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Results of surgery and adjuvant radiotherapy for pancreatic cancer

Shoichi Hishinuma, Yoshiro Ogata, Junichi Matsui, and Iwao Ozawa

Department of Surgery, Tochigi Cancer Center, 4-9-13 Yohnan, Utsunomiya 320, Japan

Abstract: We retrospectively reviewed the cases of 34 patients with pancreatic cancer who underwent resection between January 1988 and December 1996. Adjuvant radiotherapy was performed in 24 patients, with 13 receiving both intra- and postoperative radiotherapy, 2 receiving postoperative radiotherapy (PORT) alone, and 9 receiving intraoperative radiotherapy (IORT) alone. The 1- and 3-year survival rates for all 34 patients were 59% and 19%, respectively, with a median survival of 13 months. At the time of the analysis, three patients were still alive. Recurrence patterns were assessed in 25 patients who had had no distant metastases at the time of surgery, had survived more than 3 months after surgery, and had undergone close surveillance for recurrence. Based on computed tomography (CT) and autopsy findings, a total of 15 (60%) of these 25 patients had local recurrence, 13 (52%) had liver metastases, and 8 (32%) had both. Eight (62%) of the 13 patients who received IORT and/or PORT developed local recurrence, and we failed to detect any survival advantage of IORT and/or PORT over surgery alone. However, autopsies revealed a suppressive effect of radiation on cancer growth, and local recurrence was not considered to be the direct cause of death in any of the patients, nor did any of the patients develop gastrointestinal obstruction due to local recurrence. The incidence of liver metastasis in the patients with and without tumor invasion of the portal system was 80% (8/10) and 33% (5/15), respectively. The patients who did not develop liver metastasis had significantly longer survivals than who did. Further improvements of survival await effective prophylactic treatment for liver metastases.

Key words: pancreatic cancer, adjuvant therapy, resection, recurrence, survival

Offprint requests to: S. Hishinuma

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Introduction

The incidence of pancreatic cancer has increased over the past several decades, but difficult management problems still remain. In a review of 37 000 patients with pancreatic cancer, Gudjonsson[1] showed that the 5-year survival rate for all patients was 0.4%, increasing to just 3.8% for resected patients. These results show that surgical resection provides substantially better survival, but that only a few patients have a chance for cure. The Gastrointestinal Tumor Study Group (GITSG) has reported increased survival in patients treated by curative resection with adjuvant chemoradiotherapy.[2,3] There are also recent reports of encouraging results with neoadjuvant chemoradiotherapy.[4,5] However, although neoadjuvant therapy has had a possible effect of increasing tumor resectability rates, it has not significantly improved the long-term survival for patients with pancreatic cancer over that for historic controls.[6,7] Surgery and high-dose radiation therapy to the pancreatic bed alone is unlikely to further enhance survival, and some effective form of adjuvant therapy is needed.

With few opportunities for early diagnosis, aggressive therapeutic strategies should be established to improve patient outcome, based on the assessment of recurrence patterns after resection. In the present study, recurrence patterns and survival in patients with resectable pancreatic cancer were retrospectively analyzed with respect to adjuvant radiotherapy.

Patients and methods

Patients

Between January 1988 and December 1996, 143 patients with pancreatic ductal cell cancer were admitted to Tochigi Cancer Center, Utsunomiya, Japan. Thirty-four underwent resection, a resectability rate of 24%, and these 34 resection patients served as the subjects of

Table 1. Summary of surgical procedures, disease stage,[8] and adjuvant radiotherapy

