TABLE 1. Clinicopathologic Findings

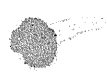
No.	Age/Sex	Location/ Size (mm)	Diagnosis/ Predominant Histology in ACC Area	Scheme	Gross Tumor-shape	Length of Intraductal Polypoid Projection (mm)	Tumor Thrombus in the Portal Vein	Extrapan-creatic Extension*	ly*	v*	ne*	TMN/ Stage (UICC)	Recurrence/ Survival
1	63/F	Phbt/	ACC		Sausage	+	+	+	+ +	+++	–	T3N0M0	Liver (3 mo) /
		145	Mix			20(Ph), 15(Pt)		rp				Stage IIA	Dead (4 mo)†
2	80/M	Phbt/	ACC		Sausage	+	–	–	–	+	–	T2N0M0	Liver (11 mo) /
		130	Mix			33(Ph), 20(Pt)						Stage IB	Dead (18 mo)
3	58/M	Ptb + Ph/	ACC		Sausage	+	–	+	–	++	–	T3N0M0	Liver (5 mo) /
		80(Pt-b) + 40(Ph)	AC			40(Ptb), 15(Ph)		rp				Stage IIA	Alive (29 mo)
4	72/M	Pbt/	ACC		Sausage	+	–	–	–	+	–	T2N0M0	LN (9 mo) /
		85	Mix			13(Pb), 10(Pt)						Stage IB	Alive (32 mo)
5	51/F	Phbt/	ACC		Ball	+	–	+	–	++	–	T3N0M0	None /
		135	Mix			50(Ph), 50(Pt)		du, ch				Stage IIA	Dead (180 mo)
6	58/M	Ph/	ACC		Ball	+	–	–	–	–	–	T2N0M0	None /
		45	AC			12(Ph)						Stage IB	Alive (32 mo)
7	64/M	Ph/	ACC		Ball	+	–	–	–	+	–	T2N0M0	None /
		30	Mix			20(Ph)						Stage IB	Alive (19 mo)
8	54/F	Pbt/	MAE		Ball	–	+	+	+	++	–	T3N0M0	Liver (5 mo) /
		155	Mix					rp				Stage IIA	Dead (7 mo)†
9	46/M	Pbt/	ACC		Ball	–	–	+	++	++	+	T3N0M1	Liver (11 mo) /
		130	Sol					Stomach, rp				Stage IV	Dead (27 mo)†
10	35/M	Ph/	ACC		Ball	–	+	+	++	++	++	T3N1M1	Liver (2 mo) /
		128	Sol					rp, du, ch				Stage IV	Dead (24 mo)†
11	54/M	Ph/	MAE		Ball	–	+	+	+	+ ++	++	T3N0M0	Liver (3 mo) /
		55	Mix					rp				Stage IIA	Allive (5 mo)

TABLE 1. (continued)

No.	Age/Sex	Location/ Size (mm)	Diagnosis/ Predominant Histology in ACC Area	Scheme	Gross Tumor-shape	Length of Intraductal Polypoid Projection (mm)	Tumor Thrombus in the Portal Vein	Extrapancreatic Extension*	ly*	v*	ne*	TMN/ Stage (UICC)	Recurrence/ Survival
12	47/M	Pb/	ACC		Ball	–	+	+	+	+ ++	++	T3N1M0	None /
13	60/F	45 Pb/	AC MAE		Ball	–	–	rp –	–	++	–	Stage IIB T2N0M1	Alive (5 mo) Liver (33 mo) /
		35	Mix									Stage IV	Alive (66 mo)

*Classified according to the classification of pancreatic carcinoma of Japan Pancreas Society.[6]
†The patient died owing to the tumor.
AC indicates acinar pattern; ch, bile duct; du, duodenum; LN, lymph node; ly, lymphatic invasion; mix, mixed acinar and solid pattern; ne, neural invasion; Phbt, pancreas head, body, and tail; rp, retropancreatic tissue; sol, solid pattern; v, venous invasion.

as confirmed by elastica staining (Fig. 2). The mean length of the intraductal polypoid projections was 24.8 mm (range 12 to 50 mm, Table 1). The tumor cells in the polypoid projections proliferated in an acinar and/or solid pattern with a scant stromal component. Adjacent to the IPG in the ducts, the tumors grew expansively and invaded and destroyed the duct wall that was present in the more central part of the tumor. Tumors invaded beyond the duct wall to the surrounding pancreatic parenchyma, and the IPG extended along the large pancreatic ducts in both directions to the duodenal ampulla and pancreatic tail. It was noteworthy that tumors showed no tendency to infiltrate beyond the pancreatic parenchyma. These findings were evident in all the tumors showing IPG. The length of the intraductal tumor projections and the extent of duct wall destruction varied from case to case, although the growth features of the tumors were similar. Extension of the intraductal polypoid projections, filling of the ducts by the tumor, and destruction of the duct wall owing to intraductal tumor expansion were also observed in the branch pancreatic ducts in these cases.

ACC, especially when developing in the pancreas body or tail, sometimes showed a unique gross tumor shape, extending along, and replacing the pancreatic parenchyma to mimic the shape of the pancreas, which we referred to as a "sausage-like" shape (Fig. 3). Grossly, this "sausage-like" shape distinguished ACC from the usual spherical or oval mass formed by the expansive growth of other pancreatic tumors, which we term hereafter as a "ball-like" shape. All 4 cases of ACC with IPG that developed in the pancreatic body or tail showed a sausage-like shape.

Tumors Without Intraductal Polypoid Growth

Six cases (cases 8 to 13 in Table 1), including 3 cases of ACC and 3 cases of MAE, did not show any IPG. In case 9, ACC invaded the main pancreatic duct without intraductal polypoid or papillary growth. Grossly, all 6 of these cases showed a ball-like tumor shape, even though 4 of them developed in the body or tail of the pancreas. Tumors without IPG often invaded beyond the pancreas to the surrounding organs with frequent invasions to lymphatic vessels, veins, or nerves, even though the tumors were not so large.

ACC With Intraductal Dissemination

Intraductal dissemination was found in 1 case of ACC with IPG (Case 3). This is the first case of its kind for which tumor dissemination in pancreatic ducts has been proven. The patient was diagnosed preoperatively as having an intraductal papillary-mucinous neoplasm. Computed tomography revealed a mass in the pancreatic tail and an ill-defined lesion in the head. Endoscopic retrograde pancreatography showed a contrast medium filling defect in the dilated main pancreatic duct, and obstruction of the distal pancreatic duct (Fig. 4A). The resected specimen (Figs. 4B and C) contained 2 lesions: one was an 8-cm tumor in the pancreas tail that extended

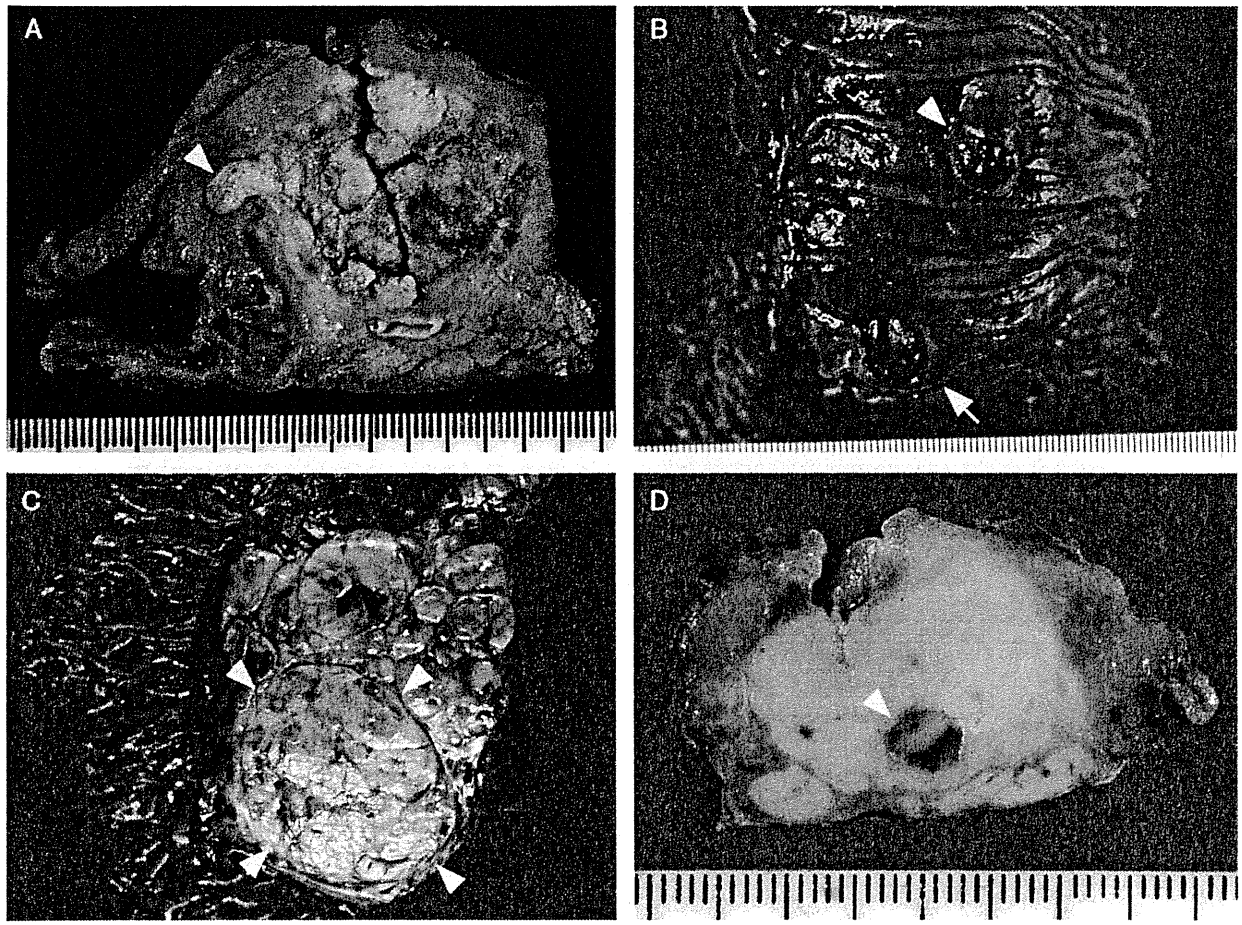


FIGURE 1. Gross appearance of intraductal polypoid growth in the large pancreatic ducts. A, An intraductal polypoid projection (arrowhead) in the Santorini duct near the accessory papilla protrudes from the main tumor mass in a horizontal section of the specimen in case 6. B, View of the duodenum mucosal surface of the fresh specimen in case 5, showing that both the accessory papilla (arrowhead) and papilla of Vater (arrow) are swollen and protrude into the lumen owing to pressure from tumors in the pancreatic ducts. C, Frontally cut surface of the fresh pancreas head specimen in case 5 reveals a polypoid tumor filling the dilated main pancreatic duct (arrowheads). D, Sagittally cut surface of the pancreas body specimen in case 4 shows an intraductal polypoid projection (arrowhead) filling the main pancreatic duct. full color

