this study with those of previous Western trials, gemcitabine was approved for pancreatic cancer treatment in Japan in 2001.

Despite worldwide agreement on the role of gemcitabine as a first-line treatment in advanced pancreatic cancer, therapies that can achieve more significant survival advantages are needed because prognosis for patients with this disease still remains very poor. Based on preclinical and clinical data showing favorable antitumor effects of gemcitabine in combination with other cytotoxic agents, additional trials of gemcitabine-based regimens, including gemcitabine plus S-1, are in progress in Japan. Several trials of new agents arising from our increased understanding of the pathobiology of pancreatic cancer are also underway to identify compounds with activity against this disease.

RESULTS IN PATIENTS WITH RESECTABLE DISEASE

Although surgical resection has offered the only curative strategy for pancreatic cancer, the long-term outcome after resection remains poor. Chemotherapy can play a role as an adjuvant treatment after resection for pancreatic cancer; there is hope that postoperative local recurrence and metastasis will be reduced with addition of chemotherapy, resulting in improved survival.

Takada et al[24] conducted a randomized, controlled trial to evaluate postoperative adjuvant chemotherapy with mitomycin C and 5-FU in patients with resected pancreaticobiliary cancer. In this trial, patients were stratified according to disease and institution. One-hundred fifty-eight patients with resected pancreatic cancer were then randomly assigned to adjuvant chemotherapy (81 patients) or surgery alone (77 patients). The 5-year survival rate in pancreatic cancer patients was 11.5% in the adjuvant group and 18.0% in the no-adjuvant group, with no significant difference noted between the groups.

A multicenter randomized trial in 89 Japanese patients with resected pancreatic cancer compared adjuvant cisplatin and 5-FU for 2 courses after pancreatectomy with surgery alone. No statistical differences in survival were seen between the 2 groups, although the 5-year survival rate for patients with adjuvant therapy was somewhat better than for those treated with surgery alone (unpublished data). Given gemcitabine's favorable results in patients with advanced pancreatic cancer, we are now conducting an additional cooperative group study comparing adjuvant chemotherapy using gemcitabine and observation alone after pancreatic resection. Ten centers are participating in this study, which began accrual in 2002. Final analysis of the study is expected in 2006.

CONCLUSION

Pancreatic cancer is a major cause of cancer-related mortality in Japan and remains the most virulent disease in the world. At present, chemotherapy is of limited value in the treatment of pancreatic cancer, although gemcitabine has been accepted as first-line chemotherapy for advanced pancreatic cancer. However, various trials are being attempted that we hope will result in improving patient survival. Clinical trials of novel agents or gemcitabine-based regimens may be mandatory for the further development of chemotherapy for pancreatic cancer. Moreover, the evolving understanding of molecular and genetic biology should facilitate research to develop novel target-based agents and to establish individualized therapy regimens for this disease.

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Successful Outcome after Resection of Pancreatic Cancer with a Solitary Hepatic Metastasis

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SUMMARY
The presence of hepatic metastasis in pancreatic cancer has generally been considered to be a contraindication for surgery. However, the present case survived seven years after concomitant resection of pancreatic cancer and hepatic metastasis. This shows that hepatic metastasis may be a strong predictor of poor survival, but not a determinant of noncurability. Surgical resection may be an option for highly selected patients with pancreatic cancer complicated with hepatic metastasis.

KEY WORDS:
Pancreatic carcinoma; Solitary liver metastasis; Pancreatic resection

ABBREVIATIONS:
Carbohydrate Antigen (CA); Computed Tomography (CT); Ultrasonography (US)

INTRODUCTION

Pancreatic cancer of the body and tail has a poor prognosis, mainly due to progression beyond a localized resectable stage without special symptoms and a tendency for early metastasis to regional lymph nodes and the liver. Even if surgical resection in patients with pancreatic carcinoma is proposed with curative intent after an extensive preoperative evaluation, it is not unusual to first find hepatic metastasis at laparotomy. The presence of hepatic metastasis gives a dismal prognosis, and even apparently solitary metastasis seems to be a contraindication for radical surgery because other occult hepatic metastases probably exist at the same time. Recently, a few aggressive surgical approaches for pancreatic carcinoma with hepatic metastases have been reported as possible palliative options, however the outcomes were still disappointing (1,2).

We present here the first report of long-term survival after surgical treatment for pancreatic carcinoma with a simultaneous hepatic metastasis.

CASE REPORT

A 44-year-old male with a two-year history of maturity-onset diabetes mellitus complained of persistent back pain, intermittent bouts of fever up to 38°C, and a 4-kg weight loss over 2 months. A tumor was detected in the pancreas tail by computed tomography (CT) at his local hospital, and he was referred to us for further diagnostic work-up and treatment. Physical examination on admission showed neither jaundice nor anemia. Laboratory data were all within the normal range except for elevation of the serum carbohydrate antigen (CA) 19-9 level (405U/mL, normal <37U/mL), and the elastase level (486ng/dL, normal <400ng/dL). Ultrasonography (US) disclosed a hypoechoic mass with an irregular margin in the tail of the pancreas. Dynamic CT revealed a low-density mass in the pancreas tail, measuring 3.5cm at the greatest diameter (**Figure 1**). US and dynamic CT disclosed neither liver nor other distant metastases. Endoscopic retrograde pancreatography showed an abrupt obstruction in the distal side of the main pancreatic duct. Angiography revealed encasement of the splenic artery and compression of the splenic vein. Laparotomy was performed under a diagnosis of a pancreatic tail carcinoma without distant metastases. A hard tumor, 4cm in diameter, occupied the pancreas tail, with severe chronic inflammatory change on the splenic side. No lymph node swelling was noted and a cytologic study of peritoneal washing was negative for cancer cells. However, intraoperative US detected a

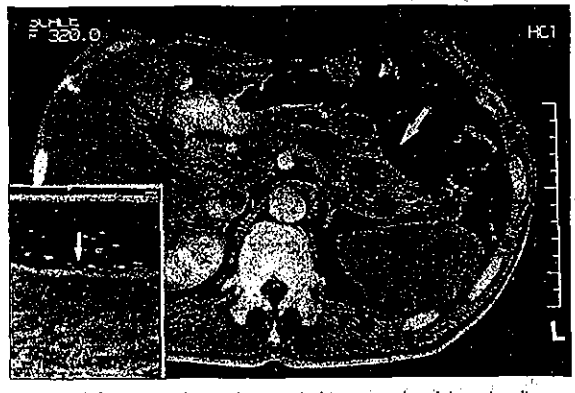

FIGURE 1 Contrast-enhanced computed tomography. A low-density mass in the pancreas tail is demonstrated.
Insert: Intraoperative ultrasonography. A hypo-echoic mass (8x7mm) (arrowhead) located the anterior superior segment of the liver is visualized just beneath the water bag.

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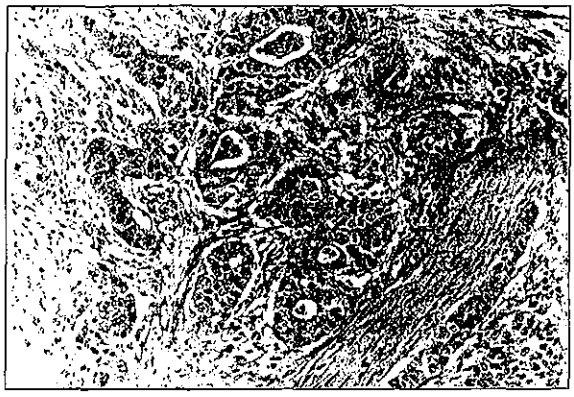

FIGURE 2 Histologic appearance of moderately differentiated tubular adenocarcinoma of the pancreas (Hematoxylin & Eosin, x200).

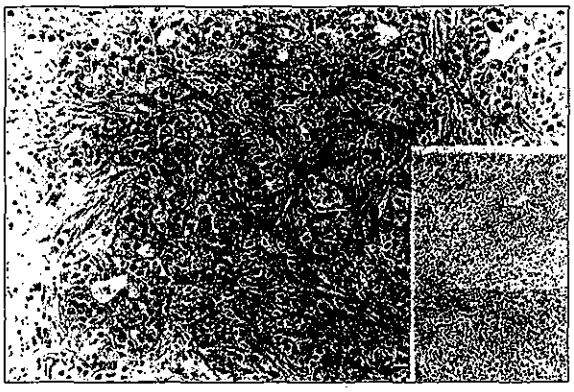

FIGURE 3 Histologic appearance of the hepatic nodule. (Hematoxylin & Eosin, x200). The morphological appearance (arrows) is similar to that in the pancreas.
Insert: Lower magnification shows normal liver and metastatic adenocarcinoma (Hematoxylin & Eosin, x100).

small solitary nodule (0.8cm in diameter) in the anterior inferior segment of the liver **(Figure 1 insert)**. A frozen section of the wedge-resected hepatic nodule strongly suggested metastatic adenocarcinoma from pancreatic carcinoma. Considering the solitary hepatic metastasis without other distant metastases, we consequently performed distal pancreatectomy, splenectomy, and left adrenectomy, with regional lymph node dissection.

The cut surface of the resected tumor of the pancreas was grayish-white, measured 40mm in the greatest diameter, with a cystic change in the center of the poorly demarcated tumor due to necrotic change. Obstructive pancreatitis was observed just distal to the tumor, with abscess formation. A wedge of liver, which was also removed at surgery, contained a grayish-white hard nodule measuring 8mm in diameter.

Pathologic examination of the pancreatic tumor revealed moderately differentiated tubular adenocarcinoma of the pancreas, partially including poorly differentiated adenocarcinoma. This carcinoma formed mainly irregular glandular and trabecular structures, accompanied by desmoplastic stroma **(Figure 2)**. A few signet-ring cells were present. The retroperitoneal connective tissue, the splenic artery and vein were involved, and invasion of lymphatics and small vessels was present. In the 37 lymph nodes harvested, nodal involvement was absent, and all of the resection margins were negative. The histological appearance of the hepatic lesion showed moderately differentiated adenocarcinoma, which was identical to that of the pancreatic tumor **(Figure 3)**. The final histopathological diagnosis was that the pancreatic tumor was pancreatic ductal carcinoma and the hepatic nodule was metastatic adenocarcinoma from the pancreas.

