CrossMark

ORIGINAL ARTICLE

Poor prognosis of common-type invasive ductal carcinomas that originate in the branching pancreatic duct

Masataka Ando · Yasuhiro Shimizu · Tsuyoshi Sano · Yoshiki Senda · Yuji Nimura · Kenji Yamao · Masato Nagino · Akio Yanagisawa

Abstract

Purpose To clarify the incidence, clinicopathological features and prognosis of pancreatic invasive ductal carcinomas (IDCs) with different tumor origin sites in the pancreatic duct.

Methods Based on the relationship between the invasive cancer area (ICA) and the main pancreatic duct (MPD), IDCs less than 2 cm in diameter were classified into two groups: type I, in which the ICA and MPD were separated, and type II, in which the MPD passed through the ICA. The clinicopathological findings and prognosis of each type were compared in a total of 37 patients.

Results The incidences of IDC types I and II were 18.9 and 81.1 %, respectively. Although there was no difference in local invasion, both node involvement and venous invasion tended to occur more frequently in type I IDC, and the three-year survival rate was significantly lower for type I (28.6 %) than type II (71.8 %) IDC.

Conclusions The prognosis of IDCs that originated in the branching pancreatic duct (BPD) distant from the MPD (type I) was worse than the prognosis of IDCs that originated in either the MPD or the BPD close to the MPD (type II). These data suggest that the progression and degree of malignancy of IDCs may vary depending on the site of tumor origin in the pancreatic duct.

Keywords Small pancreatic ductal carcinoma · Pancreatic duct · Site of tumor origin · Prognosis · Clinicopathological features

M. Ando · Y. Shimizu · T. Sano · Y. Senda · Y. Nimura
Department of Gastroenterological Surgery,
Aichi Cancer Center Hospital, 1-1 Kanokoden,
Chikusa-ku, Nagoya, Aichi 464-8681, Japan
e-mail: mando@kj8.so-net.ne.jp

K. Yamao
Department of Gastroenterology, Aichi Cancer Center Hospital,
1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681, Japan

M. Nagino
Division of Surgical Oncology, Department of Surgery, Nagoya
University Graduate School of Medicine, 65 Tsuruma-cho,
Showa-ku, Nagoya, Aichi 466-8550, Japan

A. Yanagisawa (✉)
Department of Pathology, Kyoto Prefectural Medical University
Graduate School of Medicine, Kawaramachi-Hirokoji,
Kamigyo-ku, Kyoto 602-8566, Japan
e-mail: yanagisa@koto.kpu-m.ac.jp

Introduction

Common-type invasive ductal carcinomas (IDCs) in the pancreas are advanced cancers that have invaded adjacent organs and surrounding tissue(s) at the time of diagnosis. Therefore, the treatment outcomes for IDC are poor. Interestingly, studies have indicated that patients with IDCs measuring less than 2 cm in diameter have a significantly better prognosis than patients with larger IDCs [1–3]. Therefore, the treatment outcome in patients with IDCs may be improved by early tumor detection, which requires an understanding of the characteristics and progression of small IDCs.

Many IDCs arise from the epithelium of the branching pancreatic ducts (BPDs) [4, 5]. Two types of IDCs have been defined based on their progression: IDCs that spread noninvasively through the BPD and subsequently invade the stroma [6, 7], and IDCs that invade the stroma at a relatively early stage without intraductal spread [8]. Advances in imaging modalities, such as computed tomography, endoscopic retrograde cholangiopancreatography, magnetic

resonance cholangiopancreatography and endoscopic ultra-sonography, have facilitated the detection of small IDCs that are less than 2 cm in diameter, and studies that utilize these imaging techniques continue to clarify the clinicopathological features of IDCs [3, 9]. The imaging diagnosis of small pancreatic tumors is often based on abnormal findings in the pancreatic duct [10–12]; however, the effects of the site of tumor origin in the pancreatic duct on the clinicopathological features and prognosis of IDCs remain largely unclear. The clarification of the characteristics of IDCs with respect to the site of tumor origin is important for the diagnosis of small IDCs. The purpose of this study was to clarify the incidence, clinicopathological features and prognosis of IDCs with different sites of tumor origin in the pancreatic duct. The ultimate goal of this research is to provide considerations to aid in the early detection of small IDCs, which would yield a more favorable disease prognosis.

