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Reappraisal of the Clinical Significance of Tumor Size in Patients With Pancreatic Ductal Carcinoma

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Objectives: Recent advances in diagnostic modalities have made it possible to detect small pancreatic ductal carcinoma and to increase the number of resected cases. However, the postoperative prognosis remains dismal.

Methods: Prognostic factors after pancreatectomy were retrospectively examined in 173 patients with small pancreatic ductal carcinomas (≤40 mm), and the size threshold for defining small pancreatic cancer as an early and curable disease was investigated.

Results: A Cox proportional hazard survival analysis indicated that no lymph node involvement and curative resection were important independent predictors of long-term survival. The incidence of lymph node metastasis was significantly lower in patients with tumor diameters of 20 mm or less ($P \leq 0.001$). Tumors with diameters of 15 mm or less were statistically associated with lower extension of local tumor spreading ($P = 0.001$) and less advanced stage ($P = 0.011$). The 5-year survival rate and the median survival term in patients with tumor diameters of 15 mm or less were 75% and 62 months, respectively, which were significantly better than those in patients with tumor diameter between 21 and 40 mm ($P = 0.02$).

Conclusions: A small tumor size is not always a guarantor of localized disease. However, survival after pancreatectomy is significantly favorable when the tumor diameter is 15 mm or less. A tumor diameter of 15 mm is recommended as the cutoff size as small pancreatic cancer because tumors with diameters between 16 and 20 mm should be considered comparable with tumors with diameters between 21 and 40 mm.

Key Words: small pancreatic cancer, tumor size, pancreatectomy, prognostic factors, lymph node metastases, curative resection

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The prognosis for pancreatic ductal carcinoma is extremely poor because of early metastasis.[1] With most malignant tumors, a smaller tumor size usually indicates an earlier clinical stage, and such tumors should be diagnosed and treated as early as possible to improve surgical outcome. Satake et al[2] defined small pancreatic cancer as a tumor less than 40 mm in diameter and stated that it is important to diagnose small pancreatic cancer (less than 4.0 cm) to improve prognosis. Small pancreatic cancers even with diameters of 2.0 cm or less, however, do not necessarily indicate an early disease that can be cured by surgery alone.[3–6]

Tumor size is one of the most important determinants of resectability and postoperative prognosis.[7–10] The Union International Contre le Cancer and the Japan Pancreatic Society (JPS) classification systems define small pancreatic cancer as tumors with a diameter of 20 mm or less, which is an important component in defining the primary tumor factor and the size of tumors.[11,12] However, whether this tumor size is an appropriate cutoff in defining the stage of small pancreatic cancer is questionable and of great clinical concern.[13,14]

Previously, accumulating a sufficient number of resected cases of small pancreatic cancer at a single institute was quite challenging, and most previous studies have been multi-institutional efforts.[3,6,15,16] Recent advances in diagnostic modalities, however, have made it possible to detect smaller pancreatic cancers and to increase the number of resected cases, especially in large volume centers, thereby providing more accurate clinical information.[17–20]

We retrospectively examined prognostic factors in 173 patients who underwent a pancreatectomy for pancreatic ductal carcinomas with diameters of 40 mm or less and evaluated the clinical significance of histologically measured tumor size in patients with small pancreatic cancer.

MATERIALS AND METHODS

Between January 1990 and December 2004, 403 patients underwent surgical exploration for the diagnosis of invasive pancreatic ductal cancer based on a standard preoperative evaluation consisting of contrast-enhanced computed tomography (CT), ultrasonography, magnetic resonance imaging, and arterial and portal CT angiography studies at the National Cancer Center Hospital, Tokyo, Japan. Ninety-two patients underwent only surgical exploration with biopsy or a bypass operation because of the presence of distant metastases or far-advanced local cancer extension. Limited invasion of the portal vein or superior mesenteric vein or a positive peritoneal washing cytology result was not regarded as contraindications to resection. Twenty-two patients with invasive ductal carcinoma originating in intraductal papillary-mucinous neoplasms were excluded because their lesions were regarded as

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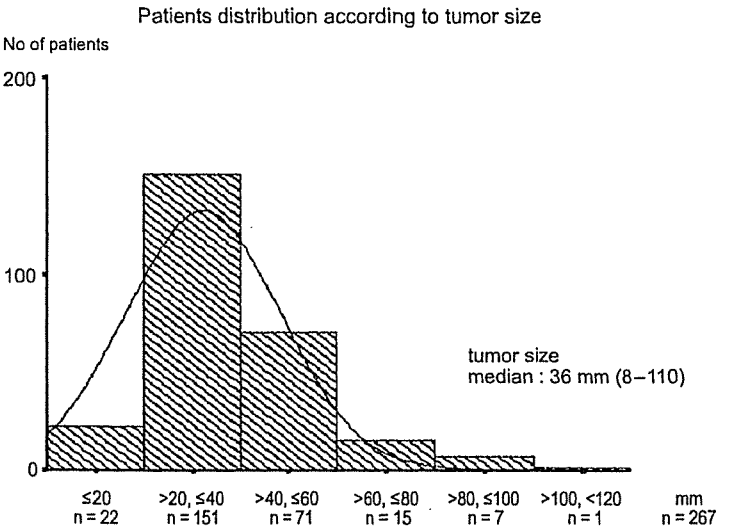

FIGURE 1. Histogram representing the distribution of tumor sizes among patients who underwent a pancreatectomy for invasive ductal carcinoma of the pancreas.

another variant of invasive ductal adenocarcinoma. Among the 289 patients who underwent resection, 3 with 30-day operative mortality and 5 with in-hospital deaths were excluded from this study of long-term survival results. In addition, 5 patients without complete follow-up data and 9 patients who died of other causes were also excluded from this study. The remaining 267 patients were enrolled in the present study.

Resected specimens were histopathologically examined and classified according to the JPS histological classification system.[12] Tumor size was measured histologically on the serial section containing the largest portion of the tumor. Tumor size was subcategorized and coded according to the JPS histological classification system as follows: TS1, 20 mm or less; TS2, from 21 to 40 mm, inclusive; TS3, from 41 to 60 mm, inclusive; and TS4, greater than 60 mm. We investigated long-term survival after surgical resection according to the tumor size (TS1–TS4). We recognized TS1 and TS2 tumors as small pancreatic cancers ($\leq$40 mm)[2] and analyzed 17 risk factors affecting survival after resection and outcome in patients with TS1 and TS2 tumors. As a further analysis of a subgroup of T1 tumors, the clinicopathologic factors of patients with pancreatic ductal carcinomas measuring 15 mm or less were also examined. The pathological features that might have influenced prognosis were classified as follows: serosal invasion (present or absent),

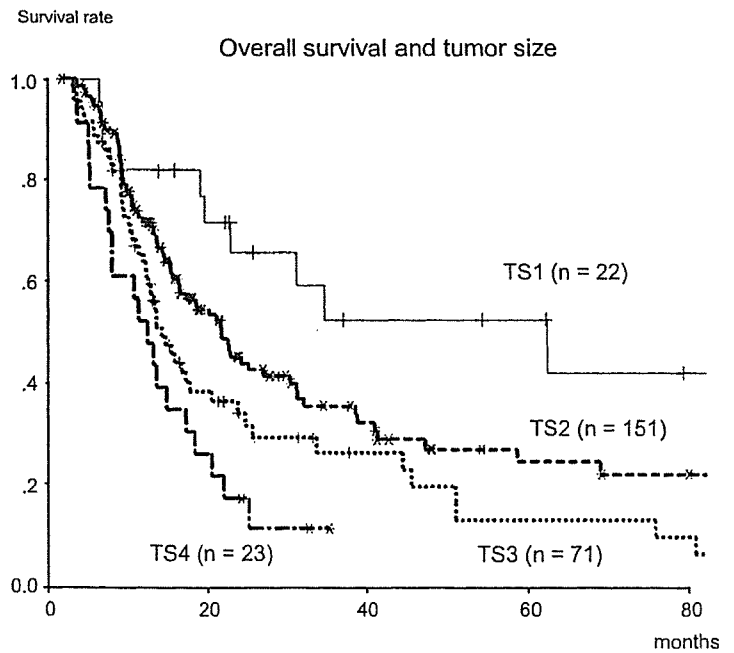

FIGURE 2. Actuarial survival curves for 267 patients who underwent a pancreatectomy for pancreatic carcinoma, compared according to tumor size (TS1–TS4): TS1 vs TS2, $P = 0.054$; TS1 vs TS3, $P = 0.003$; TS1 vs TS4, $P < 0.001$; TS2 vs TS3, $P = 0.036$; TS2 vs TS4, $P = 0.001$.

