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study, patients with no metastasis to the lymph nodes on the posterior aspect of the pancreas, on the anterior surface of the pancreas head, and along the superior mesenteric artery seldom had para-aortic lymph node metastasis. These lymph nodes could be considered as "junctional lymph nodes" to the para-aortic lymph nodes. This approach may establish more adequate criteria for dissection of para-aortic lymph nodes.

PATIENTS AND METHODS

Between July 1981 and June 2002, 178 patients with invasive ductal carcinoma of the head of the pancreas underwent extended radical surgery with systematic lymph node resection, including para-aortic lymph nodes, at the Department of Surgery II, Nagoya University. Patients with intraductal papillary mucinous neoplasms were excluded. These 178 patients consisted of 120 men and 58 women with a mean age of 62 years (range, 38-83 years). Ninety-eight pancreatoduodenectomies, 26 pylorus-preserving pancreatoduodenectomies, and 54 total pancreatectomies were performed. Portal vein resection was performed in 144 patients. The mean number of dissected lymph nodes was 45 (range, 2-139), and the mean number of dissected para-aortic lymph nodes was 7 (range, 0-33). All resected specimens were examined histopathologically after being fixed and stained with hematoxylin and eosin. Pathologic findings were evaluated in accordance with the second English edition of the *Classification of Pancreatic Carcinoma* proposed by the Japan Pancreas Society.[11] This classification scheme is more detailed than the TNM classification by Union Internationale Contre le Cancer.[12] Lymph nodes are classified into several lymph node stations named according to the anatomic location and numbered (Fig 1). These stations are further classified into several groups according to the distance from the pancreas. Lymph node Nos. 13 and 17 belong to group 1, Nos. 6, 8, 12, and 14 to group 2, and other lymph nodes to group 3. Para-aortic lymph nodes (No. 16) in this study refer to those that are surrounded by the celiac trunk, the inferior mesenteric artery, the right margin of the inferior vena cava, and the left margin of the abdominal aorta. Lymph nodes belonging to group 1, group 2, and para-aortic lymph nodes were all dissected completely at operation. Absence of a lymph node in resected specimens to be examined in a given station was treated as no metastasis to the station. The number of lymph nodes found in each station varied significantly among the patients.

Statistical analyses were performed with the use of StatView statistical software (SAS Institute Inc, Cary, NC).[13] The correlations between the incidence of metastases to various lymph node stations and those between para-aortic lymph node involvement and the other pathologic parameters were studied with the Fisher exact test. Survival rates, including postoperative death, were calculated by the Kaplan-Meier method. Differences in survival rates among the subjects were analyzed by the log-rank test, and a P value $< .05$ was considered significant.

RESULTS

Incidence of metastasis to each lymph node station and survival of patients with metastasis to a given station. Lymph node metastases occurred in 118 (66%) of 178 patients with carcinoma of the head of the pancreas. The incidence of metastasis to each of the lymph node stations defined by the second English edition of the *Classification of Pancreatic Carcinoma*[11] is given in Table I. The incidence was particularly high for lymph nodes at the posterior aspect of the head of the pancreas (No. 13, 47%), on the anterior surface of the head of the pancreas (No. 17, 29%), and along the superior mesenteric artery (No. 14, 28%). For para-aortic lymph nodes, metastases were detected in as many as 34 of 178 patients (19%); the incidence was the same as that of the lymph nodes along the hepatoduodenal ligament (No. 12, 19%) that belong to the group 2 lymph nodes.

One-year, 2-year, and 3-year survival rates of patients with metastatic involvement of each of the lymph node stations also are given in Table I. Survival of patients with lymph node metastasis, and those with metastases to the para-aortic nodes in particular, was significantly worse compared with those without node metastasis (Fig 2). One-year, 2-year, and 3-year overall survival rates for the patients with nodal metastases were 42%, 19%, and 12%, respectively. In comparison, 1-, 2-, and 3-year survival rates of patients with metastasis to the para-aortic nodes were inferior at 30%, 7%, and 3%, respectively. But, metastases to the para-aortic lymph nodes added little effect to the already poor survival rate observed among a subset with lymph node involvement. A histopathologic confirmation of the cancer-free margin at the dissected peripancreatic tissue has been reported to be a significant prognostic factor.[7] Also in this study, 1-, 2-, and 3-year survival rates of patients with a negative resection margin were relatively high at 61%, 33%, and 20%, respectively. In contrast, the prognosis of

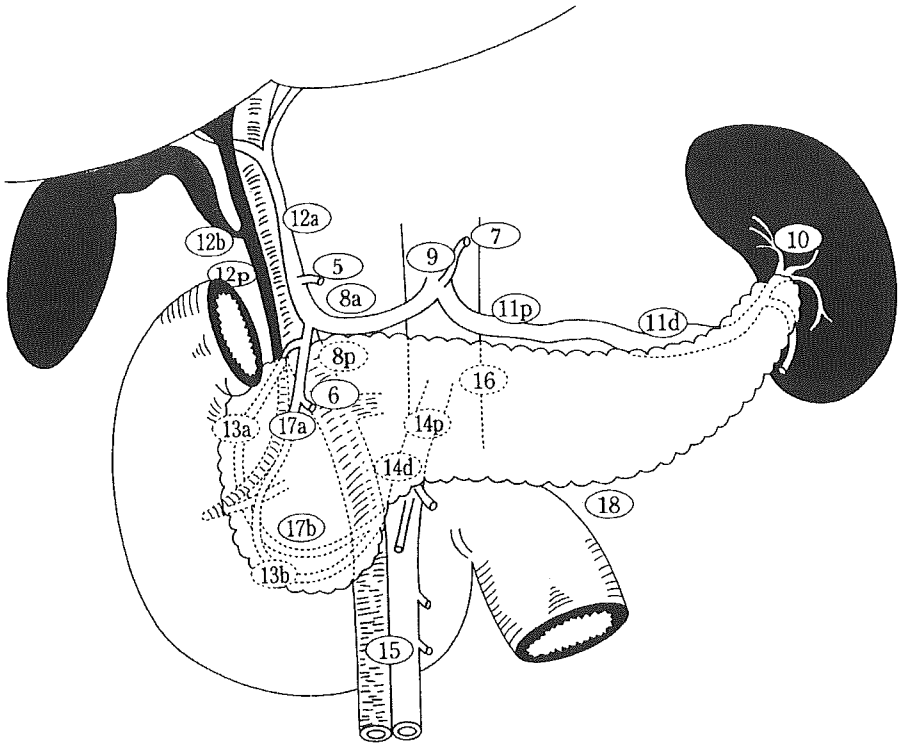

Fig 1. According to the second English edition of the *Classification of Pancreatic Carcinoma* proposed by the Japan Pancreas Society, the nomenclature of the major lymph node stations is defined as follows: *No. 5,* suprapyloric lymph nodes; *No. 6,* infrapyloric lymph nodes; *No. 7,* lymph nodes along the left gastric artery; *No. 8a,* lymph nodes in the anterosuperior group along the common hepatic artery; *No. 8p,* lymph nodes in the posterior group along the common hepatic artery; *No. 9,* lymph nodes around the celiac artery; *No. 10,* lymph nodes at the splenic hilum; *No. 11p,* lymph nodes along the proximal splenic artery; *No. 11d,* lymph nodes along the distal splenic artery; *No. 12a,* lymph nodes along the hepatic artery; *No. 12p,* lymph nodes along the portal vein; *No. 12b,* lymph nodes along the bile duct; *No. 13a,* lymph nodes on the posterior aspect of the superior portion of the head of the pancreas; *No. 13b,* lymph nodes on the posterior aspect of the inferior portion of the head of the pancreas; *No. 14p,* lymph nodes along the proximal superior mesenteric artery; *No. 14d,* lymph nodes along the distal superior mesenteric artery; *No. 15,* lymph nodes along the middle colic artery; *No. 16,* lymph nodes around the abdominal aorta; *No. 17a,* lymph nodes on the anterior surface of the superior portion of the head of the pancreas; *No. 17b,* lymph nodes on the anterior surface of the inferior portion of the head of the pancreas; and *No. 18,* lymph nodes along the inferior margin of the pancreas.

patients with a positive margin was extremely poor, with 1-, 2-, and 3-year survival rates of 13%, 2%, and 2%, respectively. Rather surprisingly, 1-, 2-, and 3-year survival rates of 16 patients with metastases to the para-aortic lymph nodes among a subset of patients with negative dissected margin were relatively high at 39%, 16%, and 8%, respectively. Nevertheless, the prognosis of 18 patients with para-aortic lymph nodes metastasis and positive dissected margin was poor, with 1-year and 2-year survival rates of 22% and 0%, respectively.

Correlation between metastases to lymph node stations and those to para-aortic nodes. We determined the correlation between metastases to each lymph node station as defined by the Classification of Pancreatic Carcinoma.[11] Strong correlations (P values < .0004) were observed between metastasis to lymph node Nos. 13 and 17, Nos. 12 and 16, Nos. 16 and 17, Nos. 13 and 16, and Nos. 12 and 13. Metastasis to the para-aortic lymph node had strong correlations with metastases to lymph nodes Nos. 12, 13, 14, and 17 (P values < .001).

