Multicenter study of early pancreatic cancer in Japan

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Abstract: Background/Objectives: The diagnosis of early-stage pancreatic ductal adenocarcinoma (PDAC) is still challenging. We conducted a multicenter study to clarify the clinical features of early-stage PDAC in Japan. Methods: We collected patients with stage 0 and stage I PDAC according to the sixth edition of the Japanese Classification of Pancreatic Carcinoma. We retrospectively analyzed the clinical profiles including opportunities for medical examination, imaging modalities and findings, methods of cytological diagnosis, and prognosis according to the stages at diagnosis. Results: Two hundred cases with Stage 0 and stage I PDAC were reported from 14 institutions, which accounted for approximately 0.7% and 3% of all PDAC cases, respectively. Overall, 20% of the early-stage PDAC cases were symptomatic. Indirect imaging findings such as dilatation of the main pancreatic duct were useful to detect early-stage PDAC. In particular, local fatty changes may be specific to early-stage PDAC. For preoperative pathologic diagnosis, cytology during endoscopic retrograde cholangiopancreatography was more commonly applied than endoscopic ultrasound fine-needle aspiration. Although the overall prognosis was favorable, new PDAC lesions developed in the remnant pancreas in 11.5% cases. Conclusions: This multicenter study revealed several key points concerning the diagnosis and management of early-stage PDAC, including screening of asymptomatic cases, importance of indirect imaging findings, application of cytology during endoscopic retrograde

cholangiopancreatography, and the risk of carcinogenesis in the remnant pancreas.

July 9, 2017

Minoti Apte,

Editor-in-Chief

Panreatology

Dear Editor:

Please find enclosed our manuscript entitled "Diagnosis of pancreatic ductal adenocarcinoma in Japan," which we request you to consider for publication as an *Original Article* in *Panreatology*.

Pancreatic ductal adenocarcinoma (PDAC) has been increasing in incidence recently; however, its prognosis could not be improved despite further research and advancement in imaging modalities. This study aimed to determine the clinical features of such patients and clarified several points such as the need to screen high-risk asymptomatic cases, identification of indirect imaging findings, importance of ERCP in screening, and the risk of carcinogenesis in the remnant pancreas. Clinical data of 200 patients with stage 0 and 1 PDAC were collected. For early-stage PDAC, endoscopic retrograde cholangiopancreatography was more commonly used than endoscopic ultrasound fine-needle aspiration for preoperative pathologic diagnosis. We found that in 14.5% of the patients, new PDAC in the postoperative remnant pancreas was observed. We conclude that the findings of this study will contribute to the early detection and improvement of prognosis of PDAC patients.

We believe that the findings of this study are relevant to the scope of your journal and will be of interest to its readership. We have approved the manuscript and agree with submission to *Panreatology*. There are no conflicts of interest to declare.

This manuscript has not been published elsewhere and is not under consideration by another journal. We have already reported some of results using a part of the cases in this study in Japanese literature. However, we added the number of cases and showed the new findings of characteristics between Stage 0 and I. The manuscript has been carefully reviewed by an experienced editor whose first language is English and who specializes in editing papers written by scientists whose native language is not English.

We look forward to hearing from you at your earliest convenience.

Sincerely,

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Disclosure of Conflict of Interest Form

All authors disclosed no financial relationships relevant to this publication.

October 21, 2017

Professor Minoti Apte,
Editor-in-Chief, *Pancreatology*,
Director, Pancreatic Research Group,
South Western Sydney Clinical School,
University of New South Wales,
Sydney, Australia

Re: PAN-D-17-00207

Dear Professor Apte,

Thank you very much for your kind and helpful comments. Attached please find our revised manuscript entitled “Multicenter study of early pancreatic cancer in Japan", which we would like to submit for publication in *Pancreatology*.

After checking the original version again, we have still found that several descriptions were ambiguous and some statistical figures were a little bit old. We therefore have revised the text more clearly, concisely and updated to increase scientific merits of this paper. In addition, because this paper deals with not only diagnosis but prognosis, we have revised the title to “Multicenter study of early pancreatic cancer in Japan”.

We have carefully checked the reviewers’ helpful and constructive comments, and the substantial issues raised have been addressed as follows.

To the Reviewer 1

This is a very interesting paper with huge potential from a relatively large cohort of patients with "early stage PDAC". This paper should be considered for publication after revisions.

-Thank you very much for your favorable comments.

1. *The authors need to report in further detail the preop imaging tests and their diagnostic value (extract some the data from table and describe in results section).*

   -As suggested, we have described the preoperative imaging tests and their diagnostic value more in detail, with some data included in the text (page 9, 2nd paragraph, page 10, 1st paragraph, and Table 3).

2. *In the methodology: Expanding on 1 they should also report on their indications for surgery based on each of these tests especially for stage 0. For example what feature on MRI or ERCP cytology or EUS FNA would prompt them to operate on these patients. They should report in further detail why these patients underwent surgery especially for stage 0.*

-Thank you for the important suggestion. Out of 200 patients included in this study, 125 (52.5%) patients underwent resection because malignancy was confirmed by cytology prior to resection. In the remaining 75 patients, decision of resection was made after informed consent with high suspicion of PDAC based on abnormal imaging findings, especially MPD dilatation and stenosis on multiple modalities. Pancreatic tumors were seldom detected by imaging modalities in stage 0 cases. These points are now stated in page 9, last paragraph, page 10, 1st and 2nd paragraphs.

3. *A table for stage 0 patients should be made showing the tests performed CT MRCP ERCP EUS PET and clearing stating which were "positive" resulting in the need for surgery*

-As suggested, we have stratified the number of positive imaging findings based on stages (stage 0 and stage 1) in Table 3.

4. *The number of tests which were "positive" should also be reported. For example 30 patients had 3 preop test indicative of PDAC, 40 patients had 2 tests indicative of PDAC etc etc*

-Thank you for the important suggestion. We counted the number of positive imaging findings out of 14 assessed in this study according to the stage. The number of positive imaging findings was 5.5±2.5 in stage 0 cases and 7.2±2.8 in stage I cases. These points are now stated in page 9, last and page 10, 1st paragraphs.

5. *Discusson: there have been some natural history papers of PANIN published in the literature which should be discussed especially PANIN 3 which corresponds to the author's stage 0.*

-As suggested, we have cited two papers describing the natural history of PDAC and PanIN (references 13 and 14), and added some description on this topic in page 12, 1st paragraph.

6. *Pg 10 Line 24 Please revise sentence to: The sentence implies that the study showed these were risk factors of early stage PDAC found in the paper (which is not true as*

there was no comparison with the normal population). Diabetes mellitus was present in 64 (32%)…..

-As suggested, we have revised the text accordingly (page 8, 1st paragraph).

To the Reviewer 2

In their manuscript entitled "Diagnosis of early-stage pancreatic ductal adenocarcinoma in Japan", Kano et al. have summarized their data on Stages 0 and I pancreatic cancer according to the Japanese Classification of Pancreatic Carcinoma. This is an interesting paper and is written in a clear way.

Thank you very much for your favorable comments.

1. *Please describe more clearly what is meant by diabetes mellitus throughout the paper. In the last decade it became clearer that new diagnosis of late onset (>50y) diabetes mellitus is a risk factor for PDAC. On the other hand DM per se, has in the literature, contradictory associations with PDAC.*

-In this study, we only asked the presence or absence of DM from the viewpoint of a risk factor for PDAC, and did not ask the interval of DM onset and PDAC diagnosis. This point is now stated in page 8, 1st paragraph.

2. *Please clarify the association of IPMN and PDAC in P9 in 52 cases. Is this a coincental finding with PDAC or are the authors reporting cancer cases developing on the background of IPMN? If the latter is the case it contradicts their methods section where they exclude patients with high grade IPMN or cancer associated with it.*

-In this study, concomitant IPMN, in which PDAC developed at a site in the pancreas different from that of the IPMN according to the imaging and/or histologic findings, was regarded as a risk factor. Patients with high-grade IPMN or IPMN-derived invasive cancer, showing a histologic transition between IPMN and PDAC, were excluded. This point is now stated in page 6, 1st paragraph.

3. *Please describe the pathologic discrimination between conincidental PDAC and IPMN and IPMN-rderived cancer.*

- In this study, concomitant IPMN, in which PDAC developed at a site in the pancreas different from that of the IPMN according to the imaging and/or histologic findings, was regarded as a risk factor. Patients with high-grade IPMN or IPMN-derived invasive

cancer, showing a histologic transition between IPMN and PDAC, were excluded. This point is now stated in page 6, 1st paragraph.

4. *Please describe the study period*

-As suggested, we have clearly stated the study period (page 6, 1st paragraph).