	IORT and PORT (n = 13)			PORT alone (n = 2)			IORT alone (n = 9)			No radiotherapy (n = 10)		
Surgical procedure	Patient number	Stage	Resected vessels	Patient number	Stage	Resected vessels	Patient number	Stage	Resected vessels	Patient number	Stage	Resected vessels
PPPD	1	III	SMV-PV	1	III	SMV-PV	1	IVa	None	1	IVa	SMV-PV
	2	III	None				2	IVb	SMV-PV, IVC	2	III	None
	3	IVa	SMV-PV, SMA				3	IVb	SMV-PV	3	III	None
	4	IVa	SMV-PV							4	IVa	None
	5	III	None									
	6	III	None									
	7	IVa	None									
	8	IVb	None									
PD	9	IVa	SMV-PV				4	IVb	SMV-PV			
	10	IVa	None				5	IVb	SMV-PV			
							6	IVb	SMV-PV			
DP	11	IVb	None				7	IVb	SMV-PV	5	I	None
	12	IVa	CA				8	IVa	none	6	IVb	None
	13	IVa	CA, SMV-PV							7	IVb	None
										8	IVa	CA
										9	IVb	None
TP				2	IVa	SMV-PV	9	IVa	SMV-PV	10	IVb	SMV-PV

PPPD, Pylorus-preserving pancreatoduodenectomy; PD, pancreatoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy; IORT, intraoperative radiotherapy; PORT, postoperative radiotherapy; SMV-PV, superior mesenteric vein and/or portal vein; SMA, superior mesenteric artery; CA, celiac axis; IVC, anterior wall of inferior vena cava

this study. There were 19 men and 15 women, ranging in age from 37 to 79 years, with a median age of 61 years.

Staging

Staging, including lymph node grouping, was performed according to the *Classification of Pancreatic Cancer* of the Japan Pancreas Society.[8] Staging was based on the histologic findings in the resected specimens.

Surgical procedures

Twenty-one patients had had cancer of the pancreatic head. Sixteen of them underwent pylorus-preserving pancreatoduodenectomy (PPPD) and 5 underwent conventional pancreatoduodenectomy (PD) (Table 1). The indication for PPPD was the intraoperative absence of detectable metastases to either the supra- or infrapyloric lymph nodes in patients who did not have tumor invasion of the distal stomach or the first portion of the duodenum. During PPPD, the right gastric artery was divided at its origin and the peripheral portions of the right gastric and right gastroepiploic arteries, including their first branches to the stomach, were divided along the gastric wall so as to completely remove both the supra- and infrapyloric lymph nodes (Fig. 1). The pancreas and bile duct were resected until negative margins were confirmed by frozen section examination. In all patients undergoing PPPD or PD, gastrointestinal continuity was restored by the Imanaga method, which entails end-to-end duodeno- or gastrojejunostomy, end-to-side pancreatojejunostomy, and choledochojejunostomy, in that order (Fig. 2).[9,10] Three patients with a tumor involving the entire pancreas underwent total pancreatectomy (TP). Ten patients with cancer of the pancreatic body or tail underwent distal pancreatectomy (DP).

The tumors were resected with an en bloc removal of group 1 and 2 lymph nodes,[8] peripancreatic soft tissue, and the nerve plexuses in the retroperitoneum. Combined resection of the adjacent vessels was performed when the tumor was inseparable from the wall of the vessels or a definite diagnosis of vascular invasion had been made based on preoperative imaging studies. Sixteen (47%) of the 34 patients (7 with PPPD, 4 with PD, 2 with DP, and 3 with TP) underwent segmental resection of the superior mesenteric vein and/or portal vein (SMV-PV) with primary anastomosis (Table 1). One each of the 7 patients who underwent resection of the SMV-PV with PPPD also underwent combined resection of the superior mesenteric artery (SMA) and the anterior wall of the inferior vena cava. Three DP patients underwent resection of the celiac axis with preser-