Distribution of metastases to other stations among patients with para-aortic lymph node involvement. We determined distribution patterns of metastatic lymph nodes among the subset of 34 patients with metastases to the para-aortic lymph nodes. Of these, 7 had involvement with only 1 other lymph node station. Of the 7 patients, 3 had metastasis to station No. 13, 3 patients to No. 14 lymph node, and the remaining 1 to No. 17 lymph node. Only 4 of the 34 patients had

Table I. Frequency of each lymph node metastasis and survival rates

Lymph node station	*Frequency of metastasis (n = 178)*	*Survival rates of patients with lymph node involvement (%)*		
		1-year	*2-year*	*3-year*
6	21 (12%)	20	0	0
7	0	—	—	—
8	17 (10%)	29	6	0
9	2 (1%)	50	0	0
10	0	—	—	—
11	14 (8%)	29	7	7
12	33 (19%)	39	0	0
13	83 (47%)	34	14	7
14	50 (28%)	34	5	2
15	2 (1%)	50	50	0
16	34 (19%)	30	7	3
17	51 (29%)	29	12	6
18	3 (2%)	33	0	0
No involvement	60 (34%)	57	32	23

neither No. 13 nor No. 14 node involvement, indicating the significance of these nodes as predictive factors of metastases to the para-aortic lymph nodes. Metastases to No. 12 lymph node stations also had a strong correlation with involvement of the para-aortic lymph node, but all patients with involvement of stations Nos. 12 and 16 also had metastasis to either No. 13 or No. 17. Only 2 patients had metastasis to the para-aortic region with no other lymph nodes involved.

Finally, Table II shows the incidences of para-aortic lymph node involvement among the patients with or without metastasis to lymph node station Nos. 12, 13, 14, or 17. Patients with metastases to any of station Nos. 12, 13, 14, and 17 had a high risk of metastases to the para-aortic lymph nodes. Conversely, the incidence was very low at 5% for a subset of patients who had no metastasis to station Nos. 13 and 14, and 3% for those who had no metastasis to station Nos. 13, 14, and 17.

Correlation between para-aortic lymph node involvement and other macroscopic pathologic parameters. We next analyzed the correlation between para-aortic lymph node involvement and other macroscopic findings as defined by the Classification of Pancreatic Carcinoma of the Japan Pancreas Society.[11] These findings included tumor diameter, serosal invasion, retropancreatic tissue invasion, distal bile duct invasion, duodenal invasion, and portal venous system invasion. Macroscopic invasion of the distal bile duct and tumor diameter had a significant correlation with para-aortic lymph node involvement (P value < .05).

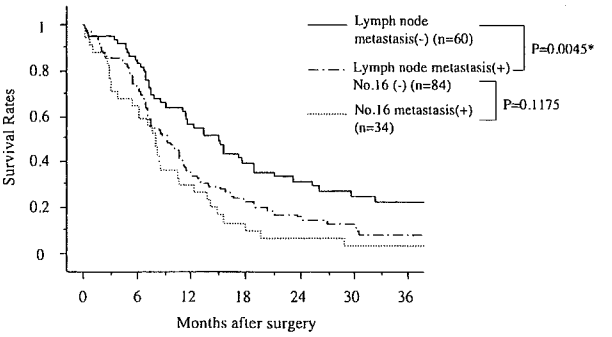

Fig 2. Survival rates of the patients with or without No. 16 lymph node metastasis. Prognosis of the patients with any lymph node metastasis was significantly inferior. No significant difference in the survival rates of the patients with or without para-aortic lymph node involvement was found among patients who had lymph node involvement.

Table II. Rates of para-aortic lymph node involvement

	n	*Rates of metastasis to para-aortic lymph node (%)*
LN12		
metastasis(+)	33	46
metastasis(−)	145	13
LN13		
metastasis(+)	83	31
metastasis(−)	95	8
LN14		
metastasis(+)	50	36
metastasis(−)	128	13
LN17		
metastasis(+)	51	41
metastasis(−)	127	10
LN13 and LN14		
metastasis(−)	79	5
LN13, LN14, and LN17		
metastasis(−)	70	3

DISCUSSION

Since Fortner[14] advocated an extended radical surgical procedure for pancreatic head cancer in 1973, we have performed extended radical surgery with wide dissection of lymph nodes, including the para-aortic lymph nodes, to improve the prognosis of patients with this disease.[3,7-9] In the current study, 118 of 178 patients had lymph node involvement, and 34 patients had para-aortic node metastasis. The mean number of lymph nodes retrieved was 45, including 7 para-aortic nodes for each patient. Despite these efforts, the prognosis of our patients did not surpass that of those treated with more limited lymphadenectomy,[2] pointing to the fact that extended lymphadenectomy has little

survival benefit for patients with pancreatic head cancer. These findings and experience with other cancer types[15,16] suggest that the indication for extended lymphadenectomy should be reconsidered seriously.

In this study, as indicated by several other reporters from Japanese institutions,[4-6] the incidences of metastasis exceeded 10% in lymph node station Nos. 12, 13, 14, 16, and 17. These lymph nodes belong either to group 1 or 2 according to the *Classification of Pancreatic Carcinoma* of the Japan Pancreas Society,[11] with the exception of para-aortic nodes (No. 16). Resection of the lymph node stations belonging to groups 1 and 2 has been recommended as a standard procedure in Japan, whereas the indication of extensive resection of No. 16 has been a matter of controversy. We therefore examined in detail various patterns of lymphatic spread in a group of patients with cancer of the pancreatic head to readjust the indication for extended lymphadenectomy that includes the para-aortic nodes.

A number of reports[5,17,18] referred to the lymphatic flow to the para-aortic lymph node. Nagakawa et al,[17] for example, injected activated carbon particles or ^{111}In colloid in their patients with pancreatic cancer to investigate the lymphatic spread from the head of the pancreas to the para-aortic lymph node and concluded that the main lymphatic route to the para-aortic lymph node was through the nodes in the posterior part of the head of the pancreas (No. 13) and around the superior mesenteric artery (No. 14). Nagai[18] found that dye injected into the posterior region of the pancreas head drained toward the right or posterior side of the superior mesenteric artery and finally to the para-aortic lymph nodes. In addition, Kayahara et al[5] indicated that the main lymphatic pathway from the head of the pancreas to the para-aortic lymph nodes was via the No. 14 lymph nodes, which harbored metastasis in all 7 patients with para-aortic lymph node involvement in their series. Together with these reports, our study also supports the hypothesis that the lymphatic pathways from the primary to the para-aortic lymph nodes were via station No. 13 or 14. So-called skip metastasis, which in this case denotes metastases to the para-aortic nodes without detectable metastases to either station No. 13, 14, or 17, was observed in only 2 of 178 patients, amounting to less than 3% of the current series. We therefore advocate that lymph nodes belonging to station Nos. 13, 14, and 17 are "junctional lymph nodes." This indicates that if no metastases to these lymph nodes are detected by surgical exploration or intraoperative pathologic examination, metastasis to para-aortic lymph nodes can be considered unlikely.

It has not been possible to define the metastatic pathway for the 2 patients with skip metastases to the para-aortic nodes within the scope of this study, but we cannot deny the possibility that microscopic metastases that are undetectable with routine histopathologic examination may have existed in the nodes that belong to station Nos. 13, 14, or 17 from which the metastases to para-aortic nodes may have occurred. This brings us to another unresolved problem of micrometastasis. It is well known that highly sensitive detection methods such as immunostaining or polymerase chain reaction-based assays have detected micrometastases in the lymph nodes that had been diagnosed as cancer negative by routine pathologic examination. Such phenomena have been reported in pancreatic cancer[19-21] as well as in several other cancer types. Niedergethmann et al[21] found through multivariate analysis that the presence of micrometastases to the para-aortic lymph nodes diagnosed through detection of K-ras mutation was an independent prognostic factor. This finding suggests that para-aortic lymphadenectomy might be indicated even in the absence of definite metastasis to the para-aortic nodes. However, other reports[22] argue against the prognostic impact of micrometastases, and the true benefit of dissecting micrometastases through extended lymphadenectomy remains an issue for future investigation.

According to our analysis of the correlation between para-aortic lymph node involvement and several macroscopic parameters, no patient without distal bile duct invasion or with a tumor diameter of less than 2 cm had para-aortic lymph node involvement. Since these parameters can be evaluated before or during operation, it may also be useful to incorporate these factors into the decision making with regard to dissection of the para-aortic lymph nodes. The correlation between tumor diameter and incidence of metastases to the para-aortic lymph nodes remains controversial, however, given the contradictory report from Nagakawa et al.[17]

CONCLUSION

The lymph nodes that predict metastases to the para-aortic lymph node in pancreatic head cancer were considered to be those on the posterior aspect of the head of the pancreas, on the anterior surface of the head of the pancreas, and along the superior mesenteric artery. In patients with no metastasis to these lymph nodes, the risk of

para-aortic lymph node metastasis is considered highly unlikely.