5. *Please describe the pathological findings of Stage0 and 1a and 1b cancers according to TNM classification as well and compare differences. Please also report the dimensions of stage 0 cancers in mm (mean, median,range)*

-As stated in page 6, 1st paragraph, stages were determined according to the according to the sixth edition of the Japanese Classification of Pancreatic Carcinoma [reference #9]. Early-stage PDAC were defined as cases with stage 0 (high-grade pancreatic intraepithelial neoplasia (PanIN)/carcinoma in situ) and stage I (invasive carcinoma with tumor diameter of <20 mm confined within the pancreas, along with no regional lymph node metastasis (N0) and distant metastasis (M0)). Stage I cases were further classified as stage I (TS1a) (tumor size ≤10 mm) and stage I (TS1b) (tumor size 11-20 mm) based on the tumor size in largest diameter [reference #5]. Stage 0 PDAC defined by the Japanese classification are similar to that diagnosed by UICC classification. Stage I PDAC is defined as the tumor limited to the pancreas with dimension of 2 cm or less. On the other hand, as per the UICC classification, stage I PDAC includes tumor limited to the pancreas of any size. The definition of staging is now clearly stated in page 6, 1st paragraph.

6. *Were there any patients that refused operation and folowed up despite suggestive findings for stage 0 cancer. Please comment on their follow-up and prognosis.*

-*We have no information about such cases.*

7. *p13 please explicitly write that asymptomatic patients should be examined UPON INCIDENTAL FINDING OF MPD dilatation etc. Otherwise it will be an overstatement to suggest examining asymptomatic patients*

-As suggested, we now clearly state that "Subjects with the risk factors, especially those with multiple risk factors, should be advised to undergo further medical examination if such findings are detected."(page 13, last paragraph)

8. *Please comment on the follow-up duration of pts after pancreatic resection, methods and its cost-effectiveness.*

-Thank you very much for pointing out the important issue. For the postoperative surveillance, the NCCN Clinical Practice Guidelines [reference #25] recommend a history and physical examination for symptom assessment every 3 to 6 months for 2 years, then every 6 to 12 months. CA 19-9 level testing and follow-up contrast-enhanced CT scans every 3 to 6 months for 2 years after surgical resection. The Japanese Guideline [reference #8] suggests tumor marker assessment and follow-up contrast-enhanced CT scans every 3 to 6 months for 2 years, then every 6 to 12 months at least for 5 years after surgical resection. Because the prognosis of patients with early-stage PDAC is much more favorable than the general PDAC cases, cost-effectiveness is another important issue for the long-term surveillance after resection [reference #26]. These points are now stated in page 14, 2nd paragraph.

We hope that our paper is now acceptable for publication in *Pancreatology.*

Very Sincerely,

Atsushi Kanno, M.D., Ph.D., and Atsushi Masamune, M.D., Ph.D.

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Multicenter study of early pancreatic cancer in Japan

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Abbreviations used are: CT, computed tomography; DM, diabetes mellitus; ENPD, endoscopic nasopancreatic duct drainage; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; FDG-PET, ^{18}F-fluorodeoxyglucose-positron emission tomography; FNA, fine needle aspiration; IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct; MRI, magnetic resonance imaging; PDAC, pancreatic ductal adenocarcinoma; US, ultrasonography.

Abstract

Background/Objectives: The diagnosis of early-stage pancreatic ductal adenocarcinoma (PDAC) is still challenging. We conducted a multicenter study to clarify the clinical features of early-stage PDAC in Japan. **Methods:** We collected patients with stage 0 and stage I PDAC according to the sixth edition of the Japanese Classification of Pancreatic Carcinoma. We retrospectively analyzed the clinical profiles including opportunities for medical examination, imaging modalities and findings, methods of cytological diagnosis, and prognosis according to the stages at diagnosis. **Results:** Two hundred cases with Stage 0 and stage I PDAC were reported from 14 institutions, which accounted for approximately 0.7% and 3% of all PDAC cases, respectively. Overall, 20% of the early-stage PDAC cases were symptomatic. Indirect imaging findings such as dilatation of the main pancreatic duct were useful to detect early-stage PDAC. In particular, local fatty changes may be specific to early-stage PDAC. For preoperative pathologic diagnosis, cytology during endoscopic retrograde cholangiopancreatography was more commonly applied than endoscopic ultrasound fine-needle aspiration. Although the overall prognosis was favorable, new PDAC lesions developed in the remnant pancreas in 11.5% cases. **Conclusions:** This multicenter study revealed several key points concerning the diagnosis and management of early-stage PDAC, including screening of asymptomatic cases, importance of indirect imaging findings, application of cytology during endoscopic retrograde cholangiopancreatography, and the risk of carcinogenesis in the remnant pancreas.

Keywords: diabetes mellitus; endoscopic retrograde cholangiopancreatography; intraductal papillary mucinous neoplasm; pancreatic ductal adenocarcinoma

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer, which is a lethal malignancy with very high mortality rates [1]. The American Cancer Society estimates that 53,670 (27,970 men and 25,700 women) cases will be diagnosed as having pancreatic cancer and 43,090 (22,300 men and 20,790 women) deaths will be caused by pancreatic cancer in 2017 [2]. According to the Vital Statistics Japan reported by the Ministry of Health, Labour and Welfare (http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/suikei15/) [3], pancreatic cancer is the fourth leading cause of cancer-related death and the mortality rate was 26.5 per 100,000 men and 24.4 per 100,000 women in 2015 in Japan.

It has been increasingly recognized that the prognosis of patients with early-stage pancreatic cancer is favorable [4, 5]. The Japan Pancreatic Cancer Registry showed that the 5-year survival rates of patients with the Union for International Cancer Control (UICC) stage 0 (*in situ*), stage IA and stage IB were 85.8%, 68.7%, and 59.7%, respectively [5]. However, the corresponding proportions of stages 0, IA, and IB cases accounted for only 1.7%, 4.1%, and 6.3%, respectively. The 5-year survival rate of cases with PDAC smaller than 10 mm (TS1a) reached 80.4%, but this accounts for only 0.8% of all PDAC cases [5]. These figures indicate that the early diagnosis of pancreatic cancer is a great challenge [4]. There are several reasons for the difficulties in the early diagnosis of pancreatic cancer including the absence of early-stage biomarkers, anatomical location in the retroperitoneum allowing invasion to the surrounding organs and blood vessels, and non-specific symptoms [6, 7]. Several risk factors for PDAC have been identified including intraductal papillary mucinous neoplasm (IPMN) and diabetes mellitus (DM) [8]. However, no effective strategy

for using these risk factors to detect early pancreatic cancer has been established.

In 2014, the Japan Study Group on the Early Detection of Pancreatic Cancer was established to clarify the clinical, imaging, and pathological characteristics of early-stage PDAC cases. We here report the results of a multicenter study to clarify the characteristic features of early-stage PDAC cases in Japan.

Methods

This was a retrospective, observational study that examined the clinic-pathologic features of patients with early-stage PDAC diagnosed between January 2006 and December 2015 at 14 participating institutions that comprised the JEDPAC. The stage of PDAC was determined histopathologically by resection according to the sixth edition of the Japanese Classification of Pancreatic Carcinoma [9]. Early-stage PDAC were defined as cases with stage 0 (high-grade pancreatic intraepithelial neoplasia (PanIN)/carcinoma *in situ*) and stage I (invasive carcinoma with tumor diameter of <20 mm confined within the pancreas, along with the absence of regional lymph node metastasis (N0) and distant metastasis (M0)). Stage I cases were further classified as stage I (TS1a) (tumor size <10 mm) and stage I (TS1b) (tumor size 11-20 mm) based on the tumor size in largest diameter [5]. The pathologic assessment of cases was left to the discretion of each institution. Concomitant IPMN, in which PDAC developed at a site in the pancreas different from that of the IPMN according to the imaging and/or histologic findings [10], was regarded as a risk factor. Patients with high-grade IPMN or IPMN-derived invasive cancer, showing a histologic transition between IPMN and PDAC, were excluded. Some patients included in this study were reported in our previous review in Japanese [11].

The following information was sent to the data center at Tohoku University Graduate School of Medicine after linkable anonymization: (i) clinical backgrounds (age, gender, absence or presence of risk factors for PDAC, etc.); (ii) opportunities for medical examination for early-stage PDAC (check-up, symptomatic or asymptomatic, incidental detection during screening for other diseases); (iii) imaging modalities used for the diagnosis; (iv) imaging findings on abdominal ultrasonography (US), computed tomography (CT), magnetic

resonance imaging (MRI), endoscopic ultrasonography (EUS), endoscopic retrograde cholangiopancreatography (ERCP), and ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET); (v) the methods for the cytological diagnosis of early-stage PDAC (ERCP or EUS-fine needle aspiration (FNA)); and (vi) prognosis.

All analyses were performed using JMP software (version 9.0.2; SAS Institute, Chicago, IL, USA). Continuous variables were compared using Student's *t* test. Chi-square test or Fisher's exact test was appropriately used for the comparison of proportions. The Kaplan–Meier survival analysis was used to compare the overall survival according to the stage. This study was approved by the institutional review boards of all participating institutions.