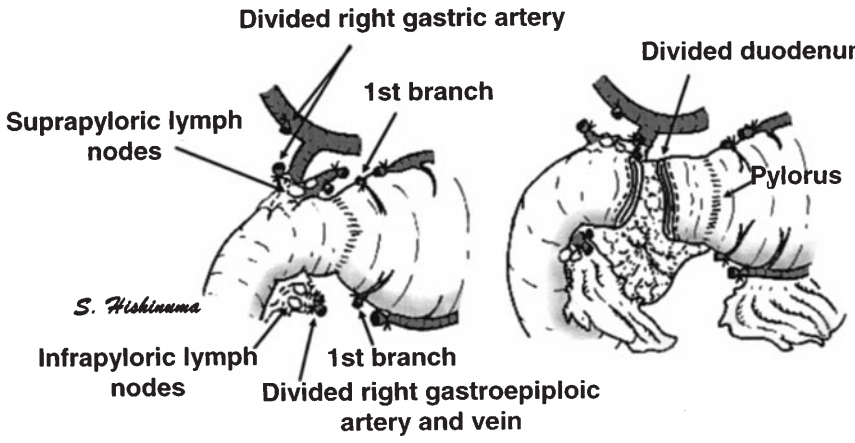

Fig. 1. Dissection of the infra- and suprapyloric lymph nodes in pylorus-preserving pancreatoduodenectomy (PPPD). The right gastric artery has been divided at its origin. The peripheral portions of the right gastric and right gastroepiploic arteries, including their first branches to the stomach, have been divided along the gastric wall so as to completely remove both the supra- and infrapyloric lymph nodes. The duodenum has been transected 2 cm distal to the pylorus

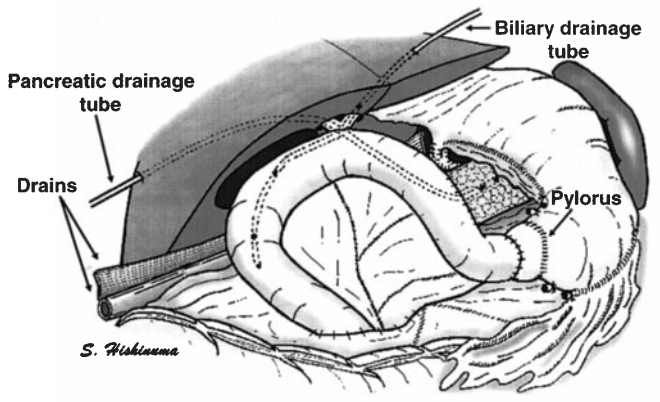

Fig. 2. Completed anastomoses following PPPD, with drains in place. Gastrointestinal continuity has been restored by the Imanaga method,[9,10] which simulates normal anatomy

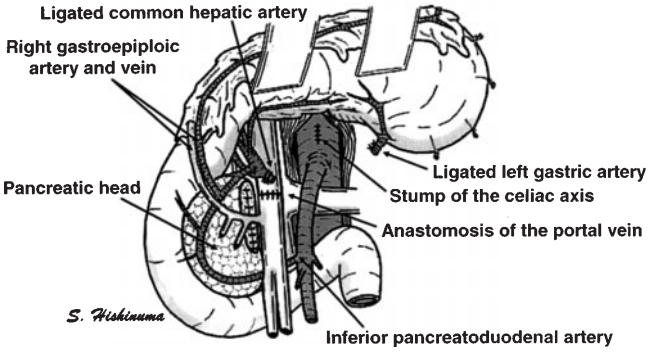

Fig. 3. Distal pancreatectomy combined with resection of the celiac axis. The entire stomach has been preserved. The blood supply to both the stomach and the liver is maintained via the inferior pancreatoduodenal artery. In this patient, the superior mesenteric vein-portal vein confluence has also been resected

vation of the entire stomach, whose blood supply as well as the blood supply of the liver was maintained via the inferior pancreatoduodenal artery (Fig. 3). One of the 3 patients also underwent resection of the SMV-PV confluence (Fig. 3).