The postoperative course was uneventful and his preoperative complaints disappeared. Two courses of adjuvant systemic chemotherapy were performed with a regimen of 5-fluorouracil (500mg/m^2/day, day 1-5, continuously, intravenously) and cisplatin (80mg/m^2, on day 1, intravenously). After discharge, the patient was closely followed until now, at 3- or 6-months intervals, including CT or US examination and the measurement of CA-19, which decreased to the normal value postoperatively. The patient is doing well more than 7 years after surgery with no clear evidence of recurrence.

DISCUSSION

With improvements in long-term survival and minimal morbidity or mortality, surgery in patients with pancreatic cancer has become an established treatment option (3). However, the presence of hepatic metastases has been generally recognized as a definitive sign of noncurability. Although sporadic attempts at resectional surgery have been reported (1,2), we found no case of long-term survival in the English literature. Thus, this is the first report of a possible surgical cure in a patient with pancreatic cancer and hepatic metastasis.

The successful result in this case may be due to the unexpectedly low biological aggressiveness of this pancreatic cancer. Therefore, such an unusual course makes a clinician wonder whether this pancreatic tumor actually represents common invasive ductal adenocarcinoma, or if the hepatic lesion can be really differentiated from bile duct adenoma or hamartoma, sometimes macroscopically mimicking metastasis (4). However, the morphological structures clearly demonstrated as typical ductal adenocarcinoma of the pancreas and its hepatic metastasis without requiring additional investigations.

A recent paper revealed that more than 70% of patients with resectable pancreatic cancer also showed occult liver metastatic lesions (5), which contributed to a disastrous post-resection outcome. In this case, however, we persisted with resective therapy, since the hepatic metastatic lesion was identified as a solitary lesion based on extensive exploration of the liver by manual and ultrasound examination. Since multiple metastatic lesions should not be resected, such a thorough exploration seems mandatory for selecting patients who are suitable for surgery.

A high probability of locally curative resection is the second necessary condition for surgery. In this case, since the primary lesion was located very distally in the pancreas tail, a wide clear surgical margin around the primary disease was feasible and regional

lymph node of the pancreas was negative, which supports our resective policy. Considering the operative procedure, only a pancreatic tumor that is resectable by distal pancreatectomy, which requires neither the removal of organs other than the pancreas nor reconstruction of the digestive tract, should be indicated. Third, the patient's youth and good performance, which would support the postoperative recovery, is considered another indispensable requirement for justifying this aggressive surgery, since the long-term results after the present treatment are not yet established.

It is impossible to judge if the adjuvant chemotherapy contributed to the successful outcome. The adjuvant treatment is considered to be most effective on minimal amounts of residual cancer after grossly curative operation, and a recent report showed adjuvant chemoradiation improved survival in patients with stage 1 pancreatic cancer by treating occult micrometastases not detected by histology (6). But an analysis of failures following adjuvant treatment in patients with resected pancreatic cancer reportedly showed an improvement in local control (7), but most patients developed liver or peritoneal metastases. Although better systemic treatment has not yet been evaluated in a controlled clinical trial, postoperative chemotherapy might contribute to the longer survival in this case, without negatively affecting the quality of life.

The present patient met very favorable criteria, was well motivated and relatively young. The surgical procedure was performed with the realization of a high probability of recurrence. The patient's wish to embark on such treatment and the lack of an alternative therapy were our major determinants in the decision to proceed. Although few patients may be suitable for such treatment, the successful outcome in the present patient has encouraged us to perform surgery for pancreatic cancer with liver metastasis, if the above requirements are met. The option of radical surgery for pancreatic cancer with liver metastasis should be considered in highly selected and otherwise healthy young patients.

ACKNOWLEDGEMENTS

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Case Report

Acute Pancreatitis Caused by Afferent Loop Herniation After Billroth II Gastrectomy: Report of a Case and Review of the Literature

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KEY WORDS:
Acute pancreatitis; Afferent loop obstruction

ABBREVIATIONS:
Acute Pancreatitis (AP); Alanine Aminotransferase (ALT); Aspartate Aminotransferase (AST); Alkaline Phosphatase (ALP); Gamma-Glutamyl Transpeptidase (GGT); Computed Tomography (CT); Ultrasound (US); Total Parenteral Nutrition (TPN)

SUMMARY
We present herein the rare case of a 44-year-old man found to have acute pancreatitis due to afferent limb obstruction caused by internal herniation, twelve years after Billroth II gastrectomy. The patient complained of nausea, vomiting, and epigastric pain in acute onset. Physical examination, laboratory studies and computed tomography imaging revealed acute pancreatitis and peritonitis. The patient had been operated on urgently and afferent limb herniation was observed between the afferent loop's meso and duodenum. The herniated segment was incarcerated and the proximal segment of the afferent limb and duodenum were markedly dilated. Microperforations were also observed in the dilated proximal afferent limb. The herniated segment of the bowel was released and longitudinal plication and serosal patching procedure were performed on the afferent limb. The patient recovered after fifteen days and remained free of acute pancreatitis for two years.

INTRODUCTION

Afferent loop obstruction after Billroth II procedure is uncommonly diagnosed as the cause of acute pancreatitis (AP) (1). Efferent loop obstruction after Whipple procedure and gastroduodenal intussusception are other rare causes of AP (2,3).

The obstruction of the afferent limb of gastroenterostomy may lead to distention and increases intraluminal pressure in proximal jejunum, duodenum and also biliary-pancreatic ducts. The resulting hyperamylasemia and hyperbilirubinemia are now being recognized with increasing facility (2).

In this article, we report a case of AP caused by afferent limb obstruction due to internal herniation 12 years after Billroth II gastrectomy.

CASE REPORT

A 44-year-old man who was admitted to our hospital with severe epigastric pain, nausea and vomiting. The pain had started suddenly and was felt in the back of the patient for three days before the admission. He had had a few previous episodes of abdominal pain and was treated conservatively. He had been operated on with Billroth II gastric resection for a duodenal ulcer 12 years before.

His abdominal examination was remarkable particularly on epigastric tenderness and guarding in the whole abdomen. The patient was febrile (axillary temperature was 38°C) and tachycardic. His laboratory work-up revealed a white blood cell count of 17800/mm^3 and platelet count 140000/mm^3. Other abnormal

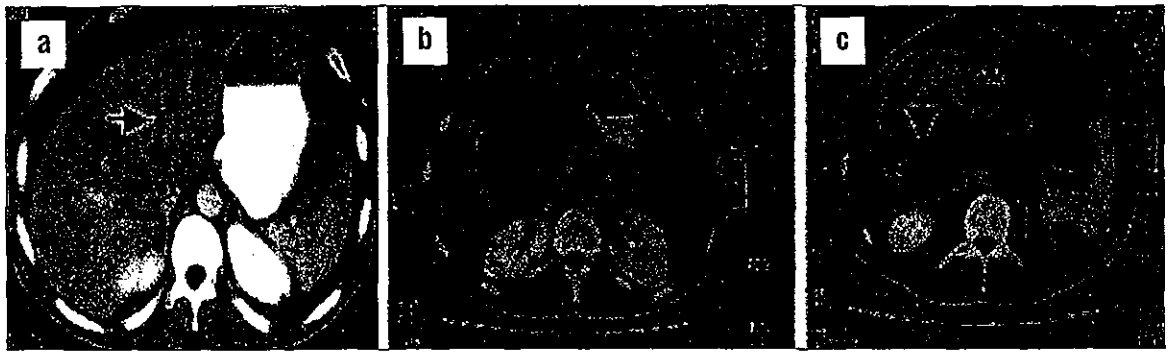

FIGURE 1 (a, b, c) Contrast enhanced abdominal CT scan of the case. CT images through the upper abdomen demonstrate fluid collection around the liver and spleen, dilatation in intrahepatic bile ducts (black arrow)(a), markedly dilated gallbladder, duodenum and pancreatic edema and pancreatic heterogeneity consistent with AP (b), and dilated duodenum and small bowel possibly afferent loop (black arrows)(c).

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Pancreatic Cancer Registry in Japan

20 Years of Experience

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Abstract: The prognosis of pancreatic cancer is defined by the histology and extent of disease. Preoperative histologic diagnosis and diagnostic imaging are fundamentals in managing the disease, but it is not rare to find unexpected peritoneal dissemination or liver metastasis at the time of operation. The overall resectability rate of pancreatic cancer is 40% in Japan. Resecting the portal vein and peripancreatic plexus were performed on 40% of the patients who underwent pancreatectomy for invasive cancer in the head of the pancreas. Long-term survival was only found in patients who underwent pancreatectomy. Radical lymph node dissection, or combined resection of the large vessels, did not seem to improve survival further than the standard resection. Multidisciplinary treatments combined with surgery were performed, and various effects of postoperative chemotherapy after pancreatectomy, intraoperative- and postoperative-radiation therapy, or postoperative chemotherapy for unresectable tumor, were shown. Development of unconventional therapies and refinement of the conventional therapy should be promoted on a randomized prospective trial basis. To promote this effort, which requires the international comparisons and cooperation, JPS developed a computerized JPS registration system downloadable from the JPS website (http://www.kojin.or.jp/suizou/index.html).