TABLE 1. Prognostic Factors for Survival

Variables	Tumor size ≤40 mm (n = 173)	Median Survival (mo)	Univariate Analysis, P	Multivariate Analysis, P
Age (median)				
≤63 yrs	87 (50)	31	0.0911	—
>63 yrs	86 (50)	21		
Sex				
Male	108 (62)	24	0.9128	—
Female	65 (38)	23		
Symptom				
Absent	61 (35)	25	0.6566	—
Present	112 (65)	23		
CA19-9 (median)				
<143 U/mL	87 (50)	31	0.0426	—
≥143 U/mL	87 (50)	20		
Site				
Head	121 (70)	23	0.1390	—
Body/tail	52 (30)	25		
Size				
≤20 mm	22 (13)	62	0.0543	—
>20 mm, ≤40 mm	151 (87)	22		
Serosal invasion				
Absent	148 (86)	25	0.0390	—
Present	25 (14)	16		
Retropancreatic tissue invasion				
Absent	16 (9)	62	0.1088	—
Present	157 (91)	23		
Vein invasion*				
Absent	102 (59)	31	0.0724	—
Present	71 (41)	16		
Artery invasion†				
Absent	159 (92)	23	0.4376	—
Present	14 (8)	39		
Plexus invasion				
Absent	126 (73)	30	0.0188	—
Present	47 (27)	16		
Lymph node metastases				
Absent	44 (25)	69	0.0007	0.002‡
Present	129 (75)	19		
Differentiation				
Well	37 (21)	23	0.3979	—
Moderate/poor	136 (79)	22		
Curative resection				
R0 (n=130)/R1 (n=29)	159 (88)	27	0.0002	<0.001§
R2	14 (12)	15		
Peritoneal cytology				
Negative	150 (92)	24	0.4979	—
Positive	13 (8)	22		
Intraoperative radiotherapy				
Yes	115 (66)	22	0.7686	—
No	58 (34)	30		
Adjuvant chemotherapy				
Yes	39 (23)	31	0.8945	—
No	134 (77)	23		

Values are given as n (%) or median.
*Portal or splenic vein.
†Gastroduodenal or splenic artery.
‡Exp (B): 2.6; 95% confidence interval; 1.4–4.9.
§Exp (B): 3.8; 95% confidence interval; 2.0–7.3.

retropancreatic tissue invasion (present or absent), splenic or portal vein invasion (present or absent), splenic artery invasion (present or absent), extrapancreatic nerve plexus invasion (absent or present), lymph node involvement (absent or present; n1, regional; n2, peripancreatic; and n3, paraaortic involvement), and differentiation of the tumor (well, moderate, or poor). Paraaortic lymph node involvement was defined as distant metastases. Pathological factors associated with tumor invasiveness, such as the growth patterns of the tumors infiltrating the surrounding tissue, lymphatic invasion, venous invasion, and intrapancreatic neural invasion, were also evaluated according to the JPS classification system. Local tumor spreading (primary tumor category) was classified as follows: T1, tumor limited to the pancreas, 2 cm or less in greatest dimension; T2, tumor limited to the pancreas, more than 2 cm in greatest dimension; T3, tumor that has extended into the bile duct, duodenum, or peripancreatic tissue, including the anterior pancreatic capsule or retroperitoneal invasion; and T4, tumor that has extended into any of the adjacent large vessels, extrapancreatic nerve plexus, stomach, spleen, or colon. A curative resection (R0) was characterized by a specimen with clear resection margins and no gross tumor mass remaining at the local site or in other organs. R1 resection was defined as positive cancer infiltration at the surgical margins. R2 resection was defined as the persistence of macroscopic tumor at the surgical site or the performance of combined resections for distant metastases. The tumors were staged according to *International Union Against Cancer (UICC): TNM Classification of Malignant Tumours*, 5th edition.[11]

Patients were closely followed every 1 to 2 months during the first year after surgery. Each follow-up visit included a physical examination, blood chemistry tests, and measurements of serum carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen. Ultrasonography and enhanced CT studies were performed at 3-month intervals, along with chest radiography.

Values are expressed as mean ± SD. Any statistical difference among the groups was analyzed using the unpaired t test or χ^2 test. Survival estimates were calculated using the Kaplan-Meier method. All variables were dichotomized for analysis. A univariate comparison of the survival curves was made using the log-rank test. Associations were considered significant if $P \leq 0.05$. A multivariate regression analysis was performed using the Cox proportional hazards model, and variables with $P < 0.10$ were entered into the final model. All statistical analyses were performed using SPSS for Windows 11.5 software (SPSS, Chicago, Ill).

RESULTS

The mean ± SD and median of histologically measured tumor sizes were 39 ± 16 mm and 36 mm (range, 8–110 mm), respectively, in 267 patients. The distribution of the histologically measured tumor sizes among patients who underwent a pancreatectomy for invasive ductal carcinoma of the pancreas is depicted in Figure 1. According to the JPS histological classification, there were 22 patients (8%) with TS1, 151 patients (57%) with TS2, 71 patients (27%) with

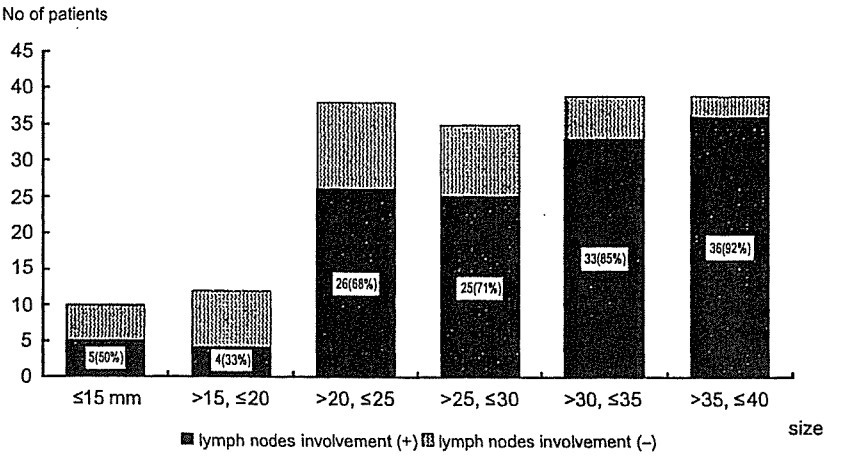

FIGURE 3. Lymph node metastasis and tumor size. Lymph node metastases were significantly present in patients with tumor diameters more than 20 mm.

TS3, and 23 patients (8%) with TS4 tumors. Ten patients (45%) with TS1 ductal carcinoma underwent pancreatectomies in the 2000s. The overall 5-year survival rate and the median survival time for each subgroup were 53% and 62 months in patients with TS1, 25% and 22 months for patients with TS2, 13% and 13 months for patients with TS3, and 0% and 12 months for patients with TS4 tumors, respectively. A significant difference in overall survival was recognized between the subgroups (Fig. 2).

Among the 173 patients (65%) with TS1 and TS2 tumors, 17 clinicopathologic factors were investigated with reference to their prognostic significance (Table 1). Indicators of a favorable prognosis in accordance to the univariate analysis included a preoperative CA19-9 value of less than 143 U/mL (median; $P = 0.043$), a tumor size of TS1 ($P = 0.054$), the absence of serosal invasion ($P = 0.039$), the absence of plexus invasion ($P = 0.019$), no lymph node involvement ($P = 0.001$), and a macroscopic curative resection (R0/R1; $P < 0.001$). When the significant prognostic factors in the univariate analysis were assessed using a multivariate analysis, the following factors were found to be independently associated with a favorable prognosis: no lymph node involvement and a macroscopic curative resection (R0/R1), with hazard ratios of 2.6 (95% confidence interval [CI], 1.4–4.9) and 3.8 (95% CI, 2.0–7.3), respectively (Table 1).

The relation between tumor size and lymph node involvement is shown in Figure 3. The positive rate of lymph node metastases in patients with a tumor diameter of more than 20 mm was significantly higher than in those with a tumor diameter of 20 mm or less ($P < 0.001$). The relation between tumor size and macroscopic noncurative resection (R2) is shown in Figure 4. No significant difference in R2 resections was seen among subgroups classified according to tumor size, and no R2 resections were performed in patients with a tumor diameter of 15 mm or less. Among the 10 patients with tumor diameters of 15 mm or less, the 5-year survival rate was 75% and the median survival time was 62 months compared with 33% and 23 months, respectively, in 12 patients with tumor diameters ranging from 16 to 20 mm, inclusive ($P = 0.081$; Fig. 5), and 25% and 22 months, respectively, in patients with tumor diameters ranging from 21 to 40 mm ($P = 0.016$; Fig. 5).

The clinicopathologic features of the patients with tumor diameters of 15 mm or less are summarized in Table 2. Clinical manifestations leading to diagnosis were abdominal pain (n = 3, 30%) and jaundice (n = 1, 10%). Six patients had no symptoms and were diagnosed incidentally during follow-up examinations for diabetes mellitus or during annual health checkups. Elevated CA19-9 levels were recognized in 5 patients. The pancreatic tumor locations were as follows: head

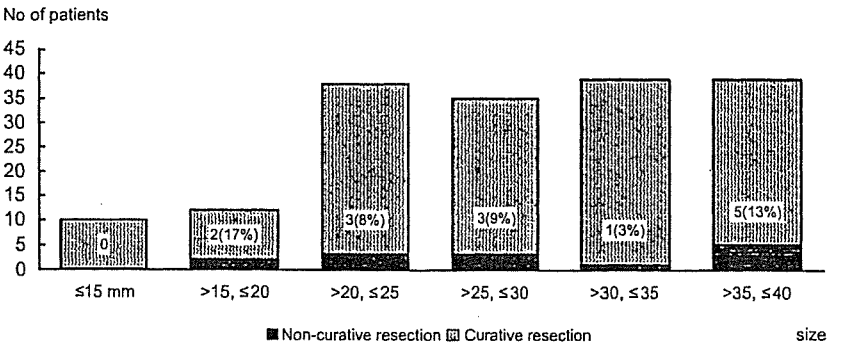

FIGURE 4. Percentage of noncurative resections according to tumor size. All 10 patients with tumor diameters of 15 mm or less received curative resections.

