	PD+PV 1	PD+PV 3 (partial)	DP+PV 1 (partial)
resected area of portal vein							
Total	63 (6) SMA 2, HA 4 CA 1	91 (3) SMA 1, HA 5	33 (1)	8 (0) CA 1	1 (0)	3 (0)	1 (0)

( ) operative death(s)

Figure 4. Extent of resected portal vein segments and associated surgical procedures. Numbers indicate the number of patients. Numbers in parentheses indicate operative deaths. TP: total pancreatectomy; PV: portal vein; SMV: superior mesenteric vein; PpTP: pylorus-preserving total pancreatectomy; PD: pancreatoduodenectomy; PpPD: pylorus-preserving pancreatoduodenectomy; DP: distal pancreatectomy; SMA: superior mesenteric artery; HA: hepatic artery; CA: celiac artery.

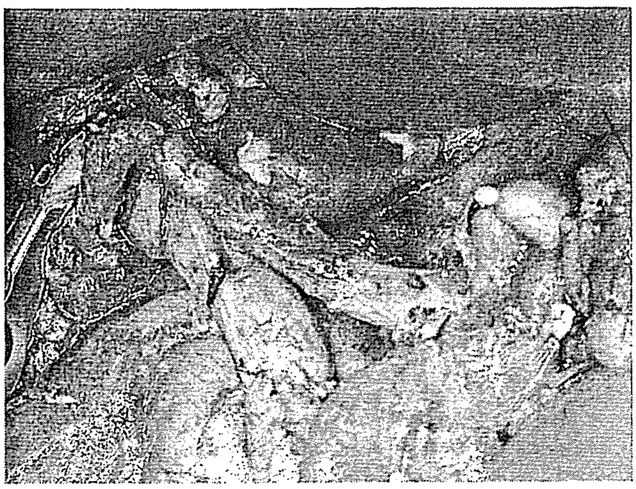


Figure 5. Operative photograph of combined resection of the portal vein and hepatic artery and reconstruction by an end-to-end anastomosis.

at a more advanced stage, and a high incidence of positive carcinoma invasion of the dissected peripancreatic margin.

Cumulative survival rates according to angiographic findings on portography are shown in Figure 7. In this respect, four types of pathology were designated: normal portal vein, unilateral narrowing, bilateral narrowing, and stenosis or obstruction with collateralization. The normal group had much higher survival rates than groups with unilateral narrowing ($P = 0.0186$), bilateral narrowing ($P < 0.0001$), or stenosis/obstruction ($P < 0.0001$) or the group with unresectable tumors ($P < 0.0001$). The unilateral narrowing group had much higher survival rates than groups with bilateral narrowing ($P = 0.0657$) or stenosis/obstruction ($P = 0.0237$) or the group with an unresectable tumor ($P < 0.0001$). Survival rates for the bilateral narrowing and stenosis/obstruction groups were similar. The stenosis/obstruction group had a slightly higher survival rate than the unresectable tumor group ($P = 0.0429$).

Cumulative survival rates based on portal invasion or invasion of the dissected peripancreatic tissue margin are shown in Figure 8. Survival for more than 1 year after surgery was seen in the group with tumor-free margins even when the portal venous system had been invaded. In contrast, cumulative survival rates for groups with tumor at the margins were quite low, showing no statistically significant difference from the rate for the 103 patients with unresectable tumors (Fig. 8). This finding shows that, barring unrelated contraindications, vascular resection is indicated when

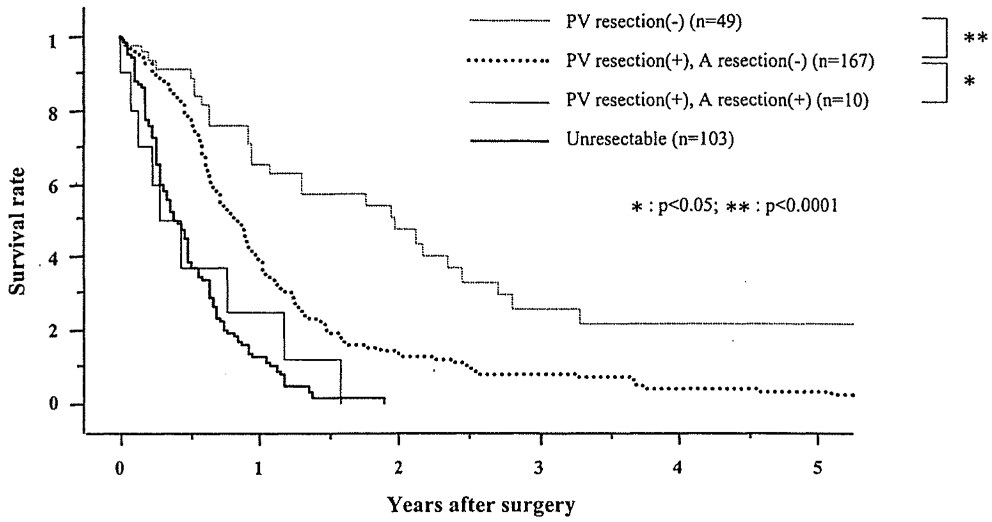


Figure 6. Comparison of cumul - ative survival rates in patients with portal vein (PV) preservation, portal vein resection, combined resection of the portal vein and artery, and an unresectable pancreatic head carcinoma.