Key Words: pancreatic cancer, registry, radical resection, chemotherapy, TNM

(*Pancreas* 2004;28:219–230)

The mortality rate of pancreatic cancer increases after 40 years of age and exceeds 120 deaths per 100,000 by the age of 80 (Fig. 1).[1] It is the fifth leading cause of cancer death in men and the sixth in women in Japan, as well as in the United States and European countries. The prognosis of this disease has not improved markedly in the past 20 years, and the development of new treatment modalities are being pursued.[2,3] The Japan Pancreas Society (JPS) and the National Cancer Center have jointly sponsored the National Pancreatic Cancer Registry since 1981. As of 2002, 23,302 cases have been registered from the leading 350 institutions nationwide.[4] During these past 20 years, JPS published the first English edition of *Classification of Pancreatic Carcinoma* in 1996,[5] and the second English edition in 2003,[6] with the goal of making classification simple, easy to understand, and acceptable by international standards, while not sacrificing any of the merits of the Japa-

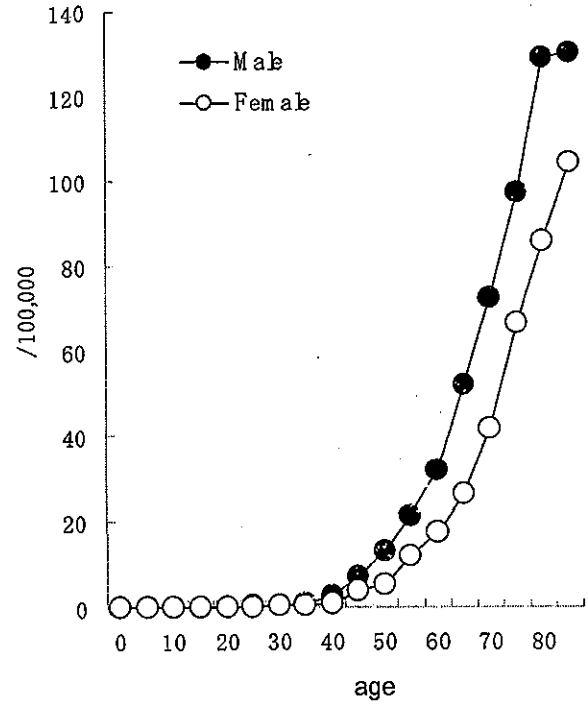

FIGURE 1. Age-corrected death due to pancreatic cancer in Japan. Modified from reference 1 and http://www.ncc.go.jp/en/statistics/.

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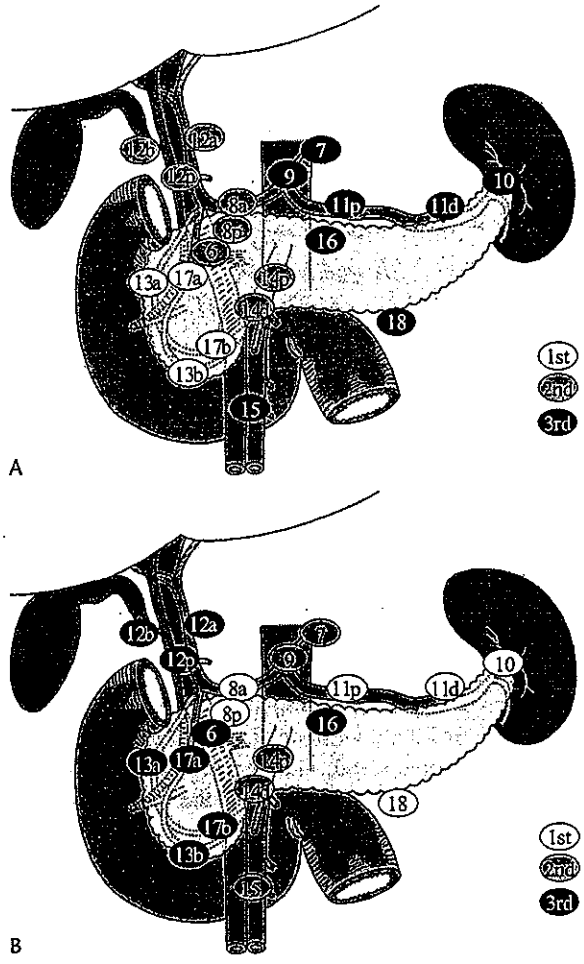

FIGURE 2. Lymph node groups for tumor of the pancreas in JPS classification system. The tumor is located in the head (A) or body and tail (B). Open circle, the 1st group; shaded circle, 2nd group; solid circle, 3rd group. Names of lymph nodes are described elsewhere.[6]

nese classification scheme. The classification of some prognostic factors has been refined and simplified, and the histologic classification is now compatible with the WHO classification system (1996). By providing standardized criteria and terminology, it facilitates comparison of clinical and pathologic data, with the ultimate goal of contributing to improving the results of treatment.[6] In this paper, current perspectives of pancreatic cancer in Japan are described based on this database according to the latest version of JPS classification.[6]

PATIENTS AND METHODS

Annually, attending physicians register patients diagnosed with pancreatic neoplasms. The questionnaire used in this study included patient history of the illness, family history, clinical symptoms and laboratory findings, extent of the disease conclusively defined by image diagnosis, surgical and pathologic findings, and pre-, intra-, and postoperative anticancer treatments. Each factor of the tumor extent was recorded as a conclusive finding from physical examination, imaging, surgical exploration, and pathologic findings. Physicians were requested to follow the patient's survival and type of recurrence annually. Registered data were entered to a database, and inappropriate cases and duplicate registrations were excluded. FilemakerPro software was used for the database and SPSS software was used for the statistical analysis. The cumulative survival rate was calculated using actuarial method and was tested by Wilcoxon-Gehan method. Any P value <0.05 was considered to be statistically significant.

JPS Classification Version 5

All data were described and analyzed according to the latest versions of JPS[6,7] and UICC[8] classifications. Both JPS and UICC independently changed their classifications in 2002. That same year, the American Joint Committee on Cancer (AJCC) revised cancer staging for exocrine pancreas, which was identical to that of the UICC classification.[9] The new JPS edition is based on data from the National Pancreatic Cancer Registry[2–4] and treatment results at individual hospitals. Additionally, to reduce human-based error in the process of registration and analysis, we developed a computerized JPS registration system based on the latest versions of classification. The application automatically calculates various factors with a simple click of buttons and checkboxes. Both Japanese and English applications can be downloaded from the JPS website (http://www.kojin.or.jp/suizou/index.html). The principal points of revision in the JPS system compared with the UICC system follow.

T Category

In the JPS classification system, the T factor is a function of 9 independent factors including tumor size (TS), distal bile duct invasion (CH), duodenal invasion (DU), serosal invasion (S), retropancreatic tissue invasion (RP), portal venous system invasion (PV), arterial system invasion (A), extrapancreatic nerve plexus invasion (PL), and invasion of other organs (OO).

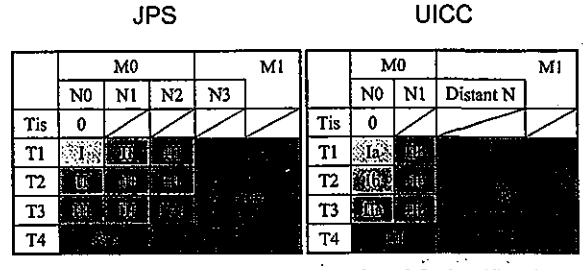

FIGURE 3. Staging system in JPS and UICC classifications Tis, noninvasive tumor. In JPS classification, metastasis to the 3rd group (N3) is equivalent to M1.

TABLE 1. Histologic Classifications of Registered Patients

I. Epithelial tumors	*11819*				
A. Exocrine tumors		11023			
1. Serous cystic tumors			*0*		
a. Serous cystadenoma				0	
b. Serous cystadenocarcinoma				0	
2. Mucinous cystic tumors			*328*		
a. Mucinous cystadenoma				0	
b. Mucinous cystadenocarcinoma				328	
3. Intraductal tumors			*229*		
a. Intraductal papillary mucinous tumors				229	
i. Intraductal papillary mucinous adenoma					*229*
With mucin hypersecretion				0	
Without mucin hypersecretion					*0*
ii. Intraductal papillary mucinous adenocarcinoma					
With mucin hypersecretion					*0*
Without mucin hypersecretion					*0*
b. Intraductal tubular tumor				0	
i. Intraductal tubular adenoma					*0*
ii. Intraductal tubular carcinoma					*0*
4. Atypical hyperplasia and carcinoma in situ			*16*		
5. Invasive ductal carcinomas			*10336*		
a. Papillary adenocarcinoma				1029	
b. Tubular adenocarcinoma				8765	
Well-differentiated type					*2148*
Moderately differentiated type					*3724*
Poorly differentiated type					*1142*
No information of differentiation					*1751*
c. Adenosquamous carcinoma				247	
d. Mucinous carcinoma				148	
e. Anaplastic carcinoma				19	
f. Invasive mucinous cystadenocarcinoma				56	
g. Invasive carcinoma originating in an intraductal tumor				72	
6. Acinar cell tumors			*87*		
a. Acinar cell adenoma				0	
b. Acinar cell adenocarcinoma				87	
B. Endocrine tumors		307			
C. Combined tumors		8			
D. Epithelial tumor with uncertain differentiation		111			
1. Solid pseudopapillary tumor				0	
2. Pancreatoblastoma				0	
3. Undifferentiated carcinoma				111	
E. Unclassifiable		44			
F. Miscellaneous		353			
II. Nonepithelial tumor	*0*				
Angioma			0		
Lymphangioma			0		
Leiomyosarcoma			0		
Malignant histiocytoma			0		
Malignant lymphoma			0		
Paraganglioma			0		
Other			0		
III. No histologic diagnosis	*11483*				

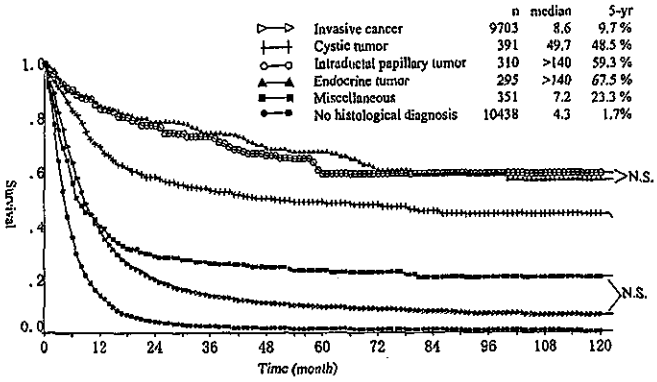

FIGURE 4. Histology and overall survival. Cumulative survival of all patients with or without pancreatectomy was calculated by actuarial method and tested by Wilcoxon-Gehan method. Any P value <0.05 is regarded as statistically significant. N.S., not significant.

