Clinical features of patients with pancreatic ductal adenocarcinoma with a history of other primary malignancies: A retrospective analysis

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Received January 16, 2021; Accepted June 23, 2021

DOI: 10.3892/mco.2021.2335

Abstract. Patients with pancreatic ductal adenocarcinoma (PDAC) that have a history of other primary malignancies are not well documented. The current study therefore aimed to evaluate the clinicopathological characteristics of patients with PDAC with or without a history of other primary malignancies. A total of 102 patients with surgically treated PDAC that presented with or without a history of other primary malignancies were retrospectively analyzed. A total of 25 patients (24.5%) had a history of other primary malignancies (age, with history of other primary malignancy vs. without, 74.2 vs. 68.9 years; P=0.005) and the reason for consultation (P<0.001) differed significantly between the groups with a history of other primary malignancies [HoM(+)] and without a history of other primary malignancies [HoM(-)]. Incidental indications during malignancy follow-up was the most common reason for the diagnosis of PDAC in the HoM(+) group. Conversely, there were no significant differences in the resectability (P=0.645), complete resection rate (P=0.774) and final stage (P=0.474) between the two groups. Disease-free survival was also not significantly different between the two groups (P=0.184). However, overall survival was significantly poorer in the HoM(+) group compared with the HoM(-) group (P=0.003). A history of other primary malignancies was also an independent predictor of poor overall survival (hazard ratio, 2.416; 95% confidence interval, 1.324-4.406; P=0.004). In conclusion, patients with PDAC and a history of other primary malignancies had significantly poorer overall survival than their counterparts, despite no differences in disease-free survival.

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Abbreviations: CI, confidence interval; HoM(+), with a history of other primary malignancies; HoM(-), without a history of other primary malignancies; HR, hazard ratio; PDAC, pancreatic ductal adenocarcinoma; TNM, tumor-node-metastasis

Key words: cancer genomics, epidemiology, multiple primary malignancies, pancreatic ductal adenocarcinoma, prognosis, surgical treatment

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is considered a poor prognostic disease with low resection and high recurrence rates (1,2). To overcome such difficulties, multidisciplinary therapeutic approaches, including surgical treatment, chemotherapy, and radiotherapy, have recently been reported, with improvements in prognosis (3-6). Prompt and accurate diagnoses of patients suitable for the aforementioned therapeutic approaches are important (2,7). Recently, PDAC arising from genetic abnormalities, such as familial pancreatic cancer, hereditary breast and ovarian cancer syndrome, Lynch syndrome, and Peutz-Jeghers syndrome, has been analyzed and reported as a representative example of such backgrounds (8-10). Approximately 10% of PDAC cases are reported to have one of the aforementioned genetic backgrounds (11). Thus, further investigation regarding such oncological viewpoints in patients with PDAC is needed.

Moreover, recent developments in cancer treatment have led to prognostic improvements in malignant diseases, including PDAC. Such improvements extend the opportunity to treat patients with malignant disease and a history of other primary malignancies (11-14). In the clinical setting, once malignant disease has been treated, periodic medical check-ups, including imaging studies, are performed for follow-up of previously treated malignancies. We hypothesized that such routine studies may beneficially affect the early diagnosis of other malignant diseases, including PDAC. However, few studies have reported the clinicopathological characteristics of patients with PDAC and a history of other primary malignancies (11-13). Therefore, further studies are needed to better understand the clinicopathological characteristics of patients with PDAC.

This study aimed to analyze the clinicopathological characteristics of patients with PDAC, with a focus on the history of other primary malignancies.

Materials and methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board of Toyama Prefectural Central Hospital (approved number: 57-52). Written informed consent was obtained from all individual participants included in the study.