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Analysis of long-term survivors after surgical resection for invasive pancreatic cancer

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Abstract

Pancreatic cancer remains a lethal disease. Although there are many reports on the survival rates of pancreatic cancer patients after surgical resection, the clinicopathological characteristics that influence long-term survival over 5 years remain controversial. Here, we clarify the favourable prognostic factors for long-term survival. One hundred and eighty-two patients with pancreatic cancer underwent surgical resections from 1981 to 1997 in our department. Among them, eight patients survived for at least 5 years after the surgery. The clinicopathological characteristics of the eight long-term survivors who underwent radical resections were studied retrospectively. R0 surgical resections, including five combined with portal vein resections (62.5%), were achieved in these eight patients. Negative invasions of the major regional artery (seven of eight, 87.5%) and to the extrapancreatic nerve plexus (seven of eight, 87.5%), and N0 or N1 lymph node metastasis (7 of 8, 87.5%) were detected as clinicopathological features of long-term survivors in our study. No exposure of carcinoma at the dissected surface and cut end (seven of eight, 87.5%) was characteristically confirmed by pathology. Portal vein invasion was seen in three of the eight patients (37.5%). For long-term survival in cases of pancreatic cancer, complete R0 resections should be performed and negative invasions in the major regional arteries and to the extrapancreatic plexus of the nerve were necessary. No invasion to the portal vein was not necessarily required if R0 was achieved by combined resection of the portal vein.

Key Words: *Pancreatic cancer, long-term survival, clinicopathological factors*

Introduction

Today, pancreatic cancer remains a highly lethal disease, and not many patients are able to live for more than 5 years after pancreatic resection. Recently, new technologies (computed tomography, ultrasonography, digital subtraction angiography, etc.) have enabled us to detect the degree of tumour invasions more accurately and to determine operability more easily [1–3]. In addition, recent improvements in surgical technologies have enabled us to better perform extended radical resections in selected cases. However, there are some scientists who maintain that the surgery is not beneficial to patients in the advanced stage of disease [4]. In our department, we have successfully and safely performed pancreatectomies combined with portal vein resections using antithrombogenic catheters for bypasses of the portal veins [5,6]. Apparent superior mesenteric arterial invasions and/or complete encasements of the portal vein were not detected during resections in the portal veins [7].

Many authors have reported prognostic factors that affect the long-term survival of pancreatic cancer patients based on macroscopic and histological findings and surgical factors [8–30]. However, most of these authors regarded 3-year survivors as long-term survivors because the prognosis of pancreatic cancer is usually very poor. In actuality, many patients who live for over 3 years after surgery still have recurrent disease.

The aim of this study was to clarify the favourable prognostic factors for long-term survival after curative resection by studying the clinical data of several patients who have survived after surgery for over 5 years, and investigating the criteria for patient selection for radical surgery. The clinicopathological factors of long-term survivors were thoroughly evaluated, and the important factors contributing to long-term survival were also investigated.

Methods

Patients

One hundred and eighty-two patients with pancreatic cancer underwent surgical resections in our department from 1981 to 1997. All the patients' medical records were retrospectively reviewed. After excluding

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the patients with intraductal papillary mucinous neoplasms (IPMNs), the long-term survivors who lived for > 5 years after the surgery were studied on the bases of surgical factors and clinicopathological findings. These were used to identify the factors that seemed to contribute to their long-term survival.

Surgical factors

Following the general rules of the Japan Pancreas Society [30], the tumour location; tumour size (TS); invasion to adjacent structures, e.g. common bile duct (CH); duodenum (DU); pancreatic serosa (S); retroperitoneum (RP); portal vein (PV); major regional artery, including the common hepatic artery, the superior mesenteric artery, the splenic artery, and the coeliac artery (A); and extrapancreatic nerve plexus (PL) were all examined. Tumour nodal metastasis (TNM) staging is determined by operative findings. The T factor is defined as follows: T1, tumour size 2 cm and the tumour is limited to the pancreas; T2, tumour size > 2 cm and the tumour is limited to the pancreas; T3, tumour is extended into CH, DU, S, or RP; and T4, the tumour is extended into PV, A, PL, or other organs. As for the severity of lymph node metastasis, N0 indicates no nodal metastasis, N1 indicates positive metastasis in the region of the tumour, N2 indicates positive metastasis in an extensive region around the N1 region, and the positive N3 node means systemic disease and is equal to M1. The degree of radicality, including the combined resection of adjacent structures, was also studied.

Pathological factors

Microscopic findings, such as the histological grade, invasion of the lymphatic duct (LY) and vessels (V), and perineural invasion (NE) were studied. In order to compare them with the operative findings, we also pathologically examined the nodal status and local invasions of adjacent structures, followed by the bile duct (CH), duodenum (DU), pancreatic serosa (S), retroperitoneum (RP), portal vein (PV), major regional artery (A), and plexus of the nerve (PL). These were studied together with the exposure of carcinoma on the pancreatic cut end margin (PCM), the cut edge of the bile duct (BCM), and the dissected peripancreatic tissue margin (DPM). The term LY0 is used to indicate that no invasion was microscopically detected in the lymphatic duct around the tumour; LY1 indicates mild invasion, LY2 indicates moderate invasion, and LY3 indicates severe invasion. The factors V and NE are also classified by the degree of invasion from V0 to V3 and from NE0 to NE3, respectively, like the factor LY. Final TNM staging and curability were determined by all of the pathological findings following the general rules for the study of pancreatic cancer, which were set by the Japan Pancreas Society [30].

Table I. Characteristics of patients.

Patient no.	Age/ sex	Survival period (years)	Outcome	Tumour site	Adjuvant therapy	Operation
1	64/M	9.5	Dead	Head	None	PD
2	68/F	8	Dead	Body	IR+FU	PD
3	46/M	5	Dead	Head, body	None	PD
4	62/M	8.9	Dead	Head	FU	PD
5	54/M	5	Dead	Head	IR+FU	PPPD
6	62/M	5.3	Alive	Head	IR+FU	PPPD
7	51/F	5	Alive	Head	None	PPPD
8	60/M	5	Alive	Head	IR+FU	PD

M, male; F, female; None, adjuvant therapy not given; PD, pancreatoduodenectomy; PPPD, pylorus-preserving pancreatoduodenectomy; IR, irradiation; FU, 5-fluorouracil administration.

Adjuvant therapy

In this study, we confirmed whether or not some adjuvant therapies, such as intraoperative radiotherapy (IORT) of 30 Gy using a linear accelerator (Linac) and/or intraportal administration of 5-fluorouracil (5-FU), were used.

Results

Twelve of the 182 pancreatic cancer patients (6.6%) survived for > 5 years after surgical resection. There were 4 IPMN patients among the 12, and they were excluded from our study. The characteristics of the remaining eight patients with invasive pancreatic cancer are shown in Table I.

There were six males and two females among the eight patients, and their mean age was 58.3 years at the time of operation (range 46–68); their mean survival period was 6.4 years after the surgery (range 5–9.5). Three of the eight patients survived without recurrence into the year 2002, three died from the recurrent disease, and two succumbed to another disease. Tumour sites were located on the pancreatic head in seven cases, and in the body in one case. Among the eight patients, one underwent a distal pancreatectomy, four received pancreatoduodenectomies (PD), and three had pylorus-preserving pancreatoduodenectomies (PPPD). Five pancreatic head cancer patients underwent combined resections of the PV, which were successfully performed without residual cancer. All eight patients underwent regional lymph node dissections that included the para-aortic region.

We performed radical resections including wide dissections of the regional lymph nodes, retroperitoneal tissues and extrapancreatic nerve plexuses for those with advanced pancreatic cancer. All eight patients macroscopically underwent *en bloc* resections without cancer exposure at the sites of the cut ends and dissected edges. The pancreatic cut end margin (PCM factor), bile duct cut end margin (BCM factor), and dissected peripancreatic tissue margin (DPM factor)

Table II. Surgical factors.

Patient no.	TS	CH	DU	S	RP	PV	A	PL	T	N	JPS stage	UICC stage	PCM BCM DPM	Combined resection
1	2	–	–	–	+	–	–	–	3	1	III	III	–	–
2	2	–	–	+	–	–	–	–	3	0	III	II	–	–
3	3	+	+	+	+	+	–	–	4	2	IVb	IV A	–	Portal vein
4	2	+	+	+	+	+	–	–	4	0	IVa	IV A	–	Portal vein
5	2	+	–	–	+	+	+	+	4	0	IVa	IV A	–	Portal vein
6	1	+	–	–	–	+	–	–	3	0	III	II	–	Portal vein
7	1	+	–	–	–	–	–	–	3	0	III	II	–	–
8	3	–	+	+	+	+	–	–	4	1	IVa	IV A	–	Portal vein

CH, choleduct; DU, duodenum; S, serosa; RP, retroperitoneum; PV, portal vein; A, major regional artery; PL, peripancreatic nerve plexus; PCM, pancreatic cut end margin; BCM, bile duct end margin; DPM, dissected peripancreatic tissue margin. The JPS stage is the TNM stage determined by the Japan Pancreas Society. The UICC stage is the TNM stage determined by UICC.

were found to be macroscopically negative for all eight patients and were microscopically proven as cancer-negative for seven of eight patients.