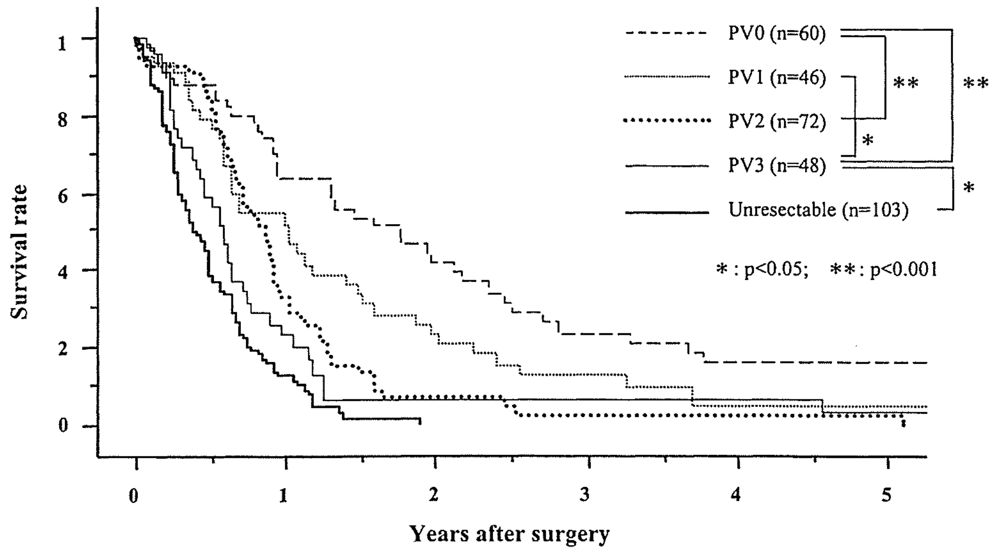


Figure 7. Comparison of cumulative survival rates in patients whose pancreatic head carcinoma shows various types of vein involvement on portography: PV0: angiograp-hically normal portal vein; PV1: unilateral narrowing; PV2: bilate-ral narrowing; PV3: stenosis or obstruction with collateralization.

it is needed to obtain a carcinoma-free surgical margin. The efficacy of arterial resection was much less than portal vein resection, and it was difficult to obtain tumor-free margins in the artery-invaded cases. The prognosis in margin-positive groups was extremely poor.

Lymph node metastases are classified as n0, n1, n2, and n3 by the Japan Pancreas Society.[7] Cumulative survival rates according to lymph node metastases are shown in Figure 9. The negative lymph node metastases group (n0) had a higher survival rate than the n2 ($P = 0.0025$) and n3 ($P = 0.0002$) lymph node-positive groups. No statistically significant difference was found in the survival rates among the n1, n2, and n3 groups.

DISCUSSION

Since 1981, we have performed isolated pancreatectomy accompanied by portal vein resection using the catheter bypass procedure.[3–6] The operability rate has risen to more than 60% during this 24-year period. During the first 12 years (1981–1993), 10 operative deaths occurred, in contrast to only 1 during the next 12 years. The cause of the latter death was cerebral hemorrhage not related directly to the surgery. Combined pancreatectomy and resection of the portal vein has become both safer and easier with catheter bypass of the portal vein.

Among patients who underwent total pancreatectomy for carcinoma of the pancreatic head, tumor spread was continuous from the head to the body or tail, with no skip