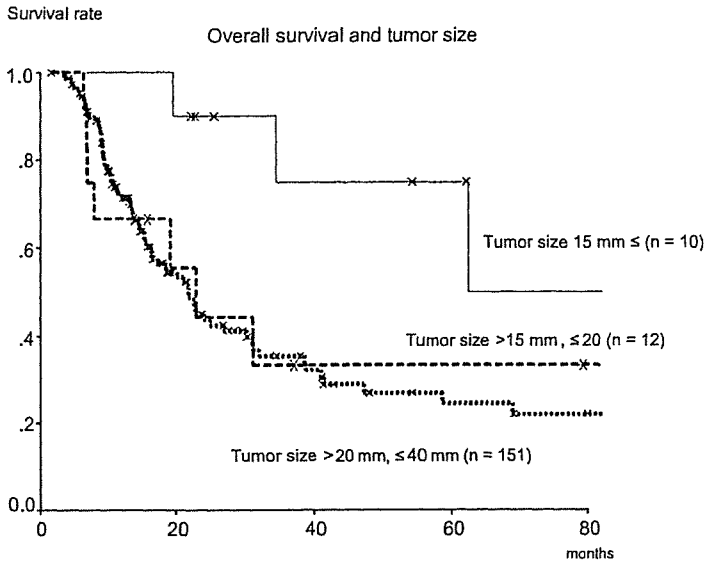

FIGURE 5. Actuarial survival curves for 173 patients who underwent a pancreatectomy for small pancreatic carcinoma, compared according to tumor size. Twenty-two TS1 patients were divided into 2 subgroups: those with a tumor diameter of 15 mm or less (n = 10) and those with a tumor diameter of 16 to 20 mm, inclusive (n = 12). The survival rate was significantly higher for patients with a tumor diameter of 15 mm or less compared with those with TS2 tumors ($P = 0.016$).

(n = 5, 50%), body (n = 4, 40%), and tail (n = 1, 10%). Peripancreatic lymph node metastases and retroperitoneal invasion were recognized in 5 and 4 patients, respectively. Positive peritoneal cytology was observed in 1 patient. Disease recurrence occurred in 4 patients (lung: n = 2, 20%; peritoneal dissemination: n = 1, 10%; and liver: n = 1, 10%). The distribution of tumor stages according to *International Union Against Cancer (UICC): TNM Classification of Malignant Tumours*, 5th edition,[11] was as follows: stage I, n = 3 (30%); II, n = 3 (30%); and III, n = 4 (40%).

A clinicopathologic comparison between 10 patients with tumor diameters of 15 mm or less and 12 patients with tumor diameters ranging from 16 to 20 mm, inclusive, is shown in Table 3. Tumors with diameters between 16 and 20 mm were statistically associated with further extension of local tumor spreading ($P = 0.001$) and more advanced stage ($P = 0.011$).

DISCUSSION

Thanks to advances in diagnostic imaging, the number of patients with small pancreatic cancers measuring 20 mm or less in diameter and identified during medical checkups, even in the absence of specific symptoms, has increased. Many of these patients subsequently undergo surgical resection. The reported 5-year survival rates after pancreatectomy in patients with TS1 tumors range from 8.0% to 59.3%, and a portion of these cases do not seem to represent early and curable cancers

TABLE 2. Clinicopathologic Features in Patients With Pancreatic Carcinoma (≤15 mm)

Patient Age/Sex	Size (mm)	Symptom	Ca19-9 Level (U/mL)	Site	Lymph Nodes Metastases	Differentiation	Rp(1)	INT(2)	Ly(3)	V(4)	Ne(5)	Peritoneal Cytology	Outcome	Stage
1. 53/M	8	Pain	1	Body	N	Poor	N	γ	N	N	P	N	54 mo AW	I
2. 68/M	10	None	119	Body	N	Poor	N	β	N	N	N	N	23 mo AW	I
3. 70/F	12	None	654	Head	P	Poor	N	γ	N	N	N	N	81 mo AW	II
4. 59/F	13	None	5	Body	N	Moderate	N	β	P	P	P	N	62 mo AW	I
5. 51/F	15	Pain	15	Head	P	Moderate	N	β	P	P	P	N	62 mo DOD, lung	II
6. 57/M	15	None	15	Body	P	Moderate	N	γ	P	P	P	P	20 mo DOD, peritoneum	II
7. 73/M	15	Jaundice	326	Head	N	Moderate	P	β	P	P	P	N	35 mo DOD, lung	III
8. 61/F	15	None	78	Head	P	Poor	P	β	P	P	P	N	26 mo AR, liver	III
9. 66/M	15	Pain	1	Tail	P	Moderate	P	β	P	P	P	N	22 mo AW	III
10. 78/M	15	None	59	Head	N	Poor	P	γ	N	P	P	NP	84 mo AW	III

Rp(1), retroperitoneal invasion; INT(2), growth pattern of tumors infiltrating the surrounding tissue; Ly(3), lymphatic invasion; V(4), venous invasion, Ne(5), intrapancreatic nerve invasion; N, negative; P, positive; β indicates an intermediate infiltrating pattern of growth; γ, a diffusely infiltrating of growth; NP, not performed; AR, alive with recurrence; AW, alive and well; DOD, dead of disease.

TABLE 3. Clinicopathologic Comparison in Patients With Small Pancreatic Ductal Carcinoma

Factors	Tumor Size ≤15 mm (n = 10)	Tumor Size >15 mm, ≤20 mm (n = 12)	*P*
Tumor size (mm), mean ± SD	13.3 ± 2.5	19.6 ± 0.8	0.003
Age (yrs), mean (range)	63 (51–78)	61 (54–78)	0.797
Sex (M/F)	6/4	9/3	0.384
CA19-9 (U/mL), mean (range)	37 (1–654)	93 (1–1673)	0.081
Symptom (present/absent)	4/6	6/6	0.969
Site (head/body/tail)	5/4/1	4/6/2	0.716
Lymph node involvement (positive/negative)	5/5	4/8	0.969
Differentiation (well/moderate/poor)	0/5/5	6/5/1	0.014
Local tumor spreading (T1/T3/T4)	6/4/0	0/5/7	0.001
Positive peritoneal cytology	1 (1/9)	1 (1/11)	1.000
Curability (R0/R1/R2)	10/0/0	9/1/2	0.235
Stage (I/II/III/IVA/IVB)	3/3/4/0/0	0/0/4/4/2	0.011
Median survival term, 5-year survival rate	62 mo, 75%	23 mo, 33%	0.081

(Table 4).[3,4,6,8,16,18–21] The major reason for this poor prognosis is probably the difficulty in determining precisely the size of pancreatic cancers, and some tumors that are actually larger than 20 mm might occasionally be included in the TS1 classification because the postoperative outcomes of patients with these tumors are sometimes similar to those of patients with TS2 tumors. Tumor size should be determined not by preoperative imaging or macroscopic inspection but by histological measurement because the boundary between tumorous and nontumorous parenchyma is usually indistinct with infiltrating tumor invasion. In the present study, only 8% of the patients had a tumor diameter of 20 mm or less, and the 5-year survival rate and median survival time for patients with TS1 tumors were 53% and 62 months, respectively; these survival results are relatively good compared with those of previous reports. Shimizu et al[18] also reported excellent survival results for TS1 tumors, with a 5-year survival rate of 59.3%. Their histological evaluation of 16 resected specimens revealed tumor sizes ranging from 9 to 20 mm (average, 13 mm), and 12 patients (75.0%) had tumor diameters of 15 mm or less.

Small pancreatic cancer was previously defined as a tumor with a diameter of 40 mm or less because the reported resectability of TS1/TS2 and TS3/TS4 tumors was 40.9% and 17.1%, respectively, according to collective series.[2,22] The present series revealed that the 5-year survival rates of TS3 (n = 71, 27%) and TS4 (n = 23, 8%) tumors were 13% and 0%, respectively; these rates are statically lower than those for TS1, and TS2 tumors. This dismal prognosis confirms the importance of early diagnosis, preferably at TS1 or TS2, and resection for pancreatic cancers.