Results

Clinical characteristics of early-stage PDAC

In the 14 participating institutions, 6942 cases with PDAC were diagnosed and 2647 cases underwent resection during the study period. There were 51 stage 0 and 149 stage I cases accounting for 0.7% and 2.3% of the all PDAC cases, respectively. Of the 200 cases with stage 0 and I PDAC, there were 109 men and 91 women, with an average age of 68.8 years (range, 39-88 years). The average observation period was 1240.8 days (range, 66–3635 days). PDAC was located in the pancreatic head in 86 (43%) cases, in the pancreatic body in 103 (51.5%) cases, and in the pancreatic tail in only 11 (5.5%) cases. One hundred thirty nine (69.5%) cases had at least one risk factor. DM was present in 64 (32.0%), smoking in 62 (31.0%), and IPMN in 52 (26.0%) cases. We only inquired about the presence or absence of DM, but did not ask about the interval of DM onset and PDAC diagnosis. The clinical characteristics were not different between stage 0 and I cases (data not shown).

Opportunities for detection of early-stage PDAC

Early-stage PDAC was detected by further medical examination due to the presence of symptoms in 50 cases (25.0%): abnormalities on medical check-up in 34 (17.0%) and abnormalities during examination or follow-up for other diseases in 103 (51.5%). The patients presented with the following symptoms: abdominal pain in 36 (72.0%), back pain in 13 (26.0%), nausea in 4 (8.0 %), diarrhea in 1 (2.0%), and jaundice in 1 (2.0%). Of the 34 patients in whom abnormalities were detected during medical check-up, 31 (91.2%) were detected by US, whereas only 1 (2.9%) case presented with an elevation of tumor marker levels. The abnormal findings detected by US were dilatation of the main pancreatic duct (MPD) in 21 (67.7%) cases, direct detection of a tumor in 9 (29.0%), and stenosis of the

MPD in 1 (3.2%). Among the 103 patients in whom an abnormality was incidentally detected during examination or follow-up for other diseases, 99 (96.1%) cases had abnormal imaging findings on CT (n=49; 49.5%) and US (n=41; 41.4%). Cases with elevated pancreatic enzyme and tumor marker levels were rare. No stage 0 PDAC case presented with elevated tumor markers.

Imaging modalities for diagnosis of early-stage PDAC

Several imaging modalities were used for the diagnosis of early-stage PDAC; in particular, CT, MRI, and EUS were performed in most cases (**Table 3**). Abnormal US findings included MPD dilatation in 101/135 (74.8%) cases, MPD stenosis in 27/135 (20.0%), and tumor detection in 71/135 (52.6%). Abnormal CT findings were MPD dilatation in 156/196 (79.6%) cases, tumor detection in 101/196 (51.5%), and local fatty changes in 82/196 (41.8%) (**Fig. 1**). Abnormal MRI findings included MPD dilatation in 143/173 (82.7%) cases and tumor detection in 78/173 (45.1%). Abnormal findings on EUS were MPD dilatation in 153/173 (88.4%) cases, MPD stenosis in 98/173 (56.6%), and tumor detection in 132/173 (76.3%). ERCP was performed after informed consent in 141 (70.5%) cases and revealed MPD dilatation in 114/141 (80.9%) and MPD stenosis in 112/141 (79.4%) cases. FDG-PET was performed in 61 (30.5%) cases and FDG accumulation was seen in 1/11 stage 0 and 30/50 (60.0%) stage I cases. We compared the number of positive imaging findings out of 14 assessed in this study (MPD dilatation, MPD stenosis, and pancreatic tumors on US; MPD dilatation, pancreatic tumors, and local fatty changes of parenchyma on CT; MPD dilatation and pancreatic tumors on MRI; MPD dilatation, MPD stenosis, and pancreatic tumors on EUS; MPD dilatation and MPD stenosis on ERCP, and FDG accumulation on FDG-PET)

between stage 0 and I cases. The number of positive imaging findings was significantly lower in stage 0 (5.5±2.5, mean±standard deviation) cases than in stage I cases (7.2±2.8) (P<0.01). Of note, pancreatic tumors were seldom detected by imaging modalities in stage 0 cases.

Cytological diagnosis of early-stage PDAC

Cytology is important for histologic confirmation of PDAC. Malignancy was confirmed by cytology prior to resection in 125 (62.5%) cases. In the remaining 75 (37.5%) cases, decision of resection was made after informed consent with high suspicion of PDAC based on abnormal imaging findings, especially MPD dilatation on multiple modalities. If stratified by stage, 27/51 (52.9%) stage 0 cases and 98/141 (65.8%) stage 1 cases underwent resection after the confirmation of malignancy. Most (26/27; 96.3%) of the stage 0 cases were diagnosed using pancreatic juice obtained by endoscopic nasopancreatic duct drainage (ENPD) and only one case was diagnosed by EUS-FNA (**Table 4**). Six stage 0 cases were also diagnosed by brushing cytology. In the stage 1 cases, 24 were diagnosed by brushing cytology, 29 using the pancreatic juice obtained by ENPD, and 53 by EUS-FNA. The proportion of malignancy by EUS-FNA was higher in stage 1 (53/63; 84.1%) than in stage 0 (1/6; 16.7%) (P=0.001).

Prognosis

Figure 3 shows the Kaplan–Meier estimates of the overall survival according to the stages. The estimated overall survival rates at 10 years after the resection for stage 0, stage I (TS1a), and stage I (TS1b) were 94.7%, 93.8%, and 78.9%, respectively (**Fig. 2**). Although the difference was not statistically significant, overall survival rates tended to be lower in the Stage I (TS1b) cases (P=0.07 vs. stage 0 cases and P=0.20 vs. stage I (TS1a) cases). Of note,

new PDAC lesions were detected in the remnant pancreas in 31 cases (15.5%) (**Fig. 3**).

Discussion

The prognosis of PDAC has not improved despite extensive research and advances in imaging modalities. PDAC develops through a stepwise progression from precursor lesions including PanIN [12]. PanIN originates in small terminal pancreatic ducts [13]. Using a mathematical model, Yachida et al. [14] estimated a period of 11.7 years on average from the initiation of pancreatic tumorigenesis until the birth of the founder cell of a parental clone, 6.8 years until the birth of the cell giving rise to the index lesion, and 2.7 years until the death of the patient. Theoretically, there is a chance to diagnose early-stage PDAC, but it is a great challenge in daily practice [6, 7]. We here reported the clinical characteristics of 200 patients with early-stage PDAC. Only 25% cases were symptomatic, indicating the importance of surveillance in asymptomatic subjects. There is a consensus that screening of PDAC should be performed within high-risk groups but not within the general population [15, 16]. There are several risk factors for PDAC including a family history of pancreatic cancer or hereditary pancreatic cancer syndrome, hereditary pancreatitis, DM, obesity, chronic pancreatitis, IPMN, pancreatic cysts, smoking, and alcohol consumption [8]. In this study, about 70% of the patients had at least one risk factor, with DM as the most common. An association between new-onset DM and pancreatic cancer has been established [17], but it remains unknown whether new-onset DM is associated with early-stage PDAC. The large number of patients with new-onset DM is an obstacle to developing an efficient screening system.

Several reports have described strategies for the surveillance of high-risk groups. Canto et al. [15] demonstrated the diagnostic utility of EUS and MRI in high-risk patients with hereditary pancreatic cancer syndrome and a family history of PDAC. Harinck et al. [18] reported the complementary roles of EUS and MRI in detecting pancreatic lesions in

such patients. Kamata et al. [19] reported that semiannual EUS was superior to annual US, CT or MRI for detecting concomitant PDAC during the follow-up of patients with IPMN. These reports confirm the utility of EUS in detecting PDAC in subjects at high risk. However, the number of facilities that can perform EUS routinely is still limited even in Japan and multiple EUS sessions per year for all IPMN cases are not realistic in the clinical setting.

Malignancy was confirmed by cytology prior to resection in 125 (62.5%) cases. Unlike PDAC cases in general, EUS-FNA was not useful for the preoperative diagnosis of malignancy in stage 0 cases, because the tumor could not be directly detected. Most of the stage 0 cases were diagnosed using pancreatic juice obtained by ENPD. Repeated pancreatic juice cytology using ENPD revealed that serial pancreatic juice aspiration cytological examination could be a feasible method for the diagnosis of pancreatic carcinoma *in situ* [20]. On the other hand, the remaining 75 (37.5%) cases underwent resection despite the absence of preoperative confirmation of malignancy. In these cases, the decision for resection was made with a high suspicion of PDAC based on abnormal imaging findings. Many imaging modalities are utilized during the diagnostic process of early-stage PDAC. Cases with stage 0 presented with fewer imaging findings than stage I cases, mainly due to the difficulty in the actual identification of tumors in stage 0 cases. Our results underscored the importance of indirect imaging findings for detecting early-stage PDAC in asymptomatic cases. The relatively low proportion of cases in the pancreatic tail (5.5%) might reflect the rarity of developing MPD dilatation due to the relatively small volume upstream of the tumor. Subjects with the risk factors, especially those with multiple risk factors, should be advised to undergo further medical examination if such findings are detected. In addition to MPD dilatation, abnormal MPD stenosis was observed on ERCP in 83% of stage 0 cases.