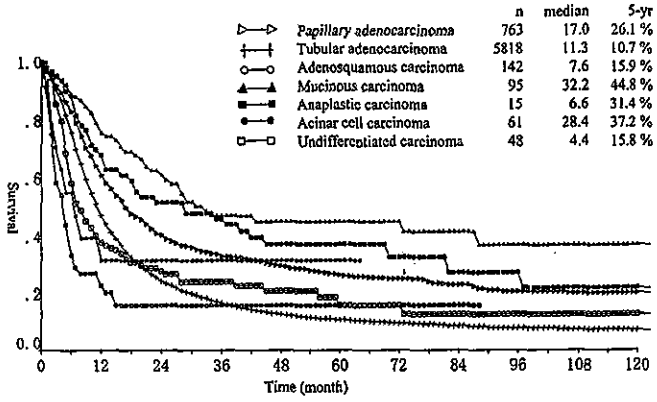

FIGURE 6. Subtype of invasive cancer and survival after pancreatectomy. Tubular adenocarcinoma includes well-, moderately, and poorly differentiated tubular adenocarcinoma together with tubular adenocarcinoma without description of differentiation, as indicated in Figure 7.

These factors are recorded as present (yes) or absent (no), except for tumor diameter size, recorded as TS1 (≤2 cm), TS2 (2.1–4.0 cm), TS3 (4.1–6.0 cm), and TS4 (>6.0 cm). Registration until year 2000 was collected using the old JPS classification system, when the 4-grade assessment (0, none; 1, suspected; 2, definite; 3, marked or adjacent organ invasion) was converted to 2 grades (grade 0 to no, other grades to yes). UICC defines a tumor that invades the celiac or superior mesenteric artery (SMA) as T4 regardless of portal vein, peripancreatic plexus, or organ invasion, while JPS regards them as T4, independently of celiac or SMA invasion.

N Category

The JPS grouping of lymph nodes has been extensively revised. Lymph nodes removed in a conventional resection are now categorized as group 1, and the other lymph nodes are categorized into groups 2 and 3, depending on lymph flow, lymph node metastasis rate, and outcome (Fig. 2). UICC regards metastasis to the regional lymph nodes as N1 regardless of the distance from the primary site. If the group 3 nodes are metastasized, it is considered to be equivalent to distant metastasis. Lymph node dissection is defined as D factor as follows: D0, no dissection or incomplete dissection of group 1 lymph nodes; D1, dissection of group 1 lymph nodes alone; D2, dissection of group 1 and 2 lymph nodes; and D3, dissection of group 1, 2, and 3 lymph nodes. The computerized JPS registration system automatically calculates the N and D factors according to each nodal status to avoid human error and subjective definition by surgeons.

M Category

Under the old classification system, distant metastasis (M1) was assessed as lymph node metastasis beyond group 3

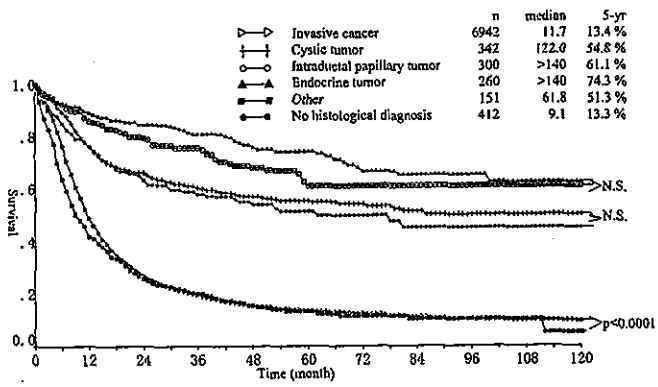

FIGURE 5. Histology and survival after pancreatectomy. Survival of the patients who underwent pancreatectomy is shown. N.S., not significant.

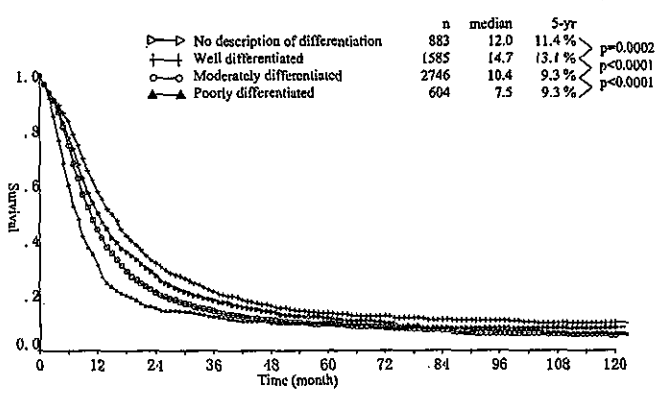

FIGURE 7. Differentiation of the tubular adenocarcinoma and survival after pancreatectomy.

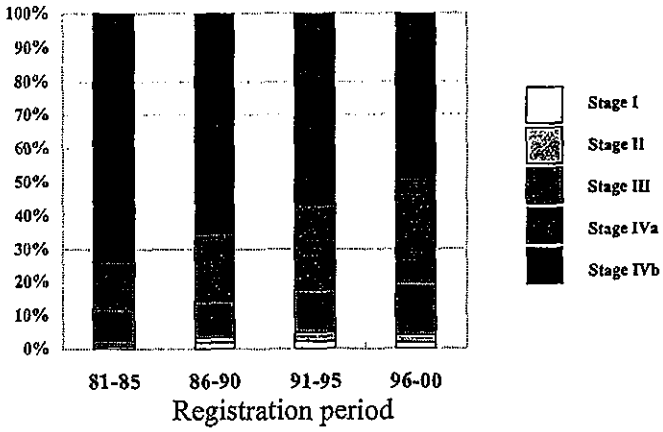

FIGURE 8. Trends of JPS stage of invasive cancer at the time of diagnosis. The stage proportion of the patients with invasive cancer is indicated according to the period of registration.

(N3), whereas in the new classification, M1 includes N3 metastasis.

Stage

Stage classifications are quite different in both systems. JPS regards the T and N factors as equivalent, while UICC regards T factors of greater prognostic value than N factors, as shown in Figure 3.

The Radicality

JPS defines the surgical margin as pancreatic cut-end margin (PCM), bile duct cut-end margin (BCM), and dissected peripancreatic tissue margin (DPM). DPM includes every surgical margin other than PCM and BCM, ie, anterior pancreatic and retropancreatic, especially along with the vessels. On the other hand, the surgical definition of the retroperitoneal (not the retropancreatic) margin in the AJCC classification is the soft tissue margin directly adjacent to the proximal 3–4 cm of the right lateral border of SMA.[9] The radicality in JPS classification system has been changed to R0, R1, and R2 similar to the UICC classification of curability A, B, and C in the old version.

RESULTS

Histologic Classification

The histologic classification of registered patients is shown in Table 1. Tumors arising from the exocrine pancreas consist of serous and mucinous cystic tumors, intraductal tumors, carcinoma in situ, invasive ductal carcinomas, and acinar cell tumors. Of 10,336 patients with invasive carcinomas, 56 patients with invasive mucinous cystadenocarcinoma and 72 patients with invasive carcinoma originating in an intraductal tumor were excluded from the analysis for invasive cancer. Instead, 87 cases of acinar cell adenocarcinoma and 111 cases of undifferentiated carcinoma were included in the analysis. Therefore, the term "invasive cancer" herein refers to most of the invasive ductal carcinomas, acinar cell tumors, and undifferentiated carcinomas, usually recognized as common phenotypes of pancreatic cancer. The excluded 2 subtypes of invasive ductal carcinomas were included in each category from which the tumors were derived. There had been no reg-

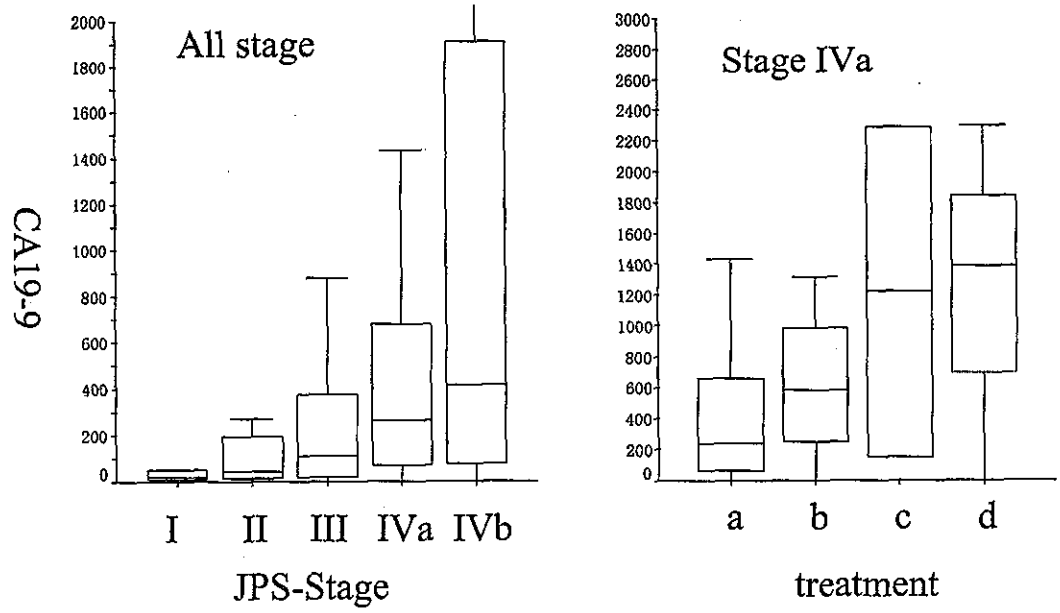

FIGURE 9. CA19-9 and the JPS stage (from cases in 2001 and 2002). The real values of CA19-9 were collected since 2001. Left: JPS stage and CA19-9. Right: Treatment of the patients with stage IVa disease and CA19-9. a, Pancreatectomy; b, palliative operation; c, exploratory laparotomy including intraoperative radiation therapy; d, no surgical procedure.

istration of nonepithelial tumors until 2002. These rare tumors may be collected by the new JPS registration system in the future. It should be noted that half of the patients were registered without histologic confirmation. These patients were excluded from the analysis even though the prognosis was very poor, as is mentioned later.