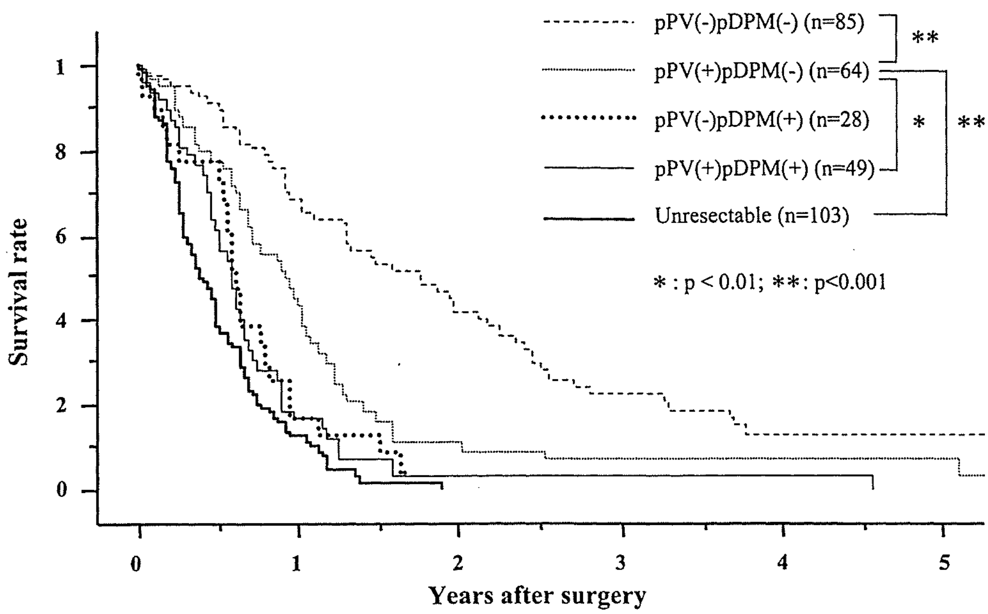


Figure 8. Comparison of cumulative survival rates in patients with and without invasion of a venous wall in the portal system (pPV) and invasion of the dissected peripancreatic tissue margin (pDPM) in patients with carcinoma of the pancreatic head.

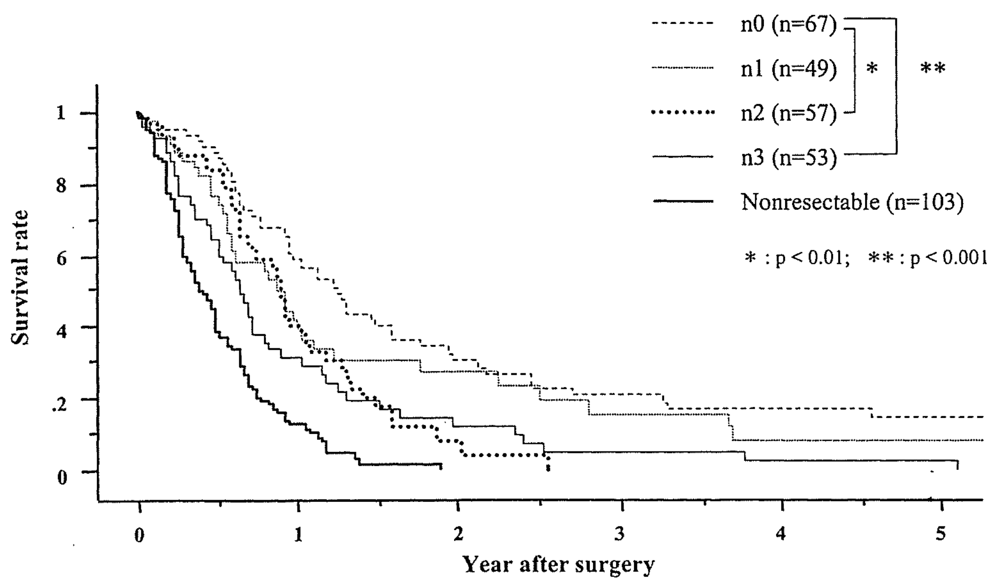


Figure 9. Comparison of cumulative survival rates of pancreatic head carcinoma according to lymph node metastasis.

areas revealed by histopathologic or immunohistochemical studies.[9] The quality of life after total pancreatectomy is much poorer than after pancreatoduodenectomy with or without sparing the pylorus. Therefore we attempt to preserve the distal pancreas whenever intrapancreatic spread from the head to the body or tail is not confirmed by intraoperative findings or immunostaining.[9,10]

The rationale for performing extensive lymphadenectomy, including the paraaortic lymph nodes, is based on the high incidence of lymph node metastases from pancreatic cancer.[11–15] However, the efficacy of this extended operation has not been established.[16–18] Extended lymphadenectomy may not be of benefit.