Methods

A total of 177 patients underwent curative (R0 or R1 [13]) resection of a common-type IDC (excluding ductal adenocarcinoma variants [14] and ductal adenocarcinomas derived from an intraductal papillary mucinous neoplasm (IPMN)) at the Aichi Cancer Center Hospital during a 14-year period from January 1996 to December 2009; a total of 37 (20.9 %) patients with a histologically invasive tumor less than 2.0 cm in diameter were included in this study. The patients had a mean age of 65.7 ± 10.8 years and included 18 males (48.6 %) and 19 females (51.4 %). The tumors were located in the pancreatic head in 25 (67.6 %) patients and in the pancreatic body or tail in 12 patients (32.4 %). The median postoperative follow-up period was 53.7 months (range 12.4–158.4 months).

To examine the relationships among the site of tumor origin in the pancreatic duct, the clinicopathological features and the prognosis of patients with IDC, full surgical specimens that were 3–6 mm thick were fixed in 10 % formalin and placed into cassettes in the plane that was perpendicular to the main pancreatic duct (MPD). The tissues were embedded in paraffin, and sections were cut at a thickness of 2–4 μm. These thin sections were mounted onto glass slides and stained with hematoxylin and eosin. The preparations were examined under a microscope, and the affected area was noted on a gross photograph. We created a diagram that reconstructed the relationship between the location of the invasive cancer area (ICA) and the MPD. If the tumor evinced a discontinuous spread from its center, the area that encircled all of the invasive fronts was considered to represent the ICA. The invasive fronts that involved blood and lymph vessels were included in the ICA; however, lymph node metastases were not included in the ICA.

Based on the ICA reconstruction diagram, the IDCs were classified according to the geographic and anatomical relationship between the ICA and MPD. The IDCs were classified either as type I, characterized by the complete separation of the ICA and the MPD by the normal pancreatic parenchyma, or type II, characterized by the passage of the MPD through the ICA.

The following clinicopathological features of the patients with IDC were assessed and correlated with the site of tumor origin in the pancreatic duct: age, sex, tumor location, CT (computed tomography) findings, EUS (endoscopic ultrasonography) findings, preoperative serum CA19-9 level, diameter of the ICA, degree of histological differentiation [13], presence or absence of pathological serosal invasion (S), retropancreatic tissue invasion (RP), lymphatic invasion (ly), venous invasion (v), intrapancreatic nerve invasion (ne), the pancreatic cut end margin (pcm) distance and the dissected pancreatic margin (dpm) distance, according to the Japan Pancreatic Society classifications [15]. Other features that were evaluated included the pathological T, N and M stages of the tumor and the R, which was assessed using the 7th edition of the TNM classification of the Union for International Cancer Control (UICC) [13]. Regarding the pcm, both the distance of the pancreatic cut end from the ICA (pcm (ICA)) and distance of the MPD cut end from the carcinoma in situ (CIS) lesion in the MPD outside of the ICA (pcm (MPD)) were investigated.

The prognoses of patients with IDC were compared based on the modes of first recurrence and postoperative recurrence and the survival rates. Continuous variables were compared using Student's t test or the Mann–Whitney U test, and discrete variables were examined by Fisher's exact test. The Kaplan–Meier method was used to calculate the recurrence and survival rates. The prognosis of each type of IDC was compared using the log-rank test. All of the p values presented were two sided, and a p value <0.05 was considered to be significant.

Results

The incidence of IDCs and the sites of tumor origin in the pancreatic duct

Among the 37 patients, the incidences of type I and type II IDC were 18.9 % (seven patients) and 81.1 % (30 patients), respectively.

The relationship between the site of tumor origin in the pancreatic duct and the clinicopathological factors

The examined prognostic and clinicopathological factors are shown in Table 1. The age, sex, tumor location and

Table 1 A comparison of the clinicopathological features of patients with type I and type II IDCs

