
Collective Review of Small Carcinomas of the Pancreas

RYOICHI TSUCHIYA, M.D., F.A.C.S.
TAKATOSHI NODA, M.D.
NOBORU HARADA, M.D., F.A.C.S.
TOSHIMITSU MIYAMOTO, M.D.

TSUTOMU TOMIOKA, M.D.
KENSUKE YAMAMOTO, M.D.
TAKASHI YAMAGUCHI, M.D.

KUNIHIDE IZAWA, M.D.
TSUKASA TSUNODA, M.D.
RYOZO YOSHINO, M.D.
TOSHIFUMI ETO, M.D.

To determine problems involved in the treatment and diagnosis of pancreatic cancer, a collective study of small carcinoma of the pancreas (2 cm or less in diameter) was performed. One hundred six cases were collected and analyzed. The results were as follows: (1) In small carcinoma of the pancreas, the resectability rate was 99.0% and the operative mortality rate was 4%. (2) Only 44% of the patients belonged to Stage I, and 14% belonged to Stage III or IV. (3) Lymph node involvement, capsular invasion, retroperitoneal invasion, and vascular invasion were found in 30, 20, 12, and 9% of the patients, respectively. (4) The postoperative cumulative 5-year survival rate was 30.3%, and that of Stage I was 37.0%. (5) A small-sized tumor of the pancreas is not always an early carcinoma, but a tumor in Stage I may be regarded as an early carcinoma. (6) Percutaneous transhepatic cholangiography and endoscopic retrograde cholangiopancreatography were the main diagnostic indicators in cases with and without jaundice, respectively. (7) There was no specific single serum test for detecting small pancreatic cancer.

IT SEEMS that the smaller the size of a solid tumor, the earlier the disease. However, is a small-sized tumor indicative of early carcinoma of the exocrine pancreas? Does such a tumor have a better prognosis after resection? How can small carcinoma of the pancreas be detected? To answer these questions, reports of 106 patients with small carcinoma—2 cm or less in diameter—were collected from major institutions in Japan and analyzed.

Materials and Methods

A detailed questionnaire in regard to small carcinoma of the pancreas—2 cm or less in diameter—was sent to

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Reprint requests: Ryoichi Tsuchiya, Second Department of Surgery, Nagasaki University School of Medicine, 7-1 Sakamoto Machi, Nagasaki City, 852 Japan.

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From the Second Department of Surgery, Nagasaki University School of Medicine, Nagasaki, Japan

871 institutions (general or university hospitals) all over Japan.

Replies from 441 institutions were obtained. The response rate was 50.6%, and reports on 106 patients with small carcinoma of the pancreas, for the 17-year period from December 1966 to September 1983, were collected and analyzed.

The total number of patients with carcinoma of the pancreas experienced in that period comprised 49 institutions and 3315 patients. Out of 3315 patients, 753 had undergone resection, including 71 patients with small carcinoma. Therefore, the overall resectability rate was 22.7%. The incidence of small carcinoma among all patients with carcinoma of the pancreas was 2.1%. It was 9.4% among the patients who had received resection. The resectability rate in patients with tumors more than 2 cm in diameter was 21.9%.

The questionnaire consisted of 30 items, as shown in Table 1. Cystadenocarcinoma, ampullary carcinoma, and islet cell tumor were excluded from this study.

The cumulative survival rate after surgery was calculated by the Kaplan-Meier method, and statistical analysis was done by the Greenwood formula.

Results

Sex and Age

Of 106 patients with small carcinoma of the pancreas, 72 were males and 34 were females. The male to female ratio was 2.1 to 1. Ages ranged from 32 to 88 years old with an average of 59.8 years. There was no significant difference in age between the sexes based on the chi square test.