to the pancreas body with protrusion into the main pancreatic duct, and the other was a 4-cm tumor in the pancreas head that did not connect to the former one and was 3-cm distant from it. The pancreas head tumor showed intraductal proliferation, filling the main pancreatic duct and its connecting branch ducts, with little invasion into the surrounding stroma (Figs. 4D–I). The pancreas head tumor showed no evidence of lymphatic, venous, or neural invasion. The tumor cell cytoplasm contained zymogen granules that were positive for diastase-resistant periodic acid-Schiff staining (Fig. 5A). These granules were immunohistochemically positive for trypsin (Fig. 5B), and proven ultrastructually to be abundant large 500-nm dense granules (Fig. 5C). Molecular analyses revealed that both the pancreas tail and head tumors had identical results, that is 1 retention of heterozygosity (D10S197) and 3 LOH (D16S408, D16S410, and D17S261) among 4 informative polymorphic genome loci in a total of 19 loci that we tested (Fig. 5D). No mutations of the *CTNNB1* (*β-catenin*) and *APC* genes were detected in either of the tumors (data not shown). These findings indicated that the 2 tumors were identical, and that the one in the pancreas head had originated from the one in the pancreas tail. We hypothesized that the tumor projection in the main pancreatic duct extending from the pancreatic tail tumor had broken free, and that the floating fragments had become implanted in the ducts of the pancreatic head. There was no evidence of multifocal tumor development.

Clinicopathologic Assessment of ACC With Intraductal Polypoid Growth

We then compared the clinicopathologic characteristics of the tumors with and without IPG (Tables 1, 3). Five of the 6 tumors without IPG infiltrated the retropancreatic tissue, and 3 of them showed additional

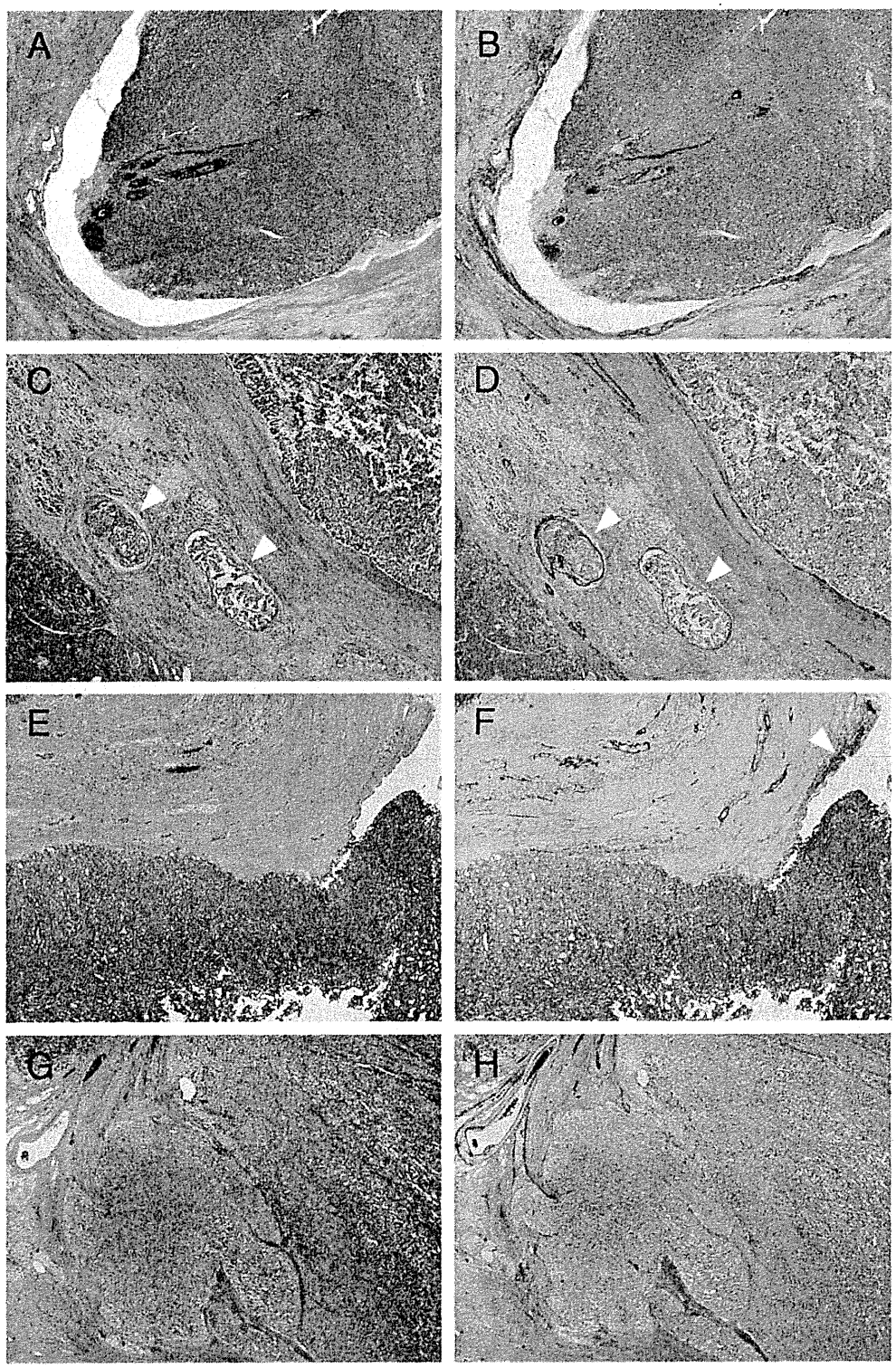


FIGURE 2. Microscopic appearance of intraductal polypoid growth in the large pancreatic duct. A and B, The advancing front of an intraductal polypoid projection in case 4 is located freely in the duct and shows no evidence of implantation to the duct wall. C and D, Intraductal tumor in case 6 fills the Santorini duct (right upper) and extends to fill in the branch ducts (arrowheads). E and F, Intraductal tumor in the main pancreatic duct in case 4 shows invasion and destruction of the duct wall (center to left). The duct wall is retained on the upper right (arrowhead). G and H, Intraductal tumor in case 2 fills the main pancreatic duct (right upper), and has disrupted the duct wall to overflow into the surrounding stroma (center to left lower). Panels A, C, E, and G show HE stain and B, D, F, and H show elastica stain. full color

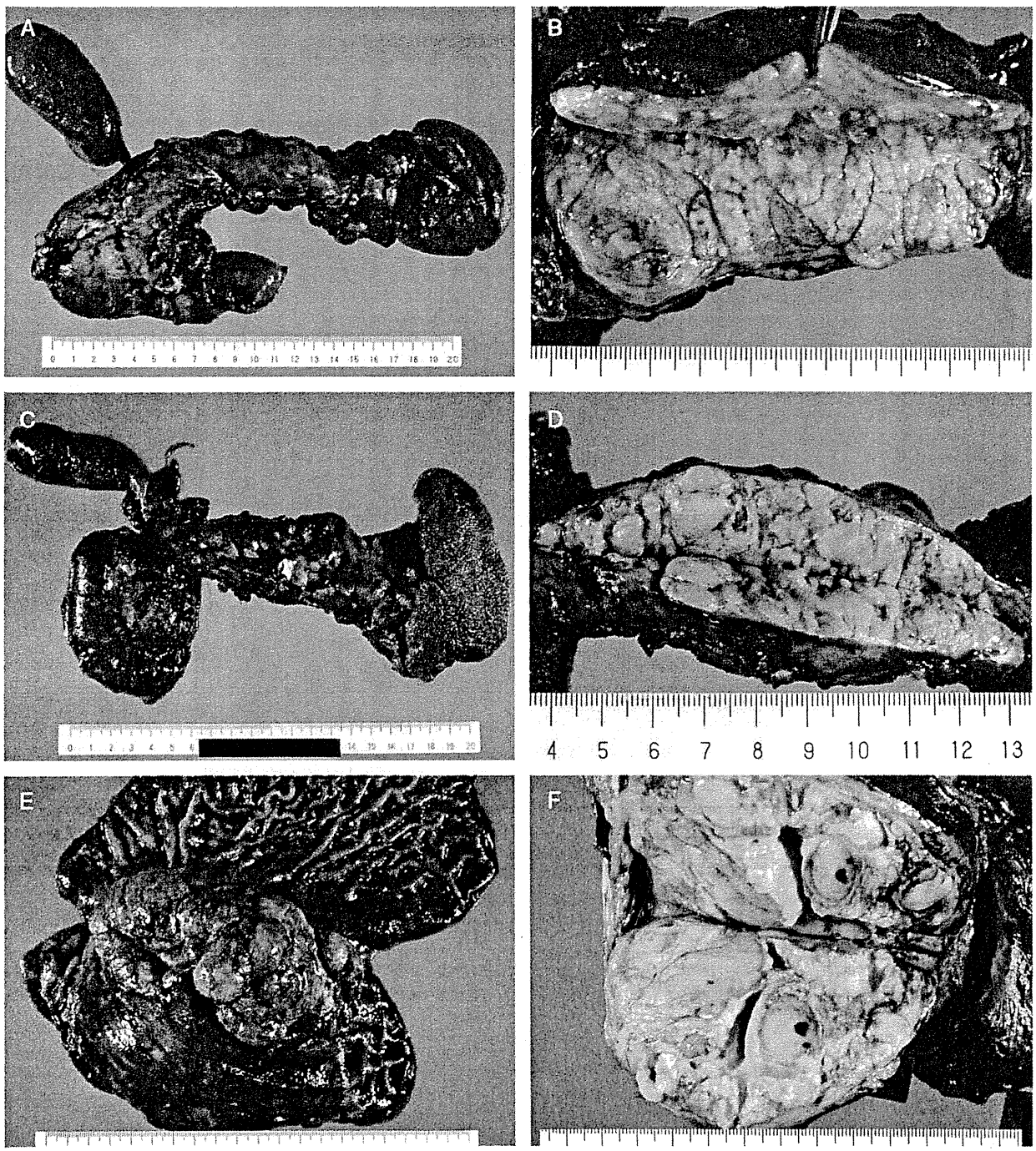
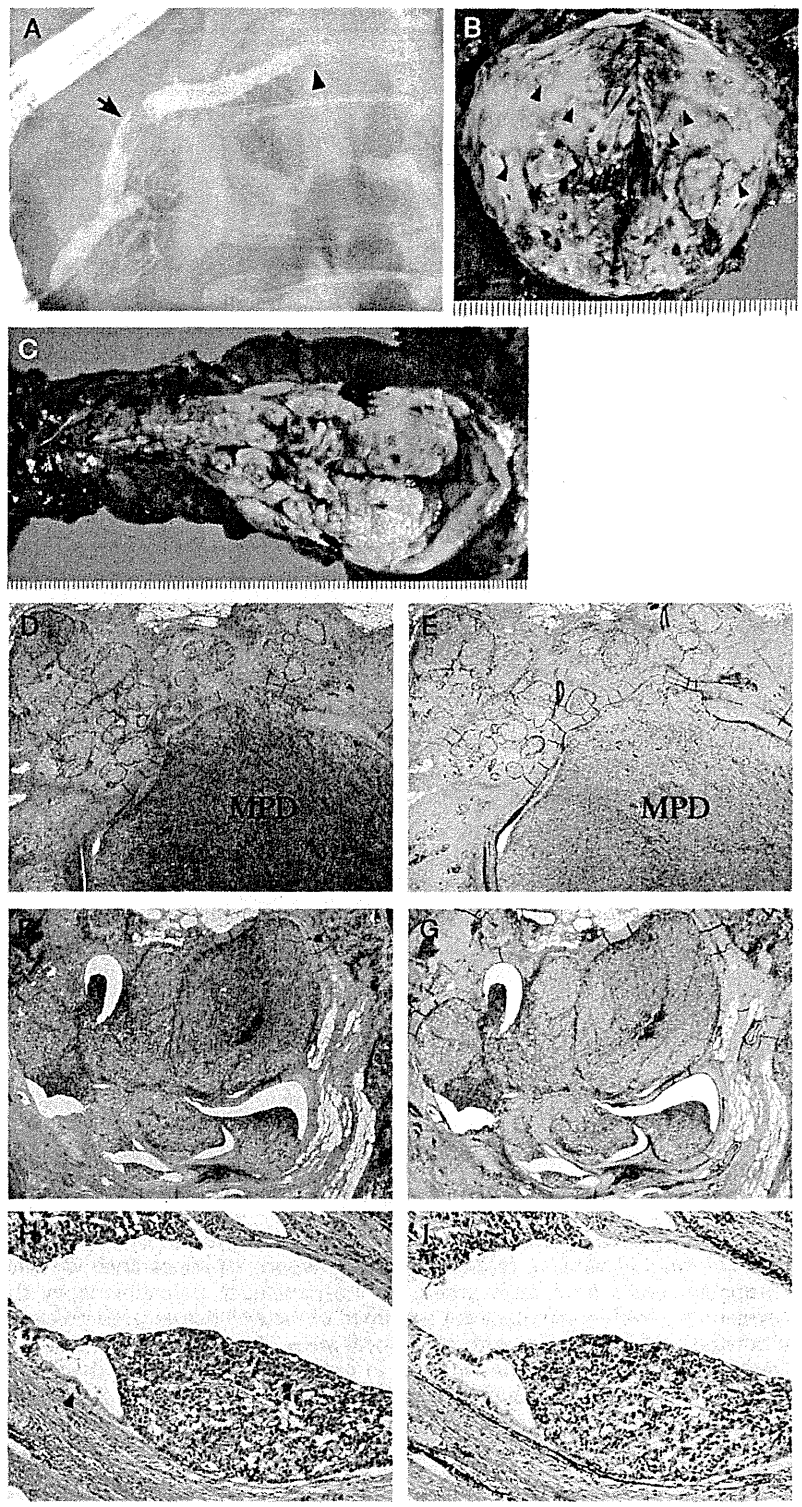


