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Results of radical distal pancreatectomy with *en bloc* resection of the celiac artery for locally advanced cancer of the pancreatic body

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Original article

Abstract

Background and aims: Locally advanced cancer of the pancreatic body involving the celiac and/or common hepatic arteries is often considered unresectable. Recently, radical distal pancreatectomy with *en bloc* resection of these arteries without reconstruction has been introduced as treatment for these tumors. However experience is small. This study reviewed the safety and the utility of this operation.

Patients: Between January 1997 and February 2003, 13 patients underwent this procedure. Data were acquired by chart review.

Results: Unplanned arterial reconstruction was required in three patients due to accidental injury. The postoperative mortality rate was 0%, despite a morbidity rate of 62%. Patient's intractable abdominal and/or back pain was completely relieved immediately after surgery. Contrary to expectations, postoperative diarrhea was mild. The surgical margins, including the retroperitoneum, were clear histologically (R0 resection) in all patients. One- and two-year survival rates were 51% and 14%, respectively, and median survival was 12.2 months. The site of recurrence was the liver in six patients and the retroperitoneum only in one.

Conclusion: Distal pancreatectomy with *en bloc* resection of the celiac artery is feasible and safe, offers a high resectability rate, and has dramatic analgesic effect. Local control of disease is excellent despite frequent hepatic recurrence.

Key Words: pancreatic cancer, distal pancreatectomy, celiac artery resection, hepatic artery resection, portal vein resection

Introduction

Most of cancers of the body and tail of the pancreas are discovered at a far advanced stage due to the lack of any specific signs or symptoms, such as obstructive jaundice caused by cancers of the head of the pancreas, and curative resection rates remain less than 22% [1-8]. Especially in cancers of the body of the pancreas, extrapancreatic extension often involves the celiac artery and/or the common hepatic artery, which are anatomically contiguous with the body of the pancreas. This situation forces the surgeon to declare the lesion unresectable in spite of the absence of distant metastasis [2,3,8]. Since Nimura et al.'s report [9], however, several authors have performed a radical distal pancreatectomy with *en bloc* resection of the celiac and common hepatic arteries for these locally advanced cancers [4,10-13]. Despite reports of a few long-term survivors [4,10,13], the overall survival benefit and the risks of this challenging operation are unknown because previous reports have included only a small number of patients (Miyakawa et al. [13]: n=8, Mayumi et al. [10]: n=6, Konishi et al. [12]: n=4, and Ozaki et al. [4]: n=2).

A distal pancreatectomy with *en bloc* resection of the celiac and common hepatic arteries was developed by Appleby [14] to achieve complete nodal clearance around the celiac artery in cases of advanced gastric cancer requiring total gastrectomy. The lack of a need for arterial reconstruction is a great advantage of this procedure because collateral pathways via the superior mesenteric artery, pancreaticoduodenal arcades, and gastroduodenal artery maintain the arterial blood supply for the hepatobiliary system. Because the collateral pathways ensure arterial flow also to the right gastroepiploic artery, the entire stomach can be preserved unless the pancreatic tumor involves the stomach.

The purpose of this retrospective study of 13 patients treated during the last 6 years was to determine the operative safety and the clinical utility of radical distal pancreatectomy with *en bloc* resection of the celiac artery for locally advanced cancer of the body of the pancreas.

Patients and Methods

Between January 1997 and February 2003, 30 patients with ductal carcinoma of the body of the pancreas, excluding intraductal papillary-mucinous neoplasms, underwent surgery. Ten patients

underwent a palliative procedure due to the presence of distant metastasis or involvement of the superior mesenteric artery; 20 patients underwent a distal pancreatectomy with curative intent. A radical distal pancreatectomy with *en bloc* resection of the celiac artery was indicated when preoperative computed tomography showed a tumor involving the celiac artery, the common hepatic artery, and/or the origin of the splenic artery (n=13); otherwise, a distal pancreatectomy without vascular resection was performed (n=7). Postoperative adjuvant therapy was not administered to most patients.

