―Report on Experiments and Clinical Cases―

Clinicopathological Features of 30 Autopsy Cases of Pancreatic Carcinoma

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Abstract

The annual incidence of pancreatic carcinoma has been increasing worldwide, and the overall 5-year survival rate has remained at approximately 5%. We re-evaluated 30 autopsy cases histologically diagnosed as pancreatic carcinoma from 1994 through 2010 at Nippon Medical School Hospital. The mean patient age was 69.5 years, with no significant differences between male and female patients. The location of the primary tumor was most often the head of the pancreas (46.7%), followed by the body (36.7%) and tail (16.7%). All patients had advanced-stage pancreatic carcinoma at diagnosis, which limited the therapeutic options. Surgical resection, radiation, and surgical resection with chemotherapy were each performed for a single patient, and chemotherapy was performed for 5 patients. The other patients received only symptomatic therapy. The mean survival time from the first medical examination to death was short (5.5 months; range, 1−40 months). The cases were classified into 28 ductal adenocarcinomas, 1 acinar cell carcinoma, and 1 intraductal papillary mucinous neoplasm (IPMN) with an associated invasive carcinoma. Death in most cases was directly related to the pancreatic carcinoma, including cachexia, carcinomatous peritonitis and pleuritis, hepatic failure and ileus due to metastasis, and malignancy-related disorders, such as coagulation disorders and immunodeficiency. The most frequent site of metastasis was the lymph nodes, followed by the liver, peritoneum, spleen, lung and/or pleura, small intestine, adrenal gland, kidney, omentum, diaphragm, and bone. We classified the autopsy cases as showing distant metastasis or local infiltration. All cases with local infiltration were located in the pancreatic head, but no difference was seen in other clinicopathological features between cases with local infiltration and cases with distant metastasis. Thus, the autopsies revealed an extremely poor prognosis for pancreatic carcinoma due to the tumor itself and malignancy-related disorders. The progression pattern (i.e., local infiltration or distant metastasis) may correlate with the location of the primary tumor.
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Key words: pancreatic carcinoma, ductal adenocarcinoma, acinar cell carcinoma, autopsy

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Introduction

The incidence and mortality from pancreatic carcinoma have been increasing worldwide[1]. Pancreatic ductal adenocarcinoma accounts for more than 95% of all malignant exocrine pancreatic tumors and is the fourth leading cause of cancer-related death in the United States and has a median survival of 6 months[2]. In Japan, pancreatic carcinoma was the sixth leading cause of cancer-related death in males and the fourth leading cause in females in 2007[3]. Most pancreatic tumors are found at advanced stages because of aggressive local infiltration and rapid progression. Treatment options for pancreatic carcinoma include surgical resection, radiation therapy, chemotherapy, and combined therapies, but the overall 5-year survival rate remains poor at approximately 5%. Even for the 15% to 20% of patients who undergo potentially curative resection, the 5-year survival is only 20%[4].

Several reports were recently published concerning the rapid autopsy in cases of pancreatic cancer. Autopsy was performed immediately after the death of patients with pancreatic carcinoma to collect high-quality tissues according to a rapid autopsy protocol[7]. Rapid autopsy of patients with pancreatic carcinoma has shown that 30% of patients die with locally destructive pancreatic cancer and that 70% die with widespread metastatic disease[8]. In addition, the Dpc4-immunolabeling status of carcinoma tissues correlates strongly with the presence of widespread metastasis but not with locally destructive tumors. Rapid autopsy studies have also revealed that the distant metastasis of pancreatic carcinoma occurs late in the genetic evolution and takes an average of 6.8 years from the cell giving rise to the parental clone to the seeding of the index metastasis[9]. The number of autopsies has decreased markedly in Japan[10], and the number of autopsies of pancreatic carcinoma has also decreased over the last 10 years at our hospital. In the present study, to clarify the clinicopathological features of the terminal phase of pancreatic carcinoma, we re-evaluated 30 autopsy cases of pancreatic carcinoma from our hospital and analyzed the metastatic status, cause of death, and other histopathological features.

Materials and Methods

Patients and Tissue Specimens

Thirty autopsy cases histologically diagnosed as pancreatic carcinoma from 1994 through 2010 at Nippon Medical School Hospital were surveyed. We analyzed the patient age and sex, location, treatment, survival time, death-related disease, postmortem time of autopsy, and patterns of metastasis. Because the criteria for classification of pancreatic tumors have changed with time, we reclassified all cases of pancreatic carcinoma according to the most recent World Health Organization classification[11]. This study was performed in accordance with the principles of the Declaration of Helsinki, 2008, and informed consent for the use of tissues was obtained from each patient's family.