Pancreatic carcinoma often invades the extrapancreatic nerve plexus.[19] With pancreatic head carcinoma, complete dissection of the extrapancreatic nerve plexus (especially the second portion) together with the nerve plexus around the superior mesenteric artery is usually necessary to obtain a carcinoma-free surgical margin. However, complete resection of the nerve plexus around the superior mesenteric artery results in severe diarrhea after surgery. Intraportal endovascular ultrasonography can diagnose invasion of the portal vein[20,21] and invasion of the second portion of the pancreatic head nerve plexus.[22] Although many imaging diagnostic modalities for pancreatic carcinoma have been developed, the diagnosis of extrapancreatic nerve plexus invasion remains difficult. Only intraportal endovascular ultrasonography can diagnose it. If this examination does not show invasion of the second portion of the pancreatic head nerve plexus, the left semicircular nerve plexus around the superior mesenteric artery is preserved to prevent postoperative diarrhea. Radical resection is not indicated when the extrapancreatic nerve plexus, especially the plexus around the superior mesenteric or celiac artery, is invaded because the surgical margin cannot be cleared.

Vascular resection has become safer and easier during pancreatic cancer surgery, but the indications for arterial resection are limited. Portal vein resection should be performed only when it is needed to create a carcinoma-free surgical margin.[22–24] If such a surgical margin cannot be obtained, even by performing extensive surgery, there is no indication for surgical resection in patients with pancreatic cancer. Extended lymphadenectomy including the paraaortic lymph nodes may not be of benefit.

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REVIEW

Oncological problems in pancreatic cancer surgery

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Abstract

Despite the development of more sophisticated diagnostic techniques, pancreatic carcinoma has not yet been detected in the early stage. Surgical resection provides the only chance for cure or long-term survival. The resection rate has increased due to recent advances in surgical techniques and the application of extensive surgery. However, the postoperative prognosis has been poor due to commonly occurring liver metastasis, local recurrence and peritoneal dissemination. Recent molecular-biological studies have clarified occult metastasis, micrometastasis and systemic disease in pancreatic cancer. Several oncological problems in pancreatic cancer surgery are discussed in the present review.

Key words: Pancreatic cancer; Extended resection; Molecular diagnosis; Micrometastasis; Adjuvant therapy

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INTRODUCTION

Over the past 30 years, the number of deaths in Japan due to pancreatic carcinoma has steadily increased from 4400 to 19000[1] (Figure 1). It is the fifth most common cause of death due to malignant neoplasms (Figure 1). Regional pancreatectomy for carcinoma of pancreatic head region, introduced by Fortner[2] in 1973, has impressed many Japanese pancreatic surgeons. Consequently, the resection rate has gradually improved, but the postoperative prognosis is still poor in spite of the development of diagnostic modalities such as CT-scan, EUS, MRI and PET. In 1980, the Japan Pancreas Society (JPS) published the first edition of its "General Rules for Surgical and Pathological Studies on Cancer of the Pancreas". The fifth edition was published in 2002. The second English edition was published in 2003[3]. The JPS also started a registration system for pancreatic carcinoma in 1981. According to the data of JPS, the 5-year survival of invasive ductal carcinoma of the pancreas after pancreatectomy is only 13.4%[4] (Figure 2). JPS and UICC stage of invasive cancer and survival after pancreatecotmy are shown in Figure 3[4]. Comparison of survival curves according to the stage reveals that stratification is much better in the JPS classification than in UICC classification.

In 1981, we developed an antithrombogenic bypass catheter for the portal vein to decompress portal congestion or prevent hepatic ischemia caused by simultaneous resection of portal vein and hepatic artery[5]. Since then, we have been aggressively performing extensive surgical resections including portal vein resection by the non touch isolation technique[7,8] using this bypass method. The resection rate has been elevated and operative mortality has remarkably decreased. However, the postoperative prognosis is still poor due to high recurrence rate. The problems of surgical therapy for pancreatic cancer are discussed in this review.

ONCOLOGICAL PROBLEMS

Intrapancreatic carcinoma development

The indications for total pancreatectomy or pancreatoduodenectomy in pancreatic head cancer are one of the key problems in pancreatic cancer surgery. It is very important to know how the carcinoma has developed from the pancreatic head to the body or tail. A high incidence of development or multicentricity of the carcinoma of the pancreatic head to the body or tail has been reported[9,10]. However, recent histopathological and immunocytochemical analysas of total pancreatectomy specimens have clarified that carcinoma development from head to body or tail is continuous[11-13]. Therefore, intraoperative quick histopathological diagnosis combined with immunohistochemical staining using frozen section can diagnose intrapancreatic carcinoma development more precisely[14,15].

Table 1 Comparative studies of extended versus standard operation for pancreatic cancer

Author	Yr	Results
Ishikawa *et al*[24]	1988	Retrospective study [standard (n = 37): 9%, 5-Y-S; extended (n = 22): 28%, 5-Y-S
Mukaiya *et al*[25]	1998	Retrospective study 77 institutions, 501 patients: NS
Henne-Bruns *et al*[26]	2000	Retrospective study [standard (n = 26); extended (n = 46)] NS
Pedrazzoli *et al*[27]	1998	RCT [standard (n = 40); extended (n = 41) — overall survival: NS; survival of node positive patients: extended > standard
Yeo *et al*[28]	2002	RCT [standard (n = 146); extended (n = 148) — mortality: NS, morbidity: extended > standard, survival: NS

RCT: Randomized controlled test; NS: Not significant.