		Type I (n = 7)		Type II (n = 30)		
		N	(%)	n	(%)	p
Age		63.1 ± 12.8		66.3 ± 10.5		0.495
Sex	Male	5	(71.4)	13	(43.3)	0.232
	Female	2	(28.6)	17	(56.7)	
Location	Ph	5	(71.4)	20	(66.7)	1.000
	Pb/t	2	(28.6)	10	(33.3)	
CT finding	Tumor (+)	5	(71.4)	21	(70.0)	0.661
EUS finding	Tumor (+)	7	(100.0)	26	(86.7)	0.415
Serum CA19-9	IU/l	62.9 ± 90.3		64.9 ± 75.3		0.951
Tumor size	(cm)	1.6 ± 0.3		1.5 ± 0.3		0.326
Pathological grade	G1/G2	5	(71.4)	17	(56.7)	0.677
	G3	2	(28.6)	13	(43.3)	
S	(+)	1	(14.3)	8	(26.7)	0.656
RP	(+)	6	(85.7)	16	(53.3)	0.204
ly	(+)	7	(100.0)	26	(86.7)	0.570
v	(+)	6	(85.7)	14	(46.7)	0.097
ne	(+)	6	(85.7)	23	(76.7)	1.000
pT	1	1	(14.3)	9	(30.0)	0.647
	3	6	(85.7)	21	(70.0)	
pN	(+)	5	(71.4)	9	(30.0)	0.080
pStage	IA	0	(0.0)	4	(13.3)	0.138
	IIA	2	(26.7)	17	(56.7)	
	IIB	5	(71.4)	9	(30.0)	
pcm (ICA)	(cm)	1.7 ± 1.1		1.3 ± 0.9		0.402
pcm (MPD)	(cm)	N/A		0.8 ± 0.7		N/A
dpm	(cm)	0.1 ± 0.1		0.2 ± 0.2		0.187
R	R1	1	(14.3)	5	(16.7)	0.685
ACT	(+)	4	(57.1)	11	(36.7)	0.283

Ph pancreatic head, *Pb/t* pancreatic body or tail, *G1* well differentiated, *G2* moderately differentiated, *G3* poorly differentiated, *S* serosal invasion, *RP* retropancreatic tissue invasion, *ly* lymphatic invasion, *v* venous invasion, *ne* intrapancreatic nerve invasion, pT, pN and the pStage were classified in accordance with the 7th edition of the UICC classification system; *pcm* pancreatic cut end margin distance, *dpm* dissected pancreatic margin distance, *ACT* postoperative adjuvant chemotherapy, *N/A* not available

preoperative serum CA19-9 level did not differ between the two IDC patient groups. Regarding the preoperative diagnosis, tumors were identified by CT in 70–71 % of cases and by EUS in 86–100 % of cases for type I and type II IDC, respectively. There were no significant differences between the two groups. In four cases of type II IDC, the tumor was not detectable by either CT or EUS.

The mean ICA diameter was 1.5 ± 0.3 cm for the 37 patients. The ICA diameter, degree of ICA histological differentiation and the nerve invasion did not differ significantly between the two IDC patient groups. With respect to vascular invasion, lymphatic invasion was observed in 87–100 % of the patients with both types of IDC, and there was no significant difference between the two types. Interestingly, venous invasion tended to occur more frequently in type I IDCs than in type II IDCs ($p = 0.097$). With respect

to local invasion, there was no significant difference in either the serosal or retropancreatic tissue invasion between the two IDC types. In addition, pT3 was frequently found in both type I and type II IDCs, and there was no significant difference between the two IDC patient groups. Although pN tended to be more frequently observed in type I than type II patients ($p = 0.080$), this difference was not significant. The stage was more advanced in type I IDCs than type II IDCs, but this difference was also insignificant (Table 1).

With respect to the surgical margin, the pcm (ICA) and dpm did not differ between the two groups. There were no CIS lesions in the MPD outside of the ICA in type I IDC, whereas, in 10 (33.3 %) cases of type II IDC, there was a CIS lesion in the MPD outside of the ICA. In the cases in which a CIS lesion was observed in the MPD outside of the ICA, the mean spread range of CIS from the ICA margin

was 1.0 ± 0.9 cm. There was no significant difference in curability, expressed as the R status.

The use of adjuvant chemotherapy with S-1 or gemcitabine (GEM) for IDC was started in 2007, with four (57.1 %) (S1: 1 and GEM: 3) patients with type I IDC and 11 (36.7 %) (S1: 3 and GEM: 8) patients with type II IDC receiving adjuvant chemotherapy after its introduction. There was no significant difference between the two IDC types.

The relationship between the site of tumor origin in the pancreatic duct and the prognosis

During the postoperative follow-up period for all 37 studied patients, recurrence occurred in 21 patients (56.8 %); in particular, recurrence was observed in six (85.7 %) of the patients with type I IDCs and 15 (50.0 %) of the patients with type II IDCs. Among the 21 recurrent cases, seven (33.3 %) involved local recurrence, five (23.8 %) involved metastasis to the liver, five (23.8 %) involved metastasis to a hematogenous organ(s) other than the liver, two (9.5 %) involved peritoneal dissemination and two (9.5 %) involved lymph node metastasis. There was no relationship between the IDC type and the mode of first recurrence (Table 2).