Adjuvant radiotherapy

Adjuvant radiotherapy was performed in 24 patients, with 13 receiving both intra- and postoperative radiotherapy, 2 receiving postoperative radiotherapy (PORT) alone, and 9 receiving intraoperative radiotherapy (IORT) alone (Table 1). IORT was combined with PORT in the resection patients whenever possible. The 2 patients with PORT alone did not receive the planned IORT because of the prolonged operation time, and the 9 patients receiving IORT alone did not receive the planned PORT because of liver metastases found at surgery in 2 patients, early liver metastases after surgery in 1, fatal postoperative complications in 3, and patients' refusal in 3. Therefore, the background and disease stage of the patient group receiving IORT alone were quite different from those of the other groups. Ten patients did not receive adjuvant radiotherapy because of their advanced age and/or poor medical condition.

IORT was administered just after tumor resection. Electron beam energies of 6–12 Mev were used to deliver 16–20 Gy to the treatment field, which included the tumor bed, root of the celiac axis and SMA, and the 2-cm-long remnant pancreas stump. PORT was usually begun 2–3 weeks after the surgery, using the same radiation field as that marked out with surgical clips for IORT at the time of surgery. Patients were treated with 10-MV X-rays using opposed anterior-posterior portals to a total dose of 45.0–57.6 Gy, administered in 1.8-Gy fractions on a Monday-through-Friday schedule. Only two patients receiving PORT were given concomitant 5-fluorouracil (5-FU).

Recurrence and survival

At the time of the analysis, three patients were still alive. Recurrence patterns were assessed in 25 patients

Table 2. Sites of pancreatic cancer recurrence demonstrated by CT

Patient no.	Surgical procedure	IORT Gy (Mev)	PORT Gy	Tumor invasion of portal system[a]	Tumor invasion of DPT (ew[8])[a]	Sites of recurrence on CT				
						Local	Liver	Peritoneum	Lung	Bone
1	PPPD	16 (9)	45.0	—	—	○	○	—	—	—
2	PPPD	18 (12)	51.2	—	+	—	○	—	—	—
3	PD	25 (9)	46.6	—	—	○	—	○	—	—
4	DP	16 (9)	40.5	+	—	—	○	—	○	○
5	DP	16 (12)	40.5	+	—	—	—	—	—	—
6	PD	20 (9)	—	+	—	○	○	○	—	—
7	PD	16 (9)	—	+	—	—	○	—	—	—
8	DP	25 (9)	—	+	+	○	○	—	—	—
9	DP	20 (6)	—	+	—	○	○	—	—	—
10	PPPD	—	—	—	+	○	—	○	—	—
11	PPPD	—	—	—	+	○	—	—	○	—
12	PPPD	—	—	—	—	—	○	—	○	—
13	PPPD	—	—	—	—	—	—	—	—	—
14	DP	—	—	—	—	—	—	—	—	—
15	DP	—	—	—	—	—	—	—	—	—
16	TP	—	—	+	—	○	○	—	—	—

PPPD, Pylorus-preserving pancreatoduodenectomy; PD, pancreatoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy; IORT, intraoperative radiotherapy; PORT, postoperative radiotherapy; CT, computed tomography; DPT, dissected peripancreatic tissue; circles denote recurrence; dashes, no recurrence

[a] Determined on resected specimens

who had had no distant metastases at the time of surgery, had survived more than 3 months after surgery, and had undergone close surveillance for recurrence. Antopsies had been performed on 9 of the 25 patients. Survival time was measured from the time of surgery, and recorded in months. Survival was analyzed by the Kaplan-Meier method, which expresses survival as cause-specific tumor mortality. The generalized Wilcoxon test was used to compare the outcomes in different groups of patients.

Results

Pathological characteristics of the tumors

Staging showed stage I in 1 (3%) patient, stage III in 7 (21%), stage IVa in 14 (41%), and stage IVb in 12 (35%) (Table 1). The difference between stages IVa and IVb was determined mainly in terms of the presence of metastasis to the group 2 and 3 lymph nodes and/or liver.[8] Tumor invasion of the dissected peripancreatic tissue was present [i.e., ew(+)[8]] in 8 patients. Tumor invasion of the retroperitoneal connective tissue (i.e., $rp_{1\text{-}3}{}^{8}$) was observed in 23 patients (68%). Involvement of the retroperitoneal nerve plexus was found in 13 (43%) of the 30 patients who underwent histologic examination of the resected plexuses. Lymph node metastases were found in 24 (71%) of the 34 patients. Two (13%) of the 16 patients who underwent PPPD had microscopic metastases in grossly negative infrapyloric lymph nodes.

