

Synchronous or Metachronous Double Cancers of the Pancreas and Other Organs: Report on 12 Cases

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Abstract Pancreatic carcinoma carries a poor prognosis, especially invasive ductal carcinoma of the pancreas. This retrospective study describes the results of the treatment and prognosis for double cancers in which cancer of the pancreas was associated with malignancies in other organs in 12 patients who were diagnosed and treated at Kurume University Hospital. The patients included 4 women and 8 men, with an average age of 67 years. Of the 12 tumors, 7 were metachronous pancreatic cancers which occurred after resections of other organ malignancies. Five patients had synchronous double cancers, one of whom was diagnosed to have gastric cancer on admission. Two other patients of this group were diagnosed to have lung cancer, while the remaining 2 patients suffered from colon cancer. By the time pancreatic cancer was diagnosed, gastrectomies had been performed in 7 patients for either gastric cancer or ulcers. In addition, one patient underwent a hysterectomy for uterine carcinoma and another received a low anterior resection for rectal carcinoma. Four of 5 patients in the synchronous group had nonresectable tumors and a palliative bypass operation was performed in 2 of these patients. Six patients who had metachronous double cancers died because of pancreatic cancer recurrence or metastases. We conclude that the prognosis of double cancers, where cancer of the pancreas is associated with other organ malignancies, primarily depends on the prognosis of the pancreatic carcinoma, and the present study suggests the necessity of long-term follow-up examinations for gastrectomy patients in order to make an early diagnosis of pancreatic cancer.

Key words Double cancer · Pancreatic cancer · Gastric cancer

Introduction

Pancreatic cancer has the poorest prognosis of all major carcinomas. Recent improvements in the prognosis of cancer patients have led to an increase in the incidence of second primary cancers, and the frequency of multiple primary malignant tumors is expected to increase as the population ages. We report herein on 12 cancers of the pancreas associated with malignancies in other organs, and also review the literature.

Patients and Methods

In this series, between 1988 and 1998, 11 patients were referred to our hospital for pancreatic cancer and one patient was referred for gastric cancer. All patients underwent metastatic screening which included taking the patient's history and performing a physical examination, blood work, including liver-associated enzymes, chest radiography, and abdominal imaging. There were 5 synchronous double-cancer patients and 7 metachronous double-cancer patients. The clinical records were retrospectively reviewed regarding patient demographics, clinical features, pathologic findings, operative details and outcomes, and survival. All patients were followed up either by return visits or by telephone interviews.

Results

Our patients consisted of 8 men and 4 women ranging in age from 59 to 78 years, with a median age of 67 years. There were 7 metachronous and 5 synchronous double-cancer patients in whom 1 patient with gastric cancer was diagnosed with synchronous double cancer intraoperatively. By the time pancreatic cancer was diagnosed, 7 patients had received gastrectomies for gastric cancer

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Received: September 24, 1999 / Accepted: March 24, 2000

Table 1. Double cancers of the pancreas and other organs

Case no.	Age/sex	Location/stage ^a	Other malignancy	Interval (years)	Phase	History of gastrectomy	Outcome	Cause of death
1	76/M	Pb, III	Stomach	3	Metachronous	+	13 months, D	Panc. Ca.
2	60/F	Ph, III	Uterus	5	Metachronous	–	34 months, D	Panc. Ca.
3	69/F	Ph, I	Stomach	12	Metachronous	+	18 months, D	Panc. Ca.
4	60/M	Pb, III	Stomach	14	Metachronous	+	13 months, D	Panc. Ca.
5	59/M	Pb, IVA	Stomach	5	Metachronous	+	3 months, D	Panc. Ca.
6	69/M	Ph, I	Rectum	5	Metachronous	–	60 months, A	
7	74/M	Pb, IVA	Colon	6	Metachronous	+	7 months, D	Panc. Ca.
8	76/M	Pb, I	Stomach	0	Synchronous	–	13 months, D	Leukemia
9	73/M	Ph, III	Lung	0	Synchronous	–	4 months, D	Panc. Ca.
10	67/F	Ph, IVB	Rectum	0	Synchronous	–	4 months, D	Panc. Ca.
11	78/M	Ph, IVB	Lung	0	Synchronous	+	13 months, A	
12	76/F	Ph, I	Colon	0	Synchronous	+	12 months, D	Colon Ca.