The cumulative three-year postoperative recurrence rates were 85.7 and 45.0 % in patients with type I and type II IDCs, respectively. The recurrence rate in patients with type I IDCs was significantly higher than that in patients with type II IDCs ($p = 0.013$) (Fig. 1). The cumulative three-year postoperative survival rates for patients with type I and type II IDCs were 28.6 and 71.8 %, respectively. Importantly, the rate was significantly lower for patients with type I IDCs than for patients with type II IDCs ($p = 0.009$) (Fig. 2).

Discussion

IDCs are refractory cancers with one of the poorest prognoses among malignant tumors. However, small IDCs that measure less than 2 cm in diameter are associated with a significantly more favorable prognosis than larger IDCs [1–3]. The clinicopathological features of small IDCs have been extensively studied [3, 9], but the effects of the site of tumor origin in the pancreatic duct on these features have not been described. Similar to IDCs, IPMNs arise from the epithelium of pancreatic ducts, and these neoplasms are classified into three categories (main duct, branch duct or mixed type) according to the site of the tumor origin [16]. The three types of IPMNs exhibit very different clinicopathological features, biological behaviors and prognoses [17, 18]. Given the similarities between IDCs and IPMNs, this study investigated whether IDCs may also differ with

Table 2 The first sites of recurrence of type 1 and type II IDCs

All cases ($n = 21$)	Type I ($n = 6$)		Type II ($n = 15$)		p
	N	(%)	n	(%)	
Local ($n = 7$)	2	(33.3)	5	(33.3)	1.000
Liver ($n = 5$)	2	(33.3)	3	(20.0)	
Distant metastasis (lung and bone) ($n = 5$)	2	(33.3)	3	(20.0)	
Peritoneum ($n = 2$)	0	(0.0)	2	(13.3)	
Lymph node ($n = 2$)	0	(0.0)	2	(13.3)	

respect to their clinicopathological features. In addition, this study examined whether the prognosis of IDC was related to the site of tumor origin in the pancreatic ducts.

Most IDCs are already in advanced stages when they are detected, with evidence of direct invasion to adjacent organs and/or distant organ metastases. Thus, the structure of the remaining pancreatic tissue is usually already destroyed by tumor cells at the time of diagnosis. Therefore, it is impossible to identify the site of tumor origin in the pancreatic duct in such advanced pancreatic cancer cases. However, in small pancreatic cancers, the structures of the pancreatic ducts and the pancreatic tissue are maintained, so it is easier to determine the site of tumor origin in the pancreatic duct. We investigated only small cancers less than 2 cm in diameter (T1 [13]) in the present study to clarify the incidence, clinicopathological features and prognosis associated with IDCs with different sites of tumor origin in the pancreatic duct.

In this study, we classified IDCs into two types based on the relative locations of the ICA and MPD in each tumor. There was no invasive cancer in the MPD among the type I IDCs, suggesting that these IDCs arose in the BPD and were distant from the MPD. Although type I IDCs may spread to involve the MPD, the central portion of type II IDCs was closer to the MPD than the type I IDCs, suggesting that the type II IDCs originated in the BPD, but were close to the MPD. In type II IDCs, the location of the MPD ranged from the peripheral zone to the center of the ICA. In certain cases, the MPD was located in the center of the ICA, which suggests that the tumors arose either in the MPD or in the BPD near the MPD (Fig. 3a, b).

Many IDCs are believed to arise in the epithelium of the BPD [4, 5], and Furuta et al. [19] reported that 56 % of IDCs originate in the BPD. In this study, we found that only 18.9 % of the IDCs originated in the BPD (type I); this percentage was much smaller than the previously reported rate [19]. Although previously published studies have hypothesized that certain type II IDCs may originate in the BPD, the results from the current investigation demonstrated that at least 18 % of the IDCs (type I tumors) originated at sites in the BPD that were distal to the MPD.