Statistical Analysis

Results are given as means ± SE. The data were compared between groups using Student's t-test or the Mann-Whitney U test. The chi-square test and Fisher's exact test were used to analyze clinicopathological features. Statistical analyses were performed with the software package StatView J version 5.0 (SAS Institute, Inc., Cary, NC, USA).

Results

Characteristics of the cases of pancreatic carcinoma (17 in men and 13 in women) are shown in **Table 1**. The mean number of autopsy cases of pancreatic carcinoma per year was 1.76 (range, 0–7), and the number has tended to decrease for the past 10 years. The mean patient age was 69.5 years (range, 50–88 years), with no significant difference between men (68.6 years; range, 50–86 years) and women (70.8 years; range, 50–88 years). The most common location of the primary tumor was the head of the pancreas (n=14; 46.7%), followed by the body (n=11; 36.7%) and tail of the pancreas (n=5; 16.7%). All cases were advanced-stage pancreatic carcinoma

Table 1 Characteristics of autopsy cases of pancreatic cancer

Case no.	Age (years)	Sex	Location	Treatment (except for supportive care)	Survival (months)	Histologic type	Grade	Cause of death	Type of progression	Postmortem interval (hours)	Year
1	66	F	body, head	cisplatin + fluorouracil	6	ductal adenocarcinoma	G1	pleural effusion	distant metastasis	2.5	1994
2	83	M	head	—	4	ductal adenocarcinoma	G3	bronchopneumonia	local infiltration	18	1994
3	81	M	head	—	2	ductal adenocarcinoma	G1	ileus, bronchopneumonia, pseudomembranous colitis	local infiltration	11	1994
4	66	F	head	—	3	ductal adenocarcinoma	G2	perforation of gastric ulcer	distant metastasis	22	1994
5	67	M	head	surgical resection + fluorouracil	40	ductal adenocarcinoma	G1	kidney abscess	distant metastasis	1	1994
6	82	F	tail	—	4	ductal adenocarcinoma	G3	carcinomatous peritonitis and pleuritis	distant metastasis	2	1994
7	58	M	body	—	1	ductal adenocarcinoma	G3	carcinomatous peritonitis, ileus, sepsis	distant metastasis	2.5	1994
8	79	F	head	—	6	ductal adenocarcinoma	G1	obstructive jaundice	local infiltration	13	1995
9	88	F	head	—	4	ductal adenocarcinoma	G2	pulmonary thrombosis, heart vegetation	distant metastasis	4	1995
10	61	F	tail	—	9	ductal adenocarcinoma	G1	pulmonary infarction	distant metastasis	1.5	1995
11	68	M	body, tail	—	3	acinar cell carcinoma	GX	sepsis	distant metastasis	14.5	1995
12	65	F	tail	—	2	ductal adenocarcinoma	G2	acute myocardial infarction, cachexia	distant metastasis	2	1997
13	75	F	body, tail	—	4	ductal adenocarcinoma	G1	ileus	distant metastasis	6.5	1998
14	50	M	head	surgical resection	15	IPMN with associated invasive carcinoma	G1	pulmonary infarction, bronchopneumonia, cachexia	local infiltration	14	1998
15	60	M	body	—	2	ductal adenocarcinoma	G3	obstructive jaundice	distant metastasis	33.5	1998
16	59	M	head	—	4	ductal adenocarcinoma	G1	cachexia	distant metastasis	3.5	1998
17	55	M	tail	—	4	ductal adenocarcinoma	G1	carcinomatous peritonitis, cirrhosis	distant metastasis	33	1999
18	80	M	head	radiation	1	adenosquamous carcinoma	GX	gastric ulcer, cachexia	distant metastasis	17	2000
19	65	F	head	fluorouracil + gemcitabine	3	undifferentiated carcinoma	G4	intraperitoneal bleeding	distant metastasis	4	2001
20	67	M	head	—	7	ductal adenocarcinoma	G2	carcinomatous peritonitis, cachexia	distant metastasis	11.5	2002
21	50	F	head	—	10	ductal adenocarcinoma	G2	carcinomatous peritonitis, gastric bleeding	distant metastasis	35	2002
22	86	M	body, tail	—	2	ductal adenocarcinoma	G2	DAD	distant metastasis	8.5	2002
23	74	F	body, tail	—	6	ductal adenocarcinoma	G2	carcinomatous peritonitis and pleuritis, liver failure	distant metastasis	3	2003
24	79	M	body, tail	—	2	ductal adenocarcinoma	G2	liver failure	distant metastasis	12.5	2003
25	68	F	body, head	fluorouracil	6	ductal adenocarcinoma	G2	carcinomatous peritonitis, gastric ulcer	distant metastasis	3.5	2004
26	81	F	head	—	5	ductal adenocarcinoma	G1	carcinomatous peritonitis, bleeding tendency	distant metastasis	3	2005
27	59	M	tail	paclitaxel + carboplatin	3	ductal adenocarcinoma	G3	DAD, bronchopneumonia	distant metastasis	14.5	2006
28	74	M	head, body	—	2	ductal adenocarcinoma	G1	carcinomatous peritonitis, candida pneumonia	local infiltration	4.5	2008
29	71	M	body, tail	gemcitabine + TS-1	4	ductal adenocarcinoma	G2	carcinomatous peritonitis and pleuritis	distant metastasis	11	2008
30	69	M	body	—	1	ductal adenocarcinoma	G1	carcinomatous peritonitis, ileus, sepsis	distant metastasis	10	2010