The operative findings are listed in Table II. The tumour size (TS) factors are classified into four degrees. TS1 means a tumour size within 2.0 cm, TS2 means that it is between 2.0 cm and 4.0 cm, TS3 means that it is between 4.0 cm and 6.0 cm, and TS4 means that it is larger than 6.0 cm. These eight patients were macroscopically classified as follows: TS1, 25%; TS2, 50%; TS3, 25%; and TS4, 0%.

Five patients (62.5%) were observed with invasion to the intrapancreatic bile duct (positive CH factor), three (37.5%) with invasion to the duodenum (positive DU factor), four (50%) with invasion to the pancreatic serosa (positive S factor), four (50%) with invasion to the retroperitoneum (positive RP factor), five (62.5%) with invasion to the portal vein (positive PV factor), and one (12.5%) with invasion to a major regional artery at the splenic artery, as well as the extra-pancreatic nerve plexus (positive PL factor). The severity of lymph node metastases in the eight cases was: N0, five cases (62.5%); N1, two cases (25%); and N2, one case (12.5%).

The surgical T factors of TNM classification were found as follows: T1, no cases (0%); T2, no cases (0%); T3, four cases (50%); and T4, four cases (50%). The surgical stages of the eight patients were: stage I, no cases (0%); II, no cases (0%); III, four cases (50%); and IV, four cases (50%). All five patients with suspected PV invasion underwent combined resections of the PV. PCM, BCM, and DPM were concluded to be surgically negative in all eight cases (100%).

The pathological findings are shown in Table III. Invasive cancer was detected in all eight cases (100%). The histological types of the tumours were as follows: well differentiated tubular carcinoma was detected in one case (12.5%), moderately differentiated tubular adenocarcinoma in six cases (75%), and mucinous carcinoma in one case (12.5%). The pathological factors of the DU, A, PL, BCM and PCM were consistent with the macroscopic findings. The CH, PV, S and RP factors were not consistent with the surgical diagnoses in one case (no. 7), two cases (nos 4 and. 8), two cases (nos 2 and 8) and two cases (nos 1 and 8), respectively. The DPM was also not consistent with the macroscopic diagnosis in one case (no. 5). The factors of LY and NE were confirmed as follows: LY0,

Table III. Pathological findings.

Patient no.	Histology	CH	DU	S	RP	PV	A	PL	pT	pN	JPS f-stage	UICC f-stage	LY	V	NE	PCM BCM DCM	pR
1	Muc	–	–	–	+	–	–	–	3	1	III	III	2	0	0	–	0
2	Tub mod	–	–	–	–	–	–	–	1	0	I	I	1	1	2	–	0
3	Tub mod	+	+	+	+	+	–	–	4	2	IVb	IV A	3	1	2	–	0
4	Tub mod	+	+	+	+	+	–	–	4	0	IVa	IV A	1	1	1	–	0
5	Tub mod	+	–	–	+	+	+	+	4	0	IVa	IV A	1	0	3	+	1
6	Tub mod	+	–	–	–	–	–	–	3	0	III	II	1	0	1	–	0
7	Tub well	–	–	–	–	–	–	–	1	0	I	I	0	0	3	–	0
8	Tub mod	–	+	–	–	–	–	–	3	1	III	III	1	1	1	–	0

Muc, mucinous carcinoma; Tub mod, tubular adenocarcinoma, moderately differentiated type; Tub well, tubular adenocarcinoma, well differentiated type; CH, choleduct; DU, duodenum; S, serosa; RP, retroperitoneum; PV, portal vein; A, major regional artery; PL, peripancreatic nerve plexus; PCM, pancreatic cut end margin; BCM, bile duct end margin; DPM, dissected peripancreatic tissue margin; R, residual tumour; P, pathological diagnosis; F, final diagnosis. The JPS f-stage is the final confirmed TNM stage determined by the Japan Pancreas Society. The UICC f-stage is the TNM stage determined by UICC.

12.5%; LY1, 62.5%; LY2, 12.5%; LY3, 12.5%; NE0 12.5%; NE1, 37.5%; NE2, 25%; and NE3, 25%. Regarding the V factor, all cases were distinctively categorized within V0 (50%) and V1 (50%), whereas V2 and V3 were both 0%. The final confirmed T factors were: T1 in two cases (25%), T2 in no cases (0%), T3 in three cases (37.5%), and T4 in three cases (37.5%). Final staging confirmed by the pathological findings was as follows: stage I, two cases (25%); II, no cases (0%); III, three cases (37.5%); and IV, three cases (37.5%).

Adjuvant therapy of intraportal 5-FU infusion was given in one case (no. 4). Combined therapies consisting of intraoperative irradiation using Linac and intraportal 5-FU infusion chemotherapy were performed in the four cases (nos 2, 5, 6 and 8) who underwent radical resection. R0 was achieved in all five cases.

Discussion

Many authors have used the statistical analysis method to discuss the prognostic factors that influenced long-term survival after surgical resection for pancreatic cancer [8–30]. They presented us with several beneficial factors, as follows: radical resection *en bloc* without residual cancer [12,16], a smaller tumour size [13,17,25], an operator or institutional factor [19], a histological differentiation [25,26], no frontal invasion of the pancreatic capsule, no retroperitoneal invasion [27], negative resection margins [27–29], a negative lymph node, a positive lymph node within the limited nodal status [8–10,17,18,22–25,27,30], negative invasion of blood vessels [24], negative perineural invasion [8,11,22], and the tumour location [12,17]. However, most authors regarded patients who survived for >3 years as long-term survivors, and only a few studied and evaluated these prognostic factors in patients who survived for >5 years.

Based on our study, four of these factors were considered important for long-term survival. They are: 1) resection without residual cancer; 2) no lymph node metastasis, or if present, limited within the N1 level; 3) no invasion of major regional arteries, including the superior mesenteric artery, common hepatic artery, splenic artery, and coeliac artery; and 4) no invasion of the extrapancreatic nerve plexus. As for the portal vein, Nakao et al. reported that if it is invaded, and if R0 resection is completed by portal vein resection, the survival rate is still more favourable than in the case of negative portal invasion with positive margin invasion [28]. In the eight patients that we studied, portal invasion was histologically confirmed in three (37.5%), and the percentage was surprisingly high.

There is no validity in the argument that the true curative resection is the R0 resection, and that R0 resection is identified as a valuable factor for long-term survival [28]. To achieve R0 resection, we usually perform a radical resection with the dissection of the regional lymph node and the retropancreatic tissue, including the extrapancreatic nerve plexus for invasive pancreatic cancer. For intraoperative diagnosis of the portal vein and PL invasion, intraportal endovascular ultrasonography (IPEUS) is helpful [2,32]. Portal vein resection is important in obtaining a carcinoma-free surgical margin in pancreatic cancer surgery [7]. If such a surgical margin cannot be obtained by extensive surgery, there is no indication for surgical resection in patients with pancreatic carcinoma.

Authors of some reports have claimed that stage III pancreatic cancer defined by the UICC rules should not be resected if neoadjuvant therapy is not effective [4]. However, we do not agree with this opinion, because in our study, five of the eight cases were classified as stages III or IV according to the UICC rules. The difference of these two opinions may be because of the difference in the extent of resection that could be performed safely.

If the extent of lymph node dissection is insufficient, we may misdiagnose cancer invasion. Therefore, it is not easy to predict long-term survival by TNM staging alone. Furthermore, as demonstrated in this study, a diagnostic discrepancy between macroscopic and microscopic findings may occur, so it is important to investigate the resected specimen carefully to correctly determine the final staging and whether or not R0 resection has been achieved. As the advanced stage in TNM classification was seen in most of our eight long-term survivors, consideration of those surgical and pathological factors, as well as TNM staging, is necessary to understand the tumour characteristics and to predict the prognosis. In general, there are many local factors as regards how the cancer invades around the pancreas. From the surgical standpoint, A0, PL(–), and R0 (DPM, PCM, BCM) were important factors affecting long-term survival. Furthermore, it was suggested that portal vein invasion does not exclude operative indication. T3 and T4 of the TNM classification were identified in 100% of the eight patients on surgical findings and 75% on pathology.

In the inconsistency between surgical and pathological diagnoses, a discrepancy seen in the CH factor in one case (no. 7) might be because of the existence of pancreatitis around the tumour. In five of the eight patients who underwent portal vein resections, portal invasion was pathologically positive only in three cases (nos 3, 4 and 5). This may have been caused by misdiagnosis due to compression of the portal vein, possibly because of a large tumour or accompanying pancreatitis. IPEUS can accurately differentiate between compression and a subtle portal venous invasion and reduce this discrepancy [3]. However, portal vein resection was considered to be necessary to obtain cancer-free margins in those cases.

Some authors have explained the benefits of using adjuvant therapies, including chemotherapy and radiotherapy [18,34,35]. As already shown, we also consider radiotherapy to be an effective method to control the pain caused by the infiltration of carcinoma into the

extrapancreatic nerve plexus [36,37]. However, irradiation does not improve the prognosis. We employed intraoperative combined adjuvant therapies consisting of radiation and 5-FU chemotherapy in four of the eight patients. However, the true feasibility of adjuvant therapy for long-term survival was not clarified in this study. Protocols evaluating the efficacy of Gemcitabine (difluorodeoxycytidine; dFdC), a new chemotherapeutic agent for pancreatic cancer, are now underway in randomized controlled trials.