Fig. 1 The postoperative recurrence of type I and type II IDCs
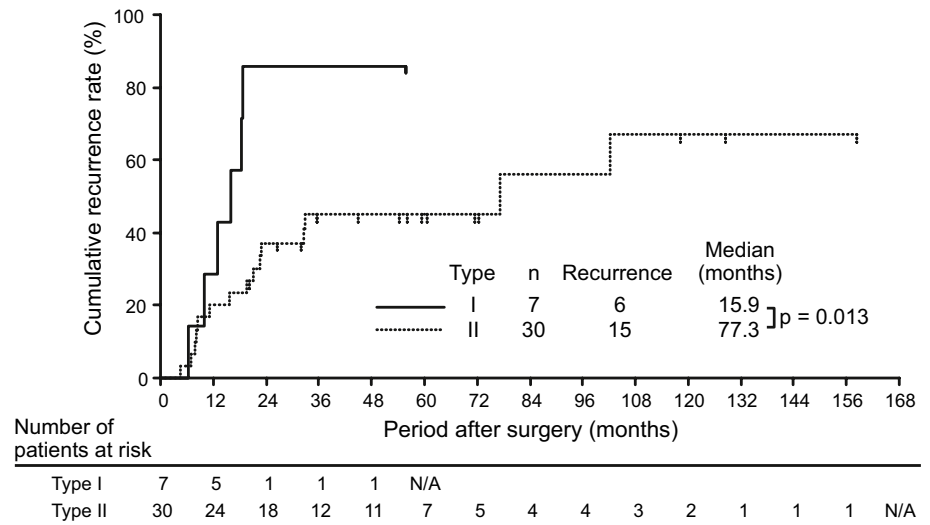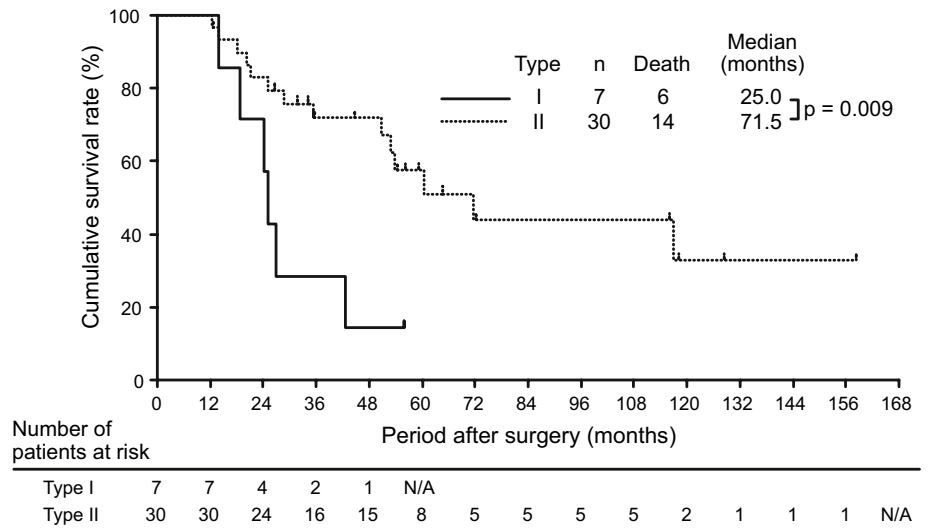

Fig. 2 The postoperative survival of patients with type I and type II IDCs

Regarding the preoperative diagnosis, there was no significant difference in the tumor detection by CT and EUS between type I and II IDCs. Although 70.2 % (26 of 37 cases) of the tumors were identified by CT, EUS revealed 89.2 % (33 of 37 cases) of the tumors. EUS was, therefore, more suitable for the detection of small pancreatic cancer than CT. However, in four cases of type II IDC, the tumor was not detectable by either CT or EUS. In these cases, obstruction and/or dilatation of the MPD in the tail of the pancreas on CT, EUS and endoscopic retrograde pancreatography findings and pancreatitis accompanying the MPD obstruction on the CT findings [2] suggested the presence of IDC. The preoperative diagnosis was confirmed as IDC or was suspected to be IDC in all 37 patients in the present study.

In 33.3 % of type II IDCs, we found diffuse CIS lesions in the MPD outside of the ICA, whereas there was no CIS in the MPD of the type I IDCs, which may simply be because the type I IDCs originated in the BPD distant from the MPD, or may suggest that these type I tumors have a reduced capacity for intraductal spread compared to type II IDCs.