We enrolled 102 consecutive patients with surgically resected and pathologically proven PDAC who were intended for curative resection between April 2013 and March 2018. PDAC patients with intraductal papillary mucinous neoplasm and those surgically treated with non-curative intent were excluded. The mean age of the enrolled patients was 70.1 years (range, 34-90 years), and the majority of patients were men (men:women ratio, 61:41). The mean follow-up period of the patients was 27.6 months (range, 1.2-80.1 months). Data from patients' medical records, including blood examinations, imaging studies, medical histories, pathological findings, and postoperative therapies, were retrospectively analyzed. Patients with a history of other primary malignancies (including concomitant diseases) were included in the HoM(+) group, and patients with no history of other primary malignancies were included in the HoM(-) group.

Staging and resectability classification were performed according to the Union for International Cancer Control Tumor-Node-Metastasis (TNM) classification (eighth edition) (15).

In this study, data are presented as mean ± standard deviation. Student's t-test was used to compare quantitative data. The Chi-square test, Fisher's exact test, or likelihood ratio test were used to compare qualitative data, as appropriate. Disease-free survival and overall survival were calculated from the date of initial surgery for PDAC to the date of relapse or death from any cause. Disease-free survival was censored at the last date on which the absence of recurrence was confirmed. Overall survival was censored at the date of last follow-up. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis was performed using a Cox proportional hazards model. All statistical analyses were conducted using SPSS version 22.0 (IBM Corp.). A P-value <0.05 was considered statistically significant.

Results

The patients' clinical characteristics are summarized in Table I. The mean age of the patients with PDAC who underwent pancreatoduodenectomy (n=71; 69.6%) and distal pancreatectomy (n=31; 30.4%) was 70 and 71 years, respectively. The median follow-up period was ~25 months.

Of the 102 patients included in the study, 25 (24.5%) had a history of other primary malignancies (including concomitant diseases). The details of the malignancies are shown in Table II.

Table I. Patient baseline characteristics.

Characteristic	Patients (n=102)
Mean ± SD age, years (range)	70.1±9.0 (34-90)
Sex (n)	
Male	61
Female	41
Tumor location (n)	
Ph	70
Pb	19
Pt	13
Preoperative therapy (n)	
Yes	11
No	91
Surgical procedure (n)	
PD	71
DP	31

DP, distal pancreatectomy; Pb, pancreatic body; PD, pancreatoduodenectomy; Ph, pancreatic head; Pt, pancreatic tail.

Table II. History of malignant diseases.

Characteristic	Patients
Total number of patients	102
History of malignant disease (including synchronous disease)	
Yes	25
No	77
Interval to diagnosis of PDAC (years)[a]	
Mean ± SD	10.5±11.8
Range	(0-48)
Details of malignant disease (n)[a,b]	
Colorectal cancer	7
Bladder cancer	4
Breast cancer	3
Gastric cancer	3
Lung cancer	3
Biliary cancer	1
Esophageal cancer	1
GIST	1
HCC	1
Lymphoma	1
Prostate cancer	1
Renal cancer	1
Thyroid cancer	1
Uterine sarcoma	1

[a]Data was obtained from the history of malignant disease group only. [b]Duplications are included where patients exhibit multiple malignancies. GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; PDAC, pancreatic ductal adenocarcinoma.

Table III. Comparison of patient baseline characteristics.

Characteristics	n (%)	HoM + (n=25)	HoM - (n=77)	P-value
Age (years)				0.005
Mean ± SD	-	74.2±7.4	68.9±9.2	
Range	-	(57-85)	(34-90)	
≤59	10 (10)	1	9	
60-74	59 (58)	10	49	
≥75	33 (32)	14	19	
Sex				0.982
Male	61 (60)	15	46	
Female	41 (40)	10	31	
Tumor location				0.380
Ph	70 (69)	15	55	
Pb/Pt	32 (31)	10	22	
Preoperative chemotherapy				0.208
Yes	11 (11)	1	10	
No	91 (89)	24	67	
Surgery				0.483
PD	71 (70)	16	55	
DP	31 (30)	9	22	

DP, distal pancreatectomy; HoM, history of other primary malignancies; Pb, pancreatic body; PD, pancreatoduodenectomy; Ph, pancreatic head; Pt, pancreatic tail.