Lymph node metastasis

Lymph node dissection is one of the important components in pancreatic cancer surgery. The high incidence of 56%[16], 70.5%[17], 73%[18], 76%[19], 77%[20], and 86.4%[21] in resected specimen of pancreatic cancer is the reason for wide dissection of lymph nodes in pancreatic cancer surgery. There are few reports about precise para-aortic lymph node metastasis. The incidence of para-aortic lymph node metastasis for pancreatic head carcinoma is reported to be 16% (7/44)[17] and 26% (23/90), respectively[20]. The incidence of pancreatic body and tail carcinoma is 13% (4/30)[22] and 17% (4/27)[21], respectively. The lymphatic flow from the pancreatic head tumor to the para-aortic lymph node via the posterior surface of the pancreatic head and around the superior mesenteric artery has been suspected[17,18,23].

The efficacy of extended lymph node dissection in pancreatic cancer surgery has been suggested in a retrospective study[24]. However, the efficacy of extended lymph node dissection has not been clarified in retrospective studies[25,26] or in recent prospective randomized controlled tests for pancreatic cancer surgery (Table 1)[27,28].

The incidence of perigastric lymph node metastasis in pancreatic cancer is relatively low[20]. Therefore, pylorus preserving pancreatoduodenectomy (PPPD) is indicated for pancreatic head carcinoma, although its advantage over the classic Whipple operation has not been clarified[29,30].

Vascular invasion

Portal vein resection is another problem in pancreatic cancer surgery. To prevent portal congestion in portal vein resection and hepatic ischemia in simultaneous resection of portal vein and hepatic artery, we developed a catheter-bypass procedure[5,6] in our department in 1981 using antithrombogenic catheter, and isolated pacreatectomy combined with portal vein resection has thus been established[8]. During the past 30 years, the operative mortality rate of pancreatoduodenectomy combined with portal vein resection has decreased, and portal vein resection in pancreatic cancer surgery has become a safe operative procedure. The reported mortality rate is 7.4% (2/27)[31], 10% (6/63)[32], 5% (3/58)[33], 0% (0/31[34], 0/14[35], 0/34[36], 0/24[37]), and 3.2% (1/31)[38]. From 1981 to 2003, 250 of 391 (63.9%) patients with pancreatic carcinoma underwent tumor resection in our department.

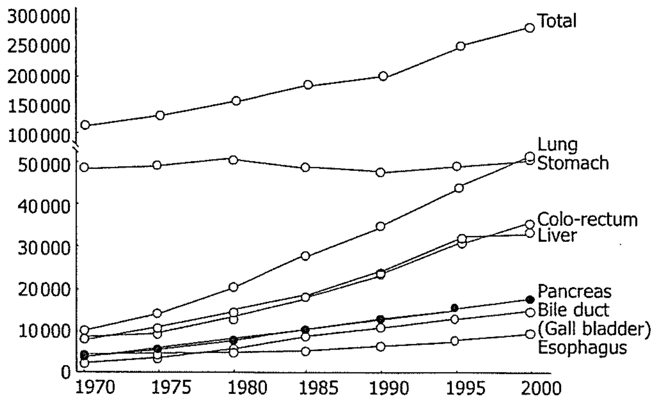

Figure 1 Trends in death due to malignant neoplasms in Japan.

Portal vein resection was performed in 171 of these 250 (68.4%) resected cases, and the mortality rate was 4.4% (11/250)[39]. The indication and contraindication for portal vein resection have not yet been clarified in pancreatic cancer surgery. There are many reports about the benefit[33,34,40] or no benefit[41] of portal vein resection for curative resection or survival. The most important indication for portal vein resection in pancreatic cancer is the ability to obtain cancer-free surgical margins[39].

In severe portal invasion cases, it is difficult to obtain cancer-free surgical margins, so the prognosis is poor[39,42-44]. A recent diagnostic modality using intraportal endovascular ultrasonography provides precise information about the relationship between the pancreatic cancer and the portal vein wall, and planning of the operative procedure[45-47].

Extrapancreatic nerve plexus invasion

Pancreatic carcinoma often invades the extrapancreatic nerve plexus[48-51]. There is continuity of the intrapancreatic neural invasion into the extrapancreatic nerve plexus[48]. The grade of intrapancreatic neural invasion correlates with the extrapancreatic nerve plexus invasion[50,51] and the manner of neural invasion has no relationship with the behavior of lymph node metastasis[50].