Interestingly, local fatty changes of the pancreatic parenchyma were detected in 21/50 (42%) stage 0 and 61/146 (41.8%) stage I cases. The underlying mechanism for the development of local fatty changes remains unknown, but might involve the interaction with the surrounding pancreatic parenchyma [21, 22].

In this study, PDAC developed in the remnant pancreas in 31 (15.5%) cases. Along with the previous case reports of metachronous cancer in the remnant pancreas [23, 24], our results suggested the importance of follow-up after surgery even in patients with early-stage PDAC. For the postoperative surveillance, the NCCN Clinical Practice Guidelines [25] recommend a history and physical examination for symptom assessment every 3 to 6 months for 2 years, then every 6 to 12 months, and then CA 19-9 level testing and follow-up contrast-enhanced CT scans every 3 to 6 months for 2 years after surgical resection. The Japanese Guidelines [8] suggest tumor marker assessment and follow-up contrast-enhanced CT scans every 3 to 6 months for 2 years, then every 6 to 12 months at least for 5 years after surgical resection. Because the prognosis of patients with early-stage PDAC is much more favorable than the general PDAC cases, cost-effectiveness is another important issue for the long-term surveillance after resection [26].

In summary, this multicenter study revealed several key points in the diagnosis and management of early-stage PDAC, including risk factors, screening of asymptomatic cases, identification of indirect imaging findings, and the risk of carcinogenesis in the remnant pancreas. Because the number of gastroenterologists specializing in pancreatic cancer is rather limited, it is important that these key points be made known to general physicians as well and prompt them to refer suspicious cases to core hospitals for further

examinations [26]. Further clarification of early-stage PDAC is warranted to improve the prognosis of this intractable disease.

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Author contributions

Kanno A, Masamune A, and Hanada K designed the study and wrote the manuscript; Kanno A, Masamune A, Hanada K, Maguchi H, Shimizu Y, Ueki T, Hasebe O, Ohtsuka T, Nakamura M, Takenaka M, Kitano M, Kikuyama M, Gabata T, Yoshida K, Sasaki T, Serikawa M, Furukawa T, Yanagisawa A, and Shimosegawa T performed data analysis. All authors read, commented, and gave approval of the final manuscript.

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Figure legends

Figure 1: A case of stage I PDAC with localized fatty changes

a. Localized tissue atrophy and fatty changes are observed in the pancreatic tail on CT (arrowhead).

b. Histologic findings reveal fatty changes in localized regions of the pancreatic parenchyma.

c. High-grade PanIN/carcinoma *in situ* is observed in a branch of the pancreatic duct.

Figure 2: Kaplan–Meier estimates of the overall survival according to the stages.

The overall survival was calculated using the Kaplan–Meier method. Censored subjects are indicated on the Kaplan-Meier curve as tick marks. The overall survival rates at 10 years after the resection were 94.7% in stage 0 cases, 93.8% in stage I (TSIa), and 78.9% in stage I (TSIb).

Figure 3: A case of newly developed PDAC in the remnant pancreas

a. CT reveals a small tumor in the pancreatic body (arrow).

b. The pancreatic tumor is detected by EUS in the pancreatic body (arrow).

c. At the age of 61 years, this patient underwent distal pancreatectomy, which revealed stage I pancreatic cancer with clear margins on pathologic examination.

d. After four years, a new tumor was detected in the pancreatic head on CT (arrowhead).

e. EUS revealed a hypoechoic lesion in the pancreatic head (arrowhead).

f. This patient underwent total remnant pancreatectomy and the pathologic diagnosis was invasive PDAC.

Table 1. Clinical characteristics of patients with stage early-stage PDAC

		All cases (n = 200)	Stage 0 cases (n = 51)	Stage I cases (n = 149)
Sex (male/female)		111/89	29/22	82/67
Age, mean ± SD (range)		68.8 ± 9.5 (38–88)	69.3 ± 8.2 (52–84)	68.5 ± 9.9 (38–88)
Observation period (days), median (range)		1240.8 (66–3635)	1392.2 (73–3546)	1189.0 (66–3635)
Location, head/body/tail, n (%)		86 (43.0)/103 (51.5)/11 (5.5)	17 (33.3)/30 (58.8)/4 (7.8)	69 (46.3)/73 (49.0)/7 (4.7)
Risk factors, n (%)*				
	DM	64 (32.0)	13 (25.5)	51 (34.2)
	Tobacco use	62 (31.0)	20 (39.2)	42 (28.2)
	IPMN	52 (26.0)	20 (39.2)	32 (21.5)
	Chronic pancreatitis	30 (15.0)	16 (31.4)	14 (9.4)
	Heavy Alcohol consumption	26 (13.0)	10 (19.6)	16 (10.7)
	Obesity	13 (6.5)	4 (7.8)	9 (6.0)
	Family history of pancreatic cancer	9 (4.5)	1 (2.0)	8 (5.4)

DM, diabetes mellitus; IPMN, intraductal papillary mucinous neoplasm; SD, standard deviation

*: Some cases had multiple risk factors.

Table

Table 2. Opportunities for medical examination in patients with early-stage PDAC

Examination opportunities			All cases (%) (n = 200)	Stage 0 cases (%) (n = 51)	Stage 1 cases (%) (n = 149)
Symptoms			50/200 (25.0)	16/51 (31.4)	34/149 (22.8)
	Abdominal pain		36/50 (72.0)	11/16 (68.8)	25/34 (73.5)
	Back pain		13/50 (26.0)	6/16 (37.5)	7/34 (20.6)
	Nausea		4/50 (8.0)	2/16 (12.5)	2/34 (5.9)
	Diarrhea		1/50 (2.0)	1/16 (6.3)	0/34 (0)
	Jaundice		1/50 (2.0)	1/16 (6.3)	0/34 (0)
	Other		7/50 (14.0)	2/16 (12.5)	5/34 (14.7)
Abnormalities identified on medical check-up			34/200 (17.0)	10/51 (19.6)	24/149 (16.1)
	Abnormal findings on US		31/34 (91.2)	10/10 (100)	21/24 (87.5)
	Findings	MPD dilatation	21/31(67.7)	10/10 (100)	11/21 (52.4)
		MPD stenosis	1/31(3.2)	0/10 (0)	1/21 (4.8)
		Detection of tumor	9/31(29.0)	0/10 (0)	9/21 (42.9)
		Other	3/31(9.7)	0/10 (0)	3/21 (14.3)
	Elevated tumor marker levels		1/34 (2.9)	0/10(0)	1/24 (4.2)
	Others		2/34 (5.9)	0/10(0)	2/24 (8.3)
Abnormalities identified during screening for other disease			103/200 (51.5)	18/51 (35.3)	85/149 (57.0)
	Abnormal imaging findings		99/103 (96.1)	17/18 (94.4)	82/85(96.5)
		CT	49/99 (49.5)	8/17 (47.1)	41/82 (50.0)
		US	41/99 (41.4)	6/17 (35.3)	35/82 (42.7)
		MRI	4/99 (4.0)	1/17 (5.9)	3/82 (3.7)
		ERCP	3/99 (3.0)	2/17 (11.8)	1/82 (1.2)
		EUS	1/99 (1.0)	0/17(0)	1/82 (1.2)
		Other	1/99 (1.0)	0/17(0)	1/82 (1.2)
	Elevated pancreatic enzymes		6/103 (5.8)	1/18 (5.6)	5/85 (5.9)
	Elevated tumor marker levels		4/103 (3.9)	0/18 (0)	4/85 (4.7)
Other			15/200 (7.5)	8/51 (15.7)	7/149 (7.5)

MPD, main pancreatic duct; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography

Table 3. Imaging modalities and findings for diagnosis of early-stage PDAC

Modalities and findings		All cases (%) (n = 200)	Stage 0 cases (%) (n = 51)	Stage I cases (%) (n = 149)
US		135/200 (67.5)	34/51 (66.7)	101/149 (67.8)
Findings	MPD dilatation	101/135 (74.8)	26/34 (76.5)	75/101 (74.3)
	MPD stenosis	27/135 (20.0)	2/34 (5.9)	25/101 (24.8)
	Pancreatic tumors	71/135 (52.6)	3/34 (8.8)	68/101 (67.3)
CT		196/200 (98.0)	50/51 (98.0)	146/149 (98.0)
Findings	MPD dilatation	156/196 (79.6)	36/50 (72.0)	120/146 (82.2)
	Pancreatic tumors	101/196 (51.5)	5/50 (10.0)	96/146 (65.8)
	Focal fatty changes of parenchyma	82/196 (41.8)	21/50 (42.0)	61/146 (41.8)
MRI		173/200 (86.5)	46/51 (90.2)	127/149 (85.2)
Findings	MPD dilatation	143/173 (82.7)	34/46 (73.9)	109/127 (85.8)
	Pancreatic tumors	78/173 (45.1)	5/46 (10.9)	73/127 (57.5)
EUS		173/200 (86.5)	41/51 (80.4)	132/149 (88.6)
Findings	MPD dilatation	153/173 (88.4)	35/41 (85.4)	118/132 (89.4)
	MPD stenosis	98/173 (56.6)	28/41 (68.3)	70/132 (53.0)
	Pancreatic tumors	132/173 (76.3)	10/41 (24.4)	122/132 (92.4)
ERCP		141/200 (70.5)	47/51 (92.2)	94/149 (63.1)
Findings	MPD dilatation	114/141 (80.9)	39/47 (83.0)	75/94 (79.8)
	MPD stenosis	112/141 (79.4)	39/47 (83.0)	73/94 (77.7)
FDG-PET		61/200 (30.5)	11/51 (21.6)	50/149 (33.6)
	FDG accumulation	31/61 (50.8)	1/11 (9.1)	30/50 (60.0)