Pb, pancreatic body; Ph, pancreatic head; D, dead; A, alive; Panc. Ca., pancreatic cancer; Colon Ca., colon cancer

^aAccording to UICC TNM classification of malignant tumors

Table 2. Treatment of double cancers

Case no.	Procedures for pancreatic cancer	Associated cancer and procedures	Others
1	Distal pancreatectomy	Gastric cancer, resection 3 years before	Gastrectomy, 3 years before
2	Pancreatoduodenectomy	Uterus carcinoma, resection 5 years before	
3	Pancreatoduodenectomy	Gastric cancer, resection 12 years before	Gastrectomy, 12 years before
4	Distal pancreatectomy, IORT	Gastric cancer, resection 14 years before	Gastrectomy, 14 years before
5	Distal pancreatectomy	Early gastric cancer, resection 5 years before	Gastrectomy, 5 years before
6	Pylorus-preserving pancreatoduodenectomy	Rectal cancer, resection 5 years before	
7	Inoperable	Colonic cancer, resection 1 year before	Gastrectomy, 6 years before
8	Distal pancreatectomy	Advanced gastric cancer, resection synchronously	
9	Bypass	op (–) Lung cancer	
10	Inoperable	op (–) Rectal cancer	
11	Inoperable	op (–) Lung cancer	Gastrectomy, 17 years before
12	Bypass	Colonic cancer, resection	Gastrectomy, 17 years before

IORT, intraoperative radiation therapy; op (–), no operative indications for cancers

or ulcers. The stages of their pancreatic cancers were as follows; 4 in stage I, 0 in stage II, 4 in stage III, and 4 in stage IVA or B according to the TNM clinical classification.¹ The seven patients in the metachronous group had all received curative operations: for gastric cancer in 4 patients, rectal or colon cancer in 2, and uterine carcinoma in 1 patient. They had undergone surgical resections for these non-pancreatic malignancies by outside surgeons 3–14 years earlier (Table 1). Six patients in the metachronous group and 1 patient in the synchronous group were considered to have localized disease after our screening, and they thus underwent a laparotomy and resection of pancreatic tumor. The treatment modalities for the pancreatic cancer patients included: a distal pancreatectomy in 4 patients, a pancreatoduodenectomy in 2, pylorus-preserving pancreatoduodenectomy in 1, and a biliojejunum bypass

operation in 2 patients (Table 2). In the synchronous group, 2 patients, one of whom had advanced colonic cancer, underwent a biliojejunum bypass operation for pancreatic cancer, and 2 had no operative indications for pancreatic cancer because of the presence of liver or bone marrow metastases. We were able to perform surgical treatment for both pancreatic and gastric cancer in the remaining patient in this group.

A resection of the pancreatic cancer was not performed in 5 cases. The reasons for not resecting the pancreatic cancer were a high age or poor general condition in 2 patients, and an advanced stage of pancreatic cancer or other organ malignancy in 3 patients.

The prognoses were poor in 10 patients. Two patients died because of advanced colonic cancer or leukemia, and 8 patients died because of either pancreatic cancer or its recurrence. Only two patients are alive at this

time. We think that the diagnosis of pancreatic carcinoma with bone marrow metastasis in case 11, one of the two surviving patients, may have been inaccurate, because he is alive now without any symptoms such as jaundice or abdominal pain, and his abdominal computed tomography (CT) findings are stable in contrast to his past results.

Discussion

There have been many reported cases of double cancers of the gastrointestinal tract. However, reported cases of double cancer involving pancreatic cancer are relatively rare.²⁻⁴ Nevertheless, according to Kamisawa et al.,⁵ pancreatic cancer was associated with a high incidence of malignancies of the gastrointestinal tract, especially the stomach.^{6,7} The overall reported incidence of pancreatic cancer associated with other organ malignancies was 1.2%–20.0% (Table 3).⁸⁻¹² According to Makino et al.,⁸ the risk of pancreatic cancer increased among gastric, thyroid, or prostatic cancer patients in Japan (Table 4).⁵⁻⁸ Regarding the risk of pancreatic cancer after a gastrectomy, some studies have suggested that a gastrectomy may be a risk factor predisposing a patient to the development of pancreatic cancer.^{13,14} An explanation of the suggested increased risk for the development