The age of the 13 patients who underwent a distal pancreatectomy with celiac artery resection ranged from 54 to 76 years, with a median of 66 years. Seven patients were male and six were female. Eight patients complained of abdominal and/or back pain and had been treated with diclophenac (n=4) or morphine (n=3). Tumor size varied from 20 to 75 mm, with a median of 55 mm. The involved arteries are summarized in **Table 1**. Tumor encasement of the celiac artery, the common hepatic artery, and/or the origin of the splenic artery was demonstrated preoperatively in 10 patients, and a tumor in continuity with these arteries was observed in the remaining 3 patients. Preoperative coil embolization of the common hepatic artery [15] was successfully performed in 8 patients, 1 to 16 days (median: 4 days) preoperatively to enhance the collateral arterial flow via the pancreatoduodenal arcades from the superior mesenteric artery.

Operative technique

After confirming the absence of hepatic and peritoneal metastasis, the superior mesenteric artery (SMA) is exposed just below the transverse mesocolon. The anterior wall of the SMA is dissected from the surrounding nerve sheath, but when this maneuver is not feasible due to tumor involvement, the operation is converted to a palliative procedure. The splenic flexure of the colon is detached from the splenocolic and gastrocolic ligaments and pulled downward. The common hepatic artery is exposed and divided just proximally to the origin of the gastroduodenal artery. After mobilization of the gastroduodenal artery to the right side, with preservation of its pancreatoduodenal branches, the neck of the pancreas is transected, ensuring a safe surgical margin. The splenic vein is divided at its confluence with the portal system. However, portal reconstruction may be required if the confluence is involved. Upward dissection of the anterior wall of the SMA with excision of the right celiac

ganglion and a part of the right crus of the diaphragm exposes the aortic wall. The origin of the celiac artery is identified just above the origin of the SMA and is divided. The left gastric artery and vein are divided at some distance from the tumor, and the gastrosplenic ligament is also divided. Turning the stump of the distal pancreas with the tumor to the left and exposing the aorta and the left crus of the diaphragm, the celiac plexus and left ganglion, and the left adrenal gland are resected *en bloc*. The left renal vein and artery are isolated, and its adrenal branches are divided. Finally, Gerota's fascia is dissected from the left kidney and the specimen is removed. Thus, this procedure includes distal pancreatectomy and *en bloc* resection of the celiac axis, common hepatic and left gastric arteries, the celiac plexus and ganglia, a part of the crus of the diaphragm and Gerota's fascia, the left adrenal gland, and the retroperitoneal soft tissue containing para-aortic lymph nodes (**Figures 1 and 2**).

When the tumor is small enough to be elevated upward and ventrally from the SMA, a left-sided approach is feasible. Subsequent to the initial dissection of the anterior wall of the SMA, the left anterior aspect of the aorta is exposed, permitting isolation of the origin of the celiac artery from the left-hand side.

Results

Surgical procedures performed

The left-sided approach was successful in only two patients (Patients #3 and 4), and the right-sided approach was required in the remaining 11 patients.

Of 9 patients with involvement of the confluence of the splenic and superior mesenteric veins, 3 patients underwent wedge resection of the portal vein and transverse primary closure, with portal vein occlusion time of 9 to 11 min, with a median of 10 min. The remaining 6 patients underwent a sleeve resection of the portal vein (**Table 1**). Direct end-to-end anastomosis was feasible in two patients, whereas interposition of a right external iliac vein graft (2.5 to 4.0 cm, with a median of 2.9 cm) was required in 4 patients. The portal vein occlusion time was 20 and 21 min in the patients who underwent direct primary anastomosis and was 26 to 31 min, with a median of 29 min, in the patients requiring graft interposition. Temporary bypass of the portal blood flow was not used in any patient.

Three patients required unplanned arterial reconstruction [16] due to iatrogenic injury to the inferior pancreaticoduodenal artery (Patients #10 and 13) or the replaced right hepatic artery (Patient #7).

