



New-Onset or Exacerbation of Diabetes Mellitus Is a Clue to the Early Diagnosis of Pancreatic Cancer

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Pancreatic ductal adenocarcinoma (PDAC), which accounts for majority of pancreatic cancers, is one of the most lethal human malignancies. Most patients are diagnosed at an advanced stage after symptom development. Early diagnosis of PDAC in asymptomatic subjects is important to improve prognosis. Diabetes mellitus (DM) is a risk factor for PDAC, and DM, especially new-onset DM, has attracted attentions as a diagnostic clue to PDAC. However, the impact of DM as a diagnostic opportunity on the prognosis of PDAC is unclear. We here retrospectively reviewed 489 PDAC patients and compared the clinical characteristics and prognosis according to the opportunities for PDAC diagnosis. PDAC was diagnosed upon presentation of symptoms, such as pain and jaundice, in 318 cases including 151 DM patients, upon new-onset or exacerbation of long-standing DM in 53 asymptomatic patients, and upon incidental detection by medical check-up or follow-up/work-up of other diseases in 118 asymptomatic patients. Asymptomatic patients including those with DM had smaller tumors, earlier disease stage, and higher resectability rates than symptomatic patients. Asymptomatic patients diagnosed in association with DM had better prognosis (median survival time, 771 days) than those diagnosed due to symptoms (343 days, $P < 0.001$), and similar to those diagnosed by incidental detection (869 days). The survival advantage was not evident in symptomatic patients with DM-associated signs. In conclusion, patients diagnosed in association with DM at asymptomatic stages had better prognosis than those diagnosed with symptoms. DM-associated signs might provide a clue to the early diagnosis of PDAC among asymptomatic subjects.

Keywords: blood glucose; early pancreatic cancer; new-onset diabetes; pancreatic ductal adenocarcinoma; pancreatic neoplasms

Tohoku J. Exp. Med., 2020 December, 252 (4), 353-364.

Introduction

Pancreatic ductal adenocarcinoma (PDAC), which accounts for the majority of pancreatic cancer cases, is one of the most lethal human malignancies (Kamisawa et al. 2016; Pereira et al. 2020; Torphy et al. 2020). Most patients are diagnosed at an advanced stage, and the prognosis is poor. According to the American Cancer Society, 57,600 individuals will be diagnosed with and approximately 47,050 will die of pancreatic cancer in 2020 (<https://www.cancer.org/cancer/pancreatic-cancer/about/key-statistics>.

<https://www.cancer.org/cancer/pancreatic-cancer/about/key-statistics>.html, accessed on September 1, 2020). Pancreatic cancer is predicted to become the second leading cause of cancer-related deaths in the United States by 2030 (Rahib et al. 2014). In Japan, the 5-year survival rate is as low as 8.5% (https://ganjoho.jp/reg_stat/statistics/dl/index.html#survival, accessed on September 1, 2020). Most patients with PDAC present with symptoms. In the Japan Pancreatic Cancer Registry (Matsuno et al. 2004), 83% of patients with invasive PDAC complained of symptoms such as abdominal pain and jaundice. In contrast, in a multi-center study of early-stage PDAC in Japan (Kanno et al.

Received September 23, 2020; revised and accepted December 2, 2020. Published online December 19, 2020; doi: 10.1620/tjem.252.353.

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2018), early-stage PDAC was diagnosed due to abnormalities during the follow-up/work-up of other diseases in 52% of cases, by symptoms in 25%, and by medical check-up in 17%. Diagnosis of PDAC among asymptomatic individuals is essential to improve survival, but this is challenging due to the absence of clinically useful biomarkers for large-scale screening of the general population. Screening of asymptomatic average-risk individuals for PDAC is not feasible or recommended with current modalities due to the relatively low prevalence of the disease (Aslanian et al. 2020).

The association between diabetes mellitus (DM) and PDAC is well known. A meta-analysis of 88 studies revealed that the relative risk of PDAC in patients with DM was 1.97, and the risk was higher with a shorter duration of DM: 6.69 for less than 1 year, 1.86 for 1-4 years, 1.72 for 5-9 years, and 1.36 for more than 10 years (Batabyal et al. 2014). The increased risk of PDAC in subjects with long-standing DM indicates that DM is a risk factor for PDAC development. However, the highest risk in new-onset DM suggests that DM is an important clinical presentation of PDAC and might provide clues to the early diagnosis of PDAC (Singhi et al. 2019). New-onset DM after 50 years of age confers a 6-8-fold increased risk of PDAC, and approximately 1% of these patients will be diagnosed with PDAC within 3 years (Chari et al. 2005; Sharma et al. 2018a). DM-associated signs including new-onset and exacerbation of long-standing DM might provide an opportunity for the early detection of PDAC. But, the impact of these DM-associated signs as a diagnostic opportunity on the prognosis of PDAC is unclear. To clarify this issue, we compared the clinical characteristics and prognosis of patients with PDAC according to their diagnostic opportunities.

Materials and Methods

Study design

This was a single-center, retrospective, observational study. This study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of Tohoku University Graduate School of Medicine (article#: 2019-1-919; 2019-1-920). Clinicopathological information of patients was obtained from medical records.

Subjects

We analyzed patients whose diagnosis was established as PDAC by pathological examination of samples obtained by surgery, endoscopic ultrasound-fine needle aspiration, brushing cytology, or pancreatic juice cytology during endoscopic retrograde cholangiopancreatography at Tohoku University Hospital between January 2013 and December 2018. We excluded patients who had intraductal papillary mucinous neoplasm (IPMN) with high-grade dysplasia or PDAC derived from IPMN, recurrent PDAC, those who received treatments for PDAC before pathological diagno-

sis, those whose diagnostic opportunities were unknown, and those who had non-curative malignancies of other organs.