FIGURE 3. Gross tumor shapes of ACC. A to D, Gross view of fresh specimen obtained by total pancreatectomy shows that the body and tail of the pancreas are roughly swollen, resembling knotty wood: an appearance we refer to as the "sausage-like" shape (A, C). This shape probably results from replacement of the pancreatic parenchyma by the tumor without massive extrapancreatic growth, as evident in a fresh horizontally cut specimen of the well demarcated yellowish-tan mass in the pancreas body and tail, showing a lobulated and solid tumor with small focal areas of necrosis (B, D). A and B show case 1, and C and D show case 2. E and F, Fresh mucosal surface of the stomach in case 9 shows a lobulated and polypoid mass covered with necrotic debris that protrudes from the mass in the pancreatic body behind the stomach wall (E). Freshly cut specimen of the mass shows that it is encapsulated and contains nodular and lobulated grayish-white tumor tissue with necrosis (F). This tumor has a ball-like shape (E, F). full color

invasion to the intrapancreatic bile duct, duodenum, or stomach. The ACC in case 9 had penetrated the gastric wall to grow in the stomach as a lobulated mass (Fig. 3). These tumors were not so large. In contrast, 3 of the 7 tumors with IPG showed infiltration to the retropancreatic tissue, duodenum, or intrapancreatic bile duct, and all of them were larger tumors. Two large tumors with IPG (cases 2 and 4) did not invade beyond the



pancreas to the surrounding organs. Portal venous invasion with a tumor thrombus-like polypoid projection was present in 5 cases, of which 4 involved tumors without IPG (Table 1).

Five of the 6 tumors without IPG showed lymphatic and neural invasion in addition to venous invasion, whereas only 1 of 7 cases of ACC with IPG showed lymphatic invasion (Tables 1, 3). Two cases of ACC showing lymph node metastasis confirmed by pathologic examination did not have IPG. Histologically, the predominant pattern of tumor growth (predominantly acinar, predominantly solid, or mixed acinar and solid)[8] was not correlated with the presence or absence of IPG.

The immunohistochemical profiles of the various cases are summarized in Table 2. All were compatible with a pathologic diagnosis of ACC, based on the immunohistochemical characteristics documented earlier.[5] The Ki-67 labeling index ranged from 15% to 95% (median: 40%). These immunohistochemical findings showed no significant correlation with the presence of IPG or with the clinical course.

Three of the 6 patients whose tumors showed no IPG died owing to the tumors, although 1 of the 7 patients whose tumor was associated with IPG also did so. The respective 1-year and 5-year disease-specific survival rates were 85.7% and 85.7% for patients having ACC with IPG, and 75% and 25% for patients whose tumors lacked IPG. Eight patients developed liver metastasis and 1 developed lymph node metastasis after surgery.

DISCUSSION

ACC is a rare pancreatic tumor, accounting for only 1% of all epithelial primary pancreatic tumors. As its malignant potential is high, being second only to that of PDC,[5,9] a precise grasp of its pathologic characteristics is necessary. Here we carried out a detailed gross and histologic review of 13 cases of ACC, and found that more than half of them showed IPG, the pancreatic duct system being closely involved in tumor growth and extension. Our findings indicated that (1) the pancreatic duct system could become a major route of tumor extension, especially in cases of ACC showing IPG, and (2) the ducts could provide a corridor for intraductal tumor dissemination. In addition, our data suggest that the presence of IPG represents a biologic characteristic of this tumor that is ACC without IPG may be potentially more aggressive than ACC with IPG.

In our series, 7 of 13 cases of ACC (54%) showed IPG in the large pancreatic ducts and its branches. All the ACCs with IPG showed similar growth and extension patterns, including intraductal polypoid projection, ducts filled with the tumor, and destruction of the walls of large pancreatic ducts and branches, although the length of the intraductal polypoid projections varied among the cases (Table 1). It is also suggested that this type of growth is an important route for extension of ACC with IPG, probably owing to the relatively low infiltrative capacity of the tumor, and that this type of growth contributes to the formation of a distinctive sausage-like gross tumor shape. In fact, all of the ACCs with IPG that developed in the body or tail of the pancreas showed this sausage-like shape (Fig. 3), in contrast to the 4 tumors without IPG, which instead developed a ball-like shape. The sausage-like shape evident on gross examination seems to be unique, and is a feature absent in other pancreatic tumors. We propose that this sausage-like shape can be used as a feature for identification of ACC, specifically that with IPG.

In our present series, ACC without IPG showed more infiltrative growth (Tables 1, 3). In contrast, most cases of ACC with IPG did not exhibit features suggestive of an infiltrative nature, and even those cases that did were limited to those involving large tumors. The presence of IPG showed a significant negative correlation with vascular and neural invasion, nodal metastasis, and liver metastasis (Table 3). None of the patients with ACC showing IPG died owing to the ACC itself, except in case 1, in contrast to 3 of 6 patients with ACC lacking IPG who did so. These findings suggest that intraductal growth indicates a less infiltrative character, and that IPG might be a hallmark that can predict the biologic character of ACC. This is consistent with earlier suggestions that ACC showing intraductal and/or papillary growth is associated with lower morbidity and mortality than typical ACC.[1,14] Similar results have been reported for PDCs; those with intraepithelial extension exceeding 10 mm in the main pancreatic duct had a better outcome than PDCs without such intraepithelial tumor extension.[12]

FIGURE 4. Gross and microscopic features of ACC in case 5. A, Endoscopic retrograde pancreatography (ERP) shows dilation of the main pancreatic duct with filling defects. The irregular filling defect in the body (arrow) is a floating tumor that has broken away from the intraductal polypoid projection of the main tumor in the tail. The round filling defect on the distal side (arrowhead) is an obstruction of the main pancreatic duct, caused by the broken-off tip of the polypoid projection. B, Sagittally cut surface of the fresh pancreas head shows an intraductal polypoid tumor (arrowheads) filling the main pancreatic duct and branch ducts, in which tumor tissue seems to be squeezed out in a "tooth paste"-like manner. These findings seem to indicate that the intraductal tumors have not become implanted into the duct wall. C, Horizontally cut specimen of the fresh pancreatic tail tumor reveals a lobulated pinkish gray-white mass in the pancreatic tail extending in the direction of the pancreas head with focal necrosis. The extending top is located in the main pancreatic duct (arrowhead). D and E, Histology of the tumor in the pancreas tail shows that it is intraductal and polypoid, filling the main pancreatic duct (MPD) and the surrounding branch duct with stromal infiltrating lesions. F to I, The tumor in the pancreas head has grown mostly in the large pancreatic duct and its branches, with occasional invasion into the stroma. Nontumorous epithelial cells are seen covering the ductal lumen (arrowhead). Sections in D, F, and H are stained with HE, and those in E, G, and I with elastica stain. full color online