MPD, main pancreatic duct; EUS, endoscopic ultrasonography; ERCP, endoscopic retrograde cholangiopancreatography; FDG-PET, ^{18}F-fluorodeoxyglucose-positron emission tomography

Table 4. Cytological diagnosis of early-stage PDAC

			All cases (%) (n = 200)	Stage 0 cases (%) (n = 51)	Stage 1 cases (%) (n = 149)
Cytology during ERCP			79/141 (56.0)	36/47 (76.6)	48/94 (51.1)
	Confirmation of malignancy	Brush	30/62 (48.4)	6/14 (42.9)	24/43 (55.8)
		ENPD	55/79 (69.6)	26/36 (72.2)	29/48 (60.4)
Cytology by EUS-FNA			69/200 (34.5)	6/51 (11.8)	63/149 (42.3)
	Confirmation of malignancy		54/69 (78.3)	1/6 (16.7)	53/63 (84.1)

ERCP, endoscopic retrograde cholangiopancreatography; ENPD, endoscopic nasopancreatic duct drainage; EUS-FNA, endoscopic ultrasonography-fine needle aspiration

Figure

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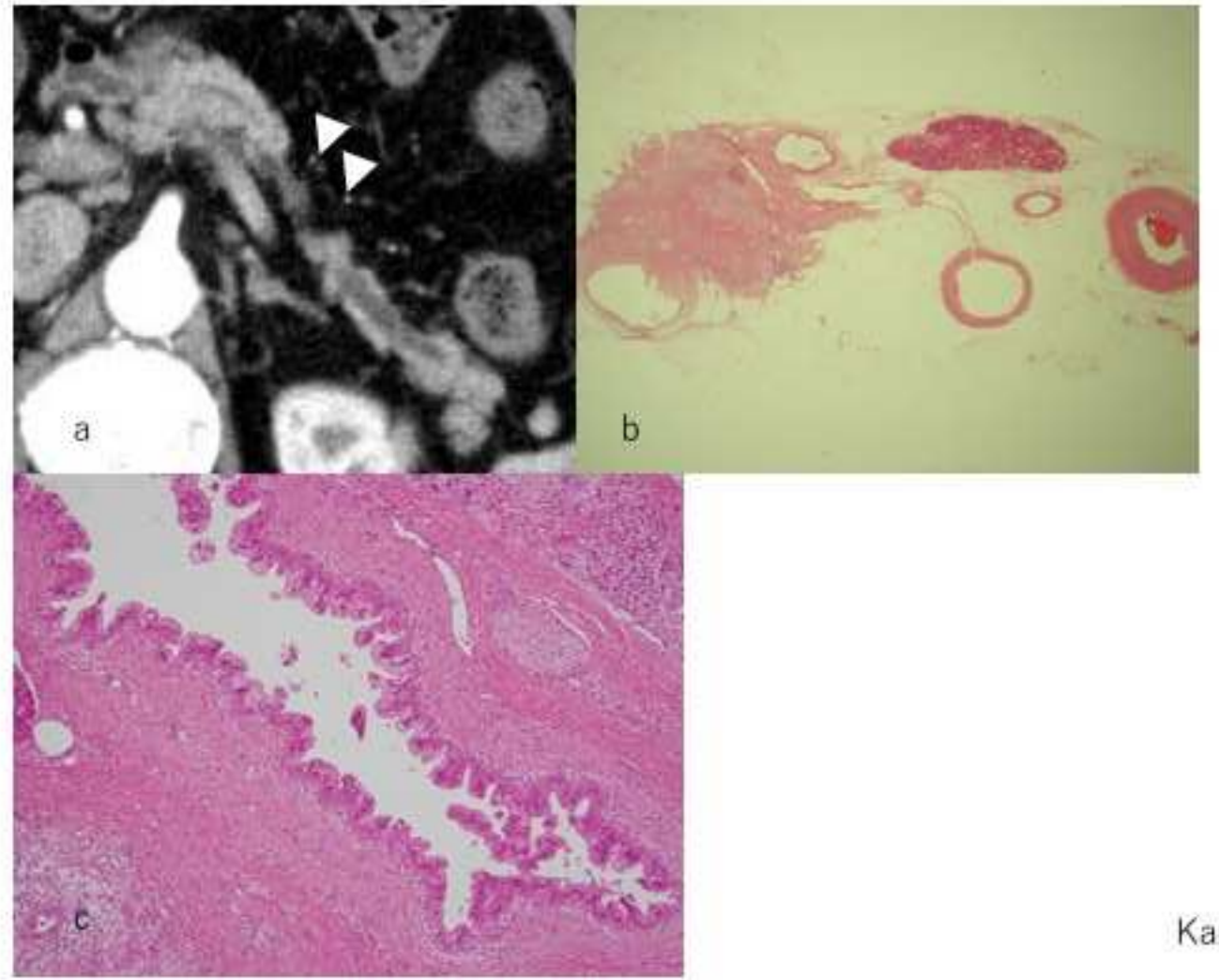

Kanno et al Figure 1

Figure

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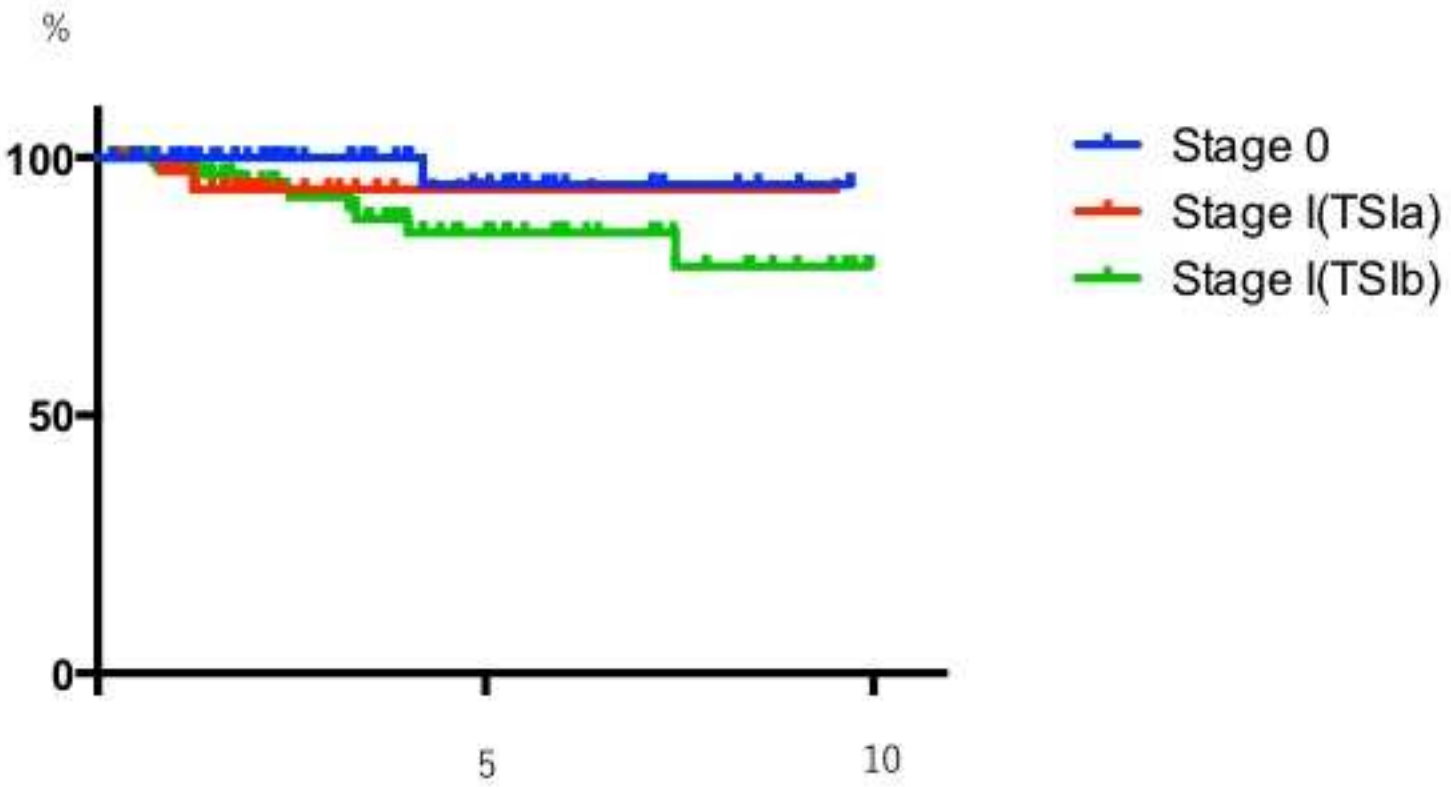