Patients were classified into three groups according to the opportunities for PDAC diagnosis: symptoms such as pain and jaundice as chief complaints (symptomatic group), asymptomatic and new-onset DM or exacerbation of long-standing DM (DM-associated group), and asymptomatic and incidental detection by medical check-up or follow-up/work-up of other diseases (incidental detection group). Patients who had symptoms and new-onset or exacerbation of DM were classified into the symptomatic group.

Definition

Tumor diameters were the largest diameter measured using surgical specimens in resected cases and that detected in multi-detector row-computed tomography or endoscopic ultrasonography in unresected cases. Clinical stages were classified according to the American Joint Committee on Cancer 8th edition (Amin et al. 2017).

We defined new-onset DM as a diagnosis of DM within 24 months of the PDAC diagnosis, and long-standing DM as a diagnosis of DM occurring more than 24 months before PDAC diagnosis as previously reported (Lee et al. 2018). DM diagnosis was made according to the criteria proposed by the American Diabetes Association (American Diabetes Association 2018). Subjects were diagnosed with DM if they had fasting blood glucose level ≥ 126 mg/dL, glycosylated hemoglobin $\geq 6.5\%$, random blood glucose ≥ 200 mg/dL, and/or if they had already received medication for DM. Herein, we refer to new-onset DM or exacerbation of long-standing DM as DM-associated signs.

Follow-up

In general, we follow the patients diagnosed with PDAC using multi-detector row-computed tomography every 2 or 3 months and tumor markers every month.

Statistical analysis

Continuous variables were expressed as mean (standard deviation [SD]) or median (interquartile range). For comparison between two groups, Student's *t*-test or Wilcoxon rank sum test was used for continuous variables, and the χ^2 test or Fisher's exact test was appropriately used for nominal variables. For comparison between the three groups, we used the analysis of variance or Kruskal-Wallis test for continuous variables, and the χ^2 test or Fisher's exact test for nominal variables. We also performed multiple comparisons using the Tukey-Kramer or Steel-Dwass test for continuous variables and the Holm method for nominal variables. The Kaplan-Meier survival analysis and a Cox proportional hazards model were used to compare the overall survival and to calculate the hazard ratio (HR) along with the 95% confidence interval (CI). Differences in survival were evaluated using the log-rank test. We per-

formed multivariate analysis using a Cox proportional hazard model with factors that were significant in univariate analysis. JMP Pro 15 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis, and a two-sided *P* value of < 0.05 was regarded as statistically significant.

Results

Patient characteristics

During the study period, 551 patients were pathologically diagnosed with PDAC at our institute and assessed for the eligibility (Fig. 1). We excluded the patients who had IPMN with high-grade dysplasia (*n* = 24) or PDAC derived from IPMN (*n* = 19), recurrent PDAC (*n* = 12), those who received treatments for PDAC before pathological diagnosis (*n* = 3), those whose diagnostic opportunities were unknown (*n* = 1), and those who had non-curative malignancies of other organs (*n* = 3). Finally, 489 patients with PDAC, whose characteristics are shown in Table 1, were enrolled. Mean patient age (SD) was 68.3 (9.4) years, and 257 (52.6%) patients were men. In 318 (65.0%) patients, PDAC was diagnosed upon presentation of symptoms, including abdominal pain (*n* = 148), jaundice (*n* = 44), back pain (*n* = 35), appetite loss (*n* = 35), abdominal discomfort (*n* = 26), nausea/vomiting (*n* = 8), malaise (*n* = 6), diarrhea (*n* = 5), fever (*n* = 3), pancreatitis (*n* = 3), and others (*n* = 5) as their chief complaints. Among the 318 symptomatic patients, 151 (47.5%) had DM and 167 (52.5%) did not have DM. The age at PDAC diagnosis was not different between the symptomatic patients with DM and those without DM (67.8 [8.2] vs. 66.4 [11.0]; *P* = 0.20). The remaining 171 (35.0%) patients were asymptomatic. PDAC was incidentally detected in 118 patients on cross-sectional imaging during a medical check-up (*n* = 32) or follow-up/work-up for other diseases (*n* = 86), and was diagnosed in

Table 1. Characteristics of the 489 patients with PDAC.

Age, mean (SD), years	68.3 (9.4)
Sex, male, n (%)	257 (52.6)
Diagnostic opportunity, n (%)	
Symptomatic	318 (65.0)
Asymptomatic	171 (35.0)
Incidental detection	118 (24.1)
In association with DM	53 (10.8)
Tumor location, n (%)	
Head	241 (49.3)
Body/tail	248 (50.7)
Tumor size, median (interquartile range), mm	30 (21-40)
Clinical stage, n (%)	
0	5 (1.0)
I	82 (16.8)
II	77 (15.7)
III	116 (23.7)
IV	209 (42.7)
Treatment, n (%)	
Surgery	197 (40.3)
Chemotherapy or chemoradiotherapy	236 (48.3)
Best supportive care	52 (10.6)
Others	4 (0.8)
DM, yes, n (%)	253 (51.7)
New-onset DM	126 (25.8)
Long-standing DM	120 (24.5)
Onset time unknown	7 (1.4)
Median survival time, days (95% CI)	445 (395-558)

CI, confidence interval; DM, diabetes mellitus; PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation.