Histology and Survival

The prognosis for invasive cancer is very poor, with an overall median survival time (MST) of 8.6 months and a 5-year survival rate of 9.7% (Fig. 4). The survival rate of patients with endocrine tumors and intraductal papillary tumors is favorable, with an MST of >10 years and a 5-year survival rate of >50%. The survival rate of patients with cystic tumors is less favorable since this population includes invasive mucinous cystadenocarcinoma. The survival rate of patients without histologic diagnosis is extremely poor, with an MST of 4.3 months and a 5-year survival rate of only 1.7%. The survival rate after pancreatectomy for each histologic type is shown in Figure 5. Of 9703 patients with invasive cancer, 6942 patients (71.5%) underwent pancreatectomy, while of 10,438 patients without histologic diagnosis, 412 patients (3.9%) underwent pancreatectomy. The survival curve of the patients lacking histologic information fits that of patients with invasive cancer, though the difference in MST is statistically significant. Survival after pancreatectomy according to the subtypes of invasive cancer is shown in Figure 6. The most frequent type is tubular adenocarcinoma for which the curve is very similar to that of all invasive cancers. Survival of patients with papillary adenocarcinoma (MST, 17.0 months; 5-year survival rate, 26.1%), mucinous carcinoma (MST, 32.2 months; 5-year survival rate, 44.8%), and acinar cell carcinoma (MST, 28.4%; 5-year survival rate, 37.2%) is significantly better than that of patients with tubular adenocarcinoma (MST, 11.3 months; 5-year survival rate, 10.7%). Survival of the patients with adenosquamous carcinoma, anaplastic carcinoma, and undifferentiated carcinoma is extremely poor, with an MST of 7.6, 6.6, and 4.4 months, respectively. Figure 7 shows survival after pancreatectomy according to the differentiation of tubular adenocarcinoma. The difference of MST between well- and moderately differentiated types is 4.3 months, while the difference between moderately and poorly differentiated types is 2.9 months. If a Japanese pathologist diagnosed a tumor as tubular adenocarcinoma without any description of differentiation, the prognosis of these patients may fall somewhere between the well- and moderately differentiated types.

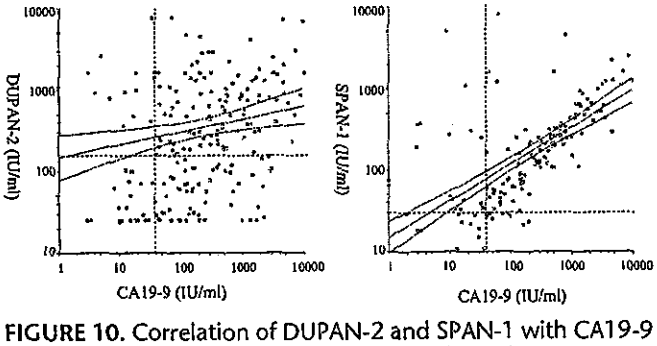

FIGURE 10. Correlation of DUPAN-2 and SPAN-1 with CA19-9 (from cases in 2001 and 2002). The real values of CA19-9 were plotted against DUPAN-2 and SPAN-1. Pearson's correlation coefficient is 0.009 for DUPAN2 (not significant) and 0.714 for SPAN-1 ($P < 0.0001$).

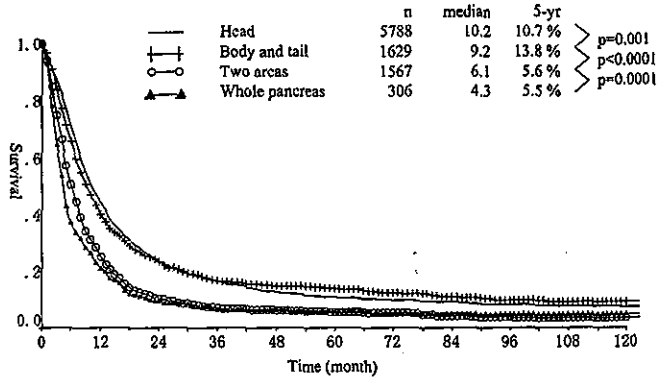

FIGURE 11. Locus of invasive carcinoma and survival. Survival according to the tumor locus is shown. Two areas: the tumor occupies the head and body or body and tail.

Diagnosis of Invasive Cancer

The most frequent reason that patients with invasive cancer visit their physicians is because of the symptoms (83.2%), while 9.7% of such patients went only for health checkups.

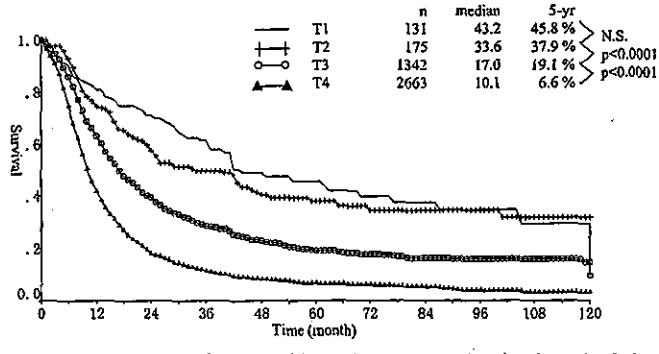

FIGURE 12. JPS T factor of invasive cancer in the head of the pancreas and survival after pancreatectomy. T1, tumor limited to the pancreas; ≤2 cm in greatest dimension; T2, tumor limited to the pancreas, >2 cm in greatest dimension; T3, tumor that has extended into any of the following: bile duct (CH), duodenum (DU), peripancreatic tissue (S, RP); T4, tumor that has extended into any of the following: adjacent large vessels (PV, A), extrapancreatic nerve plexus (PL), other organs (OO). N.S., not significant.

Only 1.7% of these patients were diagnosed because of worsening diabetes mellitus. The initial symptoms of patients with invasive cancer are abdominal pain (32.0%) and jaundice (18.1%). If the patient has a tumor in the head of the pancreas, the rate of jaundice increases to 26.3% and there is abdominal pain as well. The enthusiastic screening and progress of the imaging modalities enabled Japanese physicians to find the disease in the early stage, as shown in Figure 8. Since most of the patients are JPS stage III or more, the innovation of early diagnosis is eagerly awaited.

Using the latest data from 949 patients with invasive cancer registered in 2001 and 2002, the clinical significance of tumor markers was assessed. The correlation of CA19-9 with JPS stage and the treatment categories in stage IVa disease are shown in Figure 9. Even though there are exceptional cases, the median CA19-9 value correlates well with the JPS stage. In JPS stage IVa disease, the median CA19-9 value is 262.1 IU/mL and 412.8 IU/mL in stage IVb disease. The median CA19-9 value was significantly lower in patients who underwent pancreatectomy than in the other treatment categories. The value of CEA did not differ significantly between the stages, though there is an increasing tendency (data not shown). DUPAN-2 epitope is a syalylated mucin oligosaccharide but is distinct from Lewis antigen. So, DUPAN-2 may reflect the tumor volume in Lewis antigen–negative patients.[10] SPAN-1 is known to improve sensitivity if combined with CA19-9.[11,12] Median DUPAN-2 and SPAN-1 values were not different in the pancreatectomy group and palliative operation group. The correlation between DUPAN-2 and SPAN-1 with CA19-9 is shown in Figure 10, where the DUPAN-2 can detect the Lewis antigen–negative tumor, and SPAN-1 correlates well with CA19-9, with some exceptions. The relationship of survival and the tumor marker value will be reported shortly.

Staging of Invasive Cancer

If the tumor is localized in the head or body/tail, the MST of the patients is 10.2 and 9.2 months and the 5-year survival rate is 10.7% and 13.8%, respectively (Fig. 11). If the tumor is

TABLE 2. Lymph Node Metastases in the Resected Cases of Invasive Cancer of the Pancreatic Head

	Group	No Metastasis	Metastasis	Unknown	Metastatic Rate (%)	Total
Right cardial	3	2962	12	1936	0.2	
Left cardial	3	2760	8	2142	0.2	
Lesser curvature of the stomach	3	3748	48	1114	1.0	
Greater curvature of the stomach	3	3871	57	982	1.2	
Suprapyloric	3	3901	72	937	1.5	
Inflapyloric	2	3869	298	743	6.1	
Left gastric	3	3627	70	1213	1.4	
Anterosuperior common hepatic	2	3695	523	692	10.7	
Posterior common hepatic	2	3030	205	1675	4.2	
Celiac	3	3567	130	1213	2.6	
Splenic hilum	3	2736	23	2151	0.5	
Proximal splenic	3	3229	121	1560	2.5	
Distal splenic	3	4910	0	0	0.0	4913
Proper hepatic	2	3887	180	843	3.7	
Portal venous	2	3808	257	845	5.2	
Bile duct	2	3784	484	642	9.9	
Superior posterior pancreatic head	1	2830	1490	590	30.3	
Inferior posterior pancreatic head	1	3085	1098	727	22.4	
Proximal superior mesenteric	2	3432	526	952	10.7	
Distal superior mesenteric	2	3348	656	906	13.4	
Middle colic	3	3267	97	1546	2.0	
Abdominal aortic a2	3	3144	318	1448	6.5	
Abdominal aortic b1	3	1489	183	3238	3.7	
Superior anterior pancreatic head	1	3282	764	864	15.6	
Inferior anterior pancreatic head	1	3342	760	808	15.5	
Inferior margin of pancreas	3	3182	84	1	1.7	

The names of the lymph nodes are simplified from the original names in reference 2.