There was no significant difference in patient characteristics between the two groups, except for age [74.2 vs. 68.9 years for patients in the with [HoM(+)] and without [HoM(-)] a history of other primary malignancies groups, respectively; P=0.005] (Table III).

Table IV compares the clinical characteristics of patients with PDAC and with or without a history of other primary malignancies. In the HoM(+) group, the most common reason for consultation was the follow-up of previous malignancies (n=8; 32.0%), followed by jaundice (n=6; 24.0%), the progression of diabetes mellitus (n=4; 16.0%), and health check abnormalities (n=4; 16.0%). In the HoM(-) group, the most common reason for consultation was jaundice (n=20; 26.0%), followed by the progression of diabetes mellitus (n=16; 20.8%) and health check abnormalities (n=14; 18.2%). The difference between the two groups was significant (P<0.001).

Most cases were classified as 'resectable' (88.0% in the HoM(+) group and 76.6% in the HoM(-) group). The proportion of patients classified as 'resectable' did not differ significantly between the two groups (P=0.645).

Complete (R0) resection was achieved in 64.0% of patients in the HoM(+) group (n=16) and 64.9% of patients in the HoM(-) group (n=50). There was no significant difference between the two groups (P=0.774).

The final stage of the largest proportion of patients (36.3%) in both groups was stage 2B, with no difference between the groups (P=0.474).

Table IV. Comparison of patient clinical characteristics.

Characteristics	n (%)	HoM (+) (n=25)	HoM - (n=77)	P-value
Reason for consultation				<0.001
F/u of HoM	8 (8)	8	-	
F/u of other diseases	9 (9)	1	8	
Health check	18 (18)	4	14	
Jaundice	26 (25)	6	20	
Progression of DM	8 (8)	4	4	
Pain	13 (13)	2	11	
Others	8 (8)	0	8	
Resectability				0.645
R	81 (79)	22	59	
BR	15 (15)	2	13	
UR	6 (6)	1	5	
Margin status				0.774
R0	66 (65)	16	50	
R1	33 (32)	9	24	
R2	2 (2)	0	2	
RX	1 (1)	0	1	
UICC final stage				0.474
0	1 (1)	0	1	
IA	5 (5)	0	5	
IB	3 (3)	1	2	
IIA	18 (18)	5	13	
IIB	37 (36)	9	28	
III	27 (26)	9	18	
IV	11 (11)	1	10	
Adjuvant therapy				0.106
No	28 (27)	10	18	
Yes	74 (73)	15	59	
Recurrence				0.399
No	27 (26)	5	22	
Yes	75 (74)	20	55	

BR, borderline resectable; DM, diabetes mellitus; F/u, follow up; HoM, history of other primary malignancies; R, resectable; UICC, Union for International Cancer Control; UR, unresectable.

Adjuvant chemotherapy was administered to 60.0% of patients in the HoM(+) group (n=15) and 76.6% of patients in the HoM(-) group (n=59). There was no significant difference between the two groups (P=0.106). The recurrence rate also did not differ significantly between the two groups [80.0% in the HoM(+) group (n=20) vs. 71.4% in the HoM(-) group (n=55); P=0.399].

Postoperative disease-free survival and overall survival rates are shown in Fig. 1. Disease-free survival did not differ significantly between the two groups (P=0.184). Conversely, overall survival was significantly poorer in the HoM(+) group than in the HoM(-) group (P=0.003). In the univariate analysis, a history of other primary malignancies was associated with

Table V. Univariate and multivariate analyses of prognostic factors for the overall survival of patients with PDAC.