Another structure resected most frequently was the inferior mesenteric vein, 10 patients; followed by the transverse mesocolon, 8 patients; the middle colic artery, 5 patients; and the right gastric artery, 3 patients. Total gastrectomy was required only in one patient with massive gastric invasion, while wedge resection of the gastric wall was performed in two patients. Of the 11 patients who had not undergone cholecystectomy previously, three patients underwent prophylactic cholecystectomy for fear of postoperative ischemic cholecystitis and one underwent cholecystectomy for concomitant cholecystitis; the gallbladder was preserved in the remaining 7 patients.

Time of operation was 348 to 655 min, with a median of 458 min. Operative blood loss ranged from 532 to 1730 mL, with a median of 860 mL, and red blood cell transfusions of 2 units were administered in three patients.

Perioperative results

The serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and amylase on postoperative day 1 were 39 to 863 (median: 84), 15 to 869 (median: 53), and 162 to 1385 (median: 327) IU/L, respectively, and returned to the normal range in a few days. Serum AST and ALT concentrations in the three patients who underwent arterial reconstruction were 224 to 863 (median: 231) and 236 to 869 (median: 262), which were significantly higher than those in the patients who did not require arterial reconstruction ($P=0.017$, Mann-Whitney test).

The postoperative mortality rate was 0%, in spite of a morbidity rate of 62%. The most common complication was gastric ulcer, possibly of ischemic origin, which developed in four patients and healed within 1 to 4 weeks with anti-ulcer medication. This complication developed only in one of the seven non-gastrectomized patients who underwent preoperative coil embolization of the common hepatic artery. Pancreatic fistula, abdominal abscess, severe enteritis, sepsis derived from central line infection, and adhesive ileus occurred postoperatively in one patient each. Two patients underwent reoperation for abdominal abscess or adhesive ileus, while the others were successfully

managed medically.

Six patients received no antidiarrheal agent, whereas 6 patients were given loperamide hydrochloride (2 mg/day) and one was given tincture of opium. The intractable abdominal and/or back pain was completely relieved immediately after surgery in all patients who had reported preoperative pain, and postoperative analgesia was not necessary.

Pathologic findings

Pathologic disease stage according to 2002 UICC TNM classification system [17] is shown in **Table 1**. Five and six patients had stage IIB and III disease, respectively. Only one had stage IIA disease. A minute peritoneal nodule around the primary tumor proved to be an M1 lesion and represented stage IV disease in one patient. Six and seven patients had T3 and T4 tumors, respectively, and regional lymph node metastases were detected in eight patients but not in the para-aortic area. When using the 1997 UICC TNM classification system, 2, 1, 9, and 1 patients had stage II, III, IVA, and IVB disease, respectively.

Histopathologic grading was G1 (well-differentiated) in three patients, G2 (moderately differentiated) in seven, and G3 (poorly differentiated) in three. Extrapaneuric perineural invasion was present primarily in the nerve plexus around the celiac artery and common hepatic artery in eleven patients and extended into the left celiac ganglion in three patients. Lymphatic and venous invasion was detected in seven and eleven patients, respectively. Intramural invasion of the resected portal vein was confirmed histologically in all nine patients who underwent portal vein resection, whereas intramural invasion of the celiac or common hepatic arteries was seen only in one patient despite massive perineural invasion in the surrounding neural plexus. Direct invasion of the left adrenal gland and the crus of the diaphragm was confirmed in only two patients. The surgical margin, including the retroperitoneum and pancreas, was clear (R0 resection) in all patients based on examination of multiple serial sections.

Postoperative survival

Five patients are alive without evidence of cancer recurrence 30, 14, 8, 3, and 1 months after

surgery. One patient died of ileus in another institution 3 months after discharge from our hospital. The remaining 7 patients died of recurrent disease 5 to 16 months after surgery (median: 11 months). Main site of recurrence was the liver in 6 patients and the retroperitoneum in 1. One- and two-year survival rates for all 13 patients by the Kaplan-Meier method were 51% and 14%, respectively, and median survival was 12.2 months after surgery (**Figure 3**). Postoperative survival, with a median of 4.0 months, in the 10 patients who underwent palliative surgery was significantly worse than survival in the patients who underwent distal pancreatectomy with celiac artery resection ($P=0.003$, log rank test)