Autopsy cases were diagnosed histologically as pancreatic cancer. Survival indicates the time from the first medical examination to death. Histologic type and grade of the pancreatic cancers were determined with autopsy specimens according to World Health Organization classification. IPMN, intraductal papillary mucinous neoplasm; DAD, diffuse alveolar damage
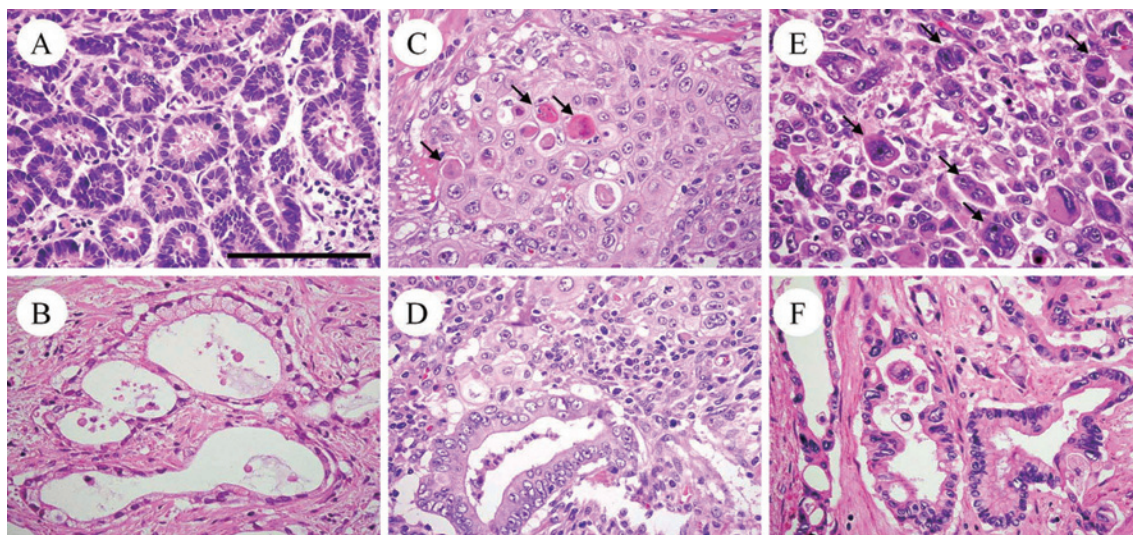
Fig. 1　Histopathological appearance of characteristic autopsy cases

(A) The case of acinar cell carcinoma (case 11) showed an acinuslike structure. (B) The case of IPMN with an associated invasive carcinoma (case 14) showed a conventional ductal adenocarcinoma (grade 1) in the remnant pancreas. (C) In the case of adenosquamous carcinoma (case 18), a moderately differentiated squamous cell carcinoma lesion with keratinization (arrows) was observed, and (D) an adenocarcinoma lesion was located in 30% of tumors. (E) In the case of undifferentiated carcinoma (case 19), anaplastic, polygonal, and osteoclastlike multinuclear cells (arrows) were observed in the pancreas, and (F) a ductal adenocarcinoma lesion was observed in the metastatic lesion. Hematoxylin and eosin staining. Scale bar=100 μm.