The two types of IDCs yielded markedly different prognoses in our patient population. The cumulative three-year postoperative recurrence rate was significantly higher in patients with type I IDCs than in patients with type II IDCs, and the survival rate was significantly lower in patients with type I IDCs than in patients with type II IDCs (Figs. 1 and 2). Although there was no significant difference in the CA19-9 level between the two IDC types in our study, recent data [20, 21] have described that an elevated level of CA19-9 is significant risk factor for peritoneal dissemination and poor survival. The prognosis of patients with type I IDC may be worse than that of patients with type II
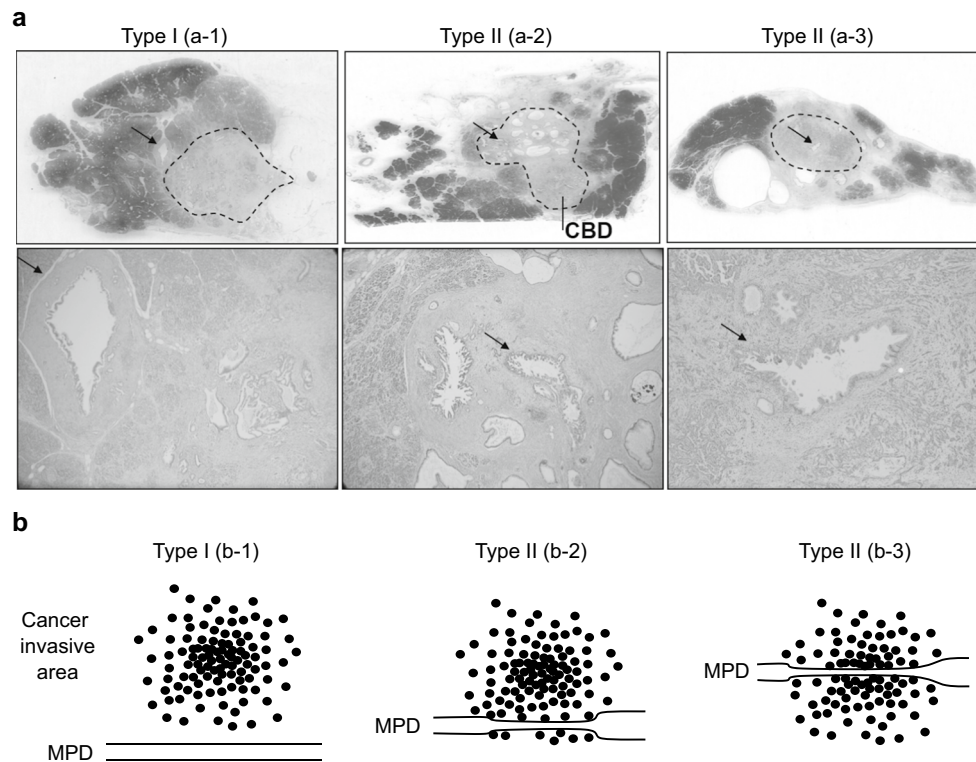
Fig. 3 The classification of the IDCs according to the site of tumor origin in the pancreatic duct. **a** A magnified view of each IDC type. *Type I* the invasive cancer area (ICA, *dashed line*) was completely separated from the main pancreatic duct (MPD, *arrow*) and invaded normal pancreatic tissue (a-1). *Type II* the MPD passed through the ICA. In certain cases of type II IDCs, the MPD passed through the peripheral zone of the ICA, which suggests that these type II IDCs originated in the BPD, but were located near the MPD (a-2). The large duct next to the duct indicated by an arrow is a branched pancreatic duct (BPD). In other cases of type II IDCs, the MPD passed through the approximate center of the ICA, suggesting that these IDCs arose either in the MPD or in the BPD at a site near the MPD (a-3). In this case, a carcinoma in situ lesion can be seen in the MPD. **b** Schematic diagrams of IDCs of type I (b-1) and type II (b-2 and b-3, which parallel Figs. 3a-2 and a-3, respectively)

IDC because, compared with type II IDCs, type I IDCs are located closer to the pancreatic capsule and can, therefore, more readily advance to the extrapancreatic tissue or veins and lymphatic vessels.

However, examinations of the T factor, *S* and *RP* revealed no significant differences in local invasion between the two IDC types in our cases. The incidence of lymphatic invasion at the primary site was high (86.7–100 %) for both IDC types, but the rate of lymph node metastasis tended to be higher for type I IDCs than for type II IDCs; further supporting the idea that the type I IDCs may be at a more advanced stage at the time of diagnosis. Recent data [22] have suggested that the increasing trend in lymph node involvement accounts for the worse prognosis of type I IDCs. The incidence of venous invasion also tended to be higher in type I cases. These factors may explain the markedly worse prognosis associated with type I IDCs.