	Univariate analysis			Multivariate analysis		
Factors	HR	95% CI	P-value	HR	95% CI	P-value
Age (<75 vs. ≥75 years)	1.139	0.626-2.072	0.670	-	-	-
Sex (male vs. female)	1.100	0.618-1.957	0.746	-	-	-
HoM (+ vs. -)	2.424	1.332-4.411	0.004	2.416	1.324-4.406	0.004
NAC (+ vs. -)	0.666	0.238-1.862	0.438	-	-	-
Tumor location (Ph vs. Pb/Pt)	1.478	0.824-2.650	0.190	-	-	-
Resectability (R vs. BR/UR)	1.712	0.411-7.135	0.460	-	-	-
Margin status (R0 vs. R1/R2/RX)	0.856	0.478-1.534	0.602	-	-	-
UICC final stage (I-II vs. III-IV)	1.719	0.975-3.031	0.061	1.644	0.929-2.908	0.088
Adjuvant chemotherapy (yes vs. no)	0.533	0.274-1.036	0.063	0.575	0.292-1.131	0.109

BR, borderline resectable; CI, confidence interval; HoM, history of other primary malignancies; HR, hazard ratio; NAC, neoadjuvant chemotherapy; Pb, pancreatic body; PDAC, pancreatic ductal adenocarcinoma; Ph, pancreatic head; Pt, pancreatic tail; R, resectable; UICC, Union for International Cancer Control; UR, unresectable.

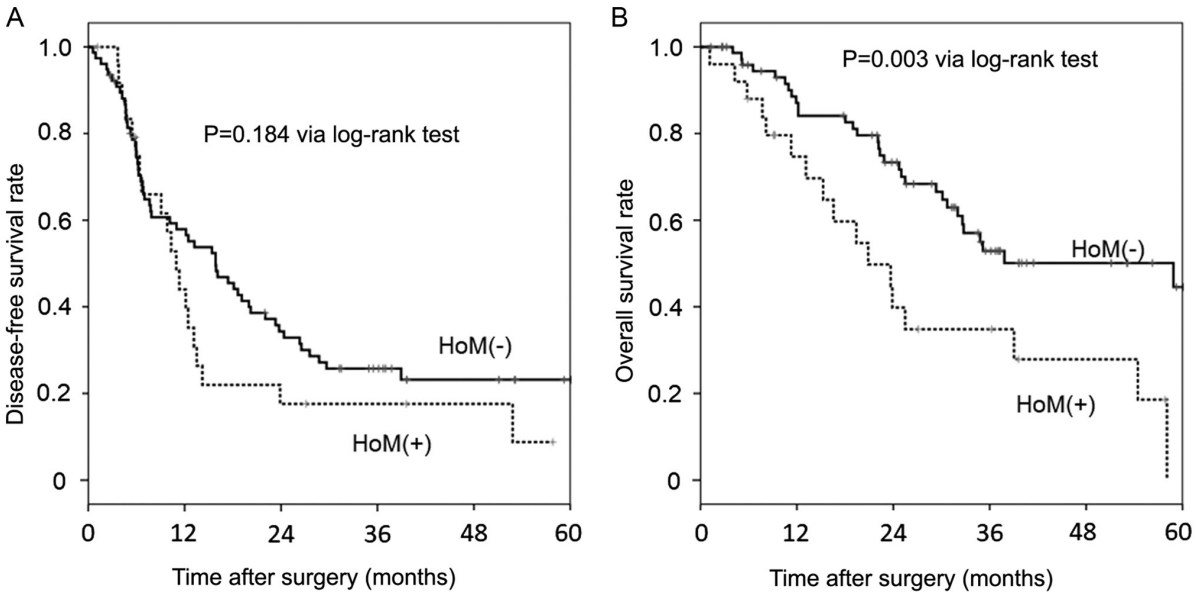

Figure 1. Comparison of (A) disease-free survival and (B) overall survival rates between HoM(+) and HoM(-) groups. Disease-free survival rates are not significantly different between the two groups (P=0.184). Conversely, overall survival rates are significantly poorer in the HoM(+) group compared with the HoM(-) group (P=0.003).