Discussion

The long-term results of radical distal pancreatectomy with *en bloc* resection of the celiac artery, with 1- and 2-year survival rates of 51% and 14% and the median survival of 12.2 months are not satisfactory, although they are significantly better than those of palliative surgery and are similar to reported survival in less advanced tumors [1-4,6,7,18]. The fact that the majority of treatment failures were due to hepatic metastases indicates a need for more effective adjuvant therapy against hepatic metastases. However, the operation provided a high resectability rate (20/30: 67%) and was locally curative, generating clear surgical margins (R0 resection) in all patients. Consequently only one patient developed retroperitoneal recurrence, even though all patients had large tumors involving the celiac and common hepatic arteries and complained of intractable abdominal and/or back pain preoperatively, which have been considered indicators of unresectability by most centers [2,3,8]. Previous studies reported that the rates of positive microscopic margins were 32 to 64% [4,5,7] and retroperitoneal recurrence accounted for 78 to 83% [6,18] of all recurrences, despite less advanced local disease. It has been suggested that this operation may help control local spread of advanced cancer of the body of the pancreas.

Pathologic findings demonstrated that extrapancreatic perineural invasion spreads via the neural plexus around the splenic, common hepatic, and celiac arteries and extends into the celiac ganglion and around the left adrenal gland. Therefore, *en bloc* resection of these structures with distal pancreatectomy has proved invaluable to achieve retroperitoneal clearance, although actual invasion of

the arterial walls and adrenal gland is uncommon.

Despite the high morbidity rate, the absence of mortality shows that distal pancreatectomy with celiac artery resection is fairly safe. None of the 21 patients reported to have undergone this procedure so far died an operative death [4,10-13]. This outcome is likely due to absence of arterial reconstruction that might cause fatal ischemia-related complications [19] and pancreatobiliary-gastrointestinal reconstruction that might develop infective complications encountered after pancreatoduodenectomy [5]. In fact, the postoperative serum concentrations of AST and ALT increased significantly in the three patients who underwent unexpected arterial reconstruction, suggesting that arterial reconstruction should be avoided to the extent possible. Gastric ulcer, possibly of ischemic origin (unpublished data), was the most common complication in the present series, but developed only in one of the seven patients who underwent preoperative coil embolization of the common hepatic artery. The embolization has the potential to prevent ischemia-related complications.

As a secondary effect of distal pancreatectomy with celiac artery resection, patients achieved perfect relief of their preoperative intractable abdominal and/or back pain [20]. This analgesic effect probably resulted from complete resection of the celiac plexus and ganglia and has been maintained throughout follow-up. Contrary to expectations, postoperative diarrhea, an adverse effect due to complete resection of the celiac plexus and ganglia [4], was mild. Preservation of gastrointestinal continuity might have contributed to this phenomenon.

These results justify further evaluation of radical distal pancreatectomy with *en bloc* resection of the celiac artery for locally advanced cancer of the body of the pancreas. Its ability to control local disease may offer selected patients the only chance for cure, and its safety and ability to control pain may improve the quality of life. However, better strategies are necessary to improve survival. First, patient selection may need to be modified. Arnoletti et al. [21] reported that aggressive surgery, including vascular reconstruction, was appropriate only in responders to neo-adjuvant chemoradiation therapy using 5-fluorouracil, mitomycin C, and/or gemcitabine. An excellent long-term result was achieved with a 5-year survival rate of 45% and median survival of 34 months. In addition to the benefit of neo-adjuvant therapy, appropriate selection of candidates for long-term survival is critical.

In their series, approximately half the patients were excluded because hepatic metastasis or local progression had developed during neo-adjuvant therapy. Currently, genetic analysis of the tumor is identifying biologic behavior that cannot be differentiated by diagnostic imaging or pathology. Progress in this area should help refine selection criteria using small biopsy specimens.

Second, indications of this operation may be extended for advanced tumors with modest local spread. Even without involvement of the great arteries, extrapancreatic extension for pancreatic cancer often results in local recurrence after curative pancreatectomy [2,6,18]. One of the most important etiologic factors is perineural invasion in the neural plexus surrounding the great arteries [22]. The ability of this operation to eradicate retroperitoneal extension, including perineural invasion, is likely to be most advantageous in patients with modest locally advanced tumor, that is, a tumor with early extrapancreatic extension without involvement of the major intraabdominal arteries.