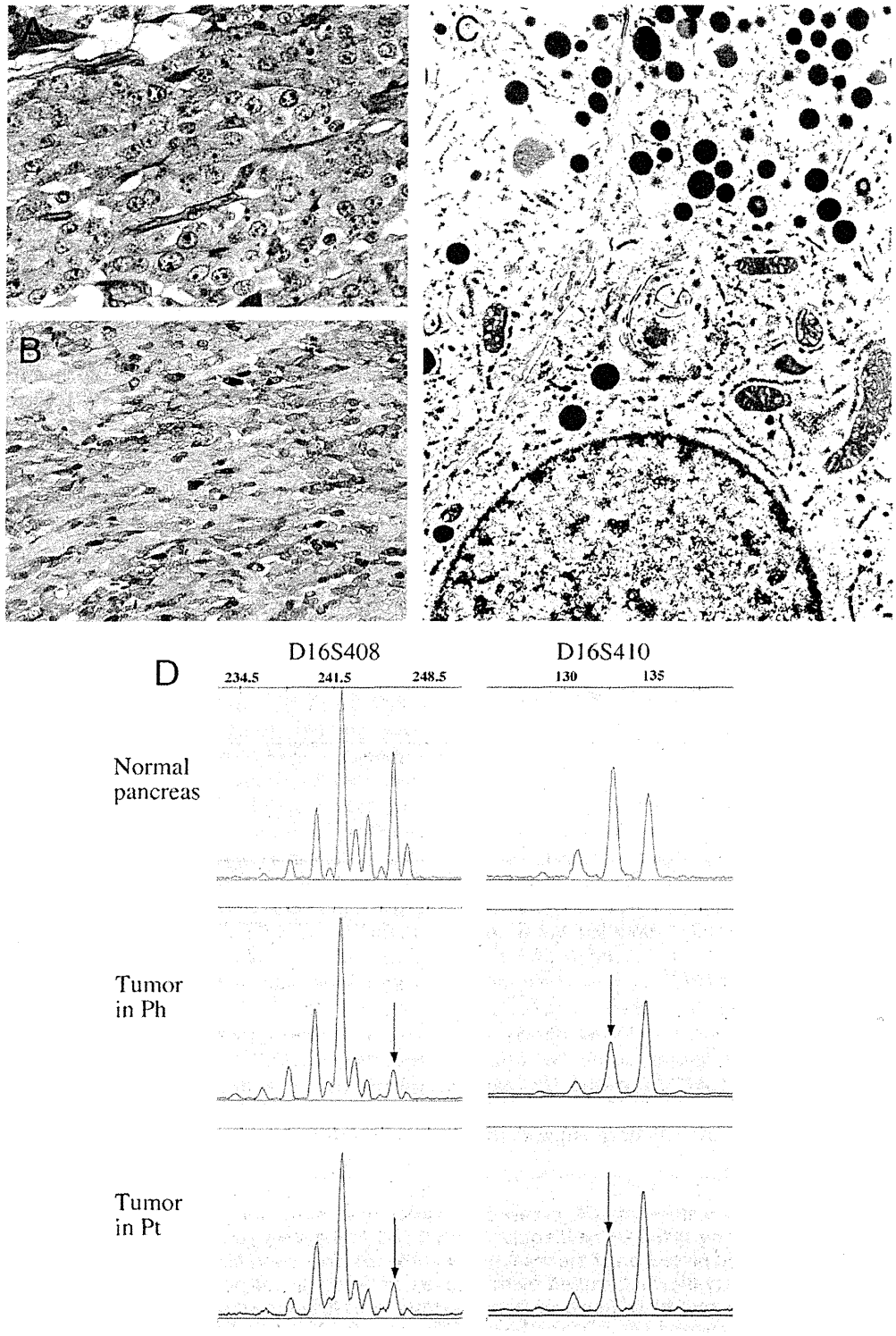


FIGURE 5. A, Periodic acid-Schiff staining with diastase digestion reveals abundant cytoplasmic granules (zymogen granules) in the tumor cells. B, Immunohistochemically, the tumor cells are strongly positive for trypsin. C, Ultrastructurally, the cells contain abundant, large, round, and homogeneous zymogen granules. D, Examples of results of LOH analyses. DNA samples obtained from normal pancreas (upper column) and tumors of the pancreas head (middle column) and tail (lower column) were amplified with markers D16S408 (left column) and D16S410 (right column). Allele sizes (bp) are indicated on the top horizontal axis. LOH is identified when the relative intensity of one allele is reduced by more than 70% in an informative case (arrows). full color online

TABLE 2. Results of Immunohistochemistry

Case	Trypsin	Lipase	β-Cat (m,c)*	β-Cat (n) (%)†	CGA	SYN	CD56	NSE	Ki-67 (%)
1	+	–	++	100	–	–	–	–	80
2	+	–	++	10	Focal+	-	Focal +	–	60
3	+	Focal+	++	0	Focal+	Focal +	–	–	90
4	+	Focal+	++	0	–	–	–	–	70
5	+	–	++	20	–	–	–	–	15
6	+	–	+	0	Focal+	–	–	–	95
7	++	+	++	60	Focal+	Focal +	–	Focal+	40
8	+	–	++	0	++	+	+	+	40
9	++	+	+	0	–	–	–	–	40
10	++	+	+	5	–	–	–	–	20
11	+	–	+	0	++	+	–	Focal+	50
12	++	+	++	0	–	Focal +	–	–	30
13	++	Focal+	++	50	++	++	Focal+	Focal+	30

*Positivity against plasma membrane and cytoplasm.
†Ratio of cells with positively stained nuclei to total cells.
β-cat indicates β-catenin; CGA, chromogranin A; Ki-67, Ki-67 labeling index; NSE, neuron-specific enolase; SYN, synaptophysin.

TABLE 3. Clinicopathologic Variables and Intraductal Polypoid Growth (IPG)

Variables	No. Patients	IPG (+)	IPG (–)	P (χ^2 test)
Sex				0.853
M	9	5	4	
F	4	2	2	
Age (year)				0.310
≥ 60	5	4	1	
< 60	8	3	5	
Tumor size				0.797
≥ 100	6	3	3	
< 100	7	4	3	
Tumor distribution (main)				0.821
Pancreatic head	5	3	2	
Pancreatic body or tail	8	4	4	
Local extension of tumor (rp, du, ch, st)*				0.135
Presence	8	3	5	
Absence	5	4	1	
Tumor thrombus in portal vein				0.053
Presence	5	1	4	
Absence	8	6	2	
Lymphatic invasion*				**0.013**
Presence	6	1	5	
Absence	7	6	1	
Venous invasion*				**0.026**
Presence	9	3	6	
Absence	4	4	0	
Neural invasion*				**0.009**
Presence	4	0	4	
Absence	9	7	2	
Local LN metastasis				0.097
Presence	2	0	2	
Absence	11	7	4	
Liver metastasis				**0.033**
Presence	3	0	3	
Absence	10	7	3	
Histology in ACC area				0.692
Predominantly acinar	3	2	1	
Predominantly solid	7	4	3	
Mixed acinar and solid	3	1	2	
TNM stage (UICC)				**0.034**
Stages IA, IB, and IIA	9	7	2	
Stages IIB	1	0	1	
Stages IV	3	0	3	

*Classified according to the classification of pancreatic cancer of Japan Pancreas Society.[6]
Bold values indicate numbers less than 0.05.
Ch indicates bile duct; du, duodenum; LN, lymph node; rp, retropancreatic tissue; st, stomach.

In case 1, ACC with IPG showed an unusually aggressive course (Table 1). Although the reasons are unclear, specific histologic features were evident. Most of the tumor cells proliferated with a usual acinar pattern, and there was focal diffuse and solid proliferation of atypical tumor cells expressing α-fetoprotein (AFP) and showing large nuclei with a high nucleo-cytoplasmic ratio, especially in areas of venous invasion and in tumor thrombi, including the portal vein. After surgery, liver metastasis developed with an exponential increase of the serum AFP level, suggesting that the aggressive behavior was owing to highly malignant AFP-positive tumor cells. This case seemed to be an exceptional one in our series, although we will need to examine a larger number of cases or conduct a prospective study to confirm our present observations.

In this series, we also showed intraductal dissemination of ACC in pancreatic ducts in 1 case of ACC with IPG. Intraductal dissemination of an epithelial neoplasm has never been proved in the duct systems of any organs, including the pancreas, bile duct, breast, or prostate. The pancreas head tumors in case 3 composed intraductal polypoid tumors in the large and small pancreatic ducts with a small degree of invasion, which were disconnected from the main tumor located in the tail, showing protrusion into the main pancreatic duct. The tumors in the pancreas head and tail showed identical histopathologic, immunohistochemical, and molecular genetic features. From these findings, we concluded that both tumors were identical and that the tumor in the pancreas head had arisen as a result of dissemination from that in the pancreas tail. Recently, Toll et al reported an intraductally growing ACC that showed diffuse involvement of the entire pancreas without formation of a distinct mass.[14] Although the tumors were multifocal, there was no description to indicate whether all of the tumors were connected, and it is possible that intraductal dissemination may have occurred.

In conclusion, more than half of the ACCs in our series had IPG, and the pancreatic duct system was closely involved in the growth and extension of the tumors. Our findings indicated that the pancreatic duct system could be an important route of tumor extension, especially for tumors with IPG, acting as a corridor for intraductal tumor dissemination. However, it is difficult to conclude from the pathologic evidence in our small series that this is a true characteristic of this rare tumor. Further pathologic analysis of a large number of cases of ACC will be necessary to confirm our observations, although the presence of IPG may represent a biologic hallmark of lower tumor aggressiveness in comparison with ACC lacking IPG.

ACKNOWLEDGMENTS

The authors thank Drs Minoru Esaki, Satoshi Nara, Hidenori Ojima, and Masahiro Gotoh for useful discussions and Ms Rie Itoh and Reiko Ogawa for excellent technical assistance.