Lymph node metastasis was a significant prognostic factor among the 173 patients with resected pancreatic carcinomas of less than 40 mm in diameter in the present study. Tumor size, which has also been reported as an important prognostic factor,[7–10] was significant in the univariate analysis but not in the multivariate analysis. This difference might have arisen from the fact that lymph node metastases were recognized in 9 TS1 patients (40.9%), although this incidence was still statistically smaller than that of patients with TS2 tumors. The previously reported incidences of lymph node involvement in resected specimens from TS1 patients range from 18.8% to 64.2% (Table 3). The relatively frequent positive rate of lymph node metastasis suggests that this tumor size does not necessarily indicate an early cancer and that an extended lymphadenectomy might be useful in patients with TS1 tumors.[15,23]

Wagener et al[24] emphasized that a curative resection was the single most important prognostic factor in patients with pancreatic adenocarcinoma. Curative resection was also an important prognostic factor in the present study, but achieving complete local control, even in patients with small tumors, was sometimes difficult. Fourteen (8.1%) of the 173 patients with TS1 or TS2 tumors received macroscopic noncurative resections; of these 14 patients, only 2 (9.1%) had TS1 tumors. However, all 10 patients with tumor diameters of 15 mm or less received curative resections, and the tumors in 6 of these patients (60%) were limited to the pancreas. Shimizu et al[18] also reported that among 12 patients with a tumor diameter of 15 mm or less and who received curative resections, 6 (50%) had tumors that were limited to the pancreas; furthermore, no local recurrences were observed in any of the patients. On the other hand, the multi-institutional study of Egawa et al[6] reported that among patients with TS1 tumors (n = 822), 172 patients (20.9%) exhibited invasion to the portal vein system, a major artery, an extrapancreatic plexus, or another organ, with a 5-year survival rate of 22.3%, despite a similar incidence of lymph node. Their poor results suggest that most of the TS1 tumors in their series consisted of tumors with a diameter of more than 15 mm. These cumulative results suggest that local cancer control

TABLE 4. Large Series Studies (n > 15) on Small Pancreatic Carcinoma of the Pancreas Less Than 20 mm in Diameter and Lymph Node Metastases, 1986–2005

Study	Year	No. Patients Who Underwent Resection	Positive Rate of Lymph Node Involvement (%)	Median Survival/ 5-Year Survival Rate
Tsuchiya et al[3]*	1986	103	31.1	30.3%
Manabe et al[4]	1988	17	41.0	37.4% (4 yrs)
Hatori et al[19]	1995	40	47.5	55% (T1), 35% (T1/T2)
Ihse et al[20]	1995	20	32.0	8.0%
Nitecki et al[8]	1995	42	26.2	20.0%
Brennan et al[21]	1996	56	64.2	24.2 mo (head: n = 51)/59.8 mo (body/tail: n = 5)
Furukawa et al[16]*	1996	31	58.1	54.4% (4 yrs)
Egawa et al[6]*	2004	822	49.1	22.3%
Shimizu et al[18]	2005	16	18.8	59.3%

*A multi-institutional study.

through surgical resections may be relatively easy when the tumor diameter is 15 mm or less. The present study revealed that tumors with diameters between 16 and 20 mm were statistically associated with further extension of local tumor spreading and more advanced stage compared with those with diameters of 15 mm or less.

When the TS1 group was divided into 2 subgroups, the median survival time and the 5-year survival rate of patients with tumor diameters between 16 and 20 mm, inclusive, were similar to those of patients with TS2 tumors, whereas the median survival time and the 5-year survival rate of patients with tumor diameters of 15 mm or less were 62 months and 75%, respectively. We recommend using 15 mm as the cutoff size between TS1 and TS2, and tumors with diameters between 16 and 20 mm should be included in the TS2 category. It also might be reasonable to regard tumors with diameters of 10 mm or less as early and curable cancers from the viewpoint of their clinicopathologic features.[14,25,26] However, among the 267 patients in this study, only 2 (0.7%) with stage I had a tumor diameter of 10 mm or less; thus, these minute carcinomas might be exceptional and are probably encountered rarely in clinical settings.

Pancreatic cancer with a histologically measured diameter of 15 mm or less should be recognized as small pancreatic cancer, and it is important to make an effort to diagnose this size of pancreatic cancer from the viewpoint of long-term survival after pancreatectomy.

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The Role of Paraaortic Lymph Node Involvement on Early Recurrence and Survival after Macroscopic Curative Resection with Extended Lymphadenectomy for Pancreatic Carcinoma

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BACKGROUND: Early recurrence of invasive pancreatic cancer is common even after curative resection. To establish appropriate selection criteria for radical surgery, it is essential to identify the patient population at risk for early recurrence.

STUDY DESIGN: One hundred thirty-three of 136 patients who underwent potentially curative pancreatectomy for invasive ductal adenocarcinoma of the pancreas between 1999 and 2003 were divided into two groups: patients whose recurrence developed within 1 year after operation and those whose recurrence did not develop within 1 year. Clinicopathologic factors were retrospectively analyzed between these groups using univariate and multivariable methods.

RESULTS: One postoperative death occurred, yielding an in-hospital mortality rate of 0.7% (of 136 patients). Eighty-one patients (61% of 133) were identified as having recurrent pancreatic carcinoma within a year. Paraaortic nodal involvement and positive washing cytology were independent predictors of early recurrence. The median survival time in 26 patients with paraaortic nodal involvement was 13 months, versus 30 months in 106 patients without paraaortic nodal involvement ($p < 0.001$). Paraaortic lymph node involvement was notably associated with elevated CA19-9 a month after operation ($p = 0.03$), larger tumor size ($p = 0.02$), and a positive surgical margin ($p = 0.04$).

CONCLUSIONS: Sampling of paraaortic lymph nodes is recommended as a routine examination at laparotomy. When positive nodes are confirmed by frozen section, early recurrence and poor survival are inevitable, even after radical operation including extended lymphadenectomy. (J Am Coll Surg 2006;203:345–352. © 2006 by the American College of Surgeons)

Invasive pancreatic cancer is one of the leading causes of cancer deaths in Western countries, and surgical resection has offered the only cure in the treatment of this disease.[1] During last 2 decades, surgical mortality after pancreaticoduodenectomy has decreased to less than 2%, and the actual 5-year survival rate after operation has been reported to be 10% to 31%.[2-5] The presence of hepatic metastases, macroscopic peritoneal dissemination, or apparent tumor involvement of the hepatic or superior mesenteric arteries has been widely accepted as an absolute contraindication for operation in patients with pancreatic adenocarcinoma. But despite these criteria for patient selection, the median survival time and 1-year survival rate are reported to be 15 to 17 months and 55% to 68%, respectively, even after macroscopic curative resection.[6-8] This short survival time may be because of the presence of other factors, which render a curative resection impossible.

Numerous prognostic factors, such as lymph node metastases,[4,5,9] histologic tumor grade,[5] vascular invasion,[4,10] positive surgical margin,[9] tumor size,[5,9,11] and peritoneal cytology[12-14] have been reported to be important determinants of longterm survival, but have not been generally used as definitive indicators for operation and treatment selection. To establish appropriate selection criteria for radical surgery and provide additional insight for adjuvant therapeutic strategies, it is impor-

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Abbreviations and Acronyms

CA19-9 = serum carbohydrate antigen 19 to 9
IORT = intraoperative radiation therapy
US = ultrasonography

tant to evaluate information about recurrent sites[15,16] and time to recurrence.[17,18]

In this study, we retrospectively examined recurrence patterns within a year and predictive factors associated with early recurrence in 133 patients who underwent macroscopic curative pancreatectomy with extended lymphadenectomy for invasive pancreatic carcinoma.

METHODS

Between January 1999 and December 2003, 227 patients were admitted to the National Cancer Center Hospital with a diagnosis of pancreatic cancer. Patients had standardized imaging assessment consisting of ultrasonography (US), contrast-enhanced CT, magnetic resonance imaging, and angiography. Transarterial portographic CT and hepatic arteriographic CT were routinely performed to examine not only local tumor extension to major vessels but small hepatic metastases. Patients with obstructive jaundice underwent preoperative transhepatic or endoscopic biliary stenting. Surgical resection was performed in the absence of macroscopic peritoneal dissemination, hepatic metastases, bulky lymph node involvement, or apparent tumor invasion around the common hepatic or superior mesenteric arteries after routine examination with intraoperative US. Peritoneal washing cytology was routinely performed just after laparotomy. Saline solution (100 mL) was instilled into the pelvis with a bulb syringe, and the specimens were aspirated from the pouch of Douglas into a sterile tube containing sodium ethylenediamine tetraacetic acid after abdominal agitation.[14] Limited invasion of the portal vein and positive peritoneal cytology were not regarded as contraindications for surgery. One hundred thirty-six of 227 patients (60%), who met the above criteria, underwent macroscopic curative pancreatectomy and had a pathologic diagnosis of invasive ductal adenocarcinoma of the pancreas.

The surgical procedures consisted of a classic Whipple procedure (n = 41), pylorus-preserving pancreaticoduodenectomy (n = 47), left-side pancreatectomy (n = 42), or total pancreatectomy (n = 6). Regional nodes, including the nodes around the common hepatic celiac, the right side of the superior mesenteric arteries, and the paraaortic lymph nodes were routinely dissected. The area of paraaortic lymph node dissection extended from the celiac trunk to the origin of the inferior mesenteric artery, and from the right margin of the inferior vena cava to the left margin of the left gonadal vein. Intraoperative radiation therapy (IORT, 30 Gy of electron beam radiation with an energy of 9 MeV) was administrated to the retroperitoneal fields in 80 patients.[19] Fifty-six patients did not receive IORT because of reconstruction of the hospital building between 1999 and 2000. No patients received external beam radiotherapy. Eight (6%) of the patients received 5-fluorouracil and cisplatinum, and 17 patients (13%) received gemcitabine as an adjuvant chemotherapy regimen under a randomized clinical trial setting during the study period.