at diagnosis, which limited the therapeutic options. One patient underwent surgical resection and chemotherapy with fluorouracil, 1 patient underwent surgical resection, 1 patient was treated with radiation, and 5 patients underwent chemotherapy (with cisplatin and fluorouracil, fluorouracil and gemcitabine, fluorouracil, paclitaxel and carboplatin, or gemcitabine and TS-1). The 2 patients who underwent surgical resection had the longest survival times of 15 and 40 months. Most patients received only symptomatic therapy, and survival from the time of first examination to death was extremely short (mean, 5.5 months; range, 1–40 months). Specimens in several cases underwent autolysis owing to the long postmortem time (mean, 11.7 hours; range, 1–33.5 hours), but they were of high enough quality for pathological diagnosis.

On pathological examination, the cases of pancreatic carcinoma were classified as 28 ductal adenocarcinomas, 1 acinar cell carcinoma, and 1 intraductal papillary mucinous neoplasm (IPMN) with an associated invasive carcinoma (**Table 1**). The case of acinar cell carcinoma (case 11) showed acinuslike structures (**Fig. 1A**) and was immunohistochemically stained for α1-antitrypsin and amylase. The case of IPMN with associated invasive carcinoma was diagnosed from the surgically resected specimen obtained 1 year before the patient's death. An intraductal lesion was not observed in the autopsy specimen of this case, whereas ductal adenocarcinomas (grade 1) were located in the remnant pancreas, peritoneum, omentum, and diaphragm (case 14, **Fig. 1B**, **Tables 1 and 2**).

Most ductal adenocarcinomas were diagnosed as conventional type, whereas 1 case was adenosquamous carcinoma, and 1 case was undifferentiated carcinoma. In the case of the adenosquamous carcinoma (case 18), a moderately differentiated squamous cell carcinoma lesion occupied a large part of the tumor (**Fig. 1C**), and an adenocarcinoma lesion comprised approximately 30% of the tumor (**Fig. 1D**). In the case of undifferentiated carcinoma (case 19), anaplastic, polygonal, and osteoclastlike multinuclear cells, which are typical of undifferentiated carcinoma, were observed in the pancreas (**Fig. 1E**). In this case, both undifferentiated carcinomas and moderately

Table 2 Major metastatic organs

	Lymph node	Liver	Peritoneum	Spleen	Lung/pleura	Small intestine	Adrenal gland	Kidney	Omentum	Diaphragm	Bone
1	+		+		+						
2	+		+								
3	+					+					
4		+									
5	+	+									
6			+	+	+	+	+				
7	+	+	+	+	+	+	+			+	
8				+		+					
9	+	+		+							
10	+	+	+	+	+						+
11	+	+			+						
12	+	+		+				+			+
13	+	+	+			+					
14	+		+						+	+	
15	+	+		+	+			+	+	+	+
16	+				+						
17	+	+	+	+	+		+				
18	+	+		+				+		+	+
19	+	+	+			+			+		
20	+	+	+			+					
21	+	+	+	+		+	+	+	+		+
22	+	+	+	+	+		+	+	+	+	
23	+	+	+	+	+	+	+		+	+	+
24	+	+						+			+
25	+	+	+	+	+		+	+	+		
26		+	+		+	+	+				
27	+	+						+		+	
28			+			+					
29	+	+	+	+			+		+		+
30		+	+			+	+			+	

Metastatic organs were determined with autopsy specimens.

differentiated adenocarcinomas were found in the metastatic lesion (**Fig. 1F**). One case of ductal adenocarcinoma (case 12) exhibited features of squamous cell carcinoma, but these lesions comprised less than 30% of the total tumor, which was diagnosed as conventional ductal adenocarcinoma according to the World Health Organization classification. Histological grade 1 was the most frequent for ductal adenocarcinomas (11 of 27 cases; 40.7%), followed by grade 2 (10 of 27 cases; 37.0%) and grade 3 (6 of 27 cases; 22.2%). The histological grade of pancreatic carcinoma cases did not correlate with age, sex, location of tumors, stage, or survival time.

Severe disorders were observed at autopsy in most cases, and determining a single cause of death was difficult. Death in most cases was directly related to the pancreatic carcinoma, including cachexia, carcinomatous peritonitis and pleuritis, hepatic failure and ileus due to metastasis, and exsanguination due to vessel invasion (**Table 1**). Malignancy-related disorders, such as thromboembolic complications, tendency to bleed, sepsis, and inflammatory disease, were also observed. In the present cases, no deaths were attributed to causes unrelated to the tumor.