REFERENCES

1. Basturk O, Zamboni G, Klimstra DS, et al. Intraductal and papillary variants of acinar cell carcinomas: a new addition to the challenging differential diagnosis of intraductal neoplasms. *Am J Surg Pathol.* 2007;31:363–370.
2. Fabre A, Sauvanet A, Flejou JF, et al. Intraductal acinar cell carcinoma of the pancreas. *Virchows Arch.* 2001;438:312–315.
3. Hashimoto M, Matsuda M, Watanabe G, et al. Acinar cell carcinoma of the pancreas with intraductal growth: report of a case. *Pancreas.* 2003;26:306–308.
4. Hiraoka N, Onozato K, Kosuge T, et al. Prevalence of FOXP3$^+$ regulatory T cells increases during the progression of pancreatic ductal adenocarcinoma and its premalignant lesions. *Clin Cancer Res.* 2006;12:5423–5434.
5. Hruban RH, Pitman MB, Klimstra DS. Acinar neoplasms. In: Hruban RH, Pitman MB, Klimstra DS. eds. *AFIP Atlas of the Tumor Pathology Fourth Series Fascicle 6: Tumors of the Pancreas.* Washington, DC: American Registry of Pathology; 2007:191–218.
6. Japan Pancreas Society. *Classification of Pancreatic Cancer.* 2nd ed. Tokyo. Japan: Kanehara; 2003.
7. Kitagami H, Kondo S, Hirano S, et al. Acinar cell carcinoma of the pancreas: clinical analysis of 115 patients from Pancreatic Cancer Registry of Japan Pancreas Society. *Pancreas.* 2007;35:42–46.
8. Klimstra DS, Heffess CS, Oertel JE, et al. Acinar cell carcinoma of the pancreas. A clinicopathologic study of 28 cases. *Am J Surg Pathol.* 1992;16:815–837.
9. Klimstra DS, Longnecker D. Acinar cell carcinoma. In: Hamilton SR, Aaltonen LA, eds. *Pathology and Genetics. Tumours of the Digestive System. World Health Organization Classification of Tumours.* Lyon, France: IARC Press; 2000:241–243.
10. Kondo Y, Kanai Y, Sakamoto M, et al. Genetic instability and aberrant DNA methylation in chronic hepatitis and cirrhosis-a comprehensive study of loss of heterozygosity and microsatellite instability at 39 loci and DNA hypermethylation on 8 CpG islands in microdissected specimens from patients with hepatocellular carcinoma. *Hepatology.* 2000;32:970–979.
11. Sekine S, Shimoda T, Nimura S, et al. High-grade dysplasia associated with fundic gland polyposis in a familial adenomatous polyposis patient, with special reference to APC mutation profiles. *Mod Pathol.* 2004;17:1421–1426.
12. Takahashi H, Oda T, Hasebe T, et al. Biologically different subgroups of invasive ductal carcinoma of the pancreas: Dpc4 status according to the ratio of intraductal carcinoma components. *Clin Cancer Res.* 2004;10:3772–3779.
13. Takahashi Y, Hiraoka N, Onozato K, et al. Solid-pseudopapillary neoplasms of the pancreas in men and women: do they differ?. *Virchows Arch.* 2006;448:561–569.
14. Toll AD, Mitchell D, Yeo CJ, et al. Acinar cell carcinoma with a prominent intraductal growth pattern: case report with review of the literature. *Int J Surg Pathol.* 2009; In press. PMID: 195484100.
15. Yamaguchi R, Okabe Y, Jimi A, et al. Pancreatic acinar cell carcinoma extending into the common bile and main pancreatic ducts. *Pathol Int.* 2006;56:633–637.

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010;40(10)949–953
doi:10.1093/jjco/hyq074
Advance Access Publication 21 May 2010

A Conundrum for Randomized Controlled Trials: Experience from a Small Hepatocellular Carcinoma Trial

Keiko Sato[1,*], Tosiya Sato[2], Junji Furuse[3], Hiroshi Kasugai[4], Masaru Konishi[5], Tomoo Kosuge[6], Akiko Saito[7], Yo Sasaki[8], Ken Takasaki[9] and Takuji Okusaka[10]

[1]Genetic Counseling and Clinical Research Unit, Kyoto University School of Public Health, [2]Department of Biostatistics, Kyoto University School of Public Health, Kyoto, [3]Department of Internal Medicine, Medical Oncology, Kyorin University School of Medicine, Tokyo, [4]Kasugai Clinic, Hyogo, [5]Digestive Surgical Oncology Division, National Cancer Hospital East, Chiba, [6]Hepatobiliary and Pancreatic Surgery Division, National Cancer Center Hospital, [7]Department of Medicine, Institute of Gastroenterology, Tokyo Women's Medical University, Tokyo, [8]Department of Surgery, Yao Municipal Hospital, Osaka, [9]Institute of Gastroenterology, Tokyo Women's Medical University and [10]Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, Tokyo, Japan

*For reprints and all correspondence: Keiko Sato, Genetic Counseling and Clinical Research Unit, Kyoto University School of Public Health, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan. E-mail: keiko.sato@kt2.ecs.kyoto-u.ac.jp

Received February 22, 2010; accepted April 15, 2010

Objective: The aim of this study was to explore why patients accepted or declined to participate in a randomized clinical trial, which was subsequently discontinued because of a low recruitment rate.

Methods: Forty-one patients were invited to participate in a randomized clinical trial that aimed to compare local ablation therapies and surgery to treat small asymptomatic hepatocellular carcinomas. These patients were then asked to answer a questionnaire that assessed patient perception and reasons for accepting or declining to enroll in the randomized clinical trial. When patients had a strong preference for a specific treatment, the questionnaire assessed why, how and when they had chosen it.

Results: The response rate was 6/6 (100%) and 30/35 (86%) for the participant and non-participant groups, respectively. Among the 30 non-participants, 23 had a strong preference for local ablation therapies, which was less invasive and offered shorter hospitalization. Patient preference for a specific treatment often stemmed from their consultations with a clinician who referred them to a specialist hospital. Patients without strong preference for a specific treatment participated in the randomized clinical trial because of altruistic motivations.

Conclusion: When new treatments that are innovative and less burdensome become widespread, they are difficult to compare with standard therapy utilizing a well-designed randomized clinical trial. Consequently, when an innovative treatment is developed, investigators should consider designing a randomized clinical trial as early as possible.

Key words: small asymptomatic hepatocellular carcinomas – local ablation therapies – liver resection – randomized clinical trial

INTRODUCTION

Randomized clinical trials (RCT) are the gold-standard to evaluate the safety and efficacy of proposed new treatments (1–3). When a new treatment shows benefits, it is introduced into general practice and is expected to improve the quality of care. However, an appropriate evaluation of an unproven new treatment through a RCT is difficult when it becomes integrated into general clinical practice because of its innovative and minimally burdensome nature (3). Consequently, the co-existence of a new treatment and a standard therapy often leads to diminished patient access to beneficial treatments.

Small asymptomatic hepatocellular carcinomas (HCC) are increasingly recognized as a problem in Japan since the initiation of periodic surveillance of high-risk populations (4). Surgical resection has been accepted as the first-line treatment for HCC. In addition, several local ablation therapies (LAT) have been developed to treat HCC, including percutaneous ethanol injection (PEI) (5) and radiofrequency ablation (RFA) (6). They are minimally invasive and have been recognized as an alternative to surgery in small HCC patients. Retrospective studies have reported that the prognosis of patients undergoing PEI (7–10) or RFA (6,11) for small HCC was equivalent to that of patients selecting surgery. However, the optimal therapeutic strategy for small HCC is under debate. Patient decisions regarding treatment are often guided by the expertise of their consulting clinician, which is frequently affected by sectionalism that is predominant in the Japanese medical community.

In 2002, a RCT (the parent study) was organized to settle the longstanding debate comparing the benefits of LAT relative to surgery in treating small HCC (i.e. three or fewer tumors, where each tumor is 3 cm in diameter or smaller). Table 1 shows the study outline. The trial was carried out in three cancer hospitals (Institutions A, B and C) and a university hospital (Institution D), where physicians and surgeons had the opportunity to build a framework for cooperation. We reached a consensus on what to include in the informed consent form and how to obtain it from patients. Specifically, we explained the clinical equipoise by noting: (i) the probability of 5-year disease-free survival associated with the two treatments was 25 and 10% for surgery and LAT, respectively; and (ii) the probability of 5-year survival associated with the two treatments was 62 and 59% for surgery and LAT, respectively (10). The purpose of the parent study and difference between two treatments were explained in informed consent form as follows; the purpose of this study is to compare the effectiveness, risk, burden and cost between surgery and LAT. Surgery has been usually performed for your type of cancer. LAT has been found to be effective and spread widely, but there is no solid evidence that LAT has a similar benefit to surgery. Currently, the proportion of recurrence in surgery is lower than LAT. However, there is little difference in long-term survival between surgery and LAT. LAT imposes less burden and invasiveness on patients than surgery. The comparative table of benefit, burden and cost in two treatments also was put on the form.

Table 1. Outline of the parent study

	Contents
Purpose	To compare local ablation therapies (RFA, PEI) with surgical resection
Eligibility	Hepatocellular carcinoma, three or fewer tumors each 3 cm in diameter or smaller, Child-Pugh class: A or B
	Age: ≥20, <80
Endpoints	
Primary endpoints	Overall survival and disease-free survival
Secondary endpoints	Medical costs, hospitalization period, Toxicity
Sample size	120 patients
Recruit period	2 year
Institutions	Cancer hospitals (Institution A, B, C), University hospital (Institution D)

Between October 2002 and April 2003, 41 patients were invited to participate in this study. Among these patients, six agreed and 35 refused to participate. Although a similar study was completed in China (12), the steering committee decided to discontinue the trial because of the low recruitment rate. Within this context, the aim of this study was to explore why patients accepted or declined to participate in the trial, and to use this information to provide insights for future research.

PATIENTS AND METHODS

We invited 41 patients, who were originally asked to participate in the parent study, to take part in this study. These patients were then asked by an attending clinician to respond to a questionnaire accompanied by an envelope. Patients were directed to place the completed questionnaire into the envelope and deliver it to the hospital staff. This study was approved by the National Cancer Center Hospital research ethics committee.

The questionnaire contained both multiple-choice and open-ended questions that aimed to assess the reasons behind patient decisions to participate in the study. We also examined views of non-participants towards random allocation. When non-participants had a strong preference towards a specific treatment, we assessed their perception by inquiring why, how and when they developed this preference. The questionnaire, developed by the investigators, was pilot-tested with laypersons to ensure clarity and comprehensibility of the questions. The questionnaires are shown in the Supplementary data, Appendix, available at http://www.jjco.oxfordjournals.org.

RESULTS

The survey was performed between May and July of 2003. Among the six participants and 35 non-participants, 6 (100%) and 30 (86%) patients, respectively, responded to the questionnaire. Table 2 shows the number of patients who accepted or declined participation in the parent-trial. Table 2 also shows the number of non-participants who chose surgery or LAT. Only 15% of patients participated in the parent-trial. There were no differences among institutions. Among the 30 respondents who declined trial entry, four had surgery, 25 had LAT and the remaining one was unknown.

Table 2. Number of patients (Pt) who accepted or declined participation

	Pt invited to RCT	Participant (%)	Non-participant		
			Total	Surgery	Local ablation therapies
Institution A	10	3 (30)	7	1	6
Institution B	8	1 (12)	7	1	6
Institution C	12	1 (8)	11	0	11
Institution D	11	1 (9)	10	4	6
Total	41	6 (15)	35	6	29

Reasons for Participation or Non-participation

Table 3 summarizes participants' reasons for deciding to participate in the parent-trial. All participants answered that they thought participation in the trial would contribute to the development of medicine. When asked about their major reason for participation, three participants marked 'the contribution to medical development' and two participants noted 'clinicians asked me to participate'.

Table 4 shows non-participants' reasons for refusing to enroll in the parent-trial. Four patients (13%) answered that they preferred surgery to LAT whereas 23 (77%) noted that they preferred LAT. One of two patients who received LAT stated 'I disliked surgery'; although the other stated 'clinicians did not ask strongly to participate'. Twelve patients (40%) stated that they were not satisfied with the random allocation into a treatment group. Among these 12 patients, 7 (58%) answered that patients should decide their own treatment whereas 3 (25%) answered that clinicians should decide. Two patients (17%) answered that randomization was inhumane. One patient (8%) stated that random allocation was problematic when two treatments were very different. One patient (8%) stated that he/she could not understand randomization.