Patients were closely followed every 1 to 2 months during the first year after operation. Each followup visit included a physical examination, blood chemistry tests, and measurement of serum carbohydrate antigen 19 to 9 (CA19-9). US and enhanced CT were performed every 3 months, along with chest radiography. Specific sites of first disease recurrence and the time to disease recurrence were analyzed. Recurrence was suspected when a new local or distant metastatic lesion was found on serial images and an increase in tumor marker level was recognized. Radiologic evidence of tumor recurrence was accepted in patients even if they did not undergo biopsy. When progression of the disease was confirmed by repeated image studies, the date of the first suspicious radiologic finding was used as the date of initial disease recurrence. One postoperative death occurred among 136 patients. Among the remaining 135 patients initially enrolled, one patient who died of causes other than cancer and one without complete followup data were excluded from this study. The median duration of followup was 21 months (range 3 to 62 months). Finally, the 133 patients enrolled in this study were divided into two groups: patients who had recurrence within a year (early recurrence) and those who had no recurrence within a year.

Clinicopathologic variables were compared between the two groups. These included age, CA19-9 levels measured immediately preoperatively and 1 month postoperatively, the type of operative procedure, portal vein resection, IORT, and the site and size of the tumor, lymph nodes status with special reference to the paraaor-

tic lymph nodes, local tumor extension, tumor differentiation, surgical margin status, peritoneal cytology, and adjuvant chemotherapy. The location and number of dissected lymph nodes were classified and recorded according to the Japanese Pancreas Society[20]: n1, regional pancreatic lymph nodes; n2, peripancreatic lymph nodes; and n3, paraaortic lymph nodes. The local tumor location and extension were also classified according to the Japanese Pancreas Society and the TNM system 5th edition[21]: t1, tumor limited to the pancreas (2 cm or less in the greatest dimension); t2, tumor limited to the pancreas (more than 2 cm in the greatest dimension); t3, tumor extending directly into the duodenum, bile duct, or peripancreatic tissues; and t4, tumor extending directly into the stomach, spleen, colon, and adjacent large vessels. Tumors were staged according to the TNM system 5th edition, and n2 and n3 lymph node involvements were defined as distant metastases.

Comparison of clinicopathologic features between these two groups was performed using the chi-square test with Yates' correction in the univariate analysis, and all major factors by univariate analysis were included in a multivariable regression analysis to identify independent factors associated with early recurrence. Odds ratios and their 95% confidence intervals were calculated using binary enter-stepwise forward logistic regression estimates. Survival estimates were calculated by the Kaplan-Meier method. Univariate comparison of the survival curves was made with the log-rank test. All statistical analyses were performed with SPSS for Windows 11.5 software. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

One postoperative death occurred in a patient who had undergone a total pancreatectomy with portal vein resection, yielding an in-hospital mortality rate of 0.7% (1 in 136), during this study period. The patient had postoperative bleeding, probably originating from a skeltonized hepatic artery on postoperative day 4. Overall 1-, 2-, 3- and 5-year survival rates were 75%, 47%, 34%, and 18%, respectively, in 133 patients. Eighty-one patients (61% of 133 patients) were identified as having recurrent pancreatic adenocarcinoma within a year. There were 50 men and 31 women; mean age was 62.3 ± 9.3 years (range 36 to 83 years). Thirty-eight patients among the 81 patients with early recurrence (47%) died within a year after pancreatic resection from recurrent disease.

Table 1. All Sites of Initial Recurrence (Within 1 Year)

Site	n	%
Total no. of recurrence lesions	94	
Liver	37	46
Peritoneum	27	33
Locoregional	16	20
Lymph nodes	7	9
Lung	3	4
Bone	2	2
Skin	1	1
Pleural	1	1
Total no. of patients with recurrence	81	100
Patients with solitary initial recurrence	66	81
Patients with multiple recurrences at initial diagnosis	15	19

Median survival was 13 months in the 81 patients with recurrence within a year, as compared with 45 months in those who had no recurrence within a year ($n = 52$, $p < 0.0001$). No patient with early recurrence survived more than 30 months after operation.

Table 1 shows the anatomic locations of all initial recurrences within 1 year. Recurrence in a single site occurred in 66 patients (81%) at initial diagnosis and at two or more sites in 15 patients (19%) among 81 patients with early recurrence. The leading recurrence site was the liver, with 37 lesions (46%). Seven patients (9%) had only local recurrence as a primary site without apparent distant metastases.

Among the 15 clinicopathologic factors compared between the two groups (Table 2), age, gender, site of tumor (head/body, tail), operative procedure, portal vein resection, IORT, adjuvant chemotherapy, tumor differentiation, and surgical margin were not notable in the univariate analysis. Six tumor factors (CA19-9 before resection > 140 U/ml, CA19-9 after resection > 37 IU/L, tumor size > 30 mm, local tumor extension T4, presence of paraaortic lymph node metastases, and positive for peritoneal cytology) were associated with higher frequencies of patients suffering recurrence within a year. For lymph node status, negative (n0), regional pancreatic (n1), peripancreatic (n2), and paraaortic (n3) lymph node metastases were recognized in 9 (11%), 34 (42%), 14 (17%), and 24 (30%) patients with early recurrence, and 17 (33%), 26 (50%), 6 (12%), and 3 (5%) patients without recurrence, respectively. According to the TNM system 5th edition, stages I, II, III, IVA,

Table 2. Risk Factors for Recurrence Within 1 Year

	Patients with early recurrence		Patients without recurrence		
Clinicopathologic factors	**n**	**%**	**n**	**%**	**p Value**
Age, y					
Mean < 62	29	36	41	79	0.60
≥ 62	52	64	11	21	
Gender					
Male	51	63	32	62	> 0.99
Female	30	37	20	38	
CA19-9 before operation, U/ml					
Mean < 140	48	59	18	35	0.01
≥ 140	33	41	34	65	
CA19-9 after operation, U/ml					
> 37	28	35	8	15	0.02
≤ 37	53	65	44	85	
Site in pancreas					
Head, whole	55	68	36	69	0.61
Body, tail	26	32	16	31	
Tumor size, mm					
≤ 30	62	77	26	50	< 0.01
> 30	19	23	26	50	
Portal vein resection					
Yes	32	40	19	37	0.73
No	49	60	33	63	
Intraoperative radiation therapy					
Yes	52	64	27	52	0.21
No	29	36	25	48	
Adjuvant chemotherapy					
Yes	13	16	12	23	0.37
No	68	84	40	77	
Tumor differentiation					
Pap, well, muc	12	15	18	35	0.11
Mod, por, adscc	69	85	34	65	
Local tumor extension					
T1, T2, and T3	40	49	19	37	0.03
T4	41	51	33	63	
Paraaortic node metastases					
Positive	24	30	3	6	< 0.01
Negative	57	70	49	94	
n0	9	11	17	33	
n1	34	42	26	50	
n2	14	17	6	12	
Peritoneal cytology					
Positive	16	20	1	2	< 0.01
Negative	65	80	51	98	
Surgical margin					
Positive	20	25	10	19	0.53
Negative	61	75	42	81	
Stage (TNM 5th edition)					
I	0	0	3	6	< 0.01
II	1	1	2	4	
III	16	20	20	38	
IVA	25	31	18	35	
IVB	39	48	9	17	

adscc, adenosquamous carcinoma; CA19-9, serum carbohydrate antigen 19 to 9; mod, moderately differentiated tubular carcinoma; pap, papillary adenocarcinoma; por, poorly differentiated tubular carcinoma; well, well differentiated tubular carcinoma.

Table 3. Distribution of Prognostic Factors According to Paraaortic Lymph Node and Peritoneal Cytology

	Paraaortic lymph node					Peritoneal cytology				
	Positive		Negative		p	Positive		Negative		
	n	%	n	%	Value	n	%	n	%	p Value
Total n	29		104			17		114		
CA19-9; after operation, U/ml										
> 37	13	45	23	22	0.03	12	71	54	47	0.08
≤ 37	16	55	81	88		5	29	60	53	
Size, mm										
≤ 30	25	86	63	61	0.02	14	82	74	65	0.05
> 30	4	14	41	39		3	18	40	35	
Local tumor spread										
t4	12	41	49	47	0.68	12	71	49	43	0.04
t1, t2, t3	17	59	55	53		5	29	65	57	
Surgical margin										
Positive	11	38	19	18	0.04	9	53	20	18	< 0.01
Negative	18	62	85	82		8	47	94	82	
Peritoneal cytology										
Positive	7	24	10	10	0.09					
Negative	22	76	94	90						

CA19-9, serum carbohydrate antigen 19 to 9.

and IVB were present in 0, 1 (1%), 16 (20%), 25 (31%), 39 (48%) patients with early recurrence, and in 3 (6%), 2 (4%), 20 (38%), 18 (35%), and 9 (17%) patients without recurrence, respectively. Univariate analysis showed that tumor stage was pronounced when comparing the two patient groups (Table 2) ($p < 0.01$).

A stepwise logistic regression analysis was performed with 15 clinicopathologic variables to determine risk factors for recurrence within a year. Presence of paraaortic lymph node metastases and positive cytology were statistically significant risk factors: peritoneal cytology, positive or negative; odds ratio, 0.067; 95% confidence interval, 0.0054 to 0.8152; $p = 0.034$ and paraaortic nodal involvement, positive or negative; odds ratio, 0.198; 95% confidence interval, 0.0532 to 0.7399; $p = 0.016$.