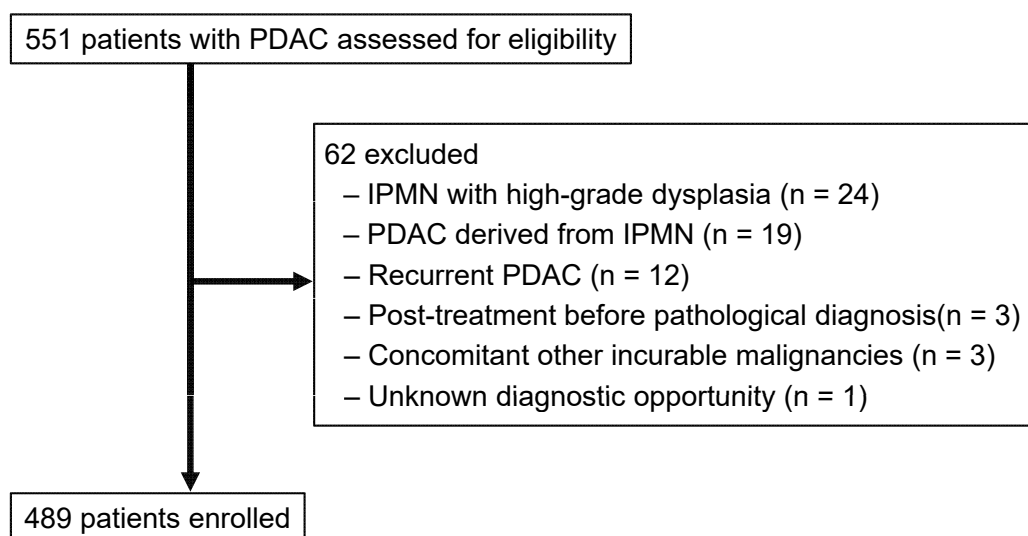


Fig. 1. Flow Diagram of the patient selection.

During the study period, 551 patients pathologically diagnosed with pancreatic ductal adenocarcinoma (PDAC) were assessed for eligibility. Sixty-two patients were excluded, and 489 patients were finally enrolled. IPMN, intraductal papillary mucinous neoplasm.

association with DM in 53 patients: new-onset DM (n = 12) or exacerbation of long-standing DM (n = 41). Among the 86 patients whose PDAC was incidentally detected during a follow-up/work-up for other diseases, 56 had benign diseases and 30 had malignancies cured by surgery or endoscopic treatment: breast cancer (n = 5), gastric cancer (n = 4), colon cancer (n = 4), lung cancer (n = 3), head and neck cancer (n = 3), esophageal cancer (n = 2), biliary cancer (n = 2), mucosa associated lymphoid tissue lymphoma of the stomach (n = 1), multiple myeloma (n = 1), ovarian cancer (n = 1), pancreatic neuroendocrine tumor (n = 1), thyroid cancer (n = 1), skin cancer (n = 1), and renal cell carcinoma (n = 1).

According to staging criteria from the American Joint Committee on Cancer 8th edition (Amin et al. 2017), the clinical stages were as follows: Stage 0 in 5 (1.0%) cases, Stage I in 82 (16.8%), Stage II in 77 (15.7%), Stage III in 116 (23.7%), and Stage IV in 209 (42.7%). Moreover, 197 (40.3%) patients received surgical resection, including 96 (19.6%) who also received preoperative treatment, 236 (48.3%) who received chemotherapy or chemoradiation,

and 52 (10.6%) who received best supportive care. Further, 253 (51.7%) patients had DM, including 126 with new-onset DM and 120 cases with long-standing DM. The onset time of DM was unknown in 7 cases. The median survival time (MST) of the 489 PDAC patients was 445 days, with cumulative survival rates of 57.8% at 1 year, 23.0% at 3 years, and 12.5% at 5 years.

Asymptomatic patients have earlier clinical stages and better prognosis than symptomatic patients

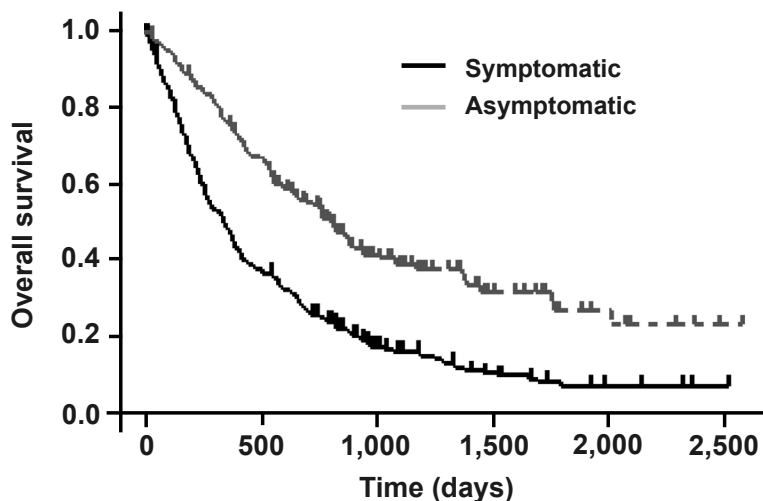
We compared the characteristics of the patients with PDAC who had symptoms (n = 318, symptomatic group) and those without symptoms (n = 171, asymptomatic group) at the time of PDAC diagnosis. As shown in Table 2, symptomatic patients were younger and more frequently presented with weight loss than asymptomatic patients. PDAC was located more frequently in the pancreatic head in symptomatic patients, which might be related to symptoms such as jaundice. On the other hand, asymptomatic patients had smaller primary tumors, earlier clinical stages, and higher resectability rates than symptomatic patients.

Table 2. Comparison of the clinical characteristics according to the presence or absence of symptoms at the time of PDAC diagnosis.