Table 3. The frequency of agreement to each statement according to participation among six patients

Statement[a]	Number of respondents (%)
I thought participation in the trial would contribute to the development of medicine	6 (100)
Clinician asked me to participate	2 (33)
I thought there were no differences between two treatments	1 (17)
Other	
I had no preference because my tumors were small	1 (17)
I could not decide which treatment to have	1 (17)

[a]More than one response was allowed.

Table 4. The reasons of 30 non-participants for refusal

Statement[a]	Number of respondents (%)
I was not satisfied to be assigned to the treatment by randomization	12 (40)
Patient should decide the treatment	7 (58)
Clinician should decide the treatment	3 (25)
Randomization was inhumane	2 (17)
Two treatments were very different	1 (8)
I could not understand randomization	1 (8)
I wanted to receive local ablation therapies	23 (77)
I wanted to receive surgery	4 (13)
Other	
Clinician did not ask me to participate	1 (3)
I disliked surgery	1 (3)

[a]More than one response was allowed.

Reasons for Refusing Trial Entry Among Non-participants

Table 5 shows non-participants' reasons for why they subsequently decided to undergo surgery or LAT. All four patients who received surgery and one patient who receive LAT answered that they had thought the probability of recurrences would be lower. Among the patients who had LAT, the majority (20/25, 75%) stated that LAT imposed a lower amount of burden and invasiveness to their body than surgery. In addition, about half of the non-participants (12/25, 48%) stated that the hospitalization period would be shorter with LAT than with surgery. One patient stated that the medical cost of LAT was fewer.

Table 6 summarizes the results of how non-participants made their treatment decisions. Among these four patients who had surgery, three answered that they followed their surgeons' recommendation and one answered he/she followed physicians' recommendation. Among these 25 patients who had LAT, 2 (8%) answered that they referred to their surgeons, 21 (84%) answered that they relied on their attending physicians' recommendation and 9 (36%) answered that they relied on general practitioners' recommendation. Thirteen out of 25 patients who had LAT answered they had already decided to obtain this treatment before they were invited to the trial.

DISCUSSION

In this study, we found that patients who declined trial entry had a strong preference for LAT, which was less invasive and offered a shorter hospitalization course. We also found that this patient preference had stemmed from patient consultations with either a clinician or general practitioner who

Table 5. The reasons of 30 non-participants for preferring surgery or local ablation therapies

Statements[a]	Number of respondents (%)	
	Pt with surgery ($n = 4$)	Pt with local ablation therapies ($n = 25$)
I thought the probability of recurrences would be lower	4 (100)	1 (4)
I thought the survival period would be longer	0	0
I thought the treatment was less burdensome	0	20 (80)
I thought the hospitalization period was shorter	0	12 (48)
I thought the medical cost was fewer	0	1 (4)
Other	0	
I heard that the prognosis were the same		1 (4)
I did not want to increase wound any more		1 (4)

[a]More than one response was allowed.

Table 6. What non-participants referred to when they made a decision

	Number of respondents (%)	
	Pt with surgery ($n = 4$)	Pt with local ablation therapies ($n = 25$)
What non-participants referred to[a]		
Informed consent form	0	13 (52)
Consultation with surgeon in charge	3 (75)	2 (8)
Consultation with physician in charge	1 (25)	21 (84)
Consultation with general practitioner	0	9 (36)
Opinion of other patients	0	2 (8)
Opinion of my family	1 (25)	3 (12)
Other		
My close friend who was clinician suggested	1 (25)	
My friend suggested		1 (4)
The explanation about the prognosis		1 (4)
The information from internet		1 (4)
The information from newspaper		2 (8)
When they made a decision		
Before invitation to the study	1 (25)	13 (52)
After invitation to the study	1 (25)	8 (32)
Do not know or no answer	2 (50)	4 (16)

[a]More than one response was allowed.

referred them to a specialist hospital. Non-participants who received surgery believed in the survival benefits from surgery and relied on surgeon recommendations. On the other hand, patients without strong preference participated in the trial largely because of altruistic motivations. In summary, we found that patients tended to choose less invasive treatment methods even if there is a lack of superiority evidence or an inferiority possibility compared with the standard treatment. Many studies have reported a number of complex barriers in appropriately conducting RCTs (13–18), and we found a couple of these factors that contributed to the incompletion of this trial.

One barrier is that LAT, which had been performed in patients with unrespectable hepatic malignancies, has become popular in treating patients with small HCC due to its superiority in local tumor control and minimal invasiveness. It has become so popular that even without appropriate evidence that LAT has equivalent survival benefits compared with surgery, many general practitioners have recommended it to their patients as an alternative therapy.

Another barrier was patient fear towards a possible allocation into a treatment group that they did not prefer. Although some studies reported that a barrier to trial entry was patient difficulty in understanding the randomization concept and associated patient uneasiness (19–21), our study did not find this as an issue. Only one in 12 respondents that disliked randomization could not understand the randomization concept. Consequently, unbiased and objective explanations by clinicians are crucial in the consent process. However, in our study, we found that the more we stressed the clinical equipoise, the more the patients preferred LAT.

Although the lack of participation was based on these simple reasons, the solution is not simple. In order to increase the number of participants, there are a few possible study designs. One is a randomized consent design, where patients are randomly allocated into a specific treatment group before they provide consent (22,23). If patients decline the allocated treatment, they are then possibly allocated to the other treatment. Even if we apply this design, apart from its ethical problems, the effort will likely fail because most patients allocated to the surgery group will decline. Another possible solution is a randomized trial with a non-randomized part. Specifically, consenting patients are randomized into the two treatment groups, and those that refuse their allocated treatment are enrolled into a non-randomized study. At the conclusion of such a study, the endpoints of the randomized group and the non-randomized group are compared. In such a design, the results may include biases. Moreover, if there is an imbalance in the number of patients between the treatment groups in the non-randomized study, it is difficult to obtain appropriate results.

Furthermore, when there is a discrepancy in results between the randomized and non-randomized study groups, there is difficulty in the interpretation of the results.

In conclusion, when innovative and less burdensome treatments become widespread, they are difficult to compare with standard therapy utilizing a RCT. In light of the increasing number of organ preserving therapies, investigators should evaluate the efficacy and safety of innovative treatments with RCTs as early as possible (24).

Acknowledgements

We dedicate this paper to the late Dr Shuichi Okada, who was the principal investigator of the parent study.

Funding

This study was supported by grants from the Ministry of Health, Labour and Welfare of Japan.

Conflict of interest statement

None declared.

References

1. Piantadosi S, Clinical Trials. A Methodologic Perspective, 2nd edn. New Jersey: John Wiley & Sons 2005.
2. Levine RJ. Ethics and Regulation of Clinical Research, 2nd edn. New Haven Connecticut: Yale University Press 1986.
3. Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials, 3rd edn. St. Louis: Mosby 1996.
4. Okuda K. Early recognition of hepatocellular carcinoma. *Hepatology* 1986;6:729–38.
5. Sugiura N, Takara K, Ohto M. Treatment of small hepatocellular carcinoma by percutaneous injection of ethanol into tumor with real-time ultrasound monitoring. *Acta Hepatol Jpn* 1983;24:920 (in Japanese).
6. Rossi S, Di Stasi M, Buscarini E, Cavanna L, Quaretti P, Squassante E, et al. Percutaneous radiofrequency interstitial thermal ablation in the treatment of small hepatocellular carcinoma. *Cancer J Sci Am* 1995;1:73–81.
7. Castells A, Bruix J, Bru C, Fuster J, Vilana R, Navasa M, et al. Treatment of small hepatocellular carcinoma in cirrhotic patients: a cohort study comparing surgical resection and percutaneous ethanol injection. *Hepatology* 1993;18:1121–6.
8. Livraghi T, Bolondi L, Buscarini L, Cottone M, Mazziotti A, Morabito A, et al. No treatment, resection and ethanol injection in hepatocellular carcinoma: a retrospective analysis of survival in 391 patients with cirrhosis. *J Hepatol* 1995;22:522–6.
9. Ryu M, Shimamura Y, Kinoshita T, Konishi M, Kawano N, Iwasaki M, et al. Therapeutic results of resection, transcatheter arterial embolization and percutaneous transhepatic ethanol injection in 3225 patients with hepatocellular carcinoma: a retrospective multicenter study. *Jpn J Clin Oncol* 1997;27:251–7.
10. Yamamoto J, Okada S, Shimada K, Okusaka T, Yamasaki S, Ueno H, et al. Treatment strategy for small hepatocellular carcinoma: comparison of long-term results after percutaneous ethanol therapy and surgical resection. *Hepatology* 2001;34:707–13.
11. Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radiofrequency ablation versus ethanol injection. *Radiology* 1999;210:655–61.
12. Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg* 2006;243:321–8.
13. Madsen SM, Mirza MR, Holm S, Hilsted KL, Kampmann K, Riis P. Attitudes towards clinical research amongst participants and nonparticipants. *J Intern Med* 2002;251:156–68.
14. Cox K, Mcgarry J. Why patients don't take part in cancer clinical trials: an overview of the literature. *Eur J Cancer Care* 2003;12:114–22.
15. Mills EJ, Seely D, Tachlis BR, Griffith L, Wu P, Wilson K, et al. Barriers to participation in clinical trials of cancer: a meta-analysis and systematic review of patient-reported factors. *Lancet Oncol* 2006;7:141–8.
16. Jenkins V, Fallowfield L. Reasons for accepting or declining to participate in randomized clinical trials for cancer therapy. *Br J Cancer* 2000;82:1783–8.
17. Ellis PM, Butow PN, Tattersall MHN, Dunn SM, Houssami N. Randomized clinical trials in oncology: understanding and attitudes predict willingness to participate. *J Clin Oncol* 2001;19:3554–61.
18. Wright JR, Whelan TJ, Schiff S, Dubois S, Crooks D, Haines PT, et al. Why cancer patients enter randomized clinical trials: exploring the factors that influence their decision. *J Clin Oncol* 2004;22:4312–8.
19. Lynoe N, Sandlund M, Dahlqvist G, Jacobsson L. Informed consent: study of quality of information given to participants in a clinical trial. *Br Med J* 1991;303:610–3.
20. Featherstone K, Donovan JD. 'Why don't they just tell me straight, why allocate it?' The struggle to make sense of participating in a randomized controlled trial. *Soc Sci Med* 2002;55:709–19.
21. Kodish E, Eder M, Noll RB, Ruccione K, Lange B, Angiolillo A, et al. Communication of randomization in childhood leukemia trials. *J Am Med Assoc* 2004;291:470–5.
22. Zelen M. A new design for randomized clinical trials. *N Engl J Med* 1979;300:1242–5.
23. Ellenberg SS. Randomization designs in comparative clinical trials. *N Engl J Med* 1984;310:1404–8.
24. Chalmers TC. Randomization of the first patients. *Med Clin North Am* 1975;59:1035–8.