poorer overall survival [hazard ratio (HR): 2.424, 95% confidence interval (CI): 1.332-4.411; P=0.004]. Advanced TNM stage (stage III-IV) (HR: 1.719, 95% CI: 0.975-3.031; P=0.061) and the initiation of adjuvant chemotherapy (HR: 0.533, 95% CI: 0.274-1.036; P=0.063) were also factors associated with overall survival. In the multivariate analysis, a history of other primary malignancies was identified as an independent predictor of poor overall survival (HR: 2.416, 95% CI: 1.324-4.406; P=0.004) (Table V).

Discussion

PDAC is still considered a poor prognostic disease, despite developments in diagnosis and treatment (1,2). To overcome such difficulties, early diagnosis, especially for identifying suitable patients for therapeutic intervention, is important (2,7). Moreover, recent advances in cancer medicine, especially in the genetic aspect, have provided new therapeutic and diagnostic modalities for specific populations of patients with PDAC (8-10). Thus, analyzing PDAC from the viewpoint of early diagnosis and different oncogenic backgrounds has been an important recent clinical issue. Therefore, we studied PDAC, focusing on patients with a history of other primary malignancies.

In this study, the HoM(+) group had significantly poorer overall survival than the HoM(-) group, and a history of other primary malignancies was a significant prognostic factor for overall survival in patients with PDAC. The results differed

from those of previous reports, as the survival rate of patients with other primary malignancies was the same or better than that of patients without other primary malignancies (11-13,16). This difference may be explained as follows. Most previous reports examined patients diagnosed and treated for PDAC before being diagnosed and treated for other primary malignancies. Thus, other primary malignancies occurred in patients who survived treatment for PDAC. Therefore, the meaning and impact of 'other primary malignancies' differed substantially from the meaning in our study. In contrast, a study by He *et al* (16) differed significantly from the above reports. The authors analyzed 67,555 PDAC cases included in the Surveillance, Epidemiology, and End Results database to determine whether these patients had a prior history of cancer. Our study differed from the He *et al* (16) study in that our study group only included patients who intended to undergo curative resection for PDAC. The characteristics of patients in the Japanese local regional hospital also differed from those in the Surveillance, Epidemiology, and End Results database. We think that the clinical information of patients with PDAC, especially their medical history prior to diagnosis and treatment, is important for early diagnosis of surgically treatable PDAC, as HoM(+) can impact the prognosis.

We hypothesized that regular imaging screening for previous diseases, which is required for follow-up, would be useful for the early detection of PDAC, as reported by Hoshimoto *et al* (17). However, our results revealed no significant beneficial effect in the HoM(+) group, both pre- and postoperatively, including that of survival. We believe that the reasons for such discouraging results may be as follows. First, the majority of patients in the HoM(+) group did not continue regular medical follow-ups for previous malignant diseases at the time of diagnosis of PDAC because half of the patients in the HoM(+) group relapsed over 5 years after treatment for other primary malignancies without recurrence. In addition, regular follow-up of patients in the HoM(+) group did not always provide useful imaging information for early diagnosis of PDAC (e.g., imaging that did not cover the upper abdomen or computed tomography without contrast enhancement).

In this study, overall survival was significantly poorer in the HoM(+) group than in the HoM(-) group, despite no significant difference in disease-free survival between the two groups. Factors according to PDAC stage, including resectability and R0 resection rate, were not significantly different between the two groups. We did not suppose that the preoperative PDAC status would differ between the two groups. Therefore, we speculate that such differences in overall survival may be due to the clinical course after recurrence of PDAC.

Patients in the HoM(+) group were significantly older than those in the HoM(-) group. Univariate and multivariate analyses showed that age was not a significant prognostic factor for patients with PDAC. The majority of deceased patients in our study died of recurrence of PDAC. Therefore, other diseases did not affect the postoperative course of PDAC. However, this fact did affect the clinical course of PDAC, as age is an important factor in selecting the therapeutic strategy. Recent studies have reported the effectiveness of adjuvant chemotherapy for improving the prognosis of PDAC after surgery (4-6). Thus, postoperative multidisciplinary therapeutic approaches may be restricted by age in the HoM(+) group.