TABLE 1. Questionnaire

1. Name of institution	16. Lymph node metastasis
2. Total number of patients, number of resectable cases	17. Capsular invasion
3. Sex, age and date of birth of patient	18. Retroperitoneal invasion
4. Family history	19. Invasion to portal veins
5. Previous history	20. Invasion to duodenum
6. Reasons for the patient's visit to your institution?	21. Invasion to choledochus
7. Date of onset of symptoms	22. Stage
8. Date of admission	23. Location of tumor
9. Date of operation	24. Macroscopic finding of tumor
10. Date of discharge	25. Curative resection?
11. Prognosis, dead or alive, date	26. Chemotherapy?
12. Operative procedure	27. Radiation therapy?
13. Grade of lymph node dissection	28. Early postoperative complications
14. Invasion at resected stump	29. Late postoperative complications
15. Size of tumor	30. Histopathological diagnosis

Location of the Tumor

In two autopsied cases, there was no description as to location of the tumor. Out of 104 patients, 92, 88.5%, had tumors located in the head of the pancreas. In seven patients, the tumor was located in the body, and in five it was found in the tail of the pancreas.

Operation

Two cases of small carcinoma of the pancreas were found at the time of autopsy. One female patient with carcinoma of the head of the pancreas had received palliative rather than excisional surgery, because of her advanced age of 88 years. All of the remaining 103 patients had undergone resection. Therefore, the resectability rate in small carcinoma of the pancreas was 103 of 104 patients or 99.0%.

The operative procedures employed in 103 patients were total pancreatectomy, pancreatoduodenectomy, and distal pancreatectomy.

Total pancreatectomy was performed on 18 of 103 patients, or 17.5%, of which 16 had carcinoma of the head

TABLE 2. Surgical Treatment for Small Carcinoma

Operative Procedure	Location of Tumor			Total	Percentage
	Head	Body	Tail		
Total pancreatectomy	16	2	—	18	17.5
Pancreatoduodenectomy	75	1	—	76	73.8
Distal pancreatectomy	—	4	5	9	8.7
Total	91	7	5	103	100%

TABLE 3. Stage and Recurrence and/or Cancer Death in Resected Cases of Small Cancer

Stage	Number	Recurrence and/or Cancer Death	Percentage
I	45	13	28.8
II	44	17	38.6
III	12	5	41.7
IV	2	0	
Total	103	35	

of the pancreas and two had carcinoma of the body. Pancreatoduodenectomy was done on 76 patients, or 73.8%, of which 75 patients received the operation for carcinoma of the head of the pancreas, and one for carcinoma of the body. Distal pancreatectomy was carried out in nine patients, or 8.7%, of which four patients had carcinoma of the body and five had carcinoma of the tail (Table 2).

Operative Results

There were four operative deaths, which occurred within 1 month after excisional surgery for carcinoma of the head of the pancreas. The operative mortality, therefore, was four out of 103, or 3.9%. Three patients had undergone pancreatoduodenectomy, and one had received total pancreatectomy. Besides the operative deaths, there were 35 deaths due to causes related to carcinoma (Table 3). The average postoperative survival period was 17.9 ± 12.0 months (mean \pm S.D.), and the range was from 42 days to 4 years. On the other hand, there were 21 deaths in which the cause of death was not related to the disease. Their average postoperative survival period was 21.5 ± 34.5 months (mean \pm S.D.), with a range from 35 days to 13 years and 8 months. Therefore, 60 out of the 103 patients had already died. Of the remaining 43 patients, two were lost to follow up. Forty-one patients were alive as of September 30, 1983. Their average postoperative survival period was 32.4 ± 36.5 months (mean \pm S.D.), with a range from 1 month to 12 years and 6 months.

Stage Classification

The Japanese Pancreatic Society¹ has proposed the stage classification of carcinoma of the pancreas as follows.

TABLE 4. Stage Classification Proposed by Japanese Pancreatic Society (April 1982)

Stage I: T ₁ (0-2 cm)	N ₀	S ₀	Rp ₀	V ₀
Stage II: T ₂ (2.1-4.0 cm)	N ₁	S ₁	Rp ₁	V ₁
Stage III: T ₃ (4.1-6.0 cm)	N ₂	S ₂	Rp ₂	V ₂
Stage IV: T ₄ (6.1 cm-)	N ₃	S ₃	Rp ₃	V ₃

TABLE 5. Location of Tumor and Stage in Resected Cases of Small Carcinoma

	Head	Body	Tail	Total	Percentage
Stage I	39	3	3	45	43.7
Stage II	40	3	1	44	42.7
Stage III	10	1	1	12	11.7
Stage IV	2			2	1.9
Total	91	7	5	103	100.0

Stage I: Size of the tumor is 2 cm or less in diameter, designated as T₁. There is no evidence of regional lymph node involvement (N₀), no capsular invasion (S₀), no retroperitoneal invasion (Rp₀), and no invasion to either portal, superior mesenteric, or splenic vein (V₀).