	Symptomatic (n = 318)	Asymptomatic (n = 171)	P value
Age, mean (SD), years	67.1 (9.8)	70.6 (8.2)	< 0.001
Sex, male, n (%)	162 (50.9)	95 (55.6)	0.33
BMI, median (IQR), kg/m ²	22.2 (19.5-24.3)	22.4 (20.2-25.3)	0.15
Weight loss, yes, n (%) [#]	126 (60.9)	48 (34.5)	< 0.001
Alcohol consumption, n (%)			0.10
Ever	130 (40.9)	83 (48.5)	
Never	188 (59.1)	88 (51.5)	
Smoking history, n (%)			0.74
Ever	165 (51.9)	86 (50.3)	
Never	153 (48.1)	85 (49.7)	
Tumor location, n (%)			< 0.001
Head	177 (55.7)	64 (37.4)	
Body/ tail	141 (44.3)	107 (62.6)	
Tumor size, median (IQR), mm	33 (24-45)	23 (16-30)	< 0.001
Clinical stage, n (%)			< 0.001
0	1 (0.3)	4 (2.3)	
I	24 (7.5)	58 (33.9)	
II	39 (12.3)	38 (22.2)	
III	85 (26.7)	31 (18.1)	
IV	169 (53.1)	40 (23.4)	
Treatment, n (%)			< 0.001
Surgery	85 (26.7)	112 (65.5)	
Chemotherapy or CRT	189 (59.4)	47 (27.5)	
Best supportive care	41 (12.9)	11 (6.4)	
Others	3 (0.9)	1 (0.6)	

BMI, body mass index; CRT, chemoradiotherapy; IQR, interquartile range; PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation.

[#]Information was available in 207 symptomatic and 139 asymptomatic cases.



Number at risk						
Symptomatic	318	111	37	14	5	1
Asymptomatic	171	112	47	18	6	2

Fig. 2. Kaplan-Meier estimates of the overall survival for patients with symptoms and those without symptoms. The cumulative overall survival in all symptomatic patients (black line) and all asymptomatic patients (gray line) was calculated using the Kaplan-Meier method. Censored subjects are indicated on the Kaplan-Meier curve as tick marks. The lower chart shows the number of subjects according to the presence or absence of symptoms at each time point.

Cumulative survival rates were 47.4% in symptomatic patients and 76.4% in asymptomatic patients at 1 year, 14.7% and 39.6% at 3 years, and 5.9% and 26.4% at 5 years, respectively. The prognosis was better in asymptomatic patients (MST: 813 days) than those in patients presenting with symptoms (MST: 343 days) ($P < 0.001$; HR = 0.46, 95% CI: 0.36-0.57) (Fig. 2).

In addition, we examined which clinical factors were associated with the prognosis of the patients with PDAC. In univariate analysis, clinical factors associated with the prognosis included age, body mass index, tumor size, clinical stage, treatment, and presence or absence of symptoms (Table 3). Among these factors, tumor size, clinical stage, treatment, and presence or absence of symptoms were associated with the prognosis in multivariate analysis.

Asymptomatic patients diagnosed in association with DM have better prognosis than those presenting with symptoms

We stratified the asymptomatic patients into those diagnosed with DM-associated signs (DM-associated group) and those whose PDAC was incidentally detected by medical check-up or follow-up/work-up for other diseases (incidental detection group). Patients in the incidental detection and DM-associated groups were older than those in the symptomatic group (Table 4). Patients in the incidental group less frequently presented weight loss and had a lower proportion of tumors in the pancreatic head than those in the other two groups. As in the case of asymptomatic patients overall, patients in the DM-associated group as

well as those in the incidental detection group had smaller primary tumors, earlier disease stages, and higher resectability rates than those in the symptomatic group. These clinical parameters were not different between patients in the DM-associated group and those in the incidental detection group. Of note, primary tumor location was different; tumors located in the pancreatic body or tail were more frequent in the incidental detection group than the other two groups.

Cumulative survival rates were 75.0% in the DM-associated group and 77.0% in the incidental detection group at 1 year, and 32.3% and 41.1% at 3 years, not available and 28.0%, at 5 years, respectively (Fig. 3). The prognosis of the patients in the DM-associated group (MST: 771 days) was better than those in the symptomatic group (MST: 343 days) ($P < 0.001$; HR = 0.50, 95% CI: 0.34-0.72). Similarly, the prognosis of the patients in the incidental detection group (MST: 869 days) was better than those in the symptomatic group ($P < 0.001$; HR = 0.44, 95% CI: 0.34-0.57). The prognosis of the patients in the DM-associated group was not different from that in the incidental detection group ($P = 0.57$; HR = 1.12, 95% CI: 0.74-1.70).

We further stratified the patients in the DM-associated group according to the duration of DM: new-onset (disease duration ≤ 24 months) DM ($n = 12$) and exacerbated long-standing (disease duration > 24 months) DM ($n = 41$). Except for younger age in patients with new-onset DM (66.0 [9.0] vs. 73.0 [7.7]; $P = 0.01$), clinical characteristics