Third, a truly effective adjuvant therapy has to be developed to treat hepatic metastasis. The majority of existing adjuvant chemoradiation regimens have yielded disappointing results [1,7,18]. However, Nukui et al. [23] have reported a new adjuvant chemoradiation regimen that uses immunotherapy with interferon-alpha, which has produced superior results in patients who underwent pancreatoduodenectomy for adenocarcinoma of the head of the pancreas: a 2-year survival rate of 84% and median survival of >24 months, though the patients had less advanced disease (1997 UICC stage III = 76%) than those in the present study (1997 UICC stage IVA = 69%). More recently, allogeneic hematopoietic stem cell transplantation has been developed to treat not only hematologic malignancies, but also solid tumors such as renal, breast, and ovarian cancer [24,25]. The immune-mediated graft-versus-tumor effect might be therapeutic in patients with pancreatic cancer as well.

In conclusion, use of distal pancreatectomy with celiac artery resection to treat locally advanced carcinoma of the body of the pancreas is feasible in terms of safety, and offers a high resectability rate and low local recurrence rate, and provides dramatic relief of pain. Because hepatic recurrence compromises long-term survival in most patients, a combination of improved patient selection, extending indications for less advanced disease, and/or the development of effective adjuvant therapy including immunotherapy should be studied.

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Figure legends

Figure 1. A cross-sectional illustration showing the resected area in radical distal pancreatectomy with *en bloc* resection of the celiac artery. Note the celiac plexus (p) and accompanying celiac ganglia (g) are cleared completely along with the celiac axis. Dotted line: line of resection, Dotted circle: a virtual tumor, ad: adrenal gland, ao: aorta, cha: common hepatic artery, gda: gastroduodenal artery, k: kidney, pv: portal vein, s: spleen, sa: splenic artery, vc: vena cava.

Figure 2. An intraoperative photograph taken at the completion of a radical distal pancreatectomy with *en bloc* resection of the celiac artery. Arrows indicate the stumps of the celiac axis and common hepatic artery. ao: aorta, crus: crus of diaphragm, gda: gastroduodenal artery, ivg: iliac vein graft, k: left kidney, panc: stump of pancreas, rv: left renal vein, sma: superior mesenteric artery, smv: superior mesenteric vein.

Figure 3. Postoperative survival calculated by the Kaplan-Meier method for the patients with pancreatic body cancer treated with distal pancreatectomy with celiac artery resection and palliative surgery ($P=0.003$, log rank test).