Stage II: Size of the tumor is from 2.1 to 4.0 cm in diameter (T₂). There is evidence of lymph node involvement in the primary group closely situated to the tumor (N₁). There is suspected invasion to the capsule (S₁), suspected invasion to the retroperitoneum (Rp₁), or suspected invasion to the veins (V₁).

Stage III: The size is from 4.1 to 6.0 cm in diameter (T₃). There is evidence of lymph node metastasis in the secondary group, which is located between the primary and tertiary groups (N₂). There is definite invasion to the capsule (S₂), the retroperitoneum (Rp₂), or the veins (V₂).

Stage IV: The size is more than 6.1 cm in diameter (T₄). There is lymph node metastasis in the tertiary group regarded as juxta-regional lymph nodes (N₃). There is evidence of direct invasion to the adjacent viscera (S₃), severe invasion to the retroperitoneum (Rp₃), or severe invasion to the veins (V₃) (Table 4).

The 103 patients who had undergone resection were grouped according to the above stage classification. Forty-five patients or 43.7% belonged to Stage I, and 44 patients or 42.7% to Stage II, 12 patients to Stage III, and two patients to Stage IV. Therefore, only about a half of the patients with small carcinoma of the pancreas 2 cm or less in diameter belonged to Stage I. On the contrary, about 14% of the patients belonged to either Stage III or IV. In two Stage IV patients, juxta-regional lymph node involvement was found (Table 5).

TABLE 6. Relationship between Stages and Factors in Small Carcinoma of the Pancreas

Stage	Points	N	S	Rp	V
I	45	0	0	0	0
II	44	26 (N ₁)	13 (S ₁)	12 (Rp ₁)	7 (V ₁)
III	12	3 (N ₂)	7 (S ₂)		2 (V ₂)
IV	2	2 (N ₃)			
Total	103	31 30.1%	20 20.0%	12 11.7%	9 8.7%

TABLE 7. Cumulative Survival Rate in Each Stage

	1 Year	3 Years	5 Years	10 Years
Stage I	89.5%	51.8%	37.0%	37.0%
II	73.8%	43.7%	26.2%	—
III	51.4%	—	—	—
IV	100%	—	—	—
Total	77.8%	44.5%	30.3%	30.3%

Relationship between Stage and Factors that Influence Prognosis (Table 6)

In 45 Stage I patients, no factors such as N, S, Rp, or V were found to occur naturally. In 44 patients of Stage II, N₁ was found in 26 patients, S₁ in 13, Rp₁ in 12, V₁ in seven. In 12 patients of Stage III, N₂ was found in three patients, S₂ in seven, V₂ in two. In two patients of Stage IV, N₃ was seen in both patients.

Therefore, even in small carcinoma, the N factor, that is, lymph node involvement, was found in 31 patients out of 103, 30.1%. Capsular invasion was seen in 20 patients, 20%, retroperitoneal invasion was found in 12 patients, 11.7%, and invasion to the portal venous system was found in nine patients, 8.9%. On the other hand, one patient who had not been operated on was found to have a pulmonary metastasis at the time of autopsy.

Therefore, more than a half of the cases of small carcinoma of the pancreas were not early carcinoma at all.

Postoperative Cumulative Survival Rate

One-, 3-, 5-, and 10-year survival rates were 77.8, 44.5, 30.3, 30.3%, respectively. Among the survival rates in each Stage, that of Stage I seemed most satisfactory, that is, 89.5% at 1 year, 51.8% at 3, and 37% at both 5 and 10 years. However, there was no statistically significant difference between Stage I and II survival rates (Table 7).