of pancreatic cancer after a gastric resection could be that a gastrectomy greatly alters both the homeostatic neural and hormonal control of pancreatic secretion, and the metabolism and absorption of the intraluminal contents. For example, the amount of nitrites and *N*-nitroso compounds, which are known pancreatic carcinogens, increases in the gastric juice after a gastrectomy, while the reflux of these substances from the duodenum into the pancreatic duct might induce pancreatic cancer.^{15,16} However, we found no strong clinical evidence to suggest that a partial gastric resection is associated with the development of pancreatic cancer. There were seven patients in the present study who had

Table 3. Incidence of pancreatic cancer associated with other organ malignancies

First author ^{Ref.}	Year	Incidence	
Kamisawa ⁵	1993	16.6%	45 (15)/270 ^a
Makino ⁸	1984	5.6%	134 (26)/2394
Yoshimori ⁷	1982	10.8%	12 (0)/111
Maruchi ⁹	1979	20.0%	23/113
Cubilla ¹⁰	1978	17.0%	65 (1)/380
Kasumi ⁶	1977	7.3%	9 (5)/123
Moertel ¹¹	1961	3.1%	29 (3)/921
Warren and Gates ¹²	1932	1.2%	15 (2)/1259

^aNumber of gastric cancers in parentheses

Table 4. Reported cases of pancreatic cancer with other organ malignancies in Japan

Malignancies of other organs	Kamisawa et al. ⁵ (<i>n</i> = 270, 16.6%)	Kasumi et al. ⁶ (<i>n</i> = 123, 7.3%)	Yoshimori et al. ⁷ (<i>n</i> = 111, 10.8%)	Makino et al. ⁸ (<i>n</i> = 2394, 5.6%)	Total
Larynx	1			2	3
Pharynx			2	1	3
Tonsil		1			1
Gingiva	1		1		2
Esophagus	2		1	2	5
Stomach	15	5		26	46
Colon	6		1	9	16
Gallbladder				4	4
Liver	2			3	5
Thyroid	9		1	25	35
Pulmonary	3			10	13
Breast	5	1		5	11
MFH	2				2
Uterus	1	1	2	9	13
Ovary				2	2
Prostate	3	1	1	14	19
Urinary bladder	1		2	4	7
Ureter			1		1
Kidney				7	7
Malignant melanoma	1				1
Multiple myeloma				1	1
AML	1				1
CML	1			1	2
Skin				1	1

n, number of cases; %, incidence

MFH, malignant fibrous histiocytosis; AML, acute myelocytic leukemia; CML, chronic myelocytic leukemia

already received gastrectomies for ulcerative or cancerous lesions of the stomach. Therefore, it is important to suspect other malignancies in gastrectomy patients during the follow-up period.

Generally, patients who undergo surgical therapy for malignant diseases receive constant follow-up examinations to check for either recurrence or metastasis from their malignancies. We therefore think that those patients who have undergone surgical treatment for malignant diseases are likely to be diagnosed with a second primary lesion earlier than patients who have had no surgical treatments. However, an early diagnosis of pancreatic cancer is very difficult because early-stage pancreatic cancer reveals no characteristic findings on ordinary examinations.

In our cases, a 59-year-old patient who underwent a gastrectomy for early gastric cancer, stage Ia, developed pancreatic cancer 5 years after a gastrectomy. He had received constant follow-up examinations including serum tumor markers and abdominal ultrasonography. However, when the diagnosis of his pancreatic cancer was made by abdominal CT, it had already reached an advanced stage and had also invaded adjacent organs. It was shown to be impossible to diagnose early-stage pancreatic cancer even though he had received constant follow-up examinations. On the other hand, patients diagnosed with pancreatic cancer have a relatively short survival period. Therefore, second primary cancer is very rare in these patients.

In conclusion, pancreatic carcinoma has a very poor prognosis and is associated with a short survival. Therefore, the prognosis of patients with double cancers involving pancreatic cancer mainly depends on the prognosis of the pancreatic cancer. The present study suggests the necessity of long-term follow-up examinations for such patients, especially for gastrectomy patients, to allow for the early diagnosis of digestive tract cancers including pancreatic cancer.

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