TABLE 3. Combination of Two Nodes in 743 Patients Who Harbored Only Two Nodal Metastases from Invasive Cancer in the Head

	1	2	3	4	5	6	7	8A	8P	9	10	11P	11D	12A	12P	12B	13A	13B	14P	14D	15	16A2	16B1	17A	17B	18
1	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
2		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3			7	0	0	0	1	0	0	0	1	0	0	1	0	1	1	0	1	0	1	0	0	0	0	0
4				5	0	1	0	1	0	0	0	0	0	0	0	1	0	0	1	0	0	0	1	0	0	0
5					3	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0
6						38	1	2	0	0	0	0	0	0	1	2	9	0	4	2	0	0	0	11	3	1
7							13	1	1	1	0	0	0	1	0	3	1	1	0	2	0	0	1	0	0	0
8A								76	5	4	0	1	0	4	4	1	15	6	6	4	1	6	2	5	7	0
8P									28	1	0	1	0	1	0	2	3	4	3	1	0	1	0	2	3	0
9										14	0	1	0	0	0	1	2	1	0	0	0	0	0	0	3	0
10											2	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0
11P												17	0	2	0	0	5	2	2	1	0	0	0	0	0	0
11D													0	0	0	0	0	0	0	0	0	0	0	0	0	0
12A														22	0	1	5	3	2	0	1	0	1	0	1	0
12P															21	4	4	0	0	1	0	1	0	4	1	0
12B																82	16	11	5	7	1	2	0	12	11	1
13A																	321	138	15	22	0	9	5	47	23	0
13B																		247	6	17	4	6	5	15	24	1
14P																			80	19	0	5	4	4	3	1
14D																				102	2	3	2	7	11	0
15																					12	1	0	1	1	0
16A2																						45	4	4	1	0
16B1																							34	3	6	0
17A																								162	45	1
17B																									149	0
18																										5

Example: Out of 321 cases with 13A involvement, 138 cases (43.0%) had 13B involvement and 47 cases (14.8%) had 17A involvement.

located in more than 2 areas, the prognosis of the patient is extremely poor.

T Factor

In 6084 patients with invasive cancer in the head of the pancreas, 638 were TS1 (10.6), 2929 were TS2 (48.1%), 1519 were TS3 (25.0%), and 652 were TS4 (10.7%). The positive rate of each factor is as follows: CH, 72.1%; DU, 47.7%; S, 49.5%; RP, 47.6%; PV, 50.8%; A, 24.8%; PL, 17.9%; OO, 16.9%, respectively. As a result, the T factors in this population are as follows: T1, 1407 cases (2.3%); T2, 209 cases (3.4%); T3, 1407 cases (23.1%); T4, 3658 cases (60.1%); and TX, 669 cases (11.0%). Survival according to the T factor after pancreatectomy for invasive cancer in the head of the pancreas is shown in Figure 12. Although the tumor size of T1 is <2 cm, the difference in MST and the 5-year survival rate between T1 and T2 was not statistically significant.

N Factor

The nodal involvement in the patients with invasive cancer in the head of the pancreas is shown in Table 2. The most frequent site is 13a and 13b (posterior pancreatic head), followed by 17a, 17b (anterior pancreatic head), 14d, 14p (superior mesenteric), 12b, 12p (hepatoduodenal ligament), and 6 (infrapyloric) nodes. In patients who had single-node metastasis, the frequencies of 13a and 13b are markedly higher, 32.3%

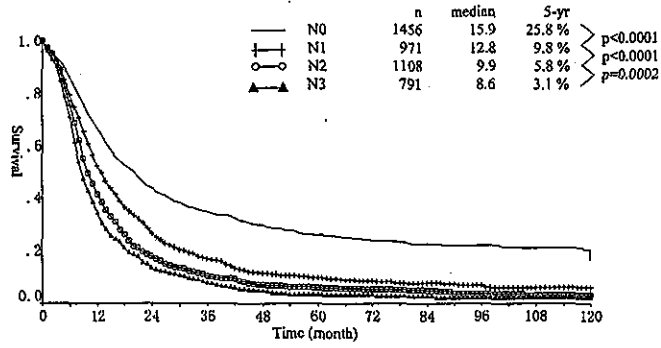

FIGURE 13. JPS N factor of invasive cancer and survival after pancreatectomy. Lymph node grouping is shown in Figure 2.

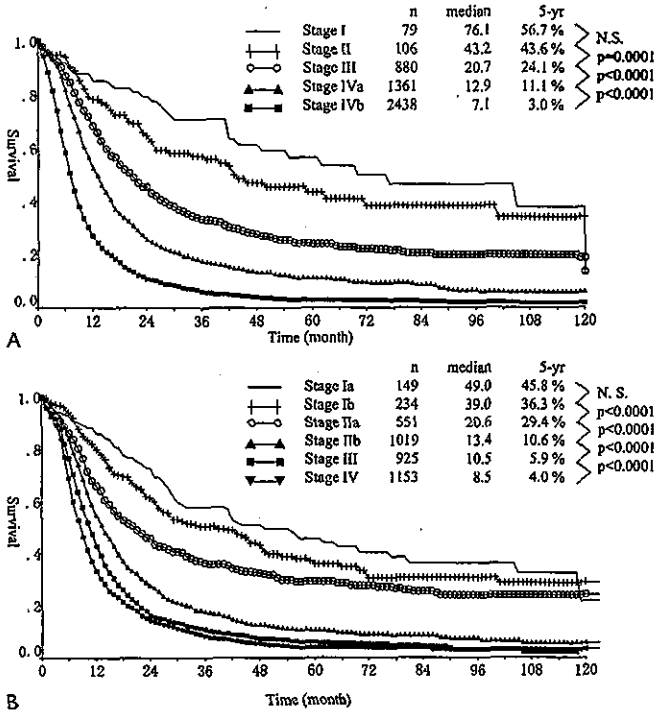

FIGURE 14. (A) JPS stage of invasive cancer and survival after pancreatectomy. (B) UICC stage and survival after pancreatectomy for invasive cancer. Definition of stages in each classification system is shown in Figure 3. N.S., not significant.

and 14.2%, respectively (data not shown). On the other hand, <2% of the patients had single-node metastasis to the paraaortic lymph nodes (16a2 or 16b1). Table 3 shows the combination of the 2 nodes in patients who had only 2-node involvement from the invasive cancer in the pancreas head. Together with the combination pattern in patients with multiple node metastases (data not shown[4]), it may be postulated that 13a and 13b can be sentinel lymph nodes of the lesion in the pancreas head.[13] Survival according to the N factor after pancreatectomy for invasive cancer in the pancreas head is shown in Figure 13. The differences between each N factor are statistically significant, suggesting that dividing the lymph nodes by the distance from the primary lesion is meaningful.

M Factor

Since Japanese surgeons aggressively dissect paraaortic lymph nodes, there are a number of patients who underwent pancreatectomy who were found (histologically or molecularly) to be metastatic to that area. The MST of patients with distant metastasis after pancreatectomy is 8.5 months, while that of the patients with unresected disease is 3.7 months (data not shown[4]).

Comparison of JPS and UICC Staging

In UICC classification, the T category reflects the distinction between potentially resectable (T3) and locally advanced (T4) primary pancreatic tumors, and the stage grouping has been changed to allow stage III to signify unresectable, locally advanced pancreatic cancer, while stage IV is reserved for patients with metastatic disease.[9] There is no definition of plexus invasion, which assigns the tumor to JPS T4 as well as SMA invasion, while it could be either T3 or T4 in the UICC classification. The survival curves of the same patients evaluated in both staging are shown in Figure 14. The JPS classification distinguishes each stage better than does the UICC classification. The 5-year survival rates in JPS stages I and III are 56.7% and 24.1%, respectively, while those of UICC stages Ia and III are 45.8% and 5.9%, respectively. The difference between UICC stage IIa and UICC stage IIb seems to be greater than the difference between IIb and III, thus making UICC stage IIb a very miserable stage. As shown in Table 4, there was no JPS stage III patient falling into the UICC stage III, while UICC stage IIb included patients with JPS stage II–IVb disease.

TABLE 4. JPS Stage and UICC Stage in Patients with Invasive Cancer in the Head of the Pancreas

	UICC							
	IA	**IB**	**IIA**	**IIB**	**III**	**IV**	**Unknown**	**Total**
JPS								
I	58	0	0	0	0	0	0	58
II	0	51	0	14	0	0	0	65
III	61	110	224	321	0	0	3	719
IVA	0	0	224	385	457	0	117	1183
IVB	0	0	0	183	284	991	64	1522
Unknown	0	0	1	1	82	0	348	432
	119	161	449	904	823	991	532	3979

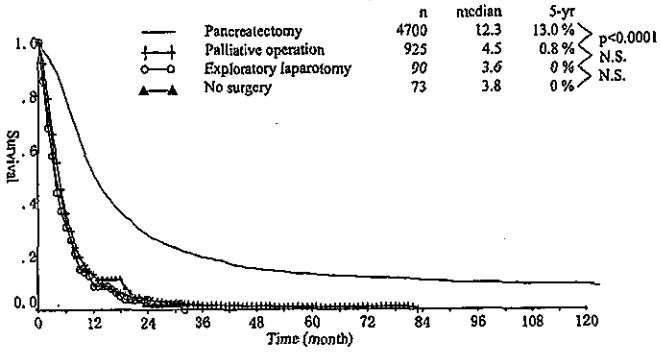

FIGURE 15. Treatment of invasive carcinoma of the head and survival. N.S., not significant.