Tumor invasion of the SMV-PV was histologically confirmed in 13 (81%) of the 16 patients who underwent segmental resection of the SMV-PV (4 with PPPD, 4 with PD, 3 with TP, 2 with DP). In the remaining 3 patients, the cancer remained outside the tunica adventitia of the SMV-PV. Tumor invasion of the splenic vein was observed in 4 of the 8 patients who underwent DP without SMV-PV resection.

Patterns of recurrence

Local recurrences included failures in the bed of the resected pancreas and in the area around the origin of the SMA and celiac axis. Failures which seemed to originate around the stump of the remnant pancreas were also considered local recurrences.

Table 2 shows the sites of recurrence, demonstrated by computed tomography (CT), in the 16 patients on whom autopsy was not performed. The two major patterns were local recurrence and liver metastasis. Two of the 5 patients who received both IORT and PORT and 3 of the 4 patients who received IORT alone developed local recurrence. Overall, 5 (55.6%) of the 9 patients who received radiotherapy had local recurrence. There was local recurrence in 3 (75%) of the 4 patients with tumor invasion of the dissected peripancreatic tissue and in 5 (42%) of the 12 patients without tumor invasion of the dissected peripancreatic tissue. Nine (56%) of the 16 patients developed liver metastases.

Autopsy disclosed local recurrence in 7 (78%) of the 9 patients (Table 3). Six (75%) of the eight patients who

Table 3. Sites of pancreatic cancer recurrence at autopsy

Patient no.	Surgical procedure	IORT Gy (Mev)	PORT Gy	Tumor invasion of portal system[a]	Tumor invasion of DPT (ew)[a]	Sites of recurrence at autopsy					
						Local	Liver	Peritoneum	Perigastric LN	Lung	Bone
1	PPPD	16 (12)	38.4	—	—	●←	●	—	—	●	—
2	PPPD	16 (9)	49.6	+	—	●←	—	●	—	—	—
3	PPPD	16 (9)	50.4	—	—	●	—	●	●	●	—
4	PPPD	16 (9)	50.4	—	—	—	●	—	—	—	●
5	PD	16 (12)	50.0	+	—	●←	●	—	—	●	—
6	DP	20 (9)	45.0	—	+	—	—	●	—	—	—
7	PPPD	—	55.8	—	—	●	—	—	●	—	●
8	TP	—	57.6	+	—	●	●	●	—	—	—
9	DP	—	—	—	—	●	—	—	—	●	—

PPPD, Pylorus-preserving pancreatoduodenectomy; PD, pancreatoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy; IORT, intraoperative radiotherapy; PORT, postoperative radiotherapy; LN, lymph nodes; DPT, dissected peripancreatic tissue; dots denote recurrence detected at autopsy; dots with arrows denote recurrence undetectable by CT; dashes, no recurrence

[a] Determined on resected specimens

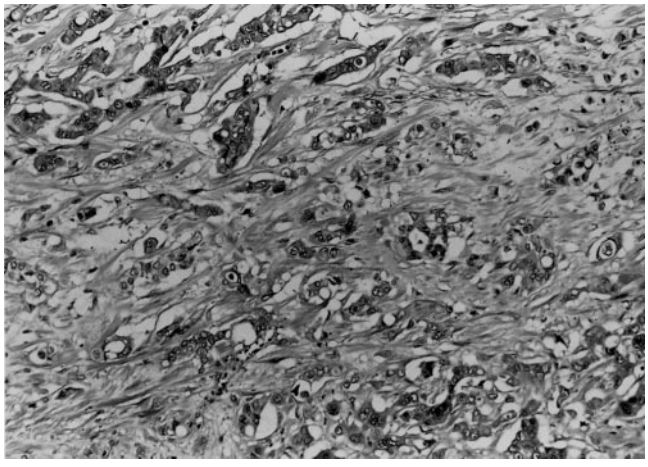

Fig. 4. Histologic findings in an autopsy specimen (patient No. 5 in Table 3) showing local recurrence in the retroperitoneum. Cancer cells are recognized in the dense fibrous stroma. (H&E, ×40)