Although the mode of the first postoperative recurrence that was observed differed from the results of various published studies, hepatic metastasis and/or local recurrence are the modes of recurrence that occur in the majority of patients with IDCs [23–25]. Indeed, previously published results have indicated that hematogenous metastasis to distant organs, such as the lungs or bones, is less common than metastasis to the liver [23]. In the present study, both types of IDC were characterized by a high incidence of distant metastasis. Recent data [26] support the notion that the metastatic potential may be present even before the formation of a visible pancreatic carcinoma, which may explain the high incidence of distant metastases in patients with small IDCs. The incidence rates of metastasis to the liver and to extrahepatic distant organs were the same (23.8 %). These modes of recurrence (i.e., lung or bone metastasis) may explain why the prognosis of patients with IDC is often unfavorable, and our findings highlight the need for vigilance in monitoring the development of both local recurrences and hepatic and distant metastases in these patients.

With respect to the mode of recurrence for each IDC type, venous invasion tended to be more common in

patients with type I IDCs than type II IDCs, but the mode of recurrence, particularly the frequency of hematogenous metastasis, did not differ significantly between the IDC types. This may be explained by the greater frequency of hematogenous metastasis and local recurrence in type I IDCs compared with type II IDCs (i.e., lymph node involvement and venous invasion tended to be more common in the type I IDCs).

This study demonstrated that the prognosis of patients with IDC depends on the site of tumor origin in the pancreatic duct. A detailed analysis of IDCs, based on our classification system, revealed that distinct types of tumors that arise in the BPD, which have previously been evaluated as a single group, demonstrated markedly different prognoses. The prognosis that was associated with IDCs that originated in the BPD at sites that were distant from the MPD (type I) was worse than the prognosis of IDCs that originated in the BPD at sites close to the MPD (type II). At the present time, abnormal findings in the MPD often trigger the detection of small IDCs. However, at least 18 % of the IDCs in this study originated from the BPD without involvement of the MPD, which suggests the importance of not only monitoring MPD stenosis or dilation, but also utilizing imaging tools to monitor changes in the BPD at sites in the pancreatic parenchyma that are distant from the MPD. This approach may facilitate the detection of IDCs at an early stage.

In conclusion, IDCs that arise in the BPD at sites that are distant from the MPD may exhibit different characteristics than those of the IDCs that arise either within the MPD or in the BPD near the MPD. Specifically, the mode of invasion and the biological malignancy of IDCs may vary with the site of tumor origin. A recent report [27] suggested that nuclear factor kB plays a role in tumor progression, and its expression may vary according to the site of tumor origin in the pancreatic duct. As this study involved a limited number of patients, studies with a large number of patients are needed to confirm our results and to explore the potential role of nuclear factor κB in the differences between the types.