We also analyzed the patterns of tumor metastasis (**Fig. 2**). Distinguishing between metastasis and direct invasion on a histological basis is difficult in advanced stages of carcinoma; therefore, we diagnosed metastasis when tumor cells were histologically detected in an organ. All cases of
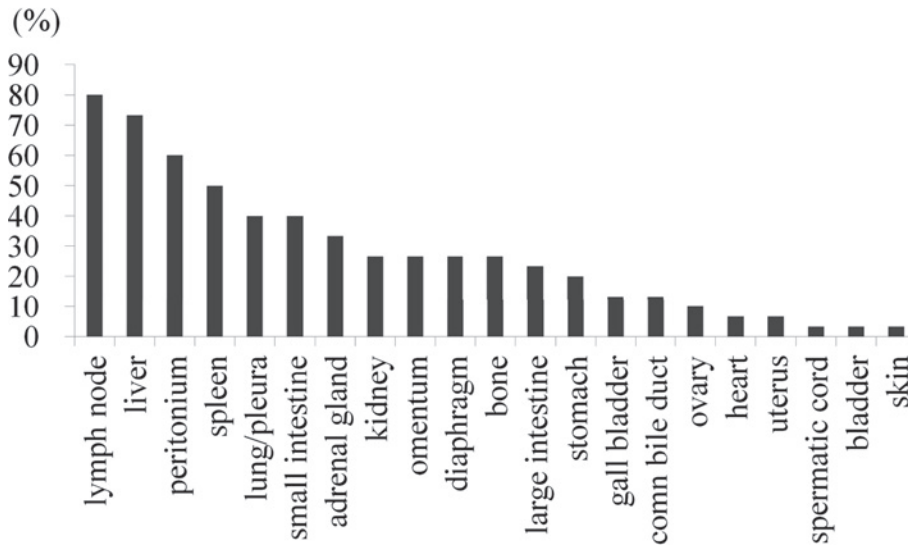
Fig. 2 Organ-segregated incidence of metastasis in cases of pancreatic carcinoma
In 30 autopsy cases of pancreatic carcinoma, the most common site of metastasis was
the lymph nodes, followed by the liver, peritoneum, spleen, lung or pleura or both, small
intestine, adrenal gland, kidney, omentum, diaphragm, and bone.

Table 3 Minor metastatic organs

	Large intestine	Stomach	Gall bladder	Common bile duct	Ovary	Heart	Uterus	Spermatic cord	Bladder	Skin
1	+			+	+		+			
2										
3										
4										
5										
6	+									
7	+		+							
8										
9										
10		+								
11										
12			+							
13									+	
14										
15	+		+	+		+				
16										
17	+	+								
18		+				+				
19										
20				+						
21										
22	+									
23	+	+								
24										
25		+			+		+			
26				+	+					+
27		+								
28			+							
29								+		
30										

Table 4 Clinicopathological features of local infiltration and distant metastasis

	Local infiltration (N=5)	Distant metastasis (N=25)
Age	73.4 ± 6.0	68.8 ± 2.0
Survival (months)	5.8 ± 2.4	5.4 ± 1.5
Sex		
male	4	13
female	1	12
Location*		
head	5	9
body + tail	0	16
Histological type		
ductal adenocarcinoma		
conventional type	4	22
adenosquamous carcinoma	0	1
undifferentiated carcinoma	0	1
IPMN with associated invasive carcinoma	1	0
acinar cell carcinoma	0	1
Histological grade		
G1	4	8
G2	0	10
G3	1	4
G4	0	1
GX	0	2

*$P=0.0088$ with chi-square test.

pancreatic carcinoma showed metastasis and were classified as stage IV. The most frequent site of metastasis was the lymph nodes (80%), followed by the liver (73.3%), peritoneum (60.0%), spleen (50.0%), lung or pleura or both (40.0%), small intestine (40.0%), adrenal gland (33.3%), kidney (26.7%), omentum (26.7%), diaphragm (26.7%), and bone (26.7%, **Fig. 2** and **Table 2**). Other metastatic sites were observed in the large intestine (23.3%), stomach (20.0%), gall bladder (13.3%), common bile duct (13.3%), ovary (10.0%), heart (6.7%), uterus (6.7%), spermatic cord (3.3%), bladder (3.3%), and skin (3.3%, **Table 3**).