Figure 1

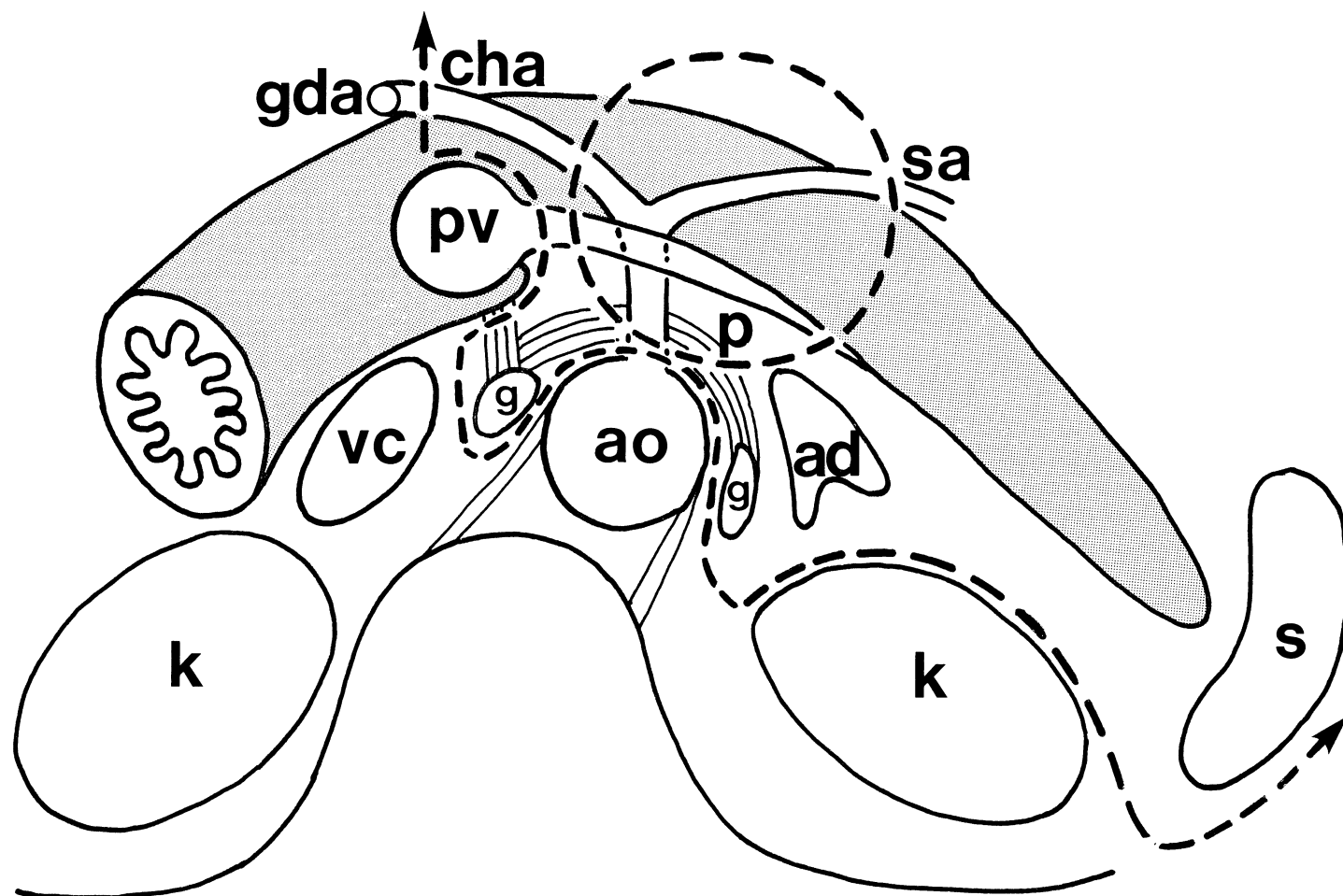


Figure 2

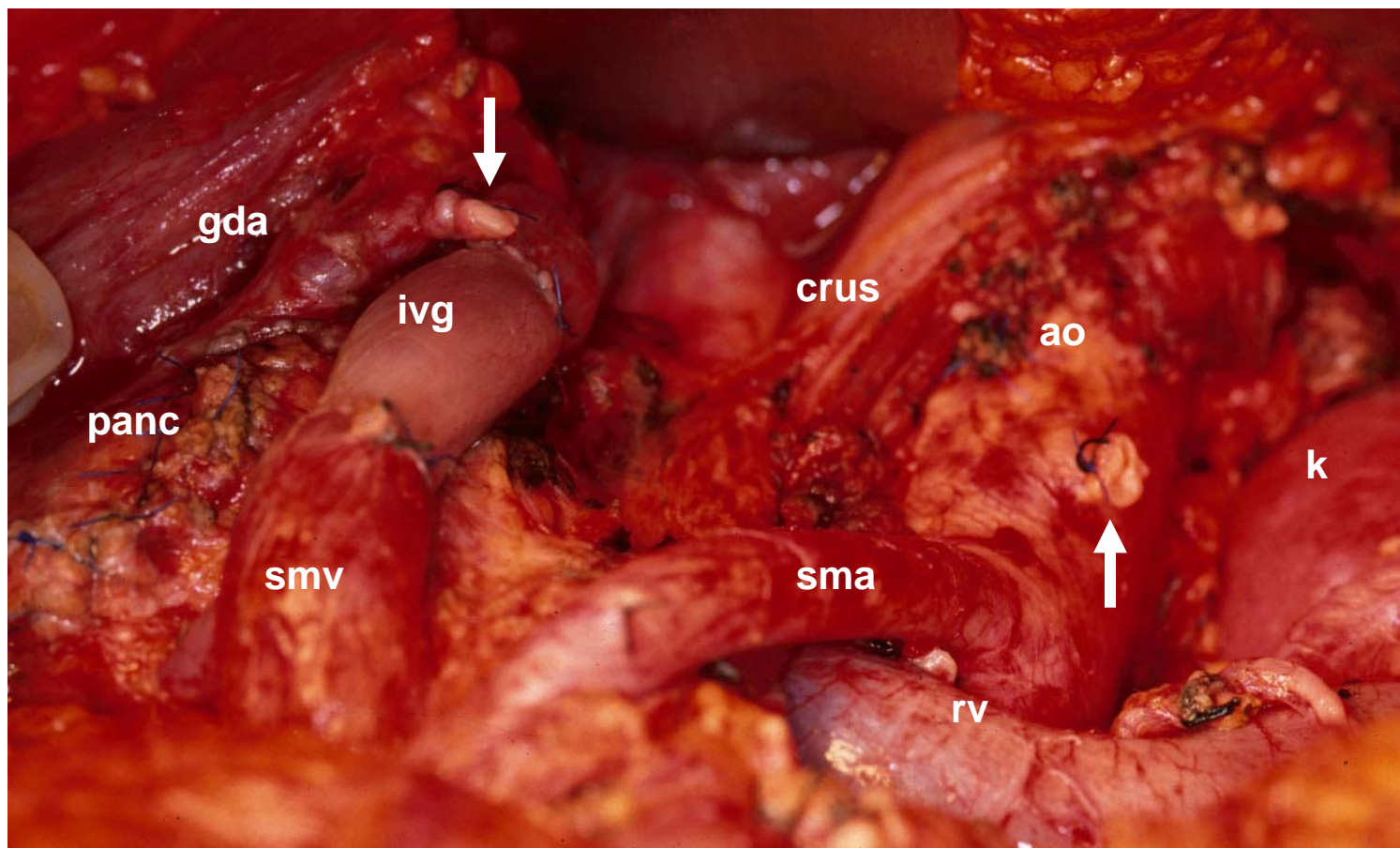


Figure 3

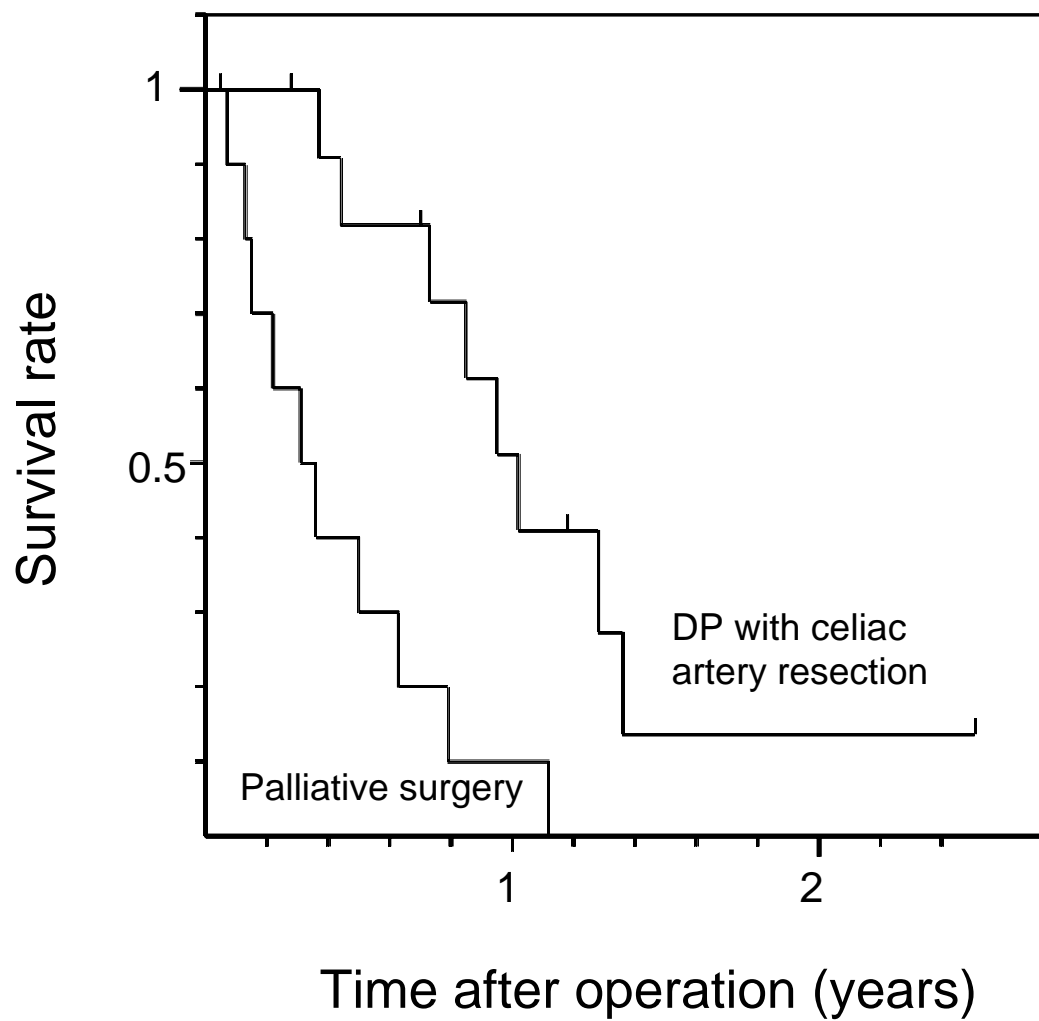


Table 1. Characteristics of patients who underwent a radical distal pancreatectomy with celiac artery resection for locally advanced cancer of the body of the pancreas.

Pt #	Age/ Gender	Tumor size (mm)	Involved and resected artery		Portal vein resection	pTNM	Residual tumor	Follow- up (mo)	Outcome
			Encased	Not encased					
1	54/F	70	CA, CHA, SA, GDA		Sleeve, grafting	T4N1M0 stageIII	R0	30	AFD
2	75/M	40		CA, CHA	Sleeve	T3N1M0 stageIIB	R0	14	AFD