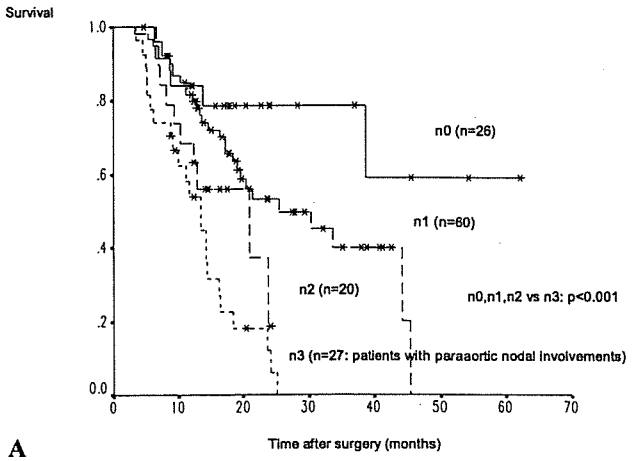
Distribution of prognostic variables according to the paraaortic lymph node and peritoneal cytology status are shown in Table 3. Paraaortic lymph node involvement was associated with elevated CA19-9 a month after operation, larger tumor size, and a positive surgical margin. Positive peritoneal cytology was notably associated with local tumor spread, and a positive surgical margin.

Survival curves for patients with paraaortic nodal involvement and positive peritoneal cytology among 133 patients are shown in Figure 1. The median survival times in 27 patients with paraaortic nodal involvement and 106 patients without paraaortic nodal involvement were 13 months and 30 months, respectively ($p < 0.001$). The median survival times in 60 patients with n1 positive metastases and 20 patients with n2 positive metastases were 26 months and 21 months, respectively (Fig. 1A). The median survival times in 17 patients with positive cytology and in 114 patients without positive cytology were 13 months and 24 months, respectively ($p = 0.004$) (Fig. 1B).

Survival curves for patients with paraaortic nodal involvement and positive peritoneal cytology among 81 patients with early recurrence are shown in Figure 2. The median survival times in 25 patients with paraaortic nodal involvement and 56 patients without paraaortic nodal involvement were 12 months and 14 months, respectively ($p = 0.03$). Median survival times in 16 patients with positive cytology and 65 patients with negative cytology were 13 months and 13 months, respectively. There was no notable difference in the survival curves between the two groups ($p = 0.25$) (Fig. 2B).

DISCUSSION

Prognostic factors in patients with pancreatic carcinoma have been analyzed on the basis of survival not but recurrence in most previously published large series reports.[3-8,10,11] Using detailed followup in 133 patients



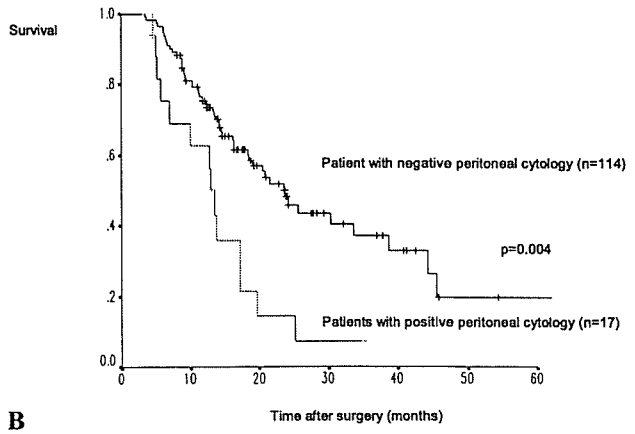
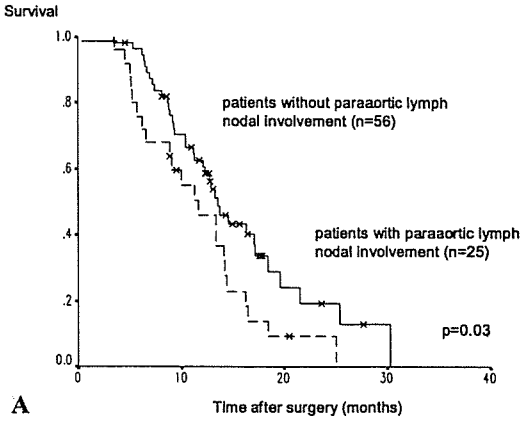


Figure 1. (A) Kaplan-Meier survival curves for patients with and without paraaortic nodal involvement among 133 patients. There was a substantial difference in the survival rate between patients with n3 and n0, n1, n2 ($p < 0.001$). (B) Kaplan-Meier survival curves for patients with and without positive cytology among 133 patients ($p = 0.004$).



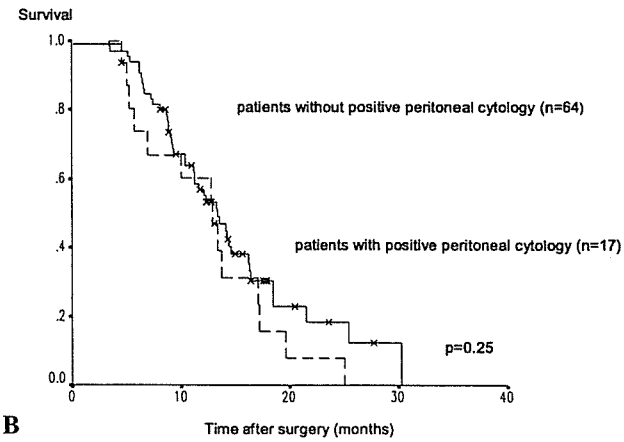


Figure 2. (A) Kaplan-Meier survival curves for patients with and without paraaortic nodal involvement among 81 patients with early recurrence. The median survival in 25 patients with paraaortic lymph nodal involvement was statistically shorter than that in 56 patients without paraaortic lymph nodal involvement ($p = 0.03$). (B) Kaplan-Meier survival curves for patients with ($n = 16$) and without ($n = 65$) positive cytology among 81 patients with early recurrence. There was no notable difference in survival rates between the two groups ($p = 0.25$).

with curative pancreatectomy in this study, we identified sites of first disease recurrence and time to disease recurrence and concluded that paraaortic lymph node involvement and positive washing cytology were statistically independent predictors of early recurrence. In addition, there is evidence suggesting that paraaortic lymph node metastases considerably affect survival. These two factors seemed to be an indicator of noncurative disease, but they cannot be evaluated by preoperative imaging studies without histologic confirmation.

In our series, more than 80% of the early recurrence was found in a distant site, of which the liver accounted for 46%. Locoregional recurrence only was recognized in 9% of patients, an apparently lower rate than in previous reports.[15,16] This suggested that microscopic metastases might already exist in the liver, peritoneal, or other distant organs at operation. Local cancer control on its own could not contribute to the longterm survival in these patients because the major cause of failure was distant metastases. Recently, postoperative systemic chemotherapy rather than chemoradiotherapy has been recommended on the basis of the result by the European Study Group for Pancreatic Cancer.[22] Application of adjuvant systemic chemotherapy rather than radiotherapy might be suitable in these patients with early recurrence on the basis of the recurrence pattern.

Extended lymphadenectomy did not adversely affect postoperative mortality, but longterm survival was possible only in patients with favorable prognostic factors.[7,23] It, as a result, permitted identification of a considerably higher percentage of nodal metastases beyond the peripancreatic node group, and the reported rate of paraaortic lymph node metastases was 19% to 26%.[24-28] Surgical outcomes after extended lymphadenectomy in patients with paraaortic nodal involvement was extremely dismal, and most of them could not survive more than 3 years, just as in our study.[24-28] Yoshida and colleagues[28] reported that the survival time for paraaortic node-positive patients with pancreatic head carcinoma was considerably shorter than that for those with bile duct adenocarcinoma (median 8 months versus 19 months, $p = 0.05$). This study revealed paraaortic lymph node metastasis was the definitive predictor of not only early recurrence but also shorter survival term (12 months). Considering these results, radical pancreatectomy including extended lymphadenectomy should not be recommended when paraaortic lymph nodal metastasis was confirmed by intraoperative frozen diagnosis.

Paraaortic lymph node involvement was associated with the CA19-9 value after operation (> 37 U/ml), tumor size, and microscopic positive surgical margin. No recovery to the normal range value of CA19-9 1 month after operation suggested the tumor residue during the operation.[29] Connor and associates[27] described LN16b1 involvement was found to be associated with a positive resection margin, and LN16b1 involvement might be a reflection of local invasion through the fascia of Treitz, rather than true second-order node involvement in lymphatic spread. In this study, 20 patients who had peripancreatic lymph node (n2) involvement had paraaortic nodal (n3) involvement. But seven patients without n2 involvement also had paraaortic nodal involvement. This might support their suggestion, but paraaortic nodal involvement seemed to be a part of wide-spread lymphatic metastases, considering the poor prognosis and recurrence pattern.