Table 3. Clinical factors associated with the prognosis of PDAC patients.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Age (years)				
< 65	1		1	
≥ 65	1.31 (1.05-1.65)	0.016	1.32 (0.99-1.76)	0.06
Male (vs. female)	0.97 (0.79-1.19)	0.75		
BMI (kg/m ²)				
< 18.5	1		1	
≥ 18.5, < 25	0.61 (0.45-0.84)	0.002	0.70 (0.47-1.05)	0.08
≥ 25	0.60 (0.42-0.87)	0.006	0.88 (0.54-1.43)	0.61
Presence of weight loss	1.42 (1.10-1.81)	0.006	1.21 (0.92-1.59)	0.17
Alcohol consumption				
Ever	1			
Never	1.03 (0.85-1.27)	0.73		
Smoking history				
Ever	1			
Never	0.99 (0.81-1.22)	0.96		
Tumor location				
Head	1			
Body/ tail	0.99 (0.81-1.22)	0.94		
Tumor size (mm)				
≤ 20	1		1	
> 20	2.85 (2.15-3.78)	< 0.001	1.43 (0.99-2.05)	0.048
Clinical stage				
0-II	1		1	
III, IV	3.52 (2.76-4.48)	< 0.001	1.67 (1.14-2.45)	0.009
Treatment				
Surgery	1			
Chemotherapy or CRT	7.00 (5.31-9.20)	< 0.001	4.45 (2.99-6.60)	< 0.001
Best supportive care	16.7 (11.70-23.95)	< 0.001	8.68 (5.00-15.08)	< 0.001
Symptoms at diagnosis				
Symptomatic	1		1	
Asymptomatic	0.43 (0.34-0.53)	< 0.001	0.75 (0.58-0.89)	0.016
Presence of DM	0.98 (0.80-1.20)	0.85		

BMI, body mass index; CI, confidence interval; CRT, chemoradiotherapy; DM, diabetes mellitus; HR, Hazard ratio; PDAC, pancreatic ductal adenocarcinoma.

were similar (data not shown). Compared to the symptomatic group (MST: 343 days), the survival advantage was seen in patients with exacerbation of long-standing DM ($P < 0.001$; MST: 768 days). In the case of patients with new-onset DM, the prognosis tended to be better (MST: 771 days) than that in the symptomatic group, but the difference was not significant ($P = 0.067$). Prognosis was not significantly different between patients with new-onset DM and those with exacerbated long-standing DM ($P = 0.91$).

Survival advantage is not evident in patients who had symptoms and DM-associated signs

New-onset DM and exacerbated DM control are often found in patients with PDAC who present with symptoms.

In this study, 119/318 (37.4%) patients presenting with symptoms had DM-associated signs (89 cases with new-onset DM and 30 cases with exacerbation of long-standing DM) at the time of PDAC diagnosis. We compared the clinical characteristics between these patients and asymptomatic patients diagnosed in association with DM. As shown in Table 5, symptomatic patients presenting with DM-associated signs had larger primary tumors, more advanced disease stages, and less resectability rates than asymptomatic patients diagnosed with DM-associated signs. Prognosis was worse in symptomatic patients with DM-associated signs than in asymptomatic patients with DM-associated signs ($P < 0.001$; HR = 2.31, 95% CI: 1.55-3.44) (Fig. 4). The survival advantage, compared to that of

Table 4. Comparison of characteristics according to the opportunities for PDAC diagnosis.

	Symptomatic group (n = 318)	Incidental detection group (n = 118)	DM-associated group (n = 53)	P value
Age, mean (SD), years	67.1 (9.8)	70.2 (8.1)	71.5 (8.5)	< 0.001*
Sex, male, n (%)	162 (50.9)	65 (55.1)	30 (56.6)	0.61
BMI, median (IQR), kg/m ²	22.2 (19.5-24.3)	22.7 (20.4-24.9)	21.7 (19.8-25.8)	0.21
Weight loss, n (%) [#]	126 (60.9)	19 (20.2)	29 (64.4)	< 0.001**
Alcohol consumption, n (%)				0.12
Ever	130 (40.9)	61 (51.7)	22 (41.5)	
Never	188 (59.1)	57 (48.3)	31 (58.5)	
Smoking history, n (%)				0.70
Ever	165 (51.9)	57 (48.3)	29 (54.7)	
Never	153 (48.1)	61 (51.7)	24 (45.3)	
Tumor location, n (%)				< 0.001**
Head	177 (55.7)	37 (31.4)	27 (50.9)	
Body/ tail	141 (44.3)	81 (68.6)	26 (49.1)	
Tumor size, median (IQR), mm	34 (25-45)	22 (16-30)	24 (16-32)	< 0.001*
Clinical stage, n (%)				< 0.001*
0	1 (0.3)	2 (1.7)	2 (3.8)	
I ^{##}	24 (7.5)	39 (33.1)	19 (35.8)	
II	39 (12.3)	27 (22.9)	11 (20.8)	
III	85 (26.7)	20 (16.9)	11 (20.8)	
IV	169 (53.1)	30 (25.4)	10 (18.9)	
Treatment, n (%)				< 0.001*
Surgery	85 (26.7)	80 (67.8)	32 (60.4)	
Chemotherapy or CRT	189 (59.4)	34 (28.8)	13 (24.5)	
Best supportive care	41 (12.9)	4 (3.4)	7 (13.2)	
Others	3 (0.9)	0 (0)	1 (1.9)	

BMI, body mass index; CRT, chemoradiotherapy; IQR, interquartile range; PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation.

*Significant difference between Symptoms group and the other two groups.

**Significant difference between incidental detection group and the other two groups.

[#]Information was available in 207 cases in the symptomatic group, 94 in the incidental detection group, and 29 in the DM-associated group.

^{##}The number (%) of Stage IA cases was 7 (2.2) in the symptomatic group, 23 (19.5) in the incidental detection group, and 8 (15.1) in the DM-associated group.

the symptomatic patients overall (MST: 343 days), was not evident in symptomatic patients with DM-associated signs (MST: 343 days) ($P = 0.44$).