In pancreatic head carcinoma, complete dissection of extrapancreatic nerve plexus , especially the second portion of pancreatic head nerve plexus and nerve plexus around the superior mesenteric artery, is sometimes necessary to obtain a carcinoma-free surgical margin. However, complete resection of the nerve plexus around

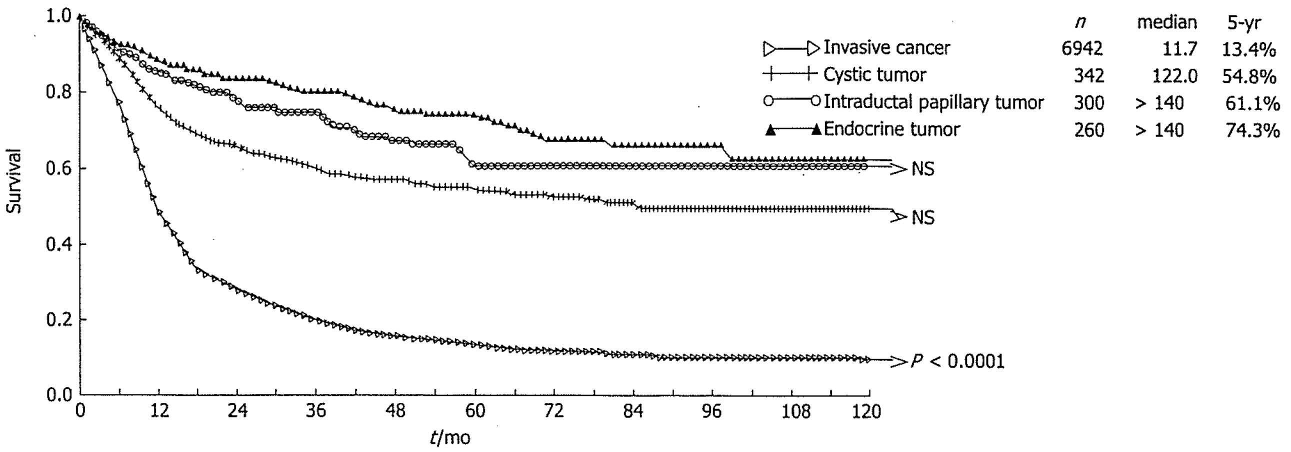

Figure 2 Histology and survival after pancreatectomy. Survival of patients who underwent pancreatectomy is shown. NS, not significant.

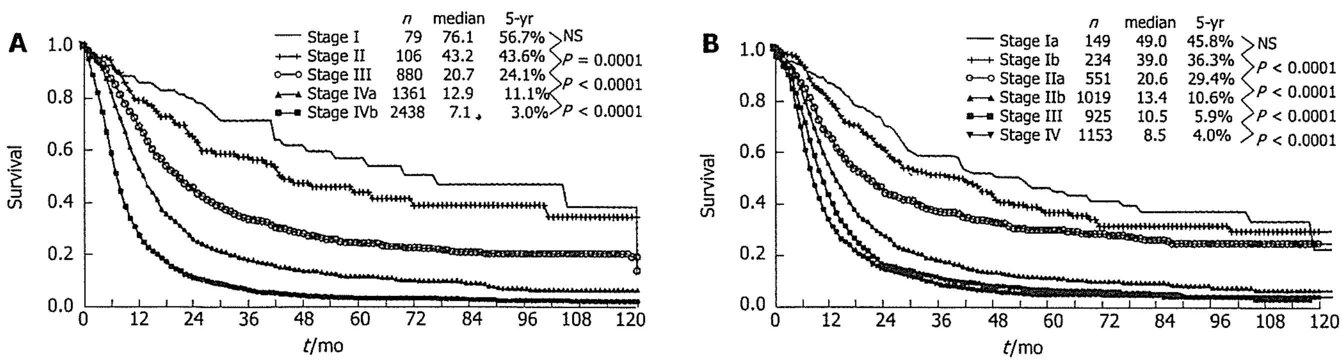

Figure 3 Survival after pancreatectomy according to JPS stage (**A**) and UICC stage (**B**). NS, not significant.

the superior mesenteric artery causes severe diarrhea after surgery, and the prognosis of positive carcinoma invasion to the extrapancreatic nerve plexus cases is very poor[39,50,51]. The greatest cause of carcinoma-positive surgical margin is extrapancreatic nerve plexus carcinoma invasion[39,48,50]. Recently, carcinoma invasion to the second portion of the pancreatic head nerve plexus can be diagnosed using intraportal endovascular ultrasonography[45-47,52]. In our department, if patients have no carcinoma invasion to the second portion of the pancreatic head nerve plexus, the left semi-circular nerve plexus around the superior mesenteric artery is preserved to prevent postoperative diarrhea.