The implication of positive cytology from peritoneal washing in the management of patients with pancreatic cancer has been assessed, and its clinical significance has been frequently evaluated. Many authors concluded that pancreatic cancer patients with peritoneal micrometastases have dismal outcomes even without macroscopic metastases, and there is no benefit from local therapy in these patients.[30-33] On the other hand, two reports from Japan demonstrated that positive cytology does not directly predict peritoneal carcinomatosis and survival, although it is associated with advanced disease.[14,34] Yachida and colleagues[14] emphasized in their cytomorphologic analysis that the presence of clusters with ragged edges and isolated carcinoma cells could indicate a high risk of peritoneal recurrence. In our study, 17 patients (94%) with positive washing cytology had recurrence within a year, and it was one of the definitive predictors of early recurrence, but among the early recurrence patients, there was no pronounced difference in postoperative survival times between patients with and without positive washing cytology. Peritoneal washing cytologic examination may be easily performed with staging laparoscopy, but it might be difficult to justify performing washing cytology examination to make a decision from the results of the currently small number of patients.

In conclusion, the result of published studies about the effectiveness of adjuvant chemotherapy remains controversial, but systemic chemotherapy might be necessary in patients with early recurrence who have no local but distant recurrence as part of a systemic disease.

Even if there is no apparent hepatic metastasis and peritoneal dissemination after surgical exploration, routine sampling of paraaortic nodes for investigation by frozen section is recommended before starting a radical operation because palpation or intraoperative US cannot predict paraaortic nodal metastases. When paraaortic nodal metastases are confirmed, radical operation including extended lymphadenectomy should be abandoned.

Author Contributions

Study conception and design: Shimada
Acquisition of data: Shimada, Sano
Analysis and interpretation of data: Shimada, Sakamoto
Drafting of manuscript: Shimada
Critical revision: Kosuge
Statistical expertise: Sano
Obtaining funding: Kosuge
Supervision: Kosuge

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A Multicenter Randomized Controlled Trial to Evaluate the Effect of Adjuvant Cisplatin and 5-Fluorouracil Therapy after Curative Resection in Cases of Pancreatic Cancer

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Background: There have been few randomized controlled clinical trials until now to determine the effectiveness of adjuvant treatments for pancreatic cancer, and the results reported so far are inconsistent.
Methods: Patients with invasive ductal pancreatic cancer who underwent radical surgery with clear histological margins at 11 Japanese institutions were enrolled and randomly assigned to one of two groups: surgery-alone group (no further treatment after surgery) and the surgery + chemotherapy group [two courses of postoperative adjuvant systemic chemotherapy with cisplatin (80 mg/m^2, Day 1) and 5-fluorouracil (500 mg/m^2/day, Days 1–5)]. Patients with a positive resectional margin or with resected distant metastases were excluded from the trial in order to minimize the influence of residual cancer.
Results: Between 1992 and 2000, 89 patients were randomized into the two arms of the trial (45 patients to the surgery + chemotherapy arm and 44 patients to the surgery-alone arm). Four patients in total were found to be ineligible (three in the surgery + chemotherapy group and one in the surgery-alone group). The baseline characteristics were comparable between the two groups. In the surgery + chemotherapy group, four patients did not receive the adjuvant treatment because of patient refusal. Toxicity was minor and acceptable among the eligible patients in the surgery + chemotherapy group. The estimated 5-year survival rates were 26.4% in the surgery + chemotherapy group and 14.9% in the surgery-alone group, and the median duration of survival was 12.5 months and 15.8 months, respectively. The recurrence rates at 5 years were 73.6 and 80.8%, respectively, in the surgery + chemotherapy and the surgery-alone groups. The differences in the survival and recurrence rates between the two groups were not statistically significant.
Conclusions: Postoperative adjuvant chemotherapy using cisplatin and 5-fluorouracil was safe and well tolerated; however, no clear survival benefit could be demonstrated.

Key words: adjuvant – chemotherapy – clinical trials – pancreatic neoplasms

INTRODUCTION

Pancreatic cancer is the fifth most common cause of death from cancer in Japan (1) and the United States (2), and its incidence is rising. Although radical resection appears to be the only means to obtain a cure, the 5-year survival rate after potentially curative resection remains extremely low, in the range of 5–30% (3–5). Therefore, effective adjuvant therapy is currently being sought. The Gastrointestinal Tumor Study Group (GITSG) performed the first multicenter randomized controlled trial to evaluate the efficacy of adjuvant treatment (6), and they concluded that adjuvant chemoradiotherapy prolonged the postoperative survival of patients with pancreatic cancer. However, the results of a few subsequent randomized controlled trials (7–10) have been inconsistent, and further evidence concerning the effectiveness of adjuvant treatments for pancreatic cancer is awaited. Combination chemotherapy with 5-fluorouracil (5-FU) and cisplatin was considered to be a promising regimen for pancreatic cancer in the early 1990s (11,12). Based on our experience of using

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this regimen in patients with unresectable pancreatic cancer, we expected that it might prove to be suitable for postoperative adjuvant treatment (13). In 1992, we initiated a multicenter randomized controlled trial to evaluate the efficacy of adjuvant chemotherapy with cisplatin and 5-FU after margin-negative resection in patients with pancreatic cancer.

METHODS

Patients and Design

Patients with ductal pancreatic cancer who underwent resectional surgery with histologically clear margins between April 1992 and March 2000 in 11 Japanese institutions were enrolled for the present study. Patients with other pancreatic and periampullary neoplasms, such as intraductal papillary mucinous neoplasm, cystadenocarcinoma and endocrine tumor, were excluded. Presence of distant metastases, even if they were resected, and presence of peritoneal seeding were regarded as criteria for exclusion from the study. After we obtained their written informed consent, the patients were registered with the randomization center by fax within 10 weeks of surgery and were then randomly assigned to one of two groups: the surgery-alone group and the surgery + chemotherapy group. They were stratified according to the institution and tumor stage using the minimization technique. The tumor stage was determined according to either the fourth or fifth edition of the UICC TNM classification, depending on the time of patient registration, and the patients were divided into two categories for stratification as follows: those with tumor in stage I or stage II according to the fifth edition (14) [equivalent to stage I of the fourth edition (15)] were assigned to one group and the remaining patients were included in the other group. Resection procedures and the range of dissection were determined according to institutional policy. Handling and histological examination of the resected specimens were carried out according to the recommendations of the Japan Pancreatic Society (16). Patients in the surgery-alone arm and those in the surgery + chemotherapy arm were followed up at 3 month intervals. Blood tests and imaging by computed tomography or ultrasound were carried out. Diagnosis of recurrence was made based on the imaging findings. Treatment after recurrence was not defined. All data were collected at a central registration office. Three pathologists performed the pathology reviews for the first 18 cases; thereafter, institutional histological diagnoses were relied upon. No external beam radiation was given to any of the patients. Intraoperative irradiation was administered on an institution-by-institution basis, and this was given to all candidates of any institution who opted to use it. The trial was conducted with the approval of the local ethics committee at each institution.

Adjuvant Chemotherapy

Chemotherapy was started within 1 week of randomization. Two courses of treatment with a combination regimen of 5-FU and cisplatin were administered. Cisplatin was administered at a dose of 80 mg/m^2 on the first day of the treatment course; 5-FU was given at a daily dose of 500 mg/m^2 as a continuous infusion for the first 5 days of the treatment course. The second course was repeated 4–8 weeks after the start of the first course. Toxicity was assessed according to the World Health Organization (WHO) guidelines (17). The second course was withheld if toxicity of grade 3 or above severity was observed or if the patient's condition did not improve sufficiently to fit the eligibility criteria for registration within 8 weeks of the start of the initial course.

Statistics

The primary endpoint of the study was the duration of survival. Duration of survival was calculated from the date of registration to the date of death due to any cause or was censored at the latest follow-up. The two treatment arms were also compared for recurrence rate. Safety analyses were performed based on data obtained from all the eligible patients who had started chemotherapy. Efficacy analyses were performed according to the intention-to-treat principle. Survival curves were drawn using the Kaplan–Meier technique. Differences in the duration of survival were compared using a two-sided log-rank test, with the significance level set at 5%. The prognostic value of the variables was tested by multivariate analysis using the Cox proportional hazards model. Assuming an overall 2-year survival rate of 15% in the surgery-alone arm, the present study was designed to enroll more than 86 patients in order to detect an absolute increase by 25% (i.e. 40% survival rate for 2 years) in the surgery + chemotherapy arm, at a significance level of 5% with 80% power.

RESULTS

Patient Characteristics

Between April 1992 and March 2000, 89 patients were randomized: 45 patients to the surgery + chemotherapy arm and 44 patients to the surgery-alone arm. Three patients in the surgery + chemotherapy group and one in the surgery-alone group were rated ineligible, resulting in 95.5% compliance. The reasons for ineligibility included resected distant metastases (two cases), histologically positive resection margin (one case) and severe postoperative complication (one case). The baseline characteristics of the patients in the two groups were comparable (Table 1).