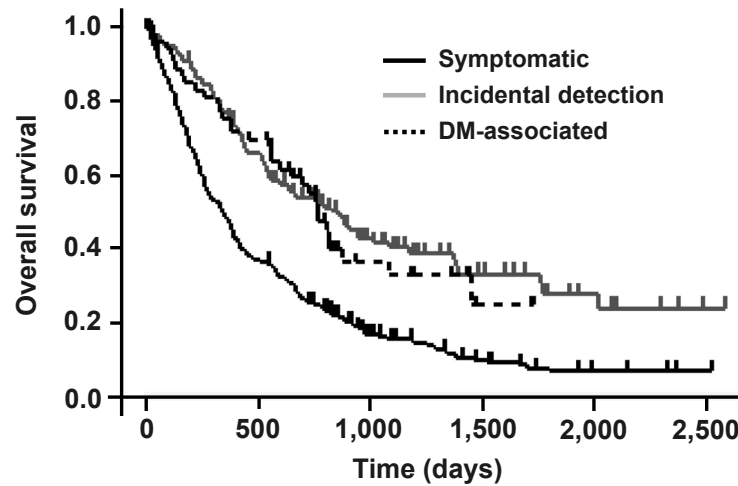
DM does not have an impact on the prognosis of patients with PDAC

Finally, we examined whether DM had an impact on the prognosis of patients with PDAC. Among the 489 enrolled patients, 253 (51.7%) had DM, and the remaining 236 (48.3%) did not have DM at the time of PDAC diagnosis. Patients who had DM were older, had higher body mass index, had more frequent weight loss, and included a higher proportion of smokers than those without DM (Table 6). Size of the primary tumor, disease stage, and resectability rate were not different between patients with DM and those without DM. Cumulative survival rates were 57.8% in patients with DM and 57.8% in those without DM at 1

year, 21.7% and 24.5% at 3 years, and 15.4% and 10.6% at 5 years, respectively. Prognosis was not different between patients with DM (MST: 420 days) and those without DM (MST: 472 days) ($P = 0.76$; HR = 1.03, 95% CI: 0.84-1.27).

Discussion

The major findings of this study are as follows. First, asymptomatic patients with PDAC had smaller primary tumors, earlier disease stages, higher resectability rates, and better prognosis than symptomatic patients. Second, compared to symptomatic patients, the survival advantage was seen in asymptomatic patients diagnosed with exacerbation of long-standing DM and it was compatible with that seen in patients whose PDAC was incidentally detected by medical check-up or follow-up/work-up of other diseases. Third, the survival advantage was seen only in asymptomatic patients diagnosed with DM and not in those presenting



Number at risk						
	0	500	1,000	1,500	2,000	2,500
Symptomatic	318	111	37	14	5	1
Incidental detection	118	76	37	16	7	2
Asymptomatic, DM-associated	53	36	10	2	0	0

Fig. 3. Kaplan-Meier estimates of the overall survival for patients according to the diagnostic opportunities. The cumulative overall survival in all symptomatic patients (black line), asymptomatic patients whose pancreatic ductal adenocarcinoma was incidentally detected (gray line), and asymptomatic patients diagnosed with DM (dashed line) was calculated using the Kaplan-Meier method. Censored subjects are indicated on the Kaplan-Meier curve as tick marks. The lower chart shows the number of subjects according to the diagnostic opportunities at each time point.

with DM-associated signs and symptoms. Lastly, the presence of DM, by itself, did not have an impact on the prognosis of patients with PDAC. Collectively, patients diagnosed in association with DM at an asymptomatic stage had better prognosis than those diagnosed after symptoms appeared, suggesting that DM-associated signs provide diagnostic opportunities for early diagnosis of PDAC among asymptomatic subjects. Among the 551 patients assessed for the eligibility, 62 patients were excluded. We assume the exclusion made this study more scientific. Natural history of IPMN with high-grade dysplasia or PDAC derived from IPMN might be different from ordinary PDAC (Omori et al. 2019). Discrimination of local recurrence from multicentric cancer is difficult in the absence of genetic analysis (Gotoh et al. 2019). Inclusion of the cases who received treatment for PDAC before pathological diagnosis would have biased the outcomes. In addition, we excluded the patients who had non-curative malignancies of other organs which seriously affect their prognosis.

The survival advantage of asymptomatic patients with PDAC was not surprising because asymptomatic patients are rare in all PDAC cases (Matsuno et al. 2004) but account for approximately 70% of early-stage cases (Kanno et al. 2018). Takeda et al. (2017) analyzed 569 cases with PDAC (250 surgically resectable and 319 unresectable cases). They showed that 163 (29%) asymptomatic patients had an earlier disease stage, higher resectability rate (64%

vs. 36%), and higher 5-year overall survival rate (18% vs. 7%) than symptomatic patients. However, it is challenging to diagnose PDAC patients while they are asymptomatic. Screening of average-risk individuals for PDAC is not recommended due to the relatively low prevalence of the disease (Aslanian et al. 2020). Alternatively, follow-up/work-up of other diseases provides important diagnostic opportunities for PDAC. Kanno et al. (2018) reported that about half of the cases with early-stage PDAC were detected due to abnormalities during the follow-up/work-up of other diseases. Kumagi et al. (2019) reported a higher detection of early-stage PDAC cases during the surveillance for hepatocellular carcinoma in patients with chronic liver disease. They emphasized that careful evaluation of the pancreas is important during the surveillance for hepatocellular carcinoma. It is increasingly recognized that the abnormalities of main pancreatic duct (MPD), such as a single localized stricture and upstream dilatation, provide clues to the early detection of PDAC (Kanno et al. 2018; Miura et al. 2020). It is reasonable to assume that such abnormalities in the pancreatic body and tail are recognized more easily because MPD is intact in the pancreatic head. MPD dilatation in the pancreatic body might be detected more easily than that in the pancreatic head by abdominal ultrasonography. Kanno et al. (2019) reported that only 2/9 (22.2%) early PDAC cases presenting MPD abnormalities were located in the pancreatic head. Symptoms such as jaundice are likely to develop if the tumor is located in the

Table 5. Comparison of the characteristics of patients who had DM-associated signs according to the presence or absence of symptoms.