Postoperative recurrence

Even in extended surgery, a high incidence of postoperative liver metastasis, local recurrence, and peritoneal metastasis has been observed with a poor postoperative prognosis (Table 2)[53-57]. The precise diagnosis of recurrence type is difficult even if modern diagnostic modalities are used. However, the local recurrence was 100% and the liver metastasis was 80% in 25 autopsy cases[55]. The first cause of poor postoperative prognosis in pancreatic cancer is liver metastasis. Although occult liver metastasis may be suspected on the basis of extensive clinical data, no criteria have been definitely determined. Surgical therapy combined with effective adjuvant therapy is necessary in view of these types of recurrence.

Adjuvant therapy

Surgical therapy currently offers the only potential cure for pancreatic cancer. However the recurrence rate is very high and the long-term survival is poor.

The potential benefit of adjuvant therapy after resection of pancreatic cancer was first recognized by the randomized trial conducted by the Gastrointestinal Tumor Study Group (GITSG) using chemoradiotherapy almost 20 years ago[58,59]. Since then, few randomized trials have shown a benefit of adjuvant treatment (Table 3)[60-65]. The study of the European Study Group for Pancreatic Cancer (ESPAC-1) concluded that postoperative chemotherapy with fluorouracil plus leucovorin confers a benefit in terms of survival, whereas postoperative chemoradiotherapy has a deleterious effect on survival[64]. The current study by Neuhaus *et al*[65] indicates that the treatment with gemcitabine in patients with resected pancreatic cancer can result in improved disease-free survival as compared to observation.

A new and more effective adjuvant therapy must be established by prospective randomized trials using newly developed drugs[66,67] or therapeutic modalities[68]. Nevertheless, the individualized adjuvant therapy is very important in pancreatic cancer treatment[69,70].

Occult metastasis and micrometastasis

Recent progress in immunohistochemistry and molecular biological studies has made it possible to clarify the occult metastasis and micrometastasis in pancreatic cancer. The

Table 2 Incidence of postoperative recurrence in pancreatic cancer

Author	Yr	Cases (*n*)	Liver (%)	Local (%)	Peritoneal (%)	Bone (%)	Lung (%)	Other (%)
Westerdahl *et al*[53]	1993	74	92	86.5				
Kayahara *et al*[54]	1993	30	60	83.3	40			
Takahashi *et al*[55]	1995	25	80	100	56	24	56	
Sperti *et al*[56]	1997	78	62	72	6			
Nakao *et al*[57]	1997	76	57	34	41	3	1	1

Table 3 Randomised controlled trials of adjuvant treatment for pancreatic ductal adenocarcinoma

Trial	Comparison	Adjuvant treatment	Number of patients	Conclusions
GITSG, 1985[58], 1987[59]	CRT *vs* OBS	2 × (20 Gy in 10 fractions + 500 mgm^{-2} 5FU d 1-3) + weekly 5FU to recurrence	49 pancreatic patients randomised	Significant increase in median survival (20 *vs* 11 mo, P = 0.035) in 43 eligible patients
Norway, 1993[60]	CT *vs* OBS	AMF (40 mgm^{-2} doxorubicin, 6 mgm^{-2} mytomycin C, 500 mgm^{-2} 5FU) once every 3 wk for six courses	61 patients (47 pancreatic, 14 ampullary) randomised 46 additional nonrandomised patients	Significant increase in median survival (23 *vs* 11 mo, P = 0.02) in 60 pancreatic and ampullary patients combined
EORTC, 1999[61]	CRT *vs* OBS	2 × (20 Gy in 10 fractions + 25 mgkg^{-1} 5FU/FA d 1-5)	218 patients (120 pancreatic, 93 ampullary) randomised	NS increase in median survival (25 *vs* 19 mo, P = 0.21) in 207 eligible patients NS increase in median survival in 114 eligible pancreatic patients (17 *vs* 13 mo, P = 0.099)
Japan, 2002[62]	CT *vs* OBS	6 mgm^{-2} mytomycin C d 1 + 310 mgm^{-2} 5FU d 1-5 and d 15-20 followed by 100 mgm^{-2} oral 5FU daily until recurrence	508 patients (173 pancreatic, 335 bile duct/gallbladder/ ampullary) randomised	Significant survival benefit in gallbladder No difference in 158 eligible pancreatic patients No difference in 48 eligible ampullary patients
ESPAC1, 2001[63], 2004[64]	CRT *vs* no CRT CT *vs* no CT	2 × (20 Gy in 10 fractions + 500 mgm^{-2} 5FU/FA d 1-3) (20 mgm^{-2} FA + 425 mgm^{-2} 5FU d 1-5) × six cycles	289 pancreatic patients randomised	NS decrease in survival for CRT (P = 0.05) in 289 patients Significant increase in survival for CT (P = 0.009) in 289 eligible patients
CONKO-001, 2005[65]	CT *vs* OBS	1 gm^{-2} GEM, d 1, 8, 15, every 4 wk for 6 mo	368 pancreatic patients randomised	Significant increase in median DFS (14.2 *vs* 7.5 mo, P < 0.05) in 356 eligible patients

CRT: Chemoradiotherapy; CT: Chemotherapy; OBS: Observation; NS: Not significant; DFS: Disease-free survival.