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Jung KW, Kim MH, Lee TY, Kwon S, Oh HC, Lee SS, et al. Clinicopathological aspects of 542 cases of pancreatic cancer: a special emphasis on small pancreatic cancer. J Korean Med Sci. 2007;22(Suppl):S79–85.
2. Shimizu Y, Yasui K, Matsueda K, Yanagisawa A, Yamao K. Small carcinoma of the pancreas is curable: new computed tomography finding, pathological study and postoperative results from a single institute. J Gastroenterol Hepatol. 2005;20:1591–4.
3. Egawa S, Takeda K, Fukuyama S, Motoi F, Sunamura M, Matsuno S. Clinicopathological aspects of small pancreatic cancer. Pancreas. 2004;28:235–40.
4. Suda K, Nobukawa B, Yamasaki S, Abe K, Matsukuma S, Suzuki F. Invasive ductal adenocarcinoma of the pancreas may originate from the larger pancreatic duct: a study of 13 tumors less than 2 cm in diameter. J Hepatobiliary Pancreat Surg. 2007;14:283–8.
5. Pour PM, Sayed S, Sayed G. Hyperplastic, preneoplastic and neoplastic lesions found in 83 human pancreases. Am J Clin Pathol. 1982;77:137–52.
6. Hisa T, Suda K, Nobukawa B, Ohkubo H, Shiozawa S, Ishigame H, et al. Distribution of intraductal lesions in small invasive ductal carcinoma of the pancreas. Pancreatology. 2007;7:341–6.
7. Yamasaki S, Suda K, Nobukawa B, Sonoue H. Intraductal spread of pancreatic cancer. Clinicopathologic study of 54 pancreatectomized patients. Pancreatology. 2002;2:407–12.
8. Ikeda M, Yanagisawa A, Seki M, Sasaki K, Takano K, Kato Y. The early state of invasive pancreatic ductal adenocarcinomas: characteristics of the low papillary type and flat type intraductal carcinoma. Pancreas. 2006;33:135–41.
9. Chiang KC, Yeh CN, Lee WC, Jan YY, Hwang TL. Prognostic analysis of patients with pancreatic head adenocarcinoma less than 2 cm undergoing resection. World J Gastroenterol. 2009;15:4305–10.
10. Takeshita K, Kutomi K, Haruyama T, Watanabe A, Furui S, Fukushima J, et al. Imaging of early pancreatic cancer on multidetector row helical computed tomography. Br J Radiol. 2010;83:823–30.
11. Ikeda S, Maeshiro K, Ryu S, Ogata K, Yasunami Y, Nakayama Y, et al. Diagnosis of small pancreatic cancer by endoscopic balloon-catheter spot pancreatography: an analysis of 29 patients. Pancreas. 2009;38:e102–13.
12. Ishikawa O, Ohigashi H, Imaoka S, Nakaizumi A, Uehara H, Kitamura T, et al. Minute carcinoma of the pancreas measuring 1 cm or less in diameter—collective review of Japanese case reports. Hepatogastroenterology. 1999;46:8–15.
13. Sobin HL, Gospodarowicz KM, Wittekind C. TNM Classification of malignant tumors. 7th ed. NY: Wiley-Liss Inc; 2009.
14. Klöppel G, Hruban RH, Longnecker DS, Adler G, Kern SE, Partanen TJ. World Health Organization classification of tumors, pathology and genetics of the digestive system. In: Hamilton SR, Aaltonen LA, editors. World Health Organization classification of tumors, pathology and genetics of the digestive system. Lyon: IARC Press; 2000. p. 221–30.
15. Japan Pancreatic Society. Classification of pancreatic carcinoma. 2nd English ed. Tokyo: Kanehara; 2003.
16. Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. Am J Surg Pathol. 2004;28:977–87.
17. Kobari M, Egawa S, Shibuya K, Shimamura H, Sunamura M, Takeda K, et al. Intraductal papillary mucinous tumors of the pancreas comprise 2 clinical subtypes: differences in clinical characteristics and surgical management. Arch Surg. 1999;134:1131–6.
18. Terris B, Ponsot P, Paye F, Hammel P, Sauvanet A, Molas G, et al. Intraductal papillary mucinous tumors of the pancreas confined to secondary ducts show less aggressive pathologic features as compared with those involving the main pancreatic duct. Am J Surg Pathol. 2000;24:1372–7.
19. Furuta K, Watanabe H, Ikeda S. Differences between solid and duct-ectatic types of pancreatic ductal carcinomas. Cancer. 1992;69:1327–33.
20. Kanda M, Fujii T, Takami H, Suenaga M, Inokawa Y, Yamada S, et al. The combination of the serum carbohydrate antigen 19-9 and carcinoembryonic antigen is a simple and accurate predictor of mortality in pancreatic cancer patients. Surg Today. 2014;44:1692–701.

21. Ko¨nigsrainer I, Zieker D, Symons S, Horlacher K, Ko¨nigsrainer A, Beckert S. Do patient- and tumor-related factors predict the peritoneal spread of pancreatic adenocarcinoma? Surg Today. 2014;44:260–3.

22. Franko J, Hugec V, Lopes T, Goldman C. Survival among pancreaticoduodenectomy patients treated for pancreatic head cancer <1 or 2 cm. Ann Surg Oncol. 2013;20:357–61.

23. Van den Broeck A, Sergeant G, Ectors N, Van Steenbergen W, Aerts R, Topal B. Patterns of recurrence after curative resection of pancreatic ductal adenocarcinoma. Eur J Surg Oncol. 2009;35:600–4.

24. Ishikawa O, Ohigashi H, Eguchi H, Sasaki Y, Yamada T, Imaoka S. Survival and late morbidity after resection of pancreatic cancer. In: Beger HG, Warshaw AL, Buchler MW, Kozarek RA, editors. The pancreas: an integrated textbook of basic science, medicine, and surgery. Malden: Blackwell Publishing Ltd; 2008. p. 776–84.

25. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Recurrence after resection for ductal adenocarcinoma of the pancreas. World J Surg. 1997;21:195–200.

26. Rhim A, Mirek E, Aiello N, Maitra A, Bailey A, McCallister F, et al. EMT and dissemination precede pancreatic tumor formation. Cell. 2012;148:349–61.

27. Furukawa K, Uwagawa T, Haruki K, Fujiwara Y, Iida T, Shiba H, et al. Nuclear factor kB activity correlates with the progression and prognosis of pancreatic cancer in a mouse model. Surg Today. 2013;43:171–7.