	Symptomatic (n = 119)	Asymptomatic (n = 53)	P value
Age, mean (SD), years	67.2 (8.6)	71.5 (8.5)	0.003
Sex, male, n (%)	71 (59.7)	30 (56.6)	0.71
BMI, median (IQR), kg/m ²	22.4 (20.4-25.5)	21.7 (19.8-25.8)	0.47
Weight loss, n (%) [#]	50 (64.1)	29 (64.4)	0.97
Alcohol consumption, n (%)			0.50
Ever	56 (47.1)	22 (41.5)	
Never	63 (52.9)	31 (58.5)	
Smoking history, n (%)			0.61
Ever	70 (58.8)	29 (54.7)	
Never	49 (41.2)	24 (45.3)	
Tumor location, n (%)			0.45
Head	68 (57.1)	27 (50.9)	
Body/ tail	51 (42.9)	26 (49.1)	
Tumor size, median (IQR), mm	35 (25-50)	24 (16-32)	< 0.001
Clinical stage, n (%)			< 0.001
0	0 (0)	2 (3.8)	
I	11 (9.2)	19 (35.8)	
II	11 (9.2)	11 (20.8)	
III	36 (30.3)	11 (20.8)	
IV	61 (51.3)	10 (18.9)	
Treatment, n (%)			< 0.001
Surgery	31 (26.1)	32 (60.4)	
Chemotherapy or CRT	73 (61.3)	13 (24.5)	
Best supportive care	14 (11.8)	7 (13.2)	
Others	1 (0.8)	1 (1.9)	

BMI, body mass index; CRT, chemoradiotherapy; DM, diabetes mellitus; IQR, interquartile range; PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation.

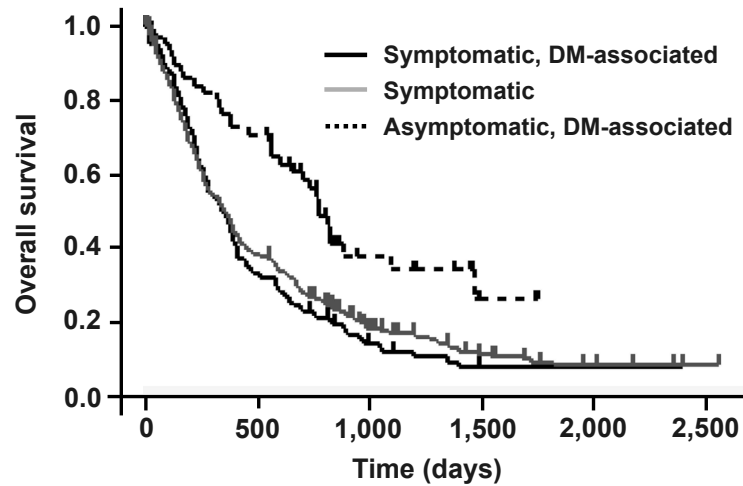
[#]Information was available in 78 symptomatic and 45 asymptomatic cases.

pancreatic head. These might explain why tumors located in the pancreatic body or tail were more frequent in the incidental detection group than the other two groups. We recently reported that focal parenchymal atrophy and fat replacement on computed tomography images provide clues to the early diagnosis of PDAC in patients who present with abnormalities of MPD (Miura et al. 2020).

The increase in blood glucose levels usually develops well before the visible appearance of the tumor, suggesting that DM development in patients with PDAC cannot be attributable merely to the destruction of the pancreatic endocrine gland (Pelaez-Luna et al. 2007). DM that develops in association with PDAC often resolves with tumor resection, and glycemic status paradoxically improves despite removal of the functional pancreatic tissue, suggesting a role of PDAC-derived factors in this phenomenon. PDAC cells cause β -cell dysfunction and insulin resistance by producing soluble factors such as adrenomedullin (Aggarwal et al. 2012) and neuromedin U (Lee et al. 2017; Zhang et al. 2020). Increased transforming growth factor- β signaling during the progression of PDAC causes erosion

of β -cell mass through apoptosis (Parajuli et al. 2020). Pancreatic stellate cells, a major collagen-producing cell type in PDAC (Erkan et al. 2012; Masamune and Shimosegawa 2013), induce apoptosis and dysfunction in β -cells (Kikuta et al. 2013). PDAC-derived exosomes might also be involved in the development of DM (Javeed et al. 2015), and Korc (2015) proposed that PDAC-induced DM might represent exosomopathy. These factors lead to the development of new-onset DM and worsened blood glucose control in patients with long-standing DM. Identification of these PDAC-derived factors would contribute to the development of biomarkers of PDAC, especially among individuals with DM.

In addition to the 53 asymptomatic cases in our study, DM-associated signs were found in 119/318 (37.4%) of symptomatic cases. Importantly, the survival advantage was not evident after the development of symptoms. These results suggest that careful follow-up of DM patients could serve as a useful diagnostic clue to the early diagnosis of PDAC, and further examination for PDAC should be performed before symptoms develop. The time window



Number at risk						
Symptomatic, DM-associated	119	36	10	3	2	0
Asymptomatic, DM-associated	53	36	10	2	0	0
Symptomatic	318	111	37	14	5	1

Fig. 4. Kaplan-Meier estimates of the overall survival for patients presenting DM-associated signs according to the presence or absence of symptoms.