Kanno et al Figure 2

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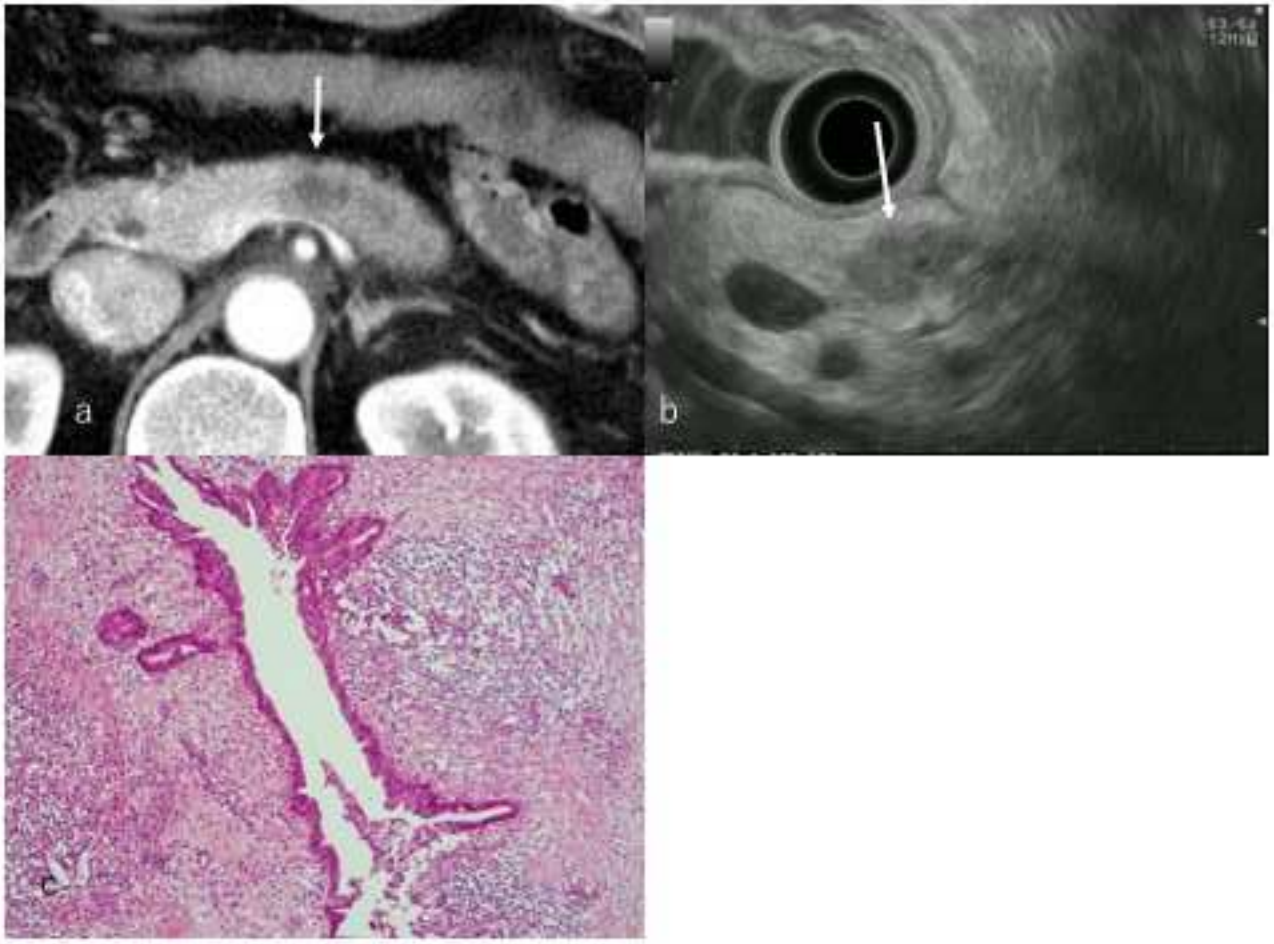

Kanno et al Figure 3

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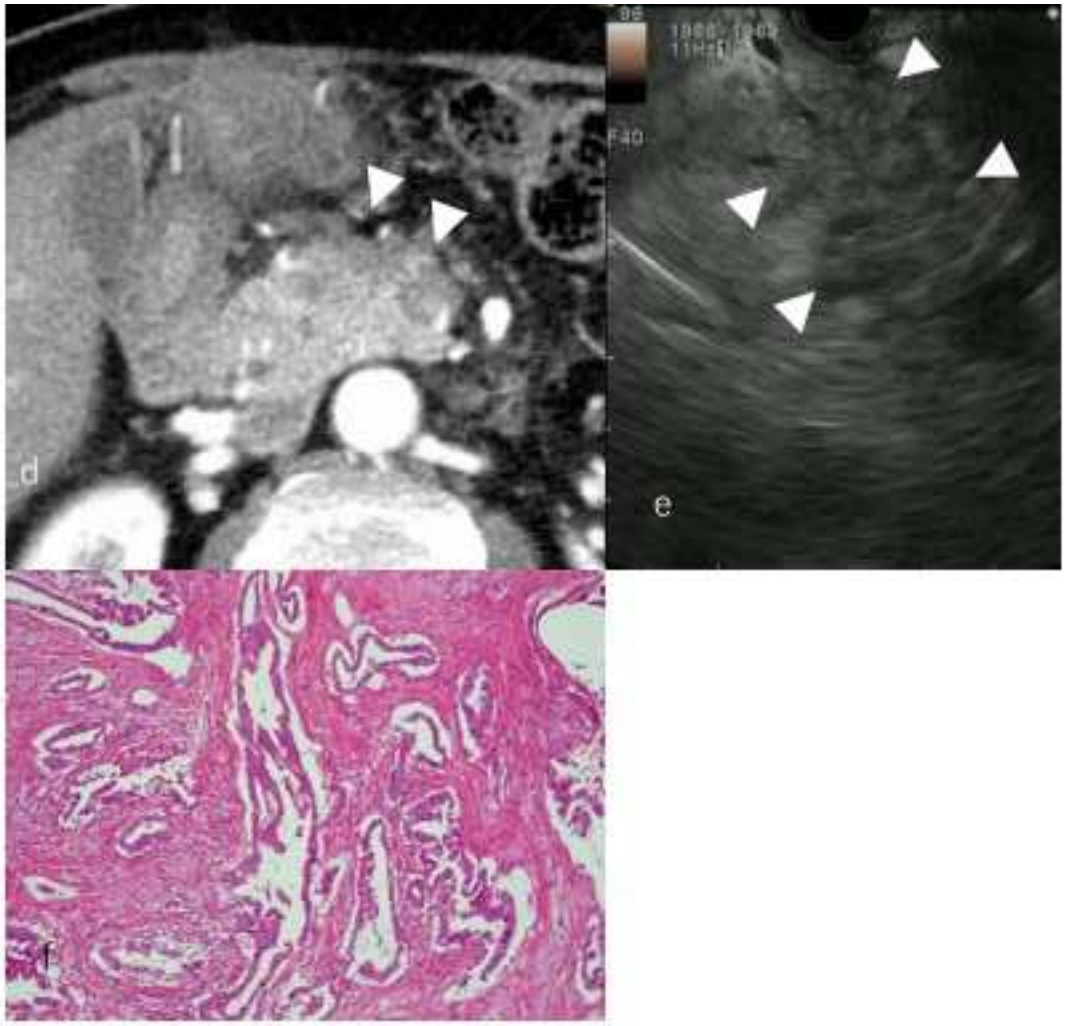

Kanno et al Figure 3

Multicenter study of early pancreatic cancer in Japan

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Abbreviations used are: CT, computed tomography; DM, diabetes mellitus; ENPD, endoscopic nasopancreatic duct drainage; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; FDG-PET, ^{18}F-fluorodeoxyglucose-positron emission tomography; FNA, fine needle aspiration; IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct; MRI, magnetic resonance imaging; PDAC, pancreatic ductal adenocarcinoma; US, ultrasonography.