World J Surg (2010) 34:1908–1915
DOI 10.1007/s00268-010-0570-9

World Journal of Surgery

Analysis of 5-Year Survivors After a Macroscopic Curative Pancreatectomy for Invasive Ductal Adenocarcinoma

Kazuaki Shimada · Yoshihiro Sakamoto · Satoshi Nara · Minoru Esaki · Tomoo Kosuge · Nobuyoshi Hiraoka

Published online: 8 April 2010

Abstract
Background Surgical resections for invasive ductal adenocarcinoma of the pancreas can provide the only chance of cure, although the 5-year survivors are not always equated with cure.
Methods A total of 229 who underwent a macroscopic curative pancreatectomy for invasive ductal adenocarcinoma between 1990 and 2003 and have been observed for more than 5 years from the time of resection were retrospectively analyzed. The data of patients who survived more than 5 years were compared with those died within 5 years. The recurrence pattern and factors that influenced an additional 5-year survival in the 5-year survivors were investigated.
Results Forty patients (17%) survived more than 5 years, and the survival rate for an additional 5 years after surviving 5 years was 72%. A multivariate Cox hazards analysis showed that negative surgical margins status, less frequency of lymphatic invasion, stage ≤ IIB, and negative lymph node involvement were independent factors associated with long-term survival. Thirty patients (75%) were alive without recurrence, and eight (20%) died of disease within 7.3 years. Intrapancreatic nerve invasion was a significant factor predicting additional long-term survival in the 40 5-year survivors.
Conclusions Limited cancer extension with negative lymph node metastases significantly contributes to the chance of surviving more than 5 years. A low incidence of intrapancreatic nerve invasion in the 5-year survivors affects the subsequent favorable survival.

K. Shimada (✉) · Y. Sakamoto · S. Nara · M. Esaki · T. Kosuge
Hepatobiliary and Pancreatic Surgery Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: kshimada@ncc.go.jp

N. Hiraoka
Pathology Division, National Cancer Center Research Institute, Tokyo, Japan

Introduction

A pancreatectomy can provide only a chance of cure for patients with invasive ductal adenocarcinoma of the pancreas, because there is a lack of effective alternatives for achieving an actual 5-year survival [1]. However, recurrence within a year after surgery might be inevitable for most patients who undergo a pancreatectomy and the long-term prognosis might be poor with very few 5-year survivors [2]. Recently, a macroscopic curative pancreatectomy with lower surgical mortality and the encouraging 5-year survival rate associated with appropriate patient's selection and additional chemotherapy have made pancreatectomy the standard choice of care for invasive ductal carcinoma of the pancreas [3, 4]. Precise data on the long-term survival and prognostic factors can be obtained by an analysis of not actuarial but actual long-term survival of 5 years or more. Large series studies have reported an actual 5-year survival ranging from 10–27% [1, 5–11]. However, 5-year survival unfortunately does not represent a cure; 16–42% of patients died of recurrent disease in the 5-year survivors [1, 5–11]. Riall et al. [6] demonstrated that patients with pancreatic primary tumors continued to die of cancer even after achieving the 5-year landmark, although at a much slower rate than in the 5 years immediately after surgery. The causes of these recurrences are still unclear and no clinicopathological analysis of recurrence and failure in the 5-year survivors has been reported.

This study retrospectively examined 229 patients who underwent a macroscopic curative pancreatectomy for invasive ductal adenocarcinoma and have been observed for more than 5 years from the time of the resection to clarify the clinicopathological characteristics of the 5-year survivors compared with those who died within 5 years. The recurrence pattern and the factors that influenced additional long-term survival in the 40 5-year survivors were also investigated.

Patients and methods

A total of 244 patients underwent a pancreatectomy for invasive ductal adenocarcinoma between January 1990 and December 2003. All patients were histologically confirmed to have the common type of invasive ductal adenocarcinoma of the pancreas. Any patients with islet cell carcinoma, mucinous cystic, intraductal papillary-mucinous neoplasms (IPMN), invasive carcinoma originating in an IPMN, or rare pancreatic malignancies were excluded. Limited numbers of hepatic metastases, invasion to the portal vein or superior mesenteric vein, was not regarded as contraindications for surgery. Four patients who underwent a noncurative resection with gross residual tumors in the surgical field were excluded. Three surgical deaths (1.2%) and three in-hospital deaths (1.2%), two patients with incomplete follow-up data, and three patients who died of noncancerous causes within 5 years after surgery (two operation-related deaths, one hypoglycemia) also were excluded from the present study of long-term survival results. The remaining 229 patients, who underwent a macroscopic curative pancreatectomy and were observed for more than 5 years from the time of the resection, were enrolled in this study.

A total of 159 patients (69%) received intraoperative radiotherapy (IORT) and 59 patients (26%) received adjuvant chemotherapy as a clinical trial setting after pancreatectomy. An aggressive multimodality treatment, including neoadjuvant chemotherapy, was not applied during this study period. Follow-up examinations included a measurement of the serum carbohydrate antigen 19-9 (CA19-9) level and ultrasound or enhanced computed tomography at 3-month intervals. The demographic and clinical variables included age, sex, CA19-9, serum carcinoembryonic antigen (CEA), location of tumor, application of IORT, or adjuvant chemotherapy. The extent of the pathological features that might influence prognosis was classified as follows[12]: historically assessed tumor size, serosal invasion (absent/present), retropancreatic tissue invasion (rp0, absent; rp1, slight invasion; rp2, wide invasion; rp3, invasion to other organs), portal vein invasion (absent/present), extrapancreatic nerve plexus invasion (absent/present), lymph node involvement (n0, absent; n1, regional; n2, peripancreatic; n3, paraaortic involvement), differentiation of the tumor, lymphatic invasion (ly0, absent; ly1, slight; ly2, moderate; ly3, marked), venous invasion (v0, absent; v1, slight; v2, moderate; v3, marked), intrapancreatic nerve invasion (ne0, absent; ne 1, slight; ne2, moderate; ne3, marked), surgical margins status (negative/positive). Lymphatic, venous, and intrapancreatic nerve invasion were classified into four groups (0, no invasion; 1, slight; 2, moderate; 3, marked) according to the following definition: 0, no cancer cell invasion seen; 1, a few cancer cell invasions (1–3 points) seen; 2, several cancer cell invasions (4–8 points) seen; 3, many cancer cell invasions (>8 points) seen in the most extensively involved area under a low power magnification (×100), on the basis of the Japan Pancreas Society classification [12]. In a case of no invasion in a representative section, all the sections were reviewed. No invasion in any section was classified "0" and a few invasions in other sections were classified "1." The tumors were staged according to the TNM system, UICC sixth edition [13]. The clinicopathological factors were compared between 5-year survivors and non-5-year survivors. The risk factors that influenced survival were examined in the 5-year survivors.

Survival was calculated using the Kaplan–Meier method and was compared between the groups by using the log-rank test. All variables were dichotomized for analysis. A multivariate survival analysis was performed using Cox's proportional hazard model. Variables with a significance of $P \leq 0.1$ in the univariate analysis were entered into the multivariate analysis. Comparisons were performed using the chi-square test with Yates' correction in the univariate analysis. All significant factors determined by the univariate analysis were entered into a multivariate regression analysis to identify independent factors. All statistical analyses were performed by using the software Package for the Social Science 11.51 J for Windows® (SPSS, Chicago, IL). $P < 0.05$ was considered to be significant.

Results

The mean survival was 3.2 ± 0.3 (median, 1.4) years and 5- and 10-year survival rates were 17% and 10%, respectively, although the 5- to 10-year survival data were actuarial. Table 1 shows a univariate analysis of factors that influenced overall survival in the 229 patients. Age, sex, location, IORT, adjuvant chemotherapy, differentiation, or plexus invasion was evaluated but were not significant in univariate analysis. The absence of portal vein invasion tended to have a better prognosis, but the difference was not statistically significant ($P = 0.0605$). Significant

Table 1 Factors affecting the long-term survival after macroscopic curative pancreatectomy in 229 patients with invasive carcinoma of the pancreas

Factor	Categories	*n*	5-yr survival (%)	Mean survival term (yr)	*P*
Age (yr)	≤64	123	18	3.3 ± 0.4	0.6422
(median 64 yr)	>64	106	16	2.8 ± 0.3	
Sex	Male	141	14	2.9 ± 0.3	0.4515
	Female	88	22	3.4 ± 0.5	
Ca19-9	≤206	115	23	4.0 ± 0.5	0.0068
(median 206 IU/dl)	>206	114	10	2.3 ± 0.3	
CEA	≤3.2	119	20	3.5 ± 0.4	0.0606
(median 3.2 IU/ml)	>3.2	110	14	2.7 ± 0.4	
Location	Head/ neck	157	15	2.9 ± 0.3	0.1058
	Body/tail	72	21	3.7 ± 0.5	
Size	≤36	118	24	4.0 ± 0.4	0.0002
(median 36 mm: 8–110)	>36	111	9	2.2 ± 0.3	
Serosal invasion	Absent	179	19	3.4 ± 0.3	0.0270
	Present	50	10	1.7 ± 0.2	
Lymph node involvement	Absent	38	42	6.0 ± 0.9	0.0000
	Present	191	12	2.6 ± 0.3	
Retroperitoneal invasion	0/1	106	25	4.1 ± 0.5	0.0026
	2/3	123	9	2.3 ± 0.3	
Portal vein invasion	Negative	120	22	3.6 ± 0.4	0.0605
	Positive	109	12	2.6 ± 0.3	
Plexus invasion	Absent	143	18	3.4 ± 0.4	0.1444
	Present	85	15	2.6 ± 0.4	
Differentiation	Well	68	22	3.6 ± 0.5	0.1026
	Mod/poor	161	15	3.0 ± 0.3	
Lymphatic invasion	0/1	102	28	4.4 ± 0.5	0.0001
	2/3	127	8	2.1 ± 0.3	
Venous invasion	0/1	102	26	4.0 ± 0.5	0.0020
	2/3	127	9	2.4 ± 0.3	
Intrapancreatic nerve invasion	0/1	97	25	3.7 ± 0.4	0.0111
	2/3	132	11	2.5 ± 0.3	
Surgical margin status	Negative	154	19	3.7 ± 0.4	0.0061
	Positive	75	12	2.1 ± 0.3	
Stage (UICC 6th) [IA ($n = 3$), 2A ($n = 32$), 2B ($n = 143$)]	<III	178	20	3.6 ± 0.3	0.0003
Stage (UICC 6th) [III ($n = 16$), IV ($n = 35$)]	≥III	51	15	1.9 ± 0.4	
Intraoperative radiotherapy	Yes	159	15	2.9 ± 0.3	0.1975
	No	70	21	3.7 ± 0.6	
Adjuvant chemotherapy	Yes	59	22	3.1 ± 0.5	0.5376
	No	170	15	3.2 ± 0.3	

association was observed between portal vein invasion and the incidence of venous invasion ($P < 0.001$). For multivariate analysis, the following factors were found to be independently associated with a favorable prognosis: negative surgical margin status, stage ≤ IIB (UICC6th), less frequency of lymphatic invasion, and negative lymph node involvement, with hazard ratios (95% confidence intervals) of 1.379 (1.026–1.853: $P = 0.033$), 1.502 (1.073–2.101: $P = 0.018$), 1.493 (1.102–2.022: $P = 0.010$), and 1.886 (1.205–2.953: $P = 0.006$), respectively. Figure 1 shows a significant difference according to the stage ($P < 0.0001$).