The cumulative overall survival in all symptomatic patients (gray line), asymptomatic patients diagnosed in association with DM (dashed line), and symptomatic patients who had DM-associated signs (black line) was calculated using the Kaplan-Meier method. Censored subjects are indicated on the Kaplan-Meier curve as tick marks. The lower chart shows the number of subjects according to the presence or absence of symptoms and DM-associated signs at each time point.

between the new-onset or exacerbation of DM and the development of symptoms is unclear but could be several months to a few years (Mizuno et al. 2013; Pelaez-Luna et al. 2007; Sharma et al. 2018b). Sharma et al. (2018b) reported that fasting blood glucose levels began to increase from 30 to 36 months before PDAC diagnosis when tumor volumes were 1-2 cm³ and crossed the threshold for DM diagnosis (126 mg/dL) about 6-12 months before diagnosis when tumor volumes reached 12 cm³. Mizuno et al. (2013) reported that elevation of glycosylated hemoglobin was observed one year before PDAC diagnosis. Pelaez-Luna et al. (2007) reported that the average interval between the onset of DM and PDAC diagnosis was 10 months (range: 5-29 months). Importantly, PDAC was still resectable as little as 6 months before its clinical diagnosis, while the patient was asymptomatic.

Previous studies have examined the impact of DM on the prognosis of PDAC patients but with conflicting results. A meta-analysis of 18 studies showed that patients with both long-standing (HR = 1.19) and new-onset DM (HR = 1.26) had worse survival (Shen et al. 2016). Another meta-analysis showed that patients with DM who underwent chemotherapy for PDAC had reduced survival, larger tumor sizes, and higher risks of death after chemotherapy (Ma et al. 2019). Lee et al. (2018) reported that the oncologic outcomes were worse in PDAC patients with new-onset DM (within 24 months before the diagnosis of PDAC) than in

those with long-standing or without DM. In our study, the prognosis was not different between the patients with DM and those without DM, suggesting that DM by itself does not contribute to the better prognosis observed in patients diagnosed with DM-associated signs.

This study has several limitations. First, this was a single-center, retrospective, observational study. Second, the number of patients diagnosed with DM was relatively small. Third, the referral to our institute was based on the discretion of the treating physicians, and the interval between the appearance of DM-associated signs and referral to our hospital varied. Nevertheless, our study showed that the patients diagnosed with DM at asymptomatic stages had better prognosis than those diagnosed at symptomatic stages. The present study suggests that the prognosis of patients with PDAC could be improved if asymptomatic patients are diagnosed with DM, although further multi-center, prospective studies are warranted. It is important to select individuals who require further examinations for PDAC because of the tremendous number of patients with DM. The Enriching New-Onset Diabetes for Pancreatic Cancer score system has been developed to stratify the risk of PDAC in patients with new-onset DM and select individuals who should undergo further examination for PDAC (Sharma et al. 2018a). This score system includes change in body weight, changes in blood glucose, and age at the onset of DM. The Consortium for the Study of Chronic

Table 6. Comparison of the characteristics in 489 patients with PDAC according to the presence or absence of DM.

	DM (n = 253)	Non-DM (n = 236)	P value
Age, mean (SD), years	69.1 (8.2)	67.4 (10.4)	0.044
Sex, male, n (%)	151 (59.7)	106 (44.9)	0.001
BMI, median (IQR), kg/m ²	22.5 (20.2-25.1)	21.9 (19.4-24.2)	0.045
Weight loss, n (%) [#]	106 (57.0)	68 (42.5)	0.007
Alcohol consumption, n (%)			0.83
Ever	109 (43.1)	104 (44.1)	
Never	144 (56.9)	132 (55.9)	
Smoking status, n (%)			0.02
Ever	143 (56.5)	108 (45.8)	
Never	110 (43.5)	128 (54.2)	
Tumor location, n (%)			0.55
Head	128 (50.6)	113 (47.9)	
Body/ tail	125 (49.4)	123 (52.1)	
Tumor size, median (IQR), mm	30 (21-42)	30 (21-40)	0.93
Clinical stage, n (%)			0.40
0	4 (1.6)	1 (0.4)	
I	47 (18.6)	35 (14.8)	
II	37 (14.6)	40 (16.9)	
III	63 (24.9)	53 (22.5)	
IV	102 (40.3)	107 (45.3)	
Treatment, n (%)			0.77
Surgery	104 (41.1)	93 (39.4)	
Chemotherapy or CRT	119 (47.0)	117 (49.6)	
Best supportive care	27 (10.7)	25 (10.6)	
Others	3 (1.2)	1 (0.4)	
Family history of PDAC, n (%) ^{###}	27 (11.7)	29 (14.3)	0.42

BMI, body mass index; CRT, chemoradiotherapy; DM, diabetes mellitus; IQR, interquartile range; PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation.

[#]Information was available in 186 DM and 160 non-DM cases.

^{###}Information was available in 231 DM and 203 non-DM cases.

Pancreatitis, Diabetes, and Pancreatic Cancer was launched to collect a cohort of 10,000 subjects aged 50 years or older with new-onset DM (Maitra et al. 2018). During the 3-year-study period, 85 to 100 incidences of PDAC are expected to be diagnosed in this cohort. These endeavors, along with new modalities and biomarkers that can detect early pancreatic cancer with high sensitivity and specificity, would contribute to overcoming this intractable disease.

Acknowledgments

This study was supported in part by a Grant-in-Aid from KUROKAWA CANCER RESEARCH FOUNDATION (to Kazuhiro Kikuta).

Conflict of Interest

The authors declare no conflict of interest.

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