Abstract

Background/Objectives: The diagnosis of early-stage pancreatic ductal adenocarcinoma (PDAC) is still challenging. We conducted a multicenter study to clarify the clinical features of early-stage PDAC in Japan. **Methods:** We collected patients with stage 0 and stage I PDAC according to the sixth edition of the Japanese Classification of Pancreatic Carcinoma. We retrospectively analyzed the clinical profiles including opportunities for medical examination, imaging modalities and findings, methods of cytological diagnosis, and prognosis according to the stages at diagnosis. **Results:** Two hundred cases with Stage 0 and stage I PDAC were reported from 14 institutions, which accounted for approximately 0.7% and 3% of all PDAC cases, respectively. Overall, 20% of the early-stage PDAC cases were symptomatic. Indirect imaging findings such as dilatation of the main pancreatic duct were useful to detect early-stage PDAC. In particular, local fatty changes may be specific to early-stage PDAC. For preoperative pathologic diagnosis, cytology during endoscopic retrograde cholangiopancreatography was more commonly applied than endoscopic ultrasound fine-needle aspiration. Although the overall prognosis was favorable, new PDAC lesions developed in the remnant pancreas in 11.5% cases. **Conclusions:** This multicenter study revealed several key points concerning the diagnosis and management of early-stage PDAC, including screening of asymptomatic cases, importance of indirect imaging findings, application of cytology during endoscopic retrograde cholangiopancreatography, and the risk of carcinogenesis in the remnant pancreas.

Keywords: diabetes mellitus; endoscopic retrograde cholangiopancreatography; intraductal papillary mucinous neoplasm; pancreatic ductal adenocarcinoma

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer, which is a lethal malignancy with very high mortality rates [1]. The American Cancer Society estimates that 53,670 (27,970 men and 25,700 women) cases will be diagnosed as having pancreatic cancer and 43,090 (22,300 men and 20,790 women) deaths will be caused by pancreatic cancer in 2017 [2]. According to the Vital Statistics Japan reported by the Ministry of Health, Labour and Welfare (http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/suikei15/) [3], pancreatic cancer is the fourth leading cause of cancer-related death and the mortality rate was 26.5 per 100,000 men and 24.4 per 100,000 women in 2015 in Japan.

It has been increasingly recognized that the prognosis of patients with early-stage pancreatic cancer is favorable [4, 5]. The Japan Pancreatic Cancer Registry showed that the 5-year survival rates of patients with the Union for International Cancer Control (UICC) stage 0 (*in situ*), stage IA and stage IB were 85.8%, 68.7%, and 59.7%, respectively [5]. However, the corresponding proportions of stages 0, IA, and IB cases accounted for only 1.7%, 4.1%, and 6.3%, respectively. The 5-year survival rate of cases with PDAC smaller than 10 mm (TS1a) reached 80.4%, but this accounts for only 0.8% of all PDAC cases [5]. These figures indicate that the early diagnosis of pancreatic cancer is a great challenge [4]. There are several reasons for the difficulties in the early diagnosis of pancreatic cancer including the absence of early-stage biomarkers, anatomical location in the retroperitoneum allowing invasion to the surrounding organs and blood vessels, and non-specific symptoms [6, 7]. Several risk factors for PDAC have been identified including intraductal papillary mucinous neoplasm (IPMN) and diabetes mellitus (DM) [8]. However, no effective strategy

for using these risk factors to detect early pancreatic cancer has been established.

In 2014, the Japan Study Group on the Early Detection of Pancreatic Cancer was established to clarify the clinical, imaging, and pathological characteristics of early-stage PDAC cases. We here report the results of a multicenter study to clarify the characteristic features of early-stage PDAC cases in Japan.

Methods

This was a retrospective, observational study that examined the clinic-pathologic features of patients with early-stage PDAC diagnosed between January 2006 and December 2015 at 14 participating institutions that comprised the JEDPAC. The stage of PDAC was determined histopathologically by resection according to the sixth edition of the Japanese Classification of Pancreatic Carcinoma [9]. Early-stage PDAC were defined as cases with stage 0 (high-grade pancreatic intraepithelial neoplasia (PanIN)/carcinoma *in situ*) and stage I (invasive carcinoma with tumor diameter of <20 mm confined within the pancreas, along with the absence of regional lymph node metastasis (N0) and distant metastasis (M0)). Stage I cases were further classified as stage I (TS1a) (tumor size <10 mm) and stage I (TS1b) (tumor size 11-20 mm) based on the tumor size in largest diameter [5]. The pathologic assessment of cases was left to the discretion of each institution. Concomitant IPMN, in which PDAC developed at a site in the pancreas different from that of the IPMN according to the imaging and/or histologic findings [10], was regarded as a risk factor. Patients with high-grade IPMN or IPMN-derived invasive cancer, showing a histologic transition between IPMN and PDAC, were excluded. Some patients included in this study were reported in our previous review in Japanese [11].

The following information was sent to the data center at Tohoku University Graduate School of Medicine after linkable anonymization: (i) clinical backgrounds (age, gender, absence or presence of risk factors for PDAC, etc.); (ii) opportunities for medical examination for early-stage PDAC (check-up, symptomatic or asymptomatic, incidental detection during screening for other diseases); (iii) imaging modalities used for the diagnosis; (iv) imaging findings on abdominal ultrasonography (US), computed tomography (CT), magnetic

resonance imaging (MRI), endoscopic ultrasonography (EUS), endoscopic retrograde cholangiopancreatography (ERCP), and ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET); (v) the methods for the cytological diagnosis of early-stage PDAC (ERCP or EUS-fine needle aspiration (FNA)); and (vi) prognosis.

All analyses were performed using JMP software (version 9.0.2; SAS Institute, Chicago, IL, USA). Continuous variables were compared using Student's *t* test. Chi-square test or Fisher's exact test was appropriately used for the comparison of proportions. The Kaplan–Meier survival analysis was used to compare the overall survival according to the stage. This study was approved by the institutional review boards of all participating institutions.

Results

Clinical characteristics of early-stage PDAC

In the 14 participating institutions, 6,942 cases with PDAC were diagnosed and 2,647 cases underwent resection during the study period. There were 51 stage 0 and 149 stage I cases accounting for 0.7% and 2.3% of the all PDAC cases, respectively. Of the 200 cases with stage 0 and I PDAC, there were 109 men and 91 women, with an average age of 68.8 years (range, 39-88 years). The average observation period was 1240.8 days (range, 66–3635 days). PDAC was located in the pancreatic head in 86 (43%) cases, in the pancreatic body in 103 (51.5%) cases, and in the pancreatic tail in only 11 (5.5%) cases. One hundred thirty nine (69.5%) cases had at least one risk factor. DM was present in 64 (32.0%), smoking in 62 (31.0%), and IPMN in 52 (26.0%) cases. We only inquired about the presence or absence of DM, but did not ask about the interval of DM onset and PDAC diagnosis. The clinical characteristics were not different between stage 0 and I cases (data not shown).

Opportunities for detection of early-stage PDAC

Early-stage PDAC was detected by further medical examination due to the presence of symptoms in 50 cases (25.0%): abnormalities on medical check-up in 34 (17.0%) and abnormalities during examination or follow-up for other diseases in 103 (51.5%). The patients presented with the following symptoms: abdominal pain in 36 (72.0%), back pain in 13 (26.0%), nausea in 4 (8.0 %), diarrhea in 1 (2.0%), and jaundice in 1 (2.0%). Of the 34 patients in whom abnormalities were detected during medical check-up, 31 (91.2%) were detected by US, whereas only 1 (2.9%) case presented with an elevation of tumor marker levels. The abnormal findings detected by US were dilatation of the main pancreatic duct (MPD) in 21 (67.7%) cases, direct detection of a tumor in 9 (29.0%), and stenosis of the

MPD in 1 (3.2%). Among the 103 patients in whom an abnormality was incidentally detected during examination or follow-up for other diseases, 99 (96.1%) cases had abnormal imaging findings on CT (n=49; 49.5%) and US (n=41; 41.4%). Cases with elevated pancreatic enzyme and tumor marker levels were rare. No stage 0 PDAC case presented with elevated tumor markers.

Imaging modalities for diagnosis of early-stage PDAC

Several imaging modalities were used for the diagnosis of early-stage PDAC; in particular, CT, MRI, and EUS were performed in most cases (**Table 3**). Abnormal US findings included MPD dilatation in 101/135 (74.8%) cases, MPD stenosis in 27/135 (20.0%), and tumor detection in 71/135 (52.6%). Abnormal CT findings were MPD dilatation in 156/196 (79.6%) cases, tumor detection in 101/196 (51.5%), and local fatty changes in 82/196 (41.8%) (**Fig. 1**). Abnormal MRI findings included MPD dilatation in 143/173 (82.7%) cases and tumor detection in 78/173 (45.1%). Abnormal findings on EUS were MPD dilatation in 153/173 (88.4%) cases, MPD stenosis in 98/173 (56.6%), and tumor detection in 132/173 (76.3%). ERCP was performed after informed consent in 141 (70.5%) cases and revealed MPD dilatation in 114/141 (80.9%) and MPD stenosis in 112/141 (79.4%) cases. FDG-PET was performed in 61 (30.5%) cases and FDG accumulation was seen in 1/11 stage 0 and 30/50 (60.0%) stage I cases. We compared the number of positive imaging findings out of 14 assessed in this study (MPD dilatation, MPD stenosis, and pancreatic tumors on US; MPD dilatation, pancreatic tumors, and local fatty changes of parenchyma on CT; MPD dilatation and pancreatic tumors on MRI; MPD dilatation, MPD stenosis, and pancreatic tumors on EUS; MPD dilatation and MPD stenosis on ERCP, and FDG accumulation on FDG-PET)

between stage 0 and I cases. The number of positive imaging findings was significantly lower in stage 0 (5.5±2.5, mean±standard deviation) cases than in stage I cases (7.2±2.8) (P<0.01). Of note, pancreatic tumors were seldom detected by imaging modalities in stage 0 cases.