Forty of the 229 patients (17%) survived more than 5 years, including 9 patients (4%) who survived more than 10 years. The median age of the patients (21 men and 19 women) was 63 (range, 27–80) years. The distribution of the tumor stages according to the TNM classification

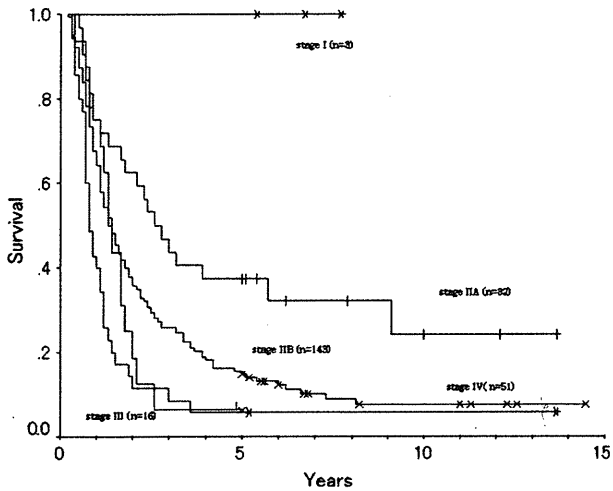


Fig. 1 Actuarial survival curve (Kaplan–Meier) for 229 patients who underwent pancreatectomies, according to UICC stage: I ($n = 3$), IIA ($n = 32$), IIB ($n = 143$), III ($n = 16$), and IV ($n = 35$; $P < 0.0001$)

(UICC 6th) was: stage IA ($n = 3$; 7%), IIA ($n = 12$; 30%), IIB ($n = 22$; 55%), III ($n = 1$; 3%), IV ($n = 2$; 5%). The pancreatic resections were a standard pancreaticoduodenectomy (Whipple procedure) in 9 patients, pylorus-preserving pancreaticoduodenectomy in 12 patients, total pancreatectomy in 4 patients, and distal pancreatectomy in 15 patients. Median tumor size was 36 (range, 8–110) mm, including ten patients (25%) with tumor diameters of ≤20 mm. Table 2 shows the chi-square test results on the clinicopathological factors between the 5-year survivors and the patients who died within 5 years after surgery. Age, sex, location, IORT, adjuvant chemotherapy, differentiation, plexus invasion, and surgical margins status were evaluated and did not reach statistical difference. The absence of portal vein invasion tended to have a better prognosis, but the difference was not significant ($P = 0.085$). Multivariate analysis showed that slight retroperitoneal invasion, less frequency of lymphatic invasion, and negative lymph node involvement were independent factors predictive of the 5-year survival, with odds ratios (95% confidence interval) of 0.429 (0.192–0.958; $P = 0.039$), 0.428 (0.186–0.986; $P = 0.046$), and 0.279 (0.122–0.635; $P = 0.002$), respectively.

Figure 2 shows the status of each 5-year survivor in the following years and the cause of death in those who did not survive. Thirty patients (75%) are alive without recurrence, eight (20%) died of disease within 8 years, and two (5%) died of a noncancerous cause. The latest disease-related death occurred at 7.3 years after surgery. Among the 40 5-year survivors, recurrence occurred in 10 patients from 0.4 to 5.3 (median, 3.5) years after surgery. All cases but two of local cancer recurrence were metastatic. One patient with local recurrence and another with solitary bone metastases who underwent radiotherapy with chemotherapy survived more than 5 years without apparent disease (Table 3). The actuarial survival rate for an additional 5 years after surviving 5 years was 72%. Of the 229 patients who underwent resection of pancreatic carcinoma, 7 patients (2%) had simultaneous hepatic resection for synchronous liver metastases located on the hepatic surface. The majority of patients ($n = 6$) was solitary and multiple (2 nodules) was observed in one patient. Pancreatic resection with partial hepatic resection included pancreaticoduodenectomy ($n = 2$) and distal pancreatectomy ($n = 5$). Surgical resection provided no survival benefit in these patients, except one patient who survived 7 years after surgery [14].

Table 4 shows a univariate analysis of factors that influenced overall survival in the 40 5-year survivors. Intrapancreatic nerve invasion was the only significant factor predicting long-term survival. Negative surgical margin status tended to have a better prognosis, but the difference was not statically significant ($P = 0.0893$).

Discussion

Invasive ductal carcinoma of the pancreas cannot be cured only with surgery in most patients [4]. The long-term prognosis is poor with very few 5-year survivors, because it often is part of a systemic disease at the time of diagnosis. It is not only difficult to achieve a 5-year survival even after a macroscopic curative resection, but also a 5-year survival does not always mean a potential cure of disease [1, 5–11]. This study identified the 40 5-year survivors after undergoing a macroscopic curative resection, but recurrence occurred in 10 patients (25%) and death with recurrent disease in 8 patients (20%). Several large series reported this pattern of dying with recurrence ranging from 16–42% of actual 5-year survivors [1, 5–11]. The cause of this failure has not been thoroughly evaluated, but it is thought to be the result of an incomplete tumor resection, the presence of occult lymph node or liver metastases, residual low grade intraductal malignancy, or de novo tumors in the pancreatic remnant [5]. In the present study, intrapancreatic nerve invasion seemed to be a significant prognostic factor influencing an additional 5 years in the 40 5-year survivors.

Cleary et al. [5] stated that they decided to examine factors related to overall survival, because they observed a greater than expected number of late (>5 years after resection) deaths from pancreatic cancer. The current study also analyzed factors related to overall survival in a multivariate Cox proportional hazard analysis, and negative surgical margin status seemed to be one of the most important factors for long-term survival, although this

factor was not significant when compared between ≥5 and <5 year survivors ($P = 0.142$) and did not statistically influence subsequent survival in the 40 5-year survivors ($P = 0.0893$). However, the extent of retroperitoneal invasion was one of the significant factors when comparing the ≥5 and <5 year survivors, which might be strongly associated with a surgical margin negative resection [15, 16]. Local cancer control with a sufficient oncologic clearance of the retroperitoneal tissue might contribute to a chance of cure for these selected patients, although long-term observation after surgery might be necessary to confirm the efficacy of such an extended resection.

Pancreatic cancer characteristically demonstrates a high potential for lymphatic invasion and intrapancreatic nerve invasion, which is defined as a part of the histological characteristics [12]. However, the clinical significance has not been fully elucidated. Helm et al. [17] reported that a simple combination of differentiation, lymphatic invasion, and local extension is predictive of survival and emphasized that the histological characteristics enhanced the predictive value of America Joint Committee on Cancer Staging in resectable pancreatic cancer (stage IA-IIB). Lymph node metastases did have predictive significance in most previous studies [7–11] as well as the current study, but not in their series. Ozaki et al. [18] reported that intrapancreatic perineural invasion was a significant prognostic factor as well as lymph node metastases and portal vein invasion according to a multivariate analysis. However, it is still controversial whether the incidence or the severity of intrapancreatic nerve invasion of cancer cells are closely related to a diminished survival in pancreatic cancer [19].

The observation period after the primary surgery securing potentially cure has not been established, because patients with invasive pancreatic carcinoma continue to die of cancer even after achieving the 5-year survival [6]. Only one patient recurred after 5 years, and a surgical cure might be expected in the case of no recurrence within 5.3 years after the initial surgery in this study. Schnelldorfer et al. [8] described that the survival beyond 10 years might suggest potential cure, because none of the 30 patients who survived beyond 7.8 years had recurrence of diseases and all survived beyond 10 years. Katz et al. [11] reported that late recurrence after 5 years occurred in seven patients, most frequently on the lung, the latest at 6.7 years and the latest cancer-related death occurred at 7.6 years.

The 5-year survivors with disease recurrence were characterized by an unexpected long-term from initial recurrence until death. No clear explanation could be obtained from this limited study, but the lack of locoregional or hepatic recurrence with isolated distant metastases might contribute to achieve a relatively long-term duration from recurrence to death. Katz et al. [11] also described that of the 17 5-year survivors who died of recurrent disease; death occurred at a median of 15 months (recurrence to last follow-up, range, 0.7–51 months). Another possibility might be due to the effectiveness of radiotherapy or radiochemotherapy for recurrence site. One patient with local recurrence and another with bone metastasis who underwent radiotherapy survived more than 5 years without disease (Table 3). Preoperative radiochemotherapy has been recently advocated, because partial and complete histopathological responses were experienced [20, 21].

Limited tumor extension and negative lymph node metastases representing an early stage have been recognized to be significantly associated with a long-term survival of 5 year, which was confirmed in the current study. However, tumors limited within the pancreas with negative node metastases were observed in only 3 patients (1%) in the current study and 280 patients (7%) among all 3,979 resected cases in the nationwide study from Japan [2]. Small pancreatic cancers with diameters ≤2.0 cm do not necessarily indicate early disease, because they are frequently associated with lymph node metastases and extrapancreatic extension [22]. Screening for early detection of this disease with negative lymph node involvement and limited invasion of the retroperitoneal space is crucial, because it will undoubtedly increase the number of 5-year survivors.

The stage of the tumor might be one of the important predictors for long-term survival but does not adequately reflect the heterogeneity in long-term outcomes, and no definitive preoperative or postoperative factors of long-term survivors have been elucidated as previously reported [1, 5, 7, 9, 10]. Adham et al. [9] in their French multicentric series reported that long-term survivors surviving more than 5 years did not always fulfill the ideal prognostic criteria and presented six patients with more advanced stages, including pT4 ($n = 5$) and synchronous liver metastases ($n = 1$). Long-term survivors in the current analysis included stage III ($n = 1$) and stage IV ($n = 2$), although it might be clinically anecdotal in the exceptional patients. Gleisner et al. [23] described that simultaneous resection of pancreatic carcinoma with liver metastases in well-selected patients did not result in long-term survival in the overwhelming majority of patients. Stitzenberg et al. [24] reported that a pancreatectomy with major arterial resection and reconstruction should be recommended for highly select younger patients with good prognostic features who underwent pancreatic resection after neoadjuvant therapy but did not result in any long-term survivors. An aggressive approach might be permitted when a macroscopic curative pancreatectomy with prompt postoperative recovery and a high likelihood of receiving any additional oncologic treatment could be expected, because it is