From this study, we conclude that in order to achieve a long-term survival goal, it is important to perform a complete R0 resection. When portal vein invasion is suspected without invasion to the major regional arteries and distant metastasis at the time of operation, a pancreatectomy with combined resection of the portal vein is to be performed to achieve a curative resection. Moreover, if PL(−), DPM, PCM and BCM(−) are microscopically confirmed in the resected specimen, a favourable outcome can be expected after the surgery.

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Transhepatic Portal Venous Angioplasty with Stenting for Bleeding Jejunal Varices

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SUMMARY
A 54-year-old woman, who had undergone pancreatoduodenectomy with resection of the portal vein and intraoperative radiation therapy for cancer of the lower bile duct 16 months before, visited our institution complaining of melena. To identify the cause of bleeding and severe anemia, we performed gastrointestinal endoscopy but could detect no obvious source. The portal phase of the superior mesenteric arteriography and percutaneous transhepatic portography revealed severe stenosis of the extrahepatic portal vein, which corresponded to the end-to-end anastomosis of the portal vein, and hepatofugal collaterals. Extravasations into the afferent loop of the jejunum were detected only with portography. These findings suggested that portal hypertension due to extrahepatic portal obstruction led to bleeding varices. Subsequent to percutaneous transhepatic portography, we dilated the stenosis of the extrahepatic portal vein using a balloon catheter and placed an expandable metallic stent there. Portography after the treatment revealed the disappearance of the hepatofugal flow to collaterals and extravasations, and the patient has had no further episodes of gastrointestinal bleeding since. In conclusion, for patients with bleeding varices due to extrahepatic portal obstruction, especially after abdominal surgery, percutaneous transhepatic angioplasty is considered to be the treatment of choice because of its efficiency and minimal invasiveness.

KEY WORDS:
Percutaneous transhepatic angioplasty; Portal vein stenosis; Bleeding varices; Expandable metallic stent

INTRODUCTION

Esophageal and gastric varices caused by portal hypertension occur frequently in patients with liver cirrhosis. Most of such varices can be controlled with endoscopic treatments such as endoscopic variceal ligation and endoscopic injection sclerotherapy. However, in patients with portal hypertension who have undergone previous abdominal surgery, varices sometimes occur at unpredictable sites through the adhesion of tissue (1-3). In such cases it is not uncommon to have difficulty identifying the bleeding point and controlling bleeding (3). We report herein a case of successful percutaneous transhepatic angioplasty for bleeding from jejunal varices of the afferent loop, caused by extrahepatic portal obstruction after pancreatoduodenectomy with the resection and reconstruction of the portal vein.

CASE REPORT

A 54-year-old woman visited our institution complaining of melena. She had undergone pancreatoduodenectomy with resection of the portal vein and intraoperative radiation therapy for cancer of the lower bile duct 16 months before. The alimentary tract was reconstructed according to Child's method, and the portal vein was reconstructed by end-to-end anastomosis. After surgery the patient was followed at our institution, and we detected no sign of recurrence.

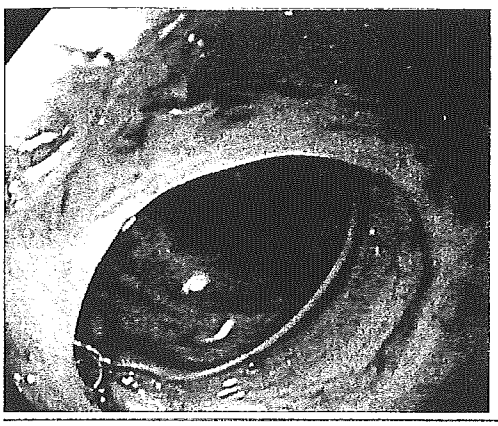

FIGURE 1
Gastrointestinal endoscopy revealed telangiectasia in the jejunal mucosa around the choledocho-jejunostomy.

On admission, a laboratory examination showed severe anemia with a hemoglobin level of 5.6g/dL and hematocrit of 17.4%. To determine the cause of melena, we performed gastrointestinal endoscopy. The examination revealed telangiectasia in the jejunal mucosa around the choledochojejunostomy (**Figure 1**), but we could not detect an obvious bleeding point. Colonoscopy and scintigraphy revealed no abnormal findings. Next we performed abdominal angiography.

Hepato-Gastroenterology 2005; 52:749-752

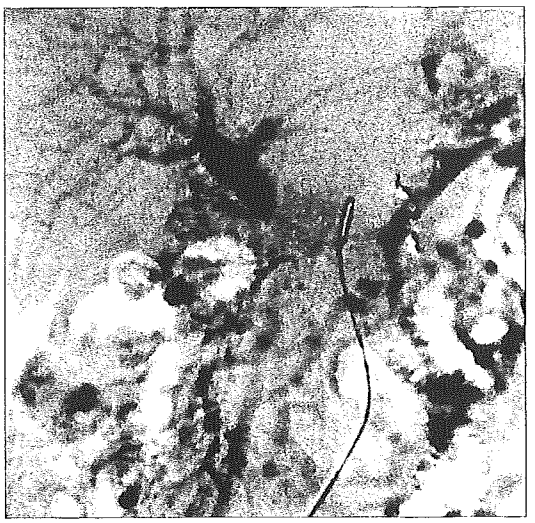

FIGURE 2
The portal phase of superior mesenteric arteriography revealed stenosis of the extrahepatic portal vein, which corresponded to the end-to-end anastomosis of the portal vein, and expanded collaterals of the portal system. The proximal portion of the splenic vein was resected in a previous surgery.

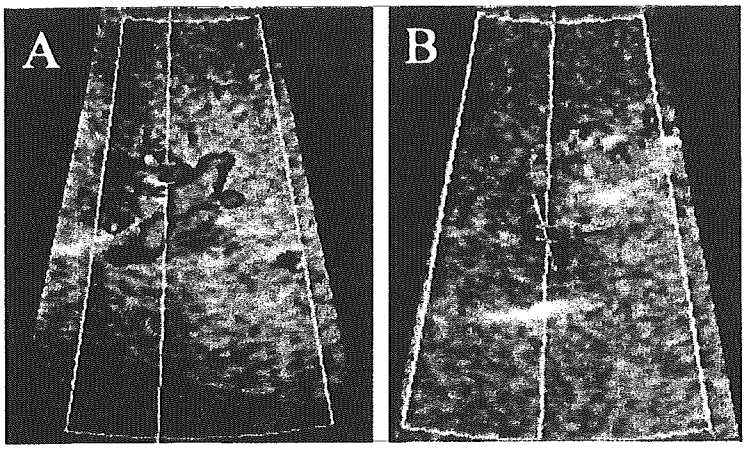

FIGURE 3 Doppler ultrasonography. Before the treatment, the portal flow in the umbilical portion was hepatofugal **(A)**. After the treatment, the portal flow in the umbilical portion changed to hepatopetal **(B)**.

The portal phase of the superior mesenteric arteriography revealed stenosis of the extrahepatic portal vein, which corresponded to the end-to-end anastomosis of the portal vein. This examination also revealed expanded collateral veins of the portal system but extravasations could not be detected **(Figure 2)**. In addition, Doppler ultrasonography revealed that the portal flow in the right branch was hepatopetal, but that in the umbilical portion was hepatofugal **(Figure 3A)**. These findings suggested portal hypertension due to extrahepatic portal obstruction, and that the flow to the intrahepatic portal vein was mainly through collateral veins. We thought that the bleeding varices were caused by portal hypertension and the clearing of the extrahepatic portal obstruction might prevent gastrointestinal bleeding. We therefore performed percutaneous transhepatic portography.

Ultrasonographic-guided puncture of the right anterior branch of the portal vein was performed through a percutaneous transhepatic approach and a 7-French sheath was placed into the intrahepatic portal vein. Then a 6-French catheter was introduced into the extrahepatic portal vein through the end-to-end anastomosis using a guidewire, and portography was performed. It revealed severe stenosis of the extrahepatic portal vein and marked hepatofugal collaterals. The length of the stenosis was approximately 30mm **(Figure 4A, B)**. It also revealed extravasations into the afferent loop of the jejunum **(Figure 4C)**. The left branch of the portal vein could not be detected. Consequentially, we attempted to dilate the stenosis of the extrahepatic portal vein. We introduced a 7-mm balloon catheter (Ultra-thin Diamond Balloon Catheter, Boston Scientific, Natick, MA, USA) into the portal vein and passed it smoothly across the stenosis. Expanding the balloon at 3 atmospheres for 30 seconds and 4 atmospheres for 30 seconds dilated the stenosis of the portal vein. After successful dilatation of the stenosis, the pressure of the extrahepatic portal vein decreased from 24 cmH_2O to 11 cmH_2O. Portography after the dilatation revealed the disappearance of the hepatofugal flow to collaterals and extravasations. In addition, a hepatopetal flow to the left branch of the portal vein was restored. To prevent re-stenosis of the extrahepatic portal vein, an expandable metallic stent (S.M.A.R.T.™ Stent, Cordis Endovascular, Miami, FL, USA) was placed at that site **(Figure 4D)**.