Fig. 5. Computed tomography (CT) scan obtained 12 months after PPPD (patient No. 5 in Table 3). Local recurrence was undetectable by CT

received IORT and/or PORT developed local recurrence. Seven (88%) of the eight patients without tumor invasion of the dissected peripancreatic tissue were found to have local recurrence, but one patient (patient No. 6 in Table 3) with tumor invasion of the dissected peripancreatic tissue who had received both IORT and PORT did not have local recurrence. In three patients who received IORT and PORT, the local recurrence confirmed by histological examination at autopsy (Fig. 4) was not demonstrated by CT (Fig. 5), because the recurrent lesions had infiltrated the retroperitoneal connective tissue without forming a tumor mass. One patient treated by PPPD (patient No. 4 in Table 3) who had had metastatic cancer in the dissected infrapyloric lymph nodes had an intact peripyloric region with no metastases to the perigastric lymph nodes. Two PPPD patients (patients Nos. 3 and 7 in Table 3) who had had no metastases in the dissected infrapyloric lymph nodes were found to have micrometastases in the lymph nodes along the lesser curvature of the stomach. These two patients also had local recurrence in the retroperitoneum. No recurrence in the peripyloric region was observed in any of the PPPD patients.

One (patient No. 6 in Table 3) of the three patients (patients Nos. 5 and 15 in Table 2, and patient No. 6 in Table 3) who underwent DP with combined resection of the celiac axis died of peritoneal dissemination without local recurrence 41 months after surgery. Patient No. 15 in Table 2 is currently alive without recurrence 12 months after surgery with good quality of life. Patient No. 5 in Table 2 committed suicide (in the absence of any evidence of recurrence) 4 months after surgery.

Based on the CT and autopsy findings, we found that a total of 15 (60%) of the 25 patients in whom recurrence patterns were assessed had local recurrence, 13 (52%) had liver metastases, and 8 (32%) had both.

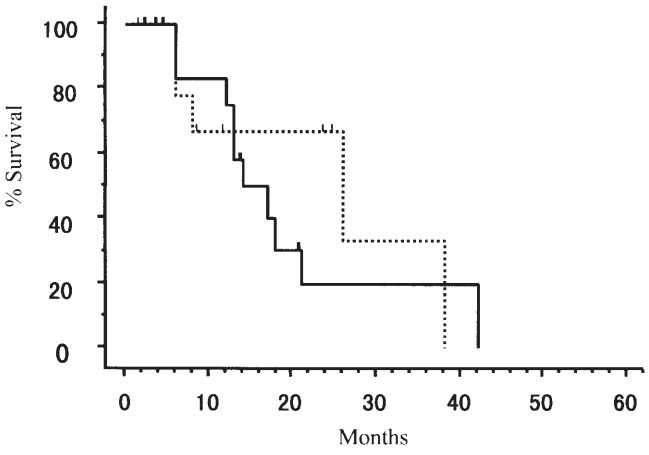

Fig. 6. Survival curves for patients who received intra- and/or postoperative radiotherapy (IORT and/or PORT) in addition to surgery (*continuous line*; $n = 15$) and for those who did not receive adjuvant radiotherapy (*dotted line*; $n = 10$). There was no difference in survival between the patients with and without adjuvant radiotherapy ($P = 0.66$)