Next, to compare the roles of local invasion and remote metastasis on aggressiveness and survival in pancreatic carcinoma, we classified the autopsy cases as showing local infiltration or distant metastasis. Local infiltration was defined when pancreatic cancer had not metastasized to distant organs, such as the liver, lung, kidney, heart, bone, ovary, uterus, testis, or bladder. We identified 5 cases (16.7%) of local infiltration and 25 cases (83.7%) of distant metastasis. In cases of local infiltration, primary tumors had tended to grow locally, and the carcinoma cells had spread via peritoneal

dissemination. **Table 4** provides the clinicopathological features of the 2 types of pancreatic carcinoma. All cases of local infiltration occurred in the pancreatic head ($P=0.0088$), but other clinicopathological features did not differ significantly between cases of local infiltration and cases of distant metastasis.

Discussion

In the present study, the mean patient age was similar to that in previous reports[12,13]. Pancreatic carcinoma is extremely rare before the age of 40 years[14]. The likely causes of death in all cases of our series were the cancer itself and tumor-related blood coagulation abnormalities and immunodeficiency, which are consistent with several previous reports[15,16]. In contrast, Blastik et al.[13] have reported on the basis of their institutional autopsy materials that most deaths in patients with pancreatic carcinoma (>75%) are unrelated to the tumor. Differences in noncurative treatments for pancreatic cancer at each institution may affect the cause of death. Thromboembolism is reported to have been

found in approximately 20% of autopsy cases of pancreatic carcinoma, and fatal pulmonary embolism develops in roughly 40% of all cases[16]. In our series, pulmonary thrombosis and infarction were observed at autopsy in only 10% of cases, and no cases of pulmonary embolism have been found since 1999. The development of techniques to diagnose and treat thromboembolism might decrease the incidence of complicating disorders.

Approximately 15% to 45% of IPMN cases are accompanied by invasive carcinomas[17]. Most cases of IPMN exhibit mucinous adenocarcinomas or conventional type ductal adenocarcinomas. Cases of IPMN associated with invasive carcinoma have a better prognosis than do cases of conventional ductal adenocarcinomas[18,19], which also have a worse prognosis than IPMNs associated with mucinous adenocarcinoma[20]. In our case of IPMN with an associated invasive carcinoma, which was conventional ductal adenocarcinoma and locally infiltrative ductal adenocarcinoma, survival was longer (15 months) than in other cases.

On the other hand, variants of ductal adenocarcinoma, adenosquamous carcinoma, and undifferentiated carcinoma had worse prognoses and widespread metastasis, as previously reported[21,22]. Both adenosquamous carcinoma and undifferentiated carcinoma are extremely rare, accounting for approximately 1% of exocrine pancreatic malignancies[11,23]. Acinar cell carcinoma is also rare (1% to 2% of exocrine pancreatic malignancies) and, with a 5-year survival rate of 25% to 50%, has a prognosis better than ductal adenocarcinoma[24]. However, the case of acinar cell carcinoma in our series had metastasized extensively.

We found metastases in all autopsy cases of pancreatic carcinoma. Liver and lymph node metastases are described in most autopsy reports of pancreatic carcinoma[13,25]. Some authors claim that 8.4% to 12.3% of cases of pancreatic carcinoma with lung metastases do not have liver metastases[15,26], and we found that 10% of our cases had such characteristics. Both aggressive local infiltration and distant metastasis are considered major causes of death in pancreatic carcinomas. Distant metastases were more frequent from tumors of the body and

tail of the pancreas than from tumors of the head, and a previous report has shown that tumors of the body and tail form more massive metastases than do tumors of the head[13]. Survival did not differ significantly between the groups in our study; therefore, both distant metastasis and local progression may contribute to the aggressiveness of pancreatic carcinomas.

Autopsy is performed for particular cases in which clinical questions are hard to solve without pathological approaches agreed upon by the family; thus, the cases indicated in this study may be biased. However, only autopsy cases provide important information on the terminal stage of diseases. The number of pathological autopsies in Japan decreased from a peak of 40,247 in 1985 to 14,098 in 2009[10]. The number of pathological autopsies has also been decreasing in our hospital, and approximately 50 autopsies are performed per year. Survey and re-evaluation of these specimens will become a precious source of novel information for diseases, such as pancreatic carcinoma.

In summary, autopsy of pancreatic carcinomas revealed an extremely poor prognosis for this disease because of the tumor and malignancy-related disorders. Two progression patterns are seen: local infiltration and distant metastasis. In addition, the progression pattern may correlate with the location of the primary tumor.

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