Table 4 Incidence of pancreatic cancer cells in peripheral blood, bone marrow, and liver tissue

Author	Yr	Incidence
Tada *et al*[71]	1993	Peripheral blood, K-*ras* 2/6 (33%)
Juhl *et al*[72]	1994	Bone marrow, immunostaining: 15/26 (58%)
Inoue *et al*[73]	1995	Liver tissue, K-*ras*: 13/17 (76%)
Nomoto *et al*[74]	1996	Peripheral blood, K-*ras*: postoperative period 10/10 (100%)
Funaki *et al*[75]	1996	Peripheral blood, CEAmRNA: 3/9 (33%)
Aihara *et al*[76]	1997	Peripheral blood, Keratin 19m RNA: 2/38 (5%)
Miyazono *et al*[77]	1999	Peripheral blood, CEAmRNA: 13-21 (61.9%)
Uemura *et al*[78]	2004	Peripheral blood, K-*ras*: 9/26 (35%)

high incidence of K-*ras* point mutation of codon 12 in pancreatic cancer has been observed. Occult pancreatic cancer cells have been detected in peripheral blood, bone marrow and liver by studies of K-*ras*, CEA mRNA, keratin 19 mRNA, along with immunocytochemical staining (Table 4)[71-78].

Occult lymph node metastasis in pancreatic cancer has been also detected by the studies of K-*ras* and immunostaining of cytokeratin or Ber-FP4 (Table 5)[79-83].

The incidence of cancer cells from abdominal washing cytology is shown in Table 6[84-89]. The incidence using conventional staining is 0%-17% (Table 6)[84,86-89]. However

Table 5 Reports of occult lymph node metastasis

Author	Yr	Results
Tian *et al*[79]	1992	HE: 8/56 (14%) Cytokeratin: 17/56 = (30%)
Ando *et al*[80]	1997	K-*ras*: paraaortic lymph nodes: 42/101 (42%)
Demeure *et al*[81]	1998	K-*ras*: Stage I (T1-2, N0, M0) 16/22 (73%)
Yamada *et al*[82]	2000	K-*ras* (-) has a better prognosis than K-*ras* (+)
Bogoevski *et al*[83]	2004	Ber-EP4: immunostaining 56/148 (37.8%)

Table 6 Incidence of occult peritoneal dissemination

Author	Yr	Results
Lei *et al*[84]	1994	Peritoneal washings, conventional cytology, 3/36 (8%), 1/11 (9%) with ascites
Juhl *et al*[72]	1994	Immunostaining (CEA, CA19-9,..., cytokeratin bone marrow 58%, peritoneal washings 58%
Vogel *et al*[85]	1999	Peritoneal washings 39%, bone marrow 38%, one of them positive: died within 19 mo, both negative: 5 y.s. 30% (P < 0.0001)
Castillo *et al*[86]	1995	Laparoscopy 16/94 (17%)
Leach *et al*[87]	1996	4/60 (7%)
Nomoto *et al*[88]	1997	Conventional: 0/18 (0%), immunostaining (CEA, CA19-9): 2/18 (11%)
Nakao *et al*[89]	1999	Conventional: 5/66 (8%), immunostaining 14/66 (22%) prognosis between cytology positive and negative: NS

a high incidence of 58%[72], 39%[85], and 22%[89] by immunocytochemical staining using monoclonal antibodies against tumor-associated antigens and cytokeratins has been reported. The difference in prognosis between positive and negative occult metastases remains controversial.

CONCLUSION

Surgical techniques for pancreatic cancer have been developed, and the resection rate has increased in Japan over the past 30 years. However, the prognosis of stage IV patients with pancreatic cancer is still poor even after aggressive surgery because of its high recurrence rate. Occult metastasis and micrometastasis have been more precisely diagnosed by immunocytochemical and molecular biological studies. On the basis of such data, adjuvant multimodal therapies targeting occult metastasis and micrometastasis with radical surgery are recommended. The effectiveness of these adjuvant multimodal therapies must be clarified and more effective adjuvant therapies must be developed.

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