Cytological diagnosis of early-stage PDAC

Cytology is important for histologic confirmation of PDAC. Malignancy was confirmed by cytology prior to resection in 125 (62.5%) cases. In the remaining 75 (37.5%) cases, decision of resection was made after informed consent with high suspicion of PDAC based on abnormal imaging findings, especially MPD dilatation on multiple modalities. If stratified by stage, 27/51 (52.9%) stage 0 cases and 98/141 (65.8%) stage 1 cases underwent resection after the confirmation of malignancy. Most (26/27; 96.3%) of the stage 0 cases were diagnosed using pancreatic juice obtained by endoscopic nasopancreatic duct drainage (ENPD) and only one case was diagnosed by EUS-FNA (**Table 4**). Six stage 0 cases were also diagnosed by brushing cytology. In the stage 1 cases, 24 were diagnosed by brushing cytology, 29 using the pancreatic juice obtained by ENPD, and 53 by EUS-FNA. The proportion of malignancy by EUS-FNA was higher in stage 1 (53/63; 84.1%) than in stage 0 (1/6; 16.7%) (P=0.001).

Prognosis

Figure 3 shows the Kaplan–Meier estimates of the overall survival according to the stages. The estimated overall survival rates at 10 years after the resection for stage 0, stage I (TS1a), and stage I (TS1b) were 94.7%, 93.8%, and 78.9%, respectively (**Fig. 2**). Although the difference was not statistically significant, overall survival rates tended to be lower in the Stage I (TS1b) cases (P=0.07 vs. stage 0 cases and P=0.20 vs. stage I (TS1a) cases). Of note,

new PDAC lesions were detected in the remnant pancreas in 31 cases (15.5%) (**Fig. 3**).

Discussion

The prognosis of PDAC has not improved despite extensive research and advances in imaging modalities. PDAC develops through a stepwise progression from precursor lesions including PanIN [12]. PanIN originates in small terminal pancreatic ducts [13]. Using a mathematical model, Yachida et al. [14] estimated a period of 11.7 years on average from the initiation of pancreatic tumorigenesis until the birth of the founder cell of a parental clone, 6.8 years until the birth of the cell giving rise to the index lesion, and 2.7 years until the death of the patient. Theoretically, there is a chance to diagnose early-stage PDAC, but it is a great challenge in daily practice [6, 7]. We here reported the clinical characteristics of 200 patients with early-stage PDAC. Only 25% cases were symptomatic, indicating the importance of surveillance in asymptomatic subjects. There is a consensus that screening of PDAC should be performed within high-risk groups but not within the general population [15, 16]. There are several risk factors for PDAC including a family history of pancreatic cancer or hereditary pancreatic cancer syndrome, hereditary pancreatitis, DM, obesity, chronic pancreatitis, IPMN, pancreatic cysts, smoking, and alcohol consumption [8]. In this study, about 70% of the patients had at least one risk factor, with DM as the most common. An association between new-onset DM and pancreatic cancer has been established [17], but it remains unknown whether new-onset DM is associated with early-stage PDAC. The large number of patients with new-onset DM is an obstacle to developing an efficient screening system.

Several reports have described strategies for the surveillance of high-risk groups. Canto et al. [15] demonstrated the diagnostic utility of EUS and MRI in high-risk patients with hereditary pancreatic cancer syndrome and a family history of PDAC. Harinck et al. [18] reported the complementary roles of EUS and MRI in detecting pancreatic lesions in

such patients. Kamata et al. [19] reported that semiannual EUS was superior to annual US, CT or MRI for detecting concomitant PDAC during the follow-up of patients with IPMN. These reports confirm the utility of EUS in detecting PDAC in subjects at high risk. However, the number of facilities that can perform EUS routinely is still limited even in Japan and multiple EUS sessions per year for all IPMN cases are not realistic in the clinical setting.

Malignancy was confirmed by cytology prior to resection in 125 (62.5%) cases. Unlike PDAC cases in general, EUS-FNA was not useful for the preoperative diagnosis of malignancy in stage 0 cases, because the tumor could not be directly detected. Most of the stage 0 cases were diagnosed using pancreatic juice obtained by ENPD. Repeated pancreatic juice cytology using ENPD revealed that serial pancreatic juice aspiration cytological examination could be a feasible method for the diagnosis of pancreatic carcinoma *in situ* [20]. On the other hand, the remaining 75 (37.5%) cases underwent resection despite the absence of preoperative confirmation of malignancy. In these cases, the decision for resection was made with a high suspicion of PDAC based on abnormal imaging findings. Many imaging modalities are utilized during the diagnostic process of early-stage PDAC. Cases with stage 0 presented with fewer imaging findings than stage I cases, mainly due to the difficulty in the actual identification of tumors in stage 0 cases. Our results underscored the importance of indirect imaging findings for detecting early-stage PDAC in asymptomatic cases. The relatively low proportion of cases in the pancreatic tail (5.5%) might reflect the rarity of developing MPD dilatation due to the relatively small volume upstream of the tumor. Subjects with the risk factors, especially those with multiple risk factors, should be advised to undergo further medical examination if such findings are detected. In addition to MPD dilatation, abnormal MPD stenosis was observed on ERCP in 83% of stage 0 cases.

Interestingly, local fatty changes of the pancreatic parenchyma were detected in 21/50 (42%) stage 0 and 61/146 (41.8%) stage I cases. The underlying mechanism for the development of local fatty changes remains unknown, but might involve the interaction with the surrounding pancreatic parenchyma [21, 22].

In this study, PDAC developed in the remnant pancreas in 31 (15.5%) cases. Along with the previous case reports of metachronous cancer in the remnant pancreas [23, 24], our results suggested the importance of follow-up after surgery even in patients with early-stage PDAC. For the postoperative surveillance, the NCCN Clinical Practice Guidelines [25] recommend a history and physical examination for symptom assessment every 3 to 6 months for 2 years, then every 6 to 12 months, and then CA 19-9 level testing and follow-up contrast-enhanced CT scans every 3 to 6 months for 2 years after surgical resection. The Japanese Guidelines [8] suggest tumor marker assessment and follow-up contrast-enhanced CT scans every 3 to 6 months for 2 years, then every 6 to 12 months at least for 5 years after surgical resection. Because the prognosis of patients with early-stage PDAC is much more favorable than the general PDAC cases, cost-effectiveness is another important issue for the long-term surveillance after resection [26].

In summary, this multicenter study revealed several key points in the diagnosis and management of early-stage PDAC, including risk factors, screening of asymptomatic cases, identification of indirect imaging findings, and the risk of carcinogenesis in the remnant pancreas. Because the number of gastroenterologists specializing in pancreatic cancer is rather limited, it is important that these key points be made known to general physicians as well and prompt them to refer suspicious cases to core hospitals for further

examinations [26]. Further clarification of early-stage PDAC is warranted to improve the prognosis of this intractable disease.

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Conflict of interests: None declared

Author contributions

Kanno A, Masamune A, and Hanada K designed the study and wrote the manuscript; Kanno A, Masamune A, Hanada K, Maguchi H, Shimizu Y, Ueki T, Hasebe O, Ohtsuka T, Nakamura M, Takenaka M, Kitano M, Kikuyama M, Gabata T, Yoshida K, Sasaki T, Serikawa M, Furukawa T, Yanagisawa A, and Shimosegawa T performed data analysis. All authors read, commented, and gave approval of the final manuscript.

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Figure legends

Figure 1: A case of stage I PDAC with localized fatty changes

a. Localized tissue atrophy and fatty changes are observed in the pancreatic tail on CT (arrowhead).

b. Histologic findings reveal fatty changes in localized regions of the pancreatic parenchyma.

c. High-grade PanIN/carcinoma *in situ* is observed in a branch of the pancreatic duct.

Figure 2: Kaplan–Meier estimates of the overall survival according to the stages.

The overall survival was calculated using the Kaplan–Meier method. Censored subjects are indicated on the Kaplan-Meier curve as tick marks. The overall survival rates at 10 years after the resection were 94.7% in stage 0 cases, 93.8% in stage I (TSIa), and 78.9% in stage I (TSIb).

Figure 3: A case of newly developed PDAC in the remnant pancreas

a. CT reveals a small tumor in the pancreatic body (arrow).

b. The pancreatic tumor is detected by EUS in the pancreatic body (arrow).

c. At the age of 61 years, this patient underwent distal pancreatectomy, which revealed stage I pancreatic cancer with clear margins on pathologic examination.

d. After four years, a new tumor was detected in the pancreatic head on CT (arrowhead).

e. EUS revealed a hypoechoic lesion in the pancreatic head (arrowhead).

f. This patient underwent total remnant pancreatectomy and the pathologic diagnosis was invasive PDAC.