Treatment Data

Four patients assigned to the surgery + chemotherapy arm refused treatment after randomization, and the detailed data for three ineligible patients were not available. As a result, a total of 38 patients were evaluated for treatment toxicity. Of these, 31 patients (81.6% of the patients who received chemotherapy) received two courses of chemotherapy, and 7 patients received only one course of chemotherapy. The reasons for treatment discontinuation were patients' withdrawal from the

Table 1. Demographic and clinical data for the patients

	Surgery + chemotherapy	Surgery alone
Gender (M:F)	29:16	21:23
Age (mean ± SD)	60.8 ± 8.1	60.1 ± 8.9
Operative procedure (pancreaticoduodenectomy:others)	37:8	34:10
Intraoperative irradiation (30:0 Gy)	30:15	27:17
Location of the tumor (head:body/tail)	35:9	34:8
Size of the tumor (<4:≥4 cm)	35:10	36:8
Histological type (papillary and well-differentiated:others)	24:21	21:23
Nodal involvement (present:absent)	12:23	9:35
pT (pT1–3:pT4)	36:9	33:11

trial (four cases), development of recurrent disease (two cases) and unresolving leucopenia (one case).

Toxicity

One ineligible patient who was suffering from a severe post-operative complication that was not documented at the time of registration died of sepsis after one course of chemotherapy. Minor toxicity was commonly observed, especially nausea and vomiting, among the 38 eligible patients who actually received the adjuvant chemotherapy. In a few patients, toxicities of grade 3 or higher severity were encountered (Table 2). However, the toxicities were reversible and resolved with conservative treatment alone in all patients.

Recurrence

Seventy-one patients died and 18 patients were alive at the end of the follow-up period. The median follow-up duration for the survivors was 44.8 months. The recurrence status remained unknown in one ineligible patient. Among the remaining 88 randomized patients, 34 (77.3%) in the surgery-alone group and 32 (71.1%) in the surgery + chemotherapy group developed recurrence. The recorded sites of recurrence are shown in Table 3. The liver was the most frequent site of recurrence for metastasis, followed by peritoneal seeding and local recurrence, in both groups. There was no significant advantage of adjuvant chemotherapy in terms of the recurrence rate (Figure 1). The median time to recurrence was 10.2 months in the 44 patients in the surgery-alone group and 8.6 months in the 44 patients in the surgery + chemotherapy group. The 5-year recurrence rates were 80.8 and 73.6%, respectively, in the two groups ($P = 0.80$).

Duration of Survival

In the randomized patients, the cause of death was recurrent disease in 63 patients (32 from the surgery-alone group and 31 from the surgery + chemotherapy group), in-hospital death in 1 patient (from the surgery + chemotherapy group), non-malignant/non-toxicity death in 5 patients (3 from the surgery-alone group and 2 from the surgery + chemotherapy group) and unknown in 2 patients (1 from each group). The duration of survival was not influenced by adjuvant chemotherapy in either the randomized or the eligible patients. The survival curves of all the randomized patients are shown in Figure 2. The median survival was 15.8 months in the surgery-alone group and 12.5 months in the surgery + chemotherapy group, and the 5-year survival rate was 14.9% in the surgery-alone group and 26.4% in the surgery + chemotherapy group ($P = 0.94$).

Table 2. Summary of toxicities according to WHO criteria ($n = 38$)

	Grade 1	Grade 2	Grade 3	Grade 4
Nausea/vomiting	15	12	5	0
Leukopenia	14	6	2	0
Granulocytopenia	6	5	3	1
Thrombocytopenia	7	2	0	0
Mucositis	1	1	2	0
Cardiac	0	0	0	0
Hepatic	17	9	3	0
Renal	3	1	0	0

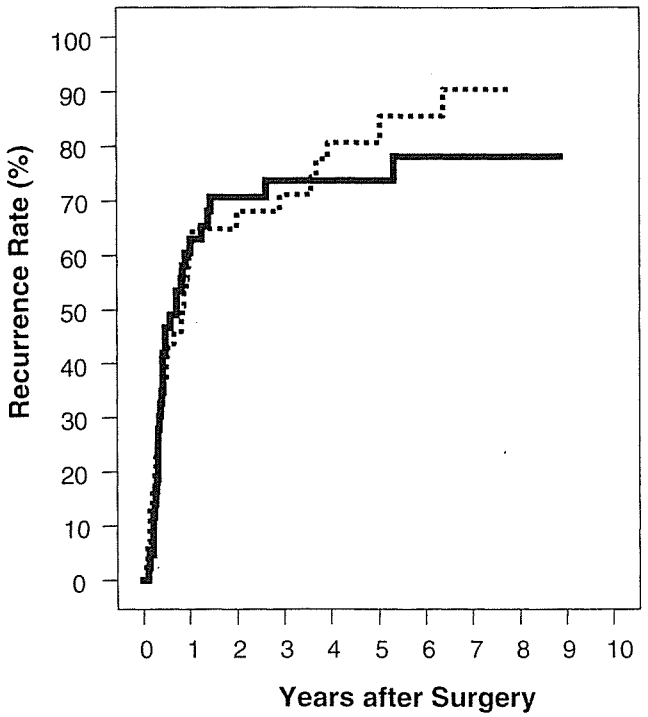
Table 3. Sites of recurrence

	Surgery + chemotherapy	Surgery alone
Liver	20	22
Peritoneum	10	9
Pleura	1	1
Local recurrence	6	7
Lymph node	3	1
Lung	1	1
Bone	1	1
Skin	0	2
Brain	1	0
Number of patients with recurrence	32	34

Prognostic Factors

In order to assess the influence of prognostic factors, the relationship of the outcomes to the following variables were investigated: gender, age, histological type, size of tumor, tumor location, pT factor, nodal involvement, type of operative procedure and administration of intraoperative radiotherapy. Calculation of the correlation coefficients (r) of pairs of variables revealed a close correlation for the tumor location and the type of

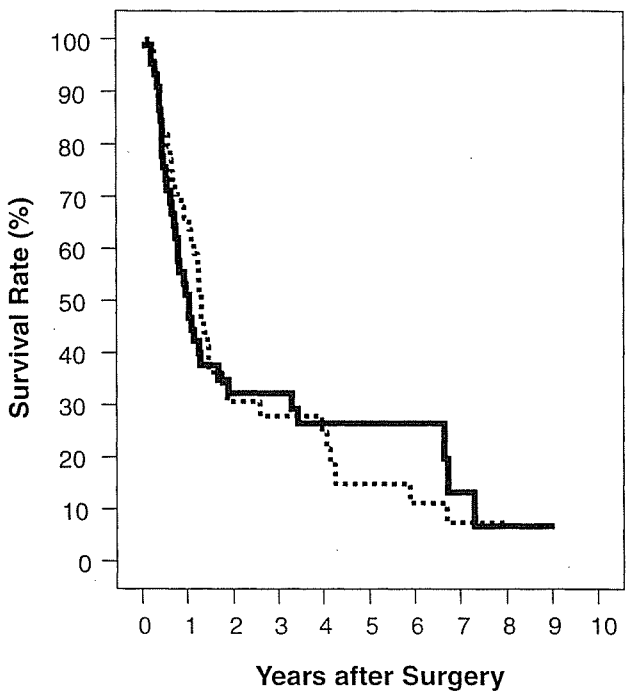
operative procedure ($r = 0.96$), whereas the coefficients for all the other pairs were less than 0.5. Consequently, 'operative procedure' was excluded from the subsequent multivariate analysis. The prognostic value of the remaining variables together with the assigned treatment arm as an additional variable was tested using multivariate analysis. The significant factors determined from this analysis were nodal involvement and the histological type of the tumor (Table 4); the effect of the pT factor was marginal. Consequently, the stage of the disease, the major determinants of which were the nodal status and the pT factor, was determined to be a good prognostic indicator. Patients with tumor in stage I or in stage II according to fifth edition of the UICC TNM classification survived significantly longer than those with more advanced disease (Figure 3). The median survival time in the two groups was 79.7 and 12.6 months, respectively ($P = 0.004$).



No. at risk

Observation	44	18	11	9	6	4	3	2
Chemotherapy	44	16	10	9	6	6	3	2

Figure 1. Cumulative recurrence rate. Solid line: surgery + chemotherapy group; dotted line: surgery-alone group.



No. at risk

Observation	44	29	11	10	8	4	3	2
Chemotherapy	45	23	12	11	7	7	5	2

Figure 2. Cumulative survival rate. Solid line: surgery + chemotherapy group; dotted line: surgery-alone group.

Table 4. Multivariate analysis

Variable	β	SE	*P*	HR	95% CI
Nodal involvement (absent versus present)	1.167	0.348	0.001	3.213	(1.626–6.350)
Histological type (papillary or well-differentiated tubular versus moderately or poorly differentiated tubular)	0.791	0.273	0.004	2.206	(1.291–3.769)
pT factor (pT1–3 versus pT4)	0.528	0.300	0.078	1.695	(0.942–3.050)
Gender (female versus male)	0.393	0.272	0.148	1.482	(0.869–2.526)
Size of tumor (<4 cm versus ≥4 cm)	0.166	0.172	0.334	1.181	(0.843–1.654)
Age	0.017	0.016	0.282	1.017	(0.986–1.049)
Chemotherapy	−0.053	0.254	0.835	0.948	(0.576–1.561)
Intraoperative radiotherapy	−0.280	0.299	0.349	0.756	(0.421–1.357)
Location of the lesion (head versus body or tail of the pancreas)	−0.354	0.291	0.224	0.702	(0.397–1.241)

SE, standard error; *P*, significance; HR, hazard ratio; CI, confidence interval.