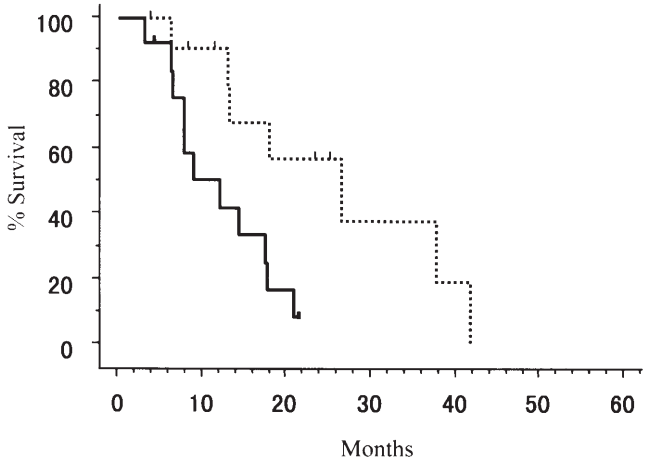

Fig. 7. Survival curves for patients who developed (*continuous line*; $n = 13$) and did not develop (*dotted line*; $n = 12$) liver metastases after resection. Patients who did not develop liver metastases had significantly longer survivals than those who did ($P = 0.02$)

Peritoneal dissemination occurred in 7 patients (28%). Eight (62%) of the 13 patients who received IORT and/or PORT developed local recurrence. However, local recurrence was not considered the direct cause of death in any of the patients, nor did any of the patients develop gastrointestinal obstruction caused by local recurrence. The incidence of liver metastasis in patients with and without tumor invasion of the portal system, including the superior mesenteric, portal, and splenic veins was 80% (8/10) and 33% (5/15), respectively. The median time to the occurrence of liver metastasis was 6 months after resection (range, 2–16 months).

Survival

The 1- and 3-year survival rates for all 34 patients were 59% and 19%, respectively, with a median survival time of 13 months. These 34 patients were divided into three groups according to the pattern of adjuvant radiotherapy (group A, IORT and/or PORT; group B, IORT alone; group C, surgery alone). Because of the quite different patient backgrounds, survival in group B could not be compared with survival in the other groups. The median survivals for the patients in groups A and C were 14 and 26 months, respectively. Although patients in group A were in better medical condition (evidenced by younger age and better nutritional status, etc) than those in group C, the comparison of survivals in groups A and C failed to yield a significant difference ($P = 0.66$) (Fig. 6).

Patients without liver metastasis ($n = 13$) had a 3-year survival rate of 38% and a median survival time of 26 months, whereas there were no 3-year survivors in the patients who developed liver metastasis ($n = 12$), and they had a median survival time of 9 months. The patients who did not develop liver metastasis had a significantly better outcome ($P = 0.02$) (Fig. 7).

Discussion

Extended resection for pancreatic cancer has been advocated in Japan in an effort to increase resectability and survival rates. However, the magnitude of this aggressive surgery causes poor nutritional status after resection and precludes patients from receiving the planned postoperative adjuvant therapy. In 1988, concern about poorer quality of life following extended resection led us to adopt PPPD with gastrointestinal reconstruction by the Imanaga method for patients with cancer of the head of the pancreas.[9,10] Our data indicate that the preservation of the pylorus with complete removal of the peripyloric lymph nodes does not give rise to recurrence at the peripyloric region as long as the indications for PPPD are observed. We also performed three DPs combined with resection of the celiac axis, which was involved by cancer of the body of the pancreas. In such patients, most surgeons would combine total gastrectomy with DP because of the decreased blood supply to the stomach. In view of the poorer nutritional status caused by DP plus total gastrectomy, we tried to preserve the entire stomach with blood supply maintained via the inferior pancreatoduodenal artery. Both PPPD and this type of DP preserve the entire stomach as a reservoir and maintain a more normal gastrointestinal hormone milieu, which in turn, results in better nutritional status. It is our consistent policy that good nutritional status in resected patients is necessary to complete planned postoperative adjuvant therapy.