The cumulative survival rates were calculated according to the grade of lymph node involvement, capsular invasion, retroperitoneal invasion, or invasion to the portal venous system.

TABLE 8. Cumulative Survival Rate and Lymph Node Involvement

	1 Year	3 Years	5 Years	10 Years
N ₀	88.6%	47.0%	29.8%	29.8%
N ₁	60.0%	40.9%	30.7%	—
N ₂	0%			
N ₃	100%			
N(-)	88.6%	47.0%	29.8%	29.8%
N(+)	58.8%	42.0%	33.6%	—

] = 95% confidence interval.

TABLE 9. Reason for Hospital Admission

	No. of Patients	Percentage
Symptoms and/or signs	99	93.4
Mass screening test	2	1.9
UGI	2	
Outpatient	2	1.9
Pancreatic stone	1	
Chronic pancreatitis	1	
After operation	3	2.8
Early gastric cancer	1	
Biliary drainage	2	
Total	106	100.0

There was a statistically significant difference in 1-year survival rate between N_0 and N_1 , and between negative lymph node involvement and positive lymph node involvement (Table 8).

There was also a significant difference in 5-year survival rate between S_0 and positive capsular invasion.

Concerning Rp and V factor, there were no significant differences in survival rates, since the number of surviving patients was so limited. 5-year survival rates for Rp and V factor could not be calculated, because their postoperative periods were less than 5 years as of September 30, 1983.

Diagnosis

Out of 106 patients with small carcinoma of the pancreas, 99 (93.4%) visited the hospital because of some complaint, and two for further examination after mass screening for gastric cancer. Two patients were found as a result of treatment for chronic pancreatitis, and three underwent laparotomy elsewhere, which led to the discovery of the pancreatic mass (Table 9). The period of their suffering disease is 3.4 months on the average.

Diagnostic tools or findings that led to the detection of the cancer were arranged in order of frequency: percutaneous transhepatic cholangiography (PTC), endoscopic retrograde cholangiopancreatography (ERCP), clinical evaluation and operative findings. In 54 jaundiced pa-

TABLE 10. Diagnostic Indications for Small Pancreatic Cancer

	With Jaundice	No Jaundice	Total
PTC	34	6	40
ERCP	6	22	28
US	3	4	7
UGI	1	3	4
Amylase	—	3	3
Clinical findings	6	4	10
Operative findings	4	5	9
Others	—	5	5
Total	54	52	106

tients, PTC was useful (34/54), as was ERCP in 52 non-jaundiced patients (22/52) (Table 10).

Table 11 shows the diagnostic sensitivity of various imaging techniques.

PTC provided correct diagnosis in all patients, with or without jaundice. ERCP correctly diagnosed 94.1% with jaundice and 100% without jaundice. Ultrasonography (US) was correct in 78.8% with jaundice and in 83.3% without jaundice. Computerized tomography (CT) provided correct findings in 79.3% with jaundice and in 72.0% without jaundice. The preoperative results of laboratory tests are shown in Table 12. A glucose tolerance test showed an abnormal value in 48 of 79 patients of 60.8%. The positive results of elastase I, ferritin, and carcinoembryonic antigen (CEA) were 57.1%, 50.0%, and 22.0%, respectively. The overall positive rate of laboratory tests in 106 patients with small cancer of the pancreas was 71.7%.

Discussion

To discuss the treatment and diagnosis of pancreatic cancer, it is most desirable to examine a large number of resectable cases that were at an early stage. However, there are limitations to obtaining cases in each institution. To overcome these limitations, a collective study² should be useful.

TABLE 11. Sensitivity of Diagnostic Procedures

	With Jaundice			Sensitivity	No Jaundice			Sensitivity
	N	A	D		N	A	D	
PTC	0	15	34	100%	0	11	9	100%
ERCP	2	10	22	94.1%	0	17	19	100%
US	7	18	8	78.8%	5	21	4	83.3%
CT	6	13	10	79.3%	7	13	5	72.0%
SCAG	20	4	12	44.4%	21	9	7	43.2%
Total	2	12	40	96.3%	3	19	30	94.2%

N = Number of examinations that were normal.

A = Number of examinations that were abnormal but nonspecific.