After portal vein angioplasty, no further episodes of variceal bleeding occurred. Doppler ultrasonography displayed sufficient hepatopetal flow in the portal vein **(Figure 3B)**. The patient has received warfarin potassium since 4 days after the treatment to prevent thrombus in the metallic stent. She maintains a normal life at present 4 months after the treatment.

DISCUSSION

Esophageal and gastric varices caused by portal hypertension occur frequently in patients with liver cirrhosis, but most can be sufficiently controlled using endoscopic treatments such as endoscopic variceal ligation and endoscopic injection sclerotherapy. On the other hand, while varices caused by extrahepatic portal obstruction after abdominal surgery are rare, they lead to bleeding at unpredictable sites through the adhesion of tissue (1-3). In the present case, bleeding varices occurred at the afferent loop of the jejunum 16 months after pancreatoduodenectomy with portal venous resection and reconstruction. For some time now, we have been safely and aggressively performing portal venous resection using catheter bypass of the portal vein for pancreatobiliary cancer (4). Since 1981, we have performed over 200 portal venous resections and reconstructions (5), but this was the first case in which we encountered bleeding varices due to stenosis of the portal vein. On admission, we suspected ulcerous bleeding around the gastrojejunostomy and performed gastrointestinal endoscopy, but we could not detect the origin of gastrointestinal bleeding in this examination. Retrospectively, the telangiectasia in the jejunal mucosa around the choledochojejunostomy suggested the presence of bleeding varices, but at that time the finding was insufficient to understand the mechanism of bleeding. Therefore it was difficult to

stop the bleeding using an endoscopic approach. Based on abdominal angiography and Doppler ultrasonography, we suspected that extrahepatic portal obstruction caused the bleeding varices. Finally, we confirmed the extravasations in percutaneous transhepatic portography, but the critical point was identifying the portal hemodynamics by angiography and Doppler ultrasonography.

Bleeding varices caused by extrahepatic portal obstruction occur congenitally and secondary to liver cirrhosis, carcinomatous invasion, pancreatitis, previous abdominal surgery and the like. Several reports refer to the treatment of such varices (2,3,6-15).

Daniel *et al.* (6) described their experience with superior mesenteric vein to intrahepatic left portal vein (Rex) shunts in children. They performed the Rex shunt procedure in 5 children with symptomatic portal hypertension caused by extrahepatic portal vein thrombosis. The Rex shunt eliminated portal hypertension and restored normal portal flow to the liver. Chen *et al.* (7) designed an end-to-side anastomosis between the proximal splenic vein and the umbilical portion of the left intrahepatic portal shunt for extrahepatic portal obstruction, and performed this simultaneously with splenectomy. They observed disappearance of the collaterals on postoperative angiography. These shunt surgeries, which were attempted to decrease extrahepatic portal pressure, are considered to be radical treatments.

Since Harville *et al.* (8) reported a balloon dilatation and stent placement in the portal vein for colon varices caused by extrahepatic portal obstruction due to chronic pancreatitis; several reports have suggested the therapeutic effectiveness of transhepatic portal dilatation and stenting for portal obstruction (2,9-13,15). Hiraoka *et al.* (2) attempted portal dilatation and stenting for bleeding jejunal varices of the afferent loop caused by extrahepatic portal stenosis in two patients who had previous abdominal surgery. In one of these patients the bleeding varices occurred 1 year after a pancreatoduodenectomy with intraoperative radiation therapy, and in the other 16 years after a choledochojejunostomy. Tsukamoto *et al.* (9) reported the efficiency of this procedure for patients with portal vein stenosis due to malignant invasion.

This procedure can be performed with a percutaneous transhepatic approach in most cases and is less invasive than other treatments. Although in the present case the stenotic area corresponded to the end-to-end anastomosis of the portal vein, the dilatation was performed smoothly and safety. To prevent re-stenosis of the extrahepatic portal vein, we placed an expandable metallic stent there. However, the long-term patency of expandable metallic stents has not been confirmed, and the indications for stenting remain to be determined.

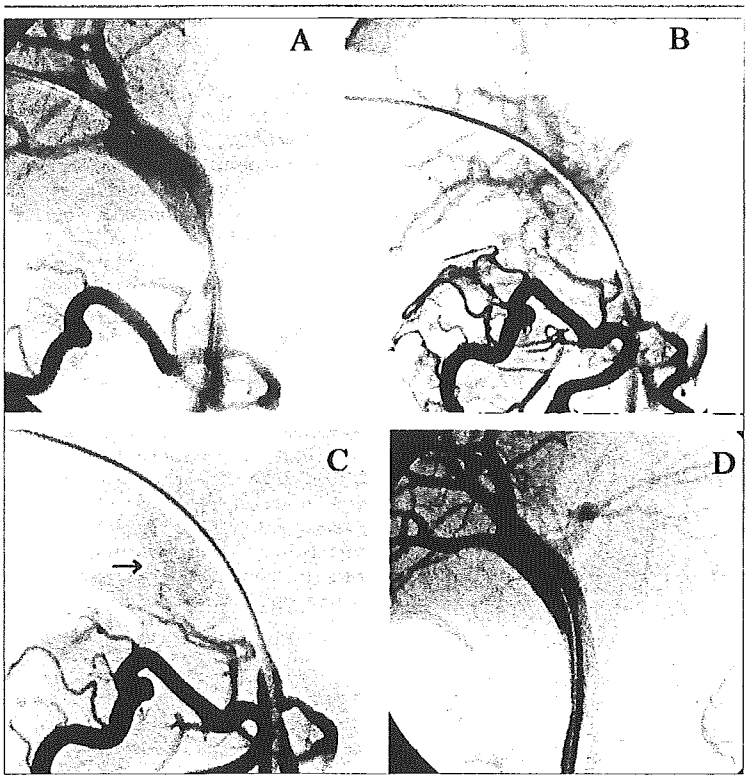

FIGURE 4 Percutaneous transhepatic portography revealed severe stenosis of the extrahepatic portal vein **(A)** and marked hepatopetal collaterals **(B)**. The length of stenosis was approximately 30mm **(A)**. Extravasations into the afferent loop of the jejunum (arrow) were also revealed **(C)**. The left branch of the portal vein could not be detected **(A)**. After portal venous angioplasty and stenting, portography revealed the disappearance of hepatofugal flow in collaterals and extravasations. In addition, a hepatopetal flow to the left branch of the portal vein was restored **(D)**.

In addition, it has been recently reported that this procedure was applied to symptomatic portal vein stenosis after liver transplantation (10,11). Because of this procedure's lower level of invasiveness, we recommend it as the first treatment choice for various patients with symptomatic extrahepatic portal obstruction.

In conclusion, when gastrointestinal bleeding is observed in patients who have had previous abdominal surgery, the possibility of bleeding varices caused by portal hypertension due to portal obstruction should be kept in mind. For patients with bleeding varices due to extrahepatic portal obstruction, percutaneous transhepatic angioplasty with stenting is thought to be effective and less invasive than other treatments. Especially for patients who have had previous abdominal surgery, this should be the procedure of choice.

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Intraportal Endovascular Ultrasound for Portal Vein Resection in Pancreatic Carcinoma

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ABSTRACT

Background/Aims: Intraportal endovascular ultrasound (IPEUS) has been reported to be the most precise diagnostic procedure for the accurate diagnosis of portal vein/superior mesenteric vein (PV/SMV) invasion in patients with pancreatic cancer. In this study, we evaluated the clinical significance of the length of PV/SMV invasion measured by IPEUS
Methodology: Twenty-six consecutive patients who underwent the pancreatic resection and IPEUS using an autopull-back device between January, 1997 and September, 2000 were retrospectively evaluated. The length of PV/ SMV invasion was measured by reviewing the videotapes recorded during the operation. Clinicopathological data and survival were analyzed.
Results: The percentage of PV/SMV invasion was 46%, all of which were treated by PV/SMV resection. The cases without PV/SMV invasion showed significantly longer survival rate. The cases with ≤18mm PV/SMV invasion, however, achieved a comparable 2-year survival rate of 28% whereas no patient with >18mm PV/SMV invasion survived more than 18 months after the resection.
Conclusions: Involvement of the PV/SMV by pancreatic carcinoma seems to be related to the extent of the disease and the PV/SMV involvement >18mm is associated with a poor prognosis due to high rate of tumor positive margin even with radical operation.

KEY WORDS: Pancreatic carcinoma; Portal vein resection; Intraportal endovascular ultrasonography

ABBREVIATIONS: Intraportal Endovascular Ultrasonography (IPEUS); Portal Vein (PV); Superior Mesenteric Vein (SMV)

INTRODUCTION

Accurate diagnosis of portal venous invasion is important to determine the operative indication and surgical procedures since portal vein (PV) resection has been advocated to achieve negative surgical margins which was shown to correlate with patient survival (1-5). With recent progress in ultrasound (US) technology, the intravascular US (IVUS) catheter has been developed and intraportal endovascular US (IPEUS) has become possible (6). IPEUS provides high-resolution, cross-sectional, real-time images of the portal vein wall and contiguous structures.