Treatment of Invasive Cancer

Surgical Resection

Japanese surgeons have challenged the resection of advanced pancreatic cancer and proved that surgery can be performed safely.[14] Many aggressive surgeons performed extended radical surgeries for various stages of pancreatic cancer, and this registry collected the resulting nationwide survival data. As shown in Figure 15, surgical resection offers the only chance of long-term survival. A number of Japanese investigators have examined pathologic factors of the resected tumor in an effort to establish reliable prognostic variables associated with decreased survival.

Vessels and Plexus Resection

Figure 16 shows the 20-year trends of the vessels and the plexus resection combined with pancreaticoduodenectomy for invasive cancer in the head of the pancreas in Japan. Portal vein resection (PVR) was performed in 17.6% cases in 1981, which increased to 33.6% in 2000. On the other hand, resection of the arteries was performed in 3.0% of all patients, which increased to 5.0% in the early 1990s. Recently, only 1.5%–2.5% of patients underwent arterial resection. Resection of the peripancreatic plexus was performed in 38.3% of patients registered after 1993, when this parameter was first recorded. These trends suggest that surgeons do not go further if the tumor involves the arterial wall and that they frequently resect the plexus to make the surgical margin negative. Survival in patients with invasive cancer in the head of the pancreas is summarized in Table 5. PVR was performed in 91 patients who were finally defined as being without portal vein invasion. The MST of these 91 patients was 13.0 months and the 5-year survival was 8.3%, while the MST of the 1656 patients without PVR was 15.9 months and the 5-year survival rate was 19.2%. PVR did not affect positively or negatively the survival of the patients without portal vein invasion. In the patients with portal vein invasion, PVR was performed in 1219 patients whose MST was 10.2 months and 5-year survival rate was 7.4%. PVR was not performed in 761 patients who underwent pancreaticoduodenectomy though they had portal vein invasion. The difference in survival in each group was not statistically significant. Similarly, resection of the arterial system and peripancreatic plexus did not increase or decrease the improvement of MST or 5-year survival, even though the resection procedure was performed on patients without the specific organ invasion.

Lymph Node Dissection

Due to the modification in lymph node grouping, most patients with invasive cancer underwent pancreatectomy with lymph node dissection of group 3. Survival in patients who underwent each extent of dissection did not differ significantly as shown in Table 6. This fact was confirmed with a stricter algorithm to calculate the D factor in which all the lymph nodes in the group should be removed (data not shown).

Radicality

One prognostic factor of greatest significance in patients who undergo pancreaticoduodenectomy is considered to be incomplete resection.[9] Incomplete resection resulting in a grossly positive retroperitoneal margin is thought to be of no survival advantage compared with those patients who receive chemoradiation and no surgery.[9] The radicality and survival of patients with UICC stage III disease (locally advanced with arterial invasion) in the head of the pancreas are shown in Figure 17. Performing R0 surgery for the disease at this stage is controversial, because correct intraoperative judgment of the disease extent is difficult, even in experienced hands. The survival rate of patients who underwent R0 surgery was signifi-

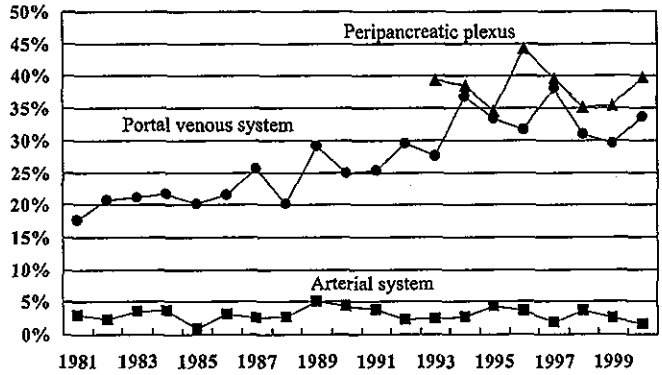

FIGURE 16. Trends of resected vessels and plexus with pancreaticoduodenectomy. Proportion of the patients with the target organ resection combined with pancreaticoduodenectomy is plotted against the registered year. The proportion includes any resection of arterial system: celiac artery, common hepatic artery, superior mesenteric artery, and splenic artery; the portal venous system: superior mesenteric vein, portal vein and splenic vein; extrapancreatic plexus: pancreatic head plexus I and II, superior mesenteric arterial plexus, plexus within the hepatoduodenal ligament, celiac plexus, common hepatic arterial plexus, and splenic plexus.

TABLE 5. Survival and the Combined Resection for Invasive Cancer in the Head of the Pancreas

Organ	Invasion	No Combined Resection n	MST	5-Year Survival (%)	Combined Resection n	MST	5-Year Survival (%)	Wilcoxon Test (A vs. B)
Portal venous system	No	1656	15.9	19.2	91	13.0	8.3	N.S.
	Yes	761	9.7	5.9	1219	10.2	7.4	N.S.
Arterial system	No	2817	13.4	14.9	37	10.3	0.0	N.S.
	Yes	636	8.6	3.8	107	8.1	3.4	N.S.
Peripancreatic plexus	No	803	15.5	18.3	571	16.8	16.9	N.S.
	Yes	264	9.1	3.5	261	9.8	7.4	N.S.

N.S., not significant.

cantly better than that of the patients who underwent R1 or R2 surgery. R1 resection did not give the same superior result as the R2 resection. However, the survival rate of patients with UICC stage III disease who underwent pancreatectomy with grossly residual tumor was significantly better than that of patients at the same stage whose tumors were not resected. Taken together, there may be a possible role of mass-reduction surgery for certain patients with locally advanced tumors.

Chemotherapy and Radiation Therapy

Postoperative chemotherapy in patients who underwent pancreatectomy for JPS stages I and II disease did not positively affect survival (data not shown[4]). In patients who underwent pancreatectomy for JPS stage III or advanced disease, postoperative chemotherapy (no specified protocol, retrospective yes or no) had a significant positive effect on survival. MST in patients who underwent pancreatectomy for JPS stages III, IVa, and IVb disease was increased by 5.4, 3.1, and 2.3 months, respectively. Currently, the Ministry of Health, Labor, and Welfare of Japan is hosting a randomized, controlled trial to examine the effectiveness of adjuvant postoperative administration of gemcitabine for patients who underwent pancreatectomy.

Patients who did not undergo pancreatectomy because of stage IV disease were subdivided into 4 categories, as shown in Table 7. Postoperative chemotherapy and radiation therapy for patients with distant lymph node metastasis but without liver metastasis or peritoneal dissemination, positively affected MST, adding 3 and 2 months, respectively. Again, these results are retrospectively archived and with no specific protocol. Conventional treatments for unresectable disease, however, are not satisfactory at all.

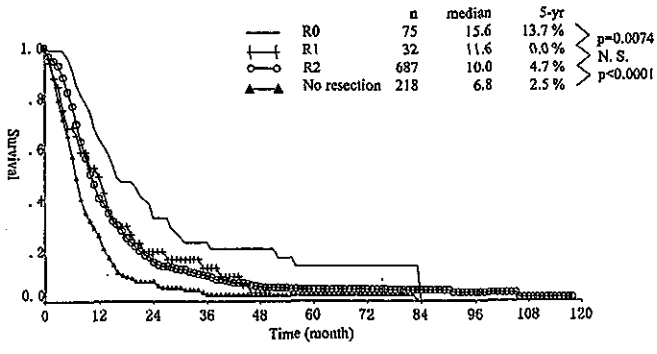

FIGURE 17. Declared radicality and survival of patients with UICC stage III invasive cancer in the head of the pancreas. R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor. N.S., not significant.

SUMMARY

In the past 20 years, Japanese physicians and surgeons have been aggressively fighting this tough disease. Thanks to improvements in perioperative management, the mortality and morbidity of pancreatectomy have been greatly reduced, even though the portal vein, peripancreatic plexus, artery, and/or retroperitoneal connective tissue was resected. However, the biology of pancreatic cancer, not the extent of resection, has been the key to defining survival so far. Improvement of im-

TABLE 6. Radicality of Lymph Node Dissection and Survival After Pancreatectomy in Patients with Invasive Cancer in the Head of the Pancreas

Dissection	n	MST	5-Year Survival Rate (%)	Wilcoxon Test
D0	106	14.4	15.6	
D1	49	12.4	19.1	N.S.
D2	231	13.8	19.7	N.S.
D3	3783	12.4	12.8	N.S.

No significant difference between D0 and D2, and D0 and D3.

TABLE 7. Chemotherapy and Radiation Therapy for Patients with Unresected Stage IV Disease

	Preoperative				Intraoperative				Postoperative			
	Chemotherapy		Radiation		Chemotherapy		Radiation		Chemotherapy		Radiation	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Stage IVa	30	1	30	1	28	3	25	6	13	17	27	2
Stage IVb												
Without M	50	4	52	3	51	5	48	7	23	33	44	11
LYM alone	159	23	175	3	139	34	139	34	71	102	149	20
		−2						**+2**		**+3**		**+2**
HEP or PER	1213	148	1317	39	1054	309	1133	219	661	691	1250	90
								+1		**+1**		**+1**

Number of patients (the bold number under each value indicates the statistically significant difference of MST (months) compared with the respective control). M, distant metastasis; LYM, distant lymph node involvement; HEP, liver metastasis; PER, peritoneal dissemination.

aging modalities has enabled us to detect smaller cancers, but these modalities were not sufficient enough to detect small metastasis to the liver or peritoneal dissemination, which is often found at the time of laparotomy. Histologic diagnosis is not easy, even in the operative cases. These factors make it difficult to expect a realistic prognosis and to define management of these patients. Apparently, management of this disease can be greatly improved. Surgery will still be at the center of management tactics, and conventional chemotherapy and radiation therapy will be employed in both resected and unresected cases. Chemotherapy and radiation therapy protocols are going to be refined in adjuvant or neoadjuvant settings on a randomized, prospective trial basis. Unconventional modalities, such as immunotherapy, gene therapy, and antiangiogenesis therapy, with or without conventional therapies, should be developed.[3] It is critically important to compare the results in a standardized manner. The computerized JPS registry system (http://www.kojin.or.jp/suizou/index.html in English and Japanese) will help mutual comparison and understanding. We strongly hope that the JPS and UICC systems will be revised similarly in the near future.