The two major patterns of recurrence following curative resection for pancreatic cancer are local recurrence and liver metastasis.[11–14] The high incidence of local recurrence has led a number of investigators to deliver adjuvant radiotherapy to the tumor bed. In an evaluation of the benefits of adjuvant therapy, the GITSG reported the results of a randomized prospective study of 43 patients with pancreatic cancer undergoing curative resection with negative surgical margins.[2] The experimental group received adjuvant therapy consisting of 40-Gy external beam radiotherapy with 5-FU postoperatively. The median survival was 20 months in the group that received adjuvant chemoradiation, versus only 11 months in the control group. The subsequent registered-to-treatment analysis by the same group confirmed the survival benefits of the adjuvant therapy.[3] However, 18 (51%) of the 35 patients in the two groups in the GITSG study that received adjuvant therapy developed local recurrence.[2,3] Spitz et al.[15] reported that none of 41 patients who underwent preoperative chemoradiation and pancreatoduodenectomy with IORT developed local recurrence, whereas two of the 19 patients who received PORT developed local recurrence. Our study showed that 54% of the patients who received both IORT and PORT developed local recurrence. It is noteworthy that autopsies disclosed local recurrence that was undetectable by CT in 3 patients who received IORT and PORT. In heavily irradiated patients, accurate retrospective diagnosis of local recurrence would seem to be achieved only with autopsy findings as well as imaging studies. We found that the local recurrences missed by CT had infiltrated the retroperitoneal soft tissue in the radiation field without forming a tumor mass. This suggests a substantial radiation effect on cancer growth, providing a rationale for radiotherapy to the tumor bed.

Local recurrence was not the direct cause of death in any of the patients in our series. The majority of the patients succumbed to distant metastases (predominantly in the liver) although local control was achieved. Spitz et al.[15] also stated that the liver was the most common site of tumor recurrence in patients who received pre- or postoperative chemoradiation. The use of adjuvant radiotherapy aimed at local control does not address the potential for treatment failure at distant sites. In this study, we found no survival advantage of adjuvant radiotherapy over surgery alone, and the development of liver metastasis after resection proved to be a significant factor affecting survival. Therefore, some effective form of prophylactic treatment of liver metastases is needed to further improve survival in patients with resectable pancreatic cancer, particularly in those with tumor invasion of the portal system, who are at high risk for liver metastasis. Ishikawa et al.[16] reported on 21 patients who received continuous 5-FU infusion therapy via both the hepatic artery and portal vein to prevent hepatic metastasis after extended pancreatectomy. The 3-year survival rate was 54%, and there were no treatment-related complications in the 20 patients who survived surgery. The cumulative mortality rate from hepatic metastasis was only 8%. Komaki et al.[17,18] showed a decreased incidence of liver metastasis in patients with locally advanced and non-metastatic cancer of the pancreas treated with prophylactic hepatic irradiation. In their series, the whole liver was treated with 23.4 Gy in 13 fractions over a 2.5-week period, in addition to 61.2 Gy to the pancreas with a continuous infusion of 5-FU. Hepatic metastasis was documented in 24 (31%) of 79 patients, with 63 of the 79 patients having died at the time of analysis.[18] The suggestion of a decreased incidence of liver metastasis as a result of hepatic irradiation has stimulated the use of this modality in adjuvant settings combined with pancreatectomy and high-dose irradiation to the pancreatic bed.[19,20] Although it is too early to draw conclusions as to the safety and efficacy of prophylactic hepatic irradiation, because of the small number of patients examined and the short follow-up period, improvement in survival over other adjuvant modalities has not been observed.[19,20]

Our study showed that further improvement of survival in patients with resectable pancreatic cancer cannot be expected without prophylactic treatment for liver metastasis. In the absence of a more effective modality for pre- or postoperative use, hepatic irradiation represents a potential treatment strategy for subclinical liver metastasis. We plan to accumulate and study prospectively a larger series of patients with resectable pancreatic cancer receiving prophylactic hepatic irradiation combined with resection and high-dose intraoperative radiotherapy.

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