Accurate discrimination between subtle invasion and compression of the tumor, which is not possible with conventional imaging modalities such as CT scan and angiography, can be achieved by IPEUS. IPEUS is reported to be the most precise diagnostic procedure for the accurate diagnosis of PV invasion peroperatively with 96-100% rates overall accuracy (6-8). In this study, we evaluated the videotapes recorded during IPEUS procedure and determined the PV/SMV invasion length in 26 consecutive patients with carcinoma of the pancreatic head who underwent surgical resection. We report the current data on clinical significance of IPEUS.

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METHODOLOGY

Patients and surgical procedures: Twenty-six consecutive patients who underwent the pancreatic resection and IPEUS using an autopull-back device between January, 1997 and September, 2000 in the Department of Surgery II, Nagoya University Hospital were retrospectively evaluated. No patients were excluded from the study. The resection of choice was partial pancreatectomy with dissection of the regional nerve plexus and lymph nodes in cases without known metastasis to distant organ or peritoneal dissemination. Using an antithrombogenic portal vein bypass catheter (Anthron, Toray, Japan), mesenteric venous blood is bypassed to the systemic circulation to prevent portal congestion during PV/SMV resection. In all cases, the PV is reconstructed by end-to-end anastomosis between PV and SMV using 5-0 or 6-0 Prolene sutures. Upon completion of the anastomosis, the bypass catheter is withdrawn (9). Segmental resection of the PV/SMV was performed to obtain surgically free margin in patients in whom invasion to the PV/SMV is diagnosed by imaging techniques or in patients in whom IPEUS revealed tumor-vessel contiguity with an intact echogenic band which is indicative of the tumor within 1mm of the adventitia of the PV/SMV

wall (10). Intraoperative radiation therapy (30 Gy against the connective tissue around superior mesenteric and celiac artery) and liver perfusion chemotherapy immediately after the operation via PV through SMV using 5-fluorouracil continuously for 3 to 4 weeks were used as adjuvant therapy. Resection margins of the pancreas, distal common bile duct, retropancreatic tissue, PV/SMV and extrapancreatic nerve plexus were marked and examined in detail microscopically by experienced pathologist (T.N.).

Clinicopathological parameters: All resected specimens were handled according to the "General Rules for the Study of Pancreatic Cancer" published by the Japan Pancreas Society (JPS) (11). The resected specimens were cut in slices perpendicular to the portal vein axis, and relationship between the tumor and the portal vein was studied on histologic examination. The following parameters were assessed according to the "Classification of Pancreatic Carcinoma" by the JPS and the "TNM Classification of Malignant Tumors" by UICC (11,12) were studied: histology, tumor size, lymph node invasion, resection margins status, extrapancreatic nerve plexus invasion and PV invasion as well as pTNM stage. According to JPS classification, briefly, tumor size was classified as TS1: less than 2.0cm in greatest diameter; TS2: 2.1-4.0cm in diameter; TS3: 4.1-6.0cm in diameter or TS4: larger than 6.1cm in diameter. The local extent of the tumor was also classified as follows; s0: anterior capsule of the pancreas not invaded; sl: invasion at one limited area; s2: numerous sites of invasion and/or extensive invasion; s3: invasion to adjacent organs and rp0: no invasion to retroperitoneal tissue; rpl: limited invasion to tissue adjacent to the pancreas; rp2: invasion not limited to tissue adjacent to the pancreas; rp3: invasion to adjacent organs. Invasion of the PV was characterized as pv0 (no invasion), pvl (invasion to the adventitia), pv2 (invasion to the media) or pv3 (invasion to the intima). Invasion to the surgical margin of resection was classified as ew (-) (no invasion) or ew (+) (invasion at the dissected peripancreatic tissue). Invasion to extrapancreatic nerve plexus was classified as absent (pl(-)) or present [pl(+)]. On the other hand, lymph node metastasis was evaluated and the stages were classified according to TNM system by UICC.

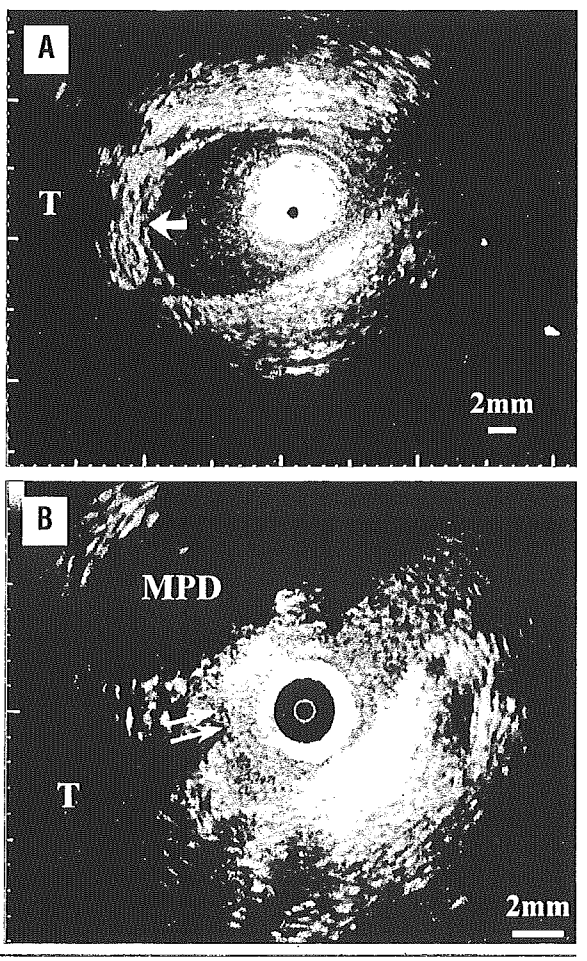

FIGURE 1 (A) Tumor is contiguous with the portal vein, but the echogenic band at vessel-parenchymal sonographic interface is intact (arrow). **(B)** The echogenic band of the portal vein is destroyed by the tumor (arrows). Note the dilated main pancreatic duct distal to the tumor. T: Tumor, MPD: Main pancreatic duct.

IPEUS: IPEUS was performed with an 8-F, 20-MHz IPEUS catheter (Boston Scientific, Boston, Mass.) from a branch of the SMV intraoperatively. The IPEUS catheter was withdrawn from the intrahepatic portion of the portal vein to superior mesenteric vein at 1 or 2mm/sec by a mechanical autopull-back device as the images were recorded on the S-VHS videotapes which were reviewed in the present study. Informed consent was obtained from all patients in the study.

The criterion for portal venous invasion at IPEUS was loss of the echogenic vessel-parenchymal sonographic interface **(Figures 1A, B)**. The length of invasion was calculated by multiplying the real-time difference recorded from counter of the video recorder and the speed of the mechanical autopull-back device used (which was either 1 or 2mm per second).

Patients were divided into three groups according to IPEUS measurements: Group I consisted of patients without PV/SMV invasion; Group II was patients with PV invasion ≤18mm and Group III >18mm, where the mean length of invasion (18mm) was selected as a cut-off point.

Statistical analysis: Statistical analysis was performed by Spearman's rank correlation test for group differences, and Student's *t*-test for mean differences using Statview software (Version 5, 1998, SAS Institute, Inc.). Survival rates were calculated by the Kaplan-Meier method, and statistical significance was examined using the log-rank test. One patient with false positive IPEUS results was excluded from statistical evaluation for survival. $P<0.05$ was considered statistically significant.

RESULTS

Patients: There were 21 men and 5 women with a mean age of 60.4 years (range, 48 to 76 years). Of 26 patients, 19 (73%) underwent segmental resection of the portal vein combined with tumor resection. Of

these 19 cases, 10 had SMV resected and 9 had combined PV/SMV resected. Pancreatoduodenectomy with distal gastrectomy was performed in 14 patients, pylorus-preserving pancreatoduodenectomy in 10 and extended distal pancreatectomy in 2.

Clinicopathological parameters: Histological examination of the surgical specimen confirmed pancreatic adenocarcinoma in all 26 patients underwent tumor resection. Differentiation was well in 3 patients, moderate in 20 and poor in 3. In most cases (22 of 26), tumor size was found >2cm. Only 4 cases had tumors ≤2cm, 3 of which were in Group I, but there was no significant difference in distribution between groups **(Table 1)**. Extrapancreatic nerve plexus invasion was found in 11 cases and this parameter lack statistical significance between 3 groups.

After resection, resection margins were tumor-free in 22 (85%) and tumor-positive in 4 (15%) three of which were in Group III. There was no significant correlation between margin status and the resected vein (SMV or PV+SMV). Lymph node invasion was seen in 15 of 26 cases (58%) most of which were in Groups II and III (9 cases). In concordance with this, the patients in Group I were mostly in Stages I-III whereas the patients in the other two groups were in Stage IV. These three parameters had statistical significance in distribution between the three groups giving evidence that PV/SMV invasion was seen mostly in advanced cases (for resection margins, lymph node invasion and pTNM stage, $p<0.05$) **(Table 1)**. There was no statistically significant difference between groups in adjuvant treatment (data not shown).