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Clinicopathological Aspects of Small Pancreatic Cancer

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Abstract: Small pancreatic cancers, intractable diseases, offer the possibility of cure. Can this be true? Through the National Pancreatic Cancer Registry, the Japan Pancreas Society (JPS) has collected 822 cases of invasive cancer with tumors <2 cm in diameter (TS1 pancreatic cancer). Papillary adenocarcinoma and the well-differentiated type of tubular adenocarcinoma are more frequent in TS1 pancreatic cancer than the larger tumors, suggesting that further genetic and phenotypic changes occur during their progression. Patients with TS1 pancreatic cancer presented with abdominal pain, jaundice, and exacerbation of diabetes, while 17.3% of them had no symptoms. Further imaging diagnosis should be employed to detect TS1 pancreatic cancer, but conventional US and ERCP play an important role in the diagnostic process. In this study, of 822 patients with TS1 pancreatic cancer, only 216 patients (26.3%) had T1 tumors because of invasion to adjacent tissue. There were 306 patients (37.2%) with lymph node metastasis, of whom 63 (7.7%) had N3 metastasis that is counted as a distant metastasis. As a result, only 136 patients (16.5%) had stage I disease with a median survival time of 78.2 months and a 5-year survival rate of 58.1%. Small pancreatic cancer does not necessarily mean early pancreatic cancer, and surgery alone is not sufficient to cure this disease.

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The Japan Pancreas Society (JPS) and the National Cancer Center have jointly sponsored the National Pancreatic Cancer Registry, and 23,302 cases were registered from 1981 to 2000.[1] During these 20 years, the imaging technology has been widely developed to be sensitive enough to detect a tumor <1 cm in size. The majority of the patients with pancreatic cancer, however, are found to have an advanced stage of disease at the time of diagnosis.[2] JPS defines a stage I tumor as confined in the pancreas and ≤2 cm in diameter, with no lymph node metastasis and no distant metastasis.[3] The tumor size (TS) is an important factor in defining the stage of this intractable disease. JPS defines the TS as 4 levels as follows: TS1, ≤2 cm; TS2, 2.1–4.0 cm; TS3, 4.1–6.0 cm; TS4, >6.0 cm. Since the number of the patients with small pancreatic cancer in each institute is quite limited, the nationwide JPS Cancer Registry gives us the insight into small pancreatic cancer. In this study, TS1 pancreatic cancer represents a small pancreatic cancer, and the clinicopathological features of TS1 pancreatic cancers are described.

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PATIENTS AND METHODS

Annually, attending physicians are requested to register patients who were diagnosed with pancreatic cancer from 1981 to 2000. The questionnaire consists of the history of illness, family history, clinical symptoms and laboratory findings, extent of the disease that is conclusively defined by the image diagnosis, surgical and pathologic findings, and pre-, intra-, and postoperative anticancer treatments. Physicians are requested to follow the patient's survival and the type of recurrence annually. Registered data are entered into a database, and inappropriate cases and duplicate registrations are excluded. According to the JPS histologic classification system, the histologic diagnosis is classified as invasive cancer, cystic tumors, intraductal tumors, endocrine tumors, and others.[4] Invasive cancer consists of the histologic subtypes, as shown in Table 1. Invasive mucinous cystadenocarcinoma and invasive carcinoma originating in an intraductal tumor are excluded from "invasive cancer." FilemakerPro software is used for the database, and SPSS software is used for the statistical analyses. Cumulative survival rate is calculated using actuarial method and tested by the Wilcoxon-Gehan method. For the frequency, the Fisher χ^2 test is used. Any P value <0.05 is considered to be statistically significant.

RESULTS

Histologic Subtypes

Of 23,302 patients, 10,406 (44.7%) had invasive cancer, while 11,483 (49.3%) patients were registered without histologic confirmation.[4] The correlation of TS and the histologic subtypes of invasive cancer are shown in Table 1. Of 10,406 patients, 822 (7.9% of all the patients with invasive cancers)

TABLE 1. Histological Subtypes of the Invasive Cancers According to Tumor Size (TS)

Histological Classification	TS1	TS2	TS3	TS4	TSX	Total
Papillary adenocarcinoma	114 (13.9%)	369 (9.7%)	221 (8.7%)	226 (10.9%)	99 (8.5%)	1029 (9.9%)
Tubular adenocarcinoma						
Well-differentiated type	218 (26.5%)	863 (22.7%)	532 (21.0%)	308 (14.8%)	227 (19.4%)	2148 (20.6%)
Moderately differentiated type	325 (39.5%)	1556 (40.9%)	930 (36.7%)	579 (27.9%)	334 (28.6%)	3724 (35.8%)
Poorly differentiated type	51 (6.2%)	305 (8.0%)	285 (11.3%)	339 (16.3%)	162 (13.9%)	1142 (11.0%)
No information of differentiation	91 (11.1%)	587 (15.4%)	427 (16.9%)	397 (19.1%)	249 (21.3%)	1751 (16.8%)
Adenosquamous carcinoma	6 (0.7%)	54 (1.4%)	67 (2.6%)	79 (3.8%)	41 (3.5%)	247 (2.4%)
Mucinous carcinoma	10 (1.2%)	30 (0.8%)	34 (1.3%)	54 (2.6%)	20 (1.7%)	148 (1.4%)
Anaplastic carcinoma	1 (0.1%)	6 (0.2%)	4 (0.2%)	8 (0.4%)	0 (0.0%)	19 (0.2%)
Acinar cell adenocarcinoma	3 (0.4%)	22 (0.6%)	17 (0.7%)	32 (1.5%)	13 (1.1%)	87 (0.8%)
Undifferentiated carcinoma	3 (0.4%)	15 (0.4%)	16 (0.6%)	53 (2.6%)	24 (2.1%)	111 (1.1%)
Total	822 (100.0%)	3807 (100.0%)	2533 (100.0%)	2075 (100.0%)	1169 (100.0%)	10,406 (100.0%)
Frequency	7.9%	36.6%	24.3%	19.9%	11.2%	100.0%

TS1, ≤2.0 cm; TS2, 2.1–4.0 cm; TS3, 4.1–6.0 cm; TS4, >6.0 cm; TSX, unknown TS.

had a TS1 pancreatic cancer. The frequency of TS1 pancreatic cancer in all invasive pancreatic cancers has been increasing from 5.6% in 1981 to 12.6% in 2000 (data not shown[1]). Papillary adenocarcinoma and a well-differentiated type of tubular adenocarcinoma are more frequent in TS1 pancreatic cancer than larger size tumors (TS2 and TS3). On the other hand, the frequencies of poorly differentiated types of tubular adenocarcinoma and undifferentiated carcinoma are increased in the TS2 and TS3 pancreatic cancers. In the largest TS4 pancreatic cancers, not only the poor prognostic histologic subtypes but also the favorable subtypes are increased. Together with the frequency of poorly differentiated tubular adenocarcinoma and adenosquamous, anaplastic, and undifferentiated carcinomas, the frequencies of mucinous carcinoma and acinar cell carcinoma are increased in TS4 pancreatic cancers.[4] Survival of patients after pancreatectomy for TS1 pancreatic cancer according to the histologic subtypes is shown in Figure 1.

Symptoms and Diagnosis

The initial symptoms according to the tumor size are shown in Table 2. Patients without any symptoms are more frequent in TS1 pancreatic cancer than in the larger size tumors. The most frequent symptom is abdominal pain, followed by jaundice and exacerbation of diabetes. The imaging modalities used to detect the tumor for the first time are shown in Table 3. In patients with TS1 pancreatic cancer, >40% of them were initially detected by abdominal US. It should be also noted that ERCP was used to make the initial diagnosis more frequently than in other tumor sizes. Currently, more sensitive methods are frequently used in Japan to detect tumors such as endoscopic ultrasonography (EUS), intraductal ultrasonography (IDUS), and magnetic resonance imaging (MRI). The latest version of the JPS Registration System (http://www.kojin.or.jp/suizou/index.html) will cover this information in the future. Since the real values of the tumor markers were not registered until 2000, data from the patients registered in 2001 and 2002 are shown in Table 4. While the sensitivities of CA19-9, CEA, DUPAN-2, and SPAN-1 in TS-1 pancreatic cancer are lower than those in other tumor sizes, the sensitivity of elastase-I is higher than that in the other tumor sizes.

Tumor Extent

In the JPS classification system, the local extent of the tumor, ie, T factor, is a function of 9 independent factors, including tumor size (TS), distal bile duct invasion (CH), duodenal invasion (DU), serosal invasion (S), retropancreatic tissue invasion (RP), portal venous system invasion (PV), arterial system invasion (A), extrapancreatic nerve plexus invasion

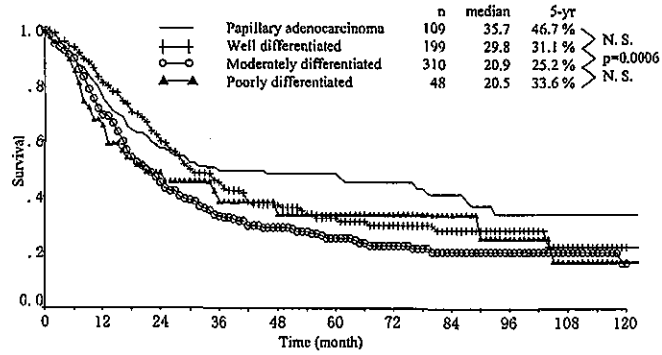

FIGURE 1. Histologic subtypes of TS1 pancreatic cancer and the survival rate after pancreatectomy. The survival rate was calculated with an actuarial method and compared by the Wilcoxon-Gehan test. TS1[3]: tumor size 1 (≤2.0 cm); N.S., statistically not significant ($P > 0.05$).