D = Number of examinations that were diagnostic of pancreatic cancer.

TABLE 12. Results of Laboratory Tests

	Number Tested	With Jaundice		No Jaundice		Percentage of A
		N	A	N	A	
Glucose tolerance test	79	16	25	15	23	60.8%
Elastase-1	14	3	3	3	5	57.1%
Ferritin	14	4	3	3	4	50.0%
CEA	59	19	9	27	4	22.0%
P-S test*	20	3	4	8	5	45.0%
PFD test†	27	8	7	7	5	44.4%
Amylase	93	31	15	28	19	36.6%
Total	106	14	40	16	36	71.7%

N = normal.

A = abnormal.

* P-S test = Pancreozymin secretin test.

† PFD = Pancreatic function diagnostant.

We collected 106 cases with small carcinoma of the pancreas and analyzed them according to the General Rules for Surgical and Pathological Studies on Cancer of the Pancreas by the Japanese Pancreatic Society.¹ As a result, it was shown that carcinoma of the pancreas, which is one of the worst in terms of curability and prognosis, has high resectability, low morbidity, and good prognosis when at an early stage. However, the facts that only 44% of the patients belonged to Stage I, and 14% belonged to Stage III or IV because of lymph node metastases (30%), capsular invasion (20%), or retroperitoneal invasion (12%), and that 13 (28.8%) of 45 Stage I patients died after operation of tumor recurrence, suggest that the small carcinoma of the pancreas is not always an early carcinoma. Thus, the operation that is sufficient to adequately remove regional lymph nodes and soft tissue adjacent to the pancreas should be chosen.

Regarding diagnosis, the results that 99 cases (93.4%) with small pancreatic cancer consulted a doctor with some symptoms and that their suffering periods were 3.4 months on the average are of importance. These suggest that patients with continuing vague symptoms should undergo further examinations for detecting the cancer within 3 months from the onset of symptoms.

The most useful diagnostic clues for small pancreatic cancer were PTC in cases with jaundice and ERCP in those without jaundice.

TABLE 13. Stage and CA 19-9 in Patients with Carcinoma of the Pancreas

Stage (no.)	CA 19-9 > 37 unit/ml
I (0)	
II (2)	2 (100%)
III (5)	3 (60%)
IV (24)	19 (79%)
Total (31)	24 (77%)

With respect to laboratory tests, individual test sensitivity was not so high and overall sensitivity was only 72% (Table 12).

Among the laboratory tests, the diagnostic clue was merely the increase of amylase activity, and that was observed in only three of 106 cases with small pancreatic cancer. These results indicate that there is presently no single specific tumor marker as a screening test sufficient for small pancreatic cancer.

Recently, the monoclonal antibody CA19-9 was prepared by Koprowski et al.³ and was found to be useful in the diagnosis of pancreatic cancer by Del Villano et al.⁴ We obtained the same results (Table 13), but this marker has a limited role in early diagnosis.

As mentioned above, most of the cases with small pancreatic cancer in this report had some symptoms and were fortunately diagnosed by consequent imaging techniques. Namely, it can be said that the cases were fortunate enough to be detected at an early stage.

It is unfortunately the present situation that most patients with small pancreatic cancer are asymptomatic and show no abnormal findings in examinations. Therefore, further investigations and efforts in detecting early pancreatic cancer should be required.

References

1. Japanese Pancreatic Society. General Rules for Surgical and Pathological Studies on Cancer of the Pancreas, 2nd ed. Tokyo: Kanehara Publishing, 1982 (in Japanese).
2. Tsuchiya R, Oribe T, Noda T. Size of the tumor and other factors influencing prognosis of carcinoma of the head of the pancreas. *Am J Gastroenterol* 1985; 80:459-462.
3. Koprowski H, Steplewski Z, Mitchell K, et al. Colorectal carcinoma antigens detected by hybridoma antibodies. *Somatic Cell Mol Genet* 1977; 5:957-972.
4. Del Villano BC, Brennan S, Brock P, et al. Radioimmunoassay for a monoclonal antibody—defined tumor marker, CA19-9. *Clin Chem* 1983; 29:549-552.