IPEUS: Tumor mass was easily detected by IPEUS in all cases without any complication. Histopathologic examination revealed the PV/SMV invasion by tumor in 12 (46.2%) of 26 patients all of whom were treated by PV/SMV resection. IPEUS detected PV/SMV invasion in all 12 patients with histologically diagnosed PV/SMV invasion. In 1 patient whom IPEUS showed tumor in contact with the portal vein and the loss of echogenic band portal venous invasion was histologically negative. Therefore, IPEUS showed 100% (12/12) sensitivity, 92.9% (13/14) specificity and 96.2% (25/26) accuracy for diagnosing portal venous invasion. False-positive rate for IPEUS was found to be 7.7%.

After excluding one case with a false-positive result, we measured the length of portal venous invasion as mentioned in Methodology. In 12 cases with portal venous invasion, the length of invasion was found between 4 to 30mm (mean: 18mm; median: 18.5mm). Positive cases further divided into two groups; Group II (invasion length <18mm) and Group III (invasion length >18mm) **(Table 1)**. Group I consisted of the patients without PV/SMV invasion.

Twenty-five cases were evaluated for survival analysis. During the follow-up period (median: 12.1 months; range: 0.4-50.3), 18 patients died of tumors from 2 weeks to 34 months after surgery. Seven

TABLE 1 Characteristics of the Patients

PV invasion	Negative Group I n=13	Positive Group II (1-18mm) n=6*	Group III (>18mm) n=6
Length of invasion (mean, mm)	0	12.8±5.6	24.2±4.1
Age (mean ±SD) †	59.5±7.5	59.8±5.9	62.7±11.1
Sex (M/F) †	11/2	5/1	4/2
Tumor differentiation†			
Well	2	-	1
Moderate	10	5	5
Poor	1	1	-
Tumor size (<2cm/>2cm) †	3/10	0/6	1/5
Nerve plexus invasion (-/+)†	8/5	4/2	2/4
Lymph node invasion (-/+)‡	7/6	2/4	1/5
Tumor-free/positive margin‡	12/1	6/0	3/3
pTNM stage‡			
I-III	12	1	0
IVa-b	1	5	6
Median survival (months)	20	12	8
50% survival rate (months)	30	17	8
1-, 2- and 3-year survival rates	62/54/36	56/28/0	33/0/0

*Data related to a patient with a false-positive result excluded from survival analysis is not shown. This patient had the following characteristics: 66, M, poorly differentiated adenocarcinoma, tumor size >2cm, no lymph node or nerve plexus invasion, no tumor at margins, pTNM stage II, died 9 months after operation, no autopsy performed.
†there is no statistically significant difference in distribution ($p>0.05$).
‡$p<0.05$.

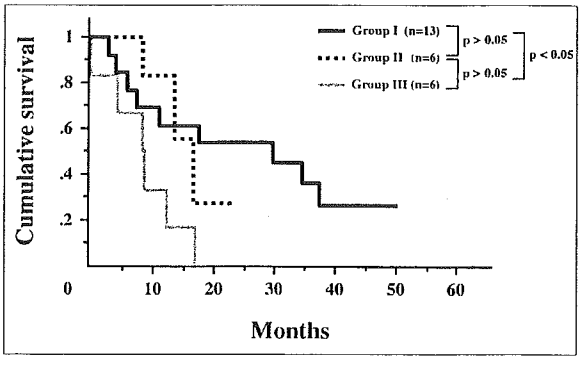

FIGURE 2 Cumulative survival rates compared between three groups. A significant difference was observed only between Group I and III ($p<0.05$). There appears to be a trend toward a better long-term survival rate in patients with ≤18mm PV/SMV invasion who underwent a PV/SMV resection.

patients remained alive as of July 2001. Among these patients, 4 were in Group I and 3 in Group II. No patients in Group III were alive; all died of tumors or tumor-related incidents from 13 to 501 days (0.4-16.7 months). When the cumulative survival rates of the three IPEUS groups compared, the difference was statistically significant between only Group I and III (**Figure 2**, Group I *vs.* II, Group II *vs.* III; $p>0.05$, whereas Group I *vs.* III; $p<0.05$).

DISCUSSION

Pancreatic carcinoma is one of the leading causes of cancer deaths despite the recent advances in diagnosis and treatment. The disease has a dismal 5-year

survival of less than 15% after resection of the tumor (13,14). Several prognostic factors were reported such as tumor size, lymph node involvement, portal vein and extrapancreatic nerve plexus invasion (1-5,15-18). The patients with tumor invasion of the portal vein by pancreatic head carcinoma historically have been regarded as not indicated for resection because of the higher morbidity and mortality. Since 1981 when we developed a pressure gradient catheter bypass from the superior mesenteric vein to the right femoral vein for combined resection of the portal vein in pancreaticoduodenectomy, PV resection and anastomosis could be performed safely without portal congestion improving the resectability rate to 64% (9,19,20).

For locally advanced pancreatic cancer, it is important to determine the extent of pancreatic cancer spread to achieve tumor-free margins with radical operation. Radical operation for pancreatic cancer which includes wide range of lymphadenectomy, retroperitoneal dissection, and when indicated, PV/SMV resection has gained many advocates in many centers around the world, particularly in Japan (20-24).

Lymph node involvement has been considered one of the limiting factors in patient survival. Cohen reported that long-term survival could not be expected in any patients with nodal involvement (25). On the other hand, Ishikawa reported that long-term survival was not hopeless, even in patients with nodal involvement when lymphatic and connective tissue resection was performed (22). Recently, Pedrazzoli *et al.* reported that there was a trend toward a longer survival in node-positive patients after extended rather than a standard lymphadenectomy (20% *vs.* 0% at 2 years) (15). Henne-Bruns *et al.* reported no significant difference in terms of survival between regional and extended lymphadenectomy in 53 patients after margin-free resection (23). In an ongoing prospective, randomized, single-institution trial, Yeo *et al.* reported a 1-year actuarial survival rate for patients surviving the immediate postoperative period of 77% for standard resection group and 83% for extended resection group (26). It appears clear that the survival benefit for patients with pancreatic cancer treated with radical or standard resection needs to be justified with prospective, multicenter trials.

Several studies evaluating prognostic factors for survival for resected pancreatic adenocarcinoma demonstrated that PV invasion is a factor for poor prognosis (2,3,23), whereas some others have reported that PV invasion is not a predictor of outcome (16). It is doubtful that PV/SMV resection improves survival since in many reports, it has been shown that the patients requiring PV/SMV resection have the same overall survival compared with those who underwent pancreatic resection without PV resection (27-29). Allema *et al.* reported no difference in survival rate between patients undergoing PV/SMV resection and those in whom PV/SMV was not resected due to macroscopic tumor involvement at the PV/SMV (27). They concluded that PV/SMV resection in patients who are suspected of having tumor invasion of the PV/SMV does not improve the rate of survival. However, it should be noted that only 15% of their patients underwent curative resection with tumor-free margin. Takahashi *et al.* reported 14% of the actuarial 5-year survival rate for 39 patients with PV/SMV resection (28). This was not significantly different from that for patients without PV/SMV resection. They concluded that PV/SMV resection should be performed if it appears to be invaded by the tumor and the prognosis tended to be related to the depth of invasion. Moreover, they also reported that 4 patients survived more than 5 years.

Harrison *et al.* described similar survival rates for patients with or without PV/SMV resection (29). Overall median survival for PV/SMV resection group was 13 months which was not found to be significantly different from the patients who underwent pancreatic resection without PV/SMV resection (17 months). In that study, however, the fact that similar survival rates was seen in two groups may be because they did not examine histologic involvement of the PV/SMV.

In 35 resectable cases, Ishikawa *et al.* reported that the overall survival rate was 29%. When they grouped the patients according to angiography data, the cases (n=17) in whom PV/SMV invasion had been angiographically diagnosed as type I, II, III or <1.2cm in length showed 54% of 3-year survival rate whereas the cases (n=18) with invasion of type IV, V or ≥1.2cm in length died within 18 months postoperatively and this rate was even lower than that of non-resected cases (30). Recently, Henne-Bruns *et al.* from Germany reported their results in 53 patients who were treated with partial pancreaticoduodenectomy with either regional or extended retroperitoneal lymphadenectomy. Although this study suggested that extended lymphadenectomy did not improve the survival rate compared to regional lymphadenectomy, PV/SMV invasion along with tumor stage and histologic grade had a significant influence on survival regardless of the type of operation (i.e. extended or regional lymphadenectomy) (23).

In the current study, we have 7 patients with a negative IPEUS who underwent PV/SMV resection. In all patients, however, IPEUS revealed tumor-vessel contiguity with an intact echogenic band which is indicative of the tumor within 1mm of the adventitia of the PV/SMV (10). Therefore, we performed PV/SMV resection in order to achieve negative margins. In our recent study, we have investigated histologically PV/SMV wall invasion and margin status and further classified 196 resected cases into four groups according to pv and ew status. As expected, pv(-)/ew(-) group had higher survival rate than did all other groups (20). In patients with pancreatic adenocarcinoma, the most important indication for radical operation combined with PV/SMV resection is justified in order to achieve negative margins when the tumor is in contact with the vessel wall (17,20,26-35).

Radical operations with major vascular resections for pancreatic carcinoma have been increasingly