3	69/F	25		SA		T3N1M0 stageIIB	R0	8	AFD
4	74/F	20		SA		T3N0M0 stageIIA	R0	3	AFD
5	60/F	75	SA	CA, CHA	Sleeve	T3N1M0 stageIIB	R0	1	AFD
6	64/M	55	SA, CA, CHA		Sleeve, grafting	T4N0M0 stageIII	R0	4	DOO
7	60/M	55	SA, CHA, LGA	GDA, PHA	Wedge	T3N1M0 stageIIB	R0	16	DOD
8	63/M	70	SA, CHA	CA	Wedge	T4N0M0 stageIII	R0	15	DOD
9	76/F	45	CA, LGA, SA	CHA	Wedge	T4N0M0 stageIII	R0	12	DOD
10	66/M	60	SA	CA		T4N1M0 stageIII	R0	11	DOD
11	71/M	65	SA	CA	Sleeve, grafting	T3N1M0 stageIIB	R0	10	DOD
12	67/M	45	SA	CA, CHA		T4N0M0 stageIII	R0	8	DOD
13	63/F	55	CHA, LGA, SA	CA	Sleeve, grafting	T4N1M1 stageIV	R0	5	DOD

This procedure usually includes distal pancreatectomy and *en bloc* resection of the celiac axis, common hepatic and left gastric arteries, the celiac plexus and ganglia, a part of the crus of the diaphragm and Gerota's fascia, the left adrenal gland, and the retroperitoneal soft tissue containing para-aortic lymph nodes.

CA: celiac axis; LGA: left gastric artery; SA: splenic artery; CHA: common hepatic artery; GDA: gastroduodenal artery; PHA: proper hepatic artery; R0: no residual tumor; DOD: died of recurrent disease; DOO: died of other cause; AFD: alive, free of disease.