Treatment of previous malignant diseases may affect some aspects of patients' condition, including the immunological and oncological status. In continuing therapeutic intervention for recurrent PDAC after resection, various factors concerning patients' condition have been shown to influence continuing anticancer therapy (18). We analyzed the neutrophil-to-lymphocyte ratio, a reliable indicator of immunological status and inflammation (19). However, no significant difference was observed between the two groups (Table SI). Therefore, we postulated that patients in the HoM(+) group may not tolerate treatment for recurrent disease owing to unknown causes.

Next, we considered the chemosensitivity of patients in the HoM(+) group, which is induced by previous treatment for other malignant diseases. The therapeutic strategy for solid organ malignant disease is usually combined with local and systemic therapy, such as surgical resection and chemotherapy. Furthermore, hematopoietic malignancies are usually treated with chemotherapy. Such anticancer drugs may affect the chemosensitivity of subsequent PDAC. However, this study lacked detailed information on the history of previous treatments for other malignant diseases. Therefore, we were unable to test this hypothesis. Further information is required.

Various genetic abnormalities associated with PDAC have recently been reported owing to advancements in genomic medicine (8-10). Genetic mutations in the oncogene *KRAS* and tumor suppressor genes *TP53*, *p16*/*CDKN2A*, and *SMAD4* are representative mutations for PDAC (20). Several studies have discussed the role of each gene mutation in the development and progression of PDAC (21,22). Epigenetic alterations have also been reported to be responsible for the dysregulation of tumor-associated genes (23,24). Some of these genes have already become therapeutic targets for selected patients (e.g., *BRCA2* and *PALB2*) (25,26). In our study, previous treatment for other primary malignancies was similar to those reported previously (11,13,17). Thus, these malignancies may have included some of the aforementioned genetic and epigenetic abnormalities. Future developments in genomic medicine will expand the indications for such therapeutic interventions. Therefore, clinicians should pay more attention to patients and patients' family history to gather potential information on PDAC with genetic abnormalities, including a history of other primary malignancies.

This study has some limitations owing to its small sample size and retrospective design. First, our study group was obtained from patients admitted to a local regional hospital in Japan. Thus, there is a bias in race and ethnicity. Second, our investigation may be subject to selection bias, as the patients selected in this study were those suitable for surgical resection. Unresectable patients were not included, including a certain proportion of patients with PDAC. Moreover, most patients included in this study were treated under the upfront surgery policy. The beneficial effect of neoadjuvant chemotherapy has recently been reported for patients with resectable PDAC (3,4). The initiation of a multidisciplinary therapeutic approach that includes neoadjuvant chemotherapy may radically change the prognosis and treatment of PDAC. The aim of this study was to examine the characteristics of patients with PDAC from a different viewpoint, including early diagnosis for better prognosis, focusing on a history of other primary malignancies. We emphasize the importance of paying attention to the medical

history of patients with PDAC, which has a significant impact on prognosis. Finally, there is ambiguity concerning the review of medical history, especially for detailed information regarding previous treatments, such as chemotherapy regimen or family history. Such information is generally dependent on patients' and family members' anamnesis. Therefore, the risk of incomplete and inaccurate information could not be avoided. Thus, the construction of a system for sharing correct information about patients' and family members' medical history is important for the future treatment of malignant diseases.

A history of other primary malignancies had a negative impact on overall survival in patients with surgically treated PDAC. Further studies, especially detailed analyses of the differences in overall survival, recurrence-free survival, previous treatments for other primary malignancies, and family history, are needed to better understand the clinical features of PDAC.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HH, KA and KS designed the current study and wrote the manuscript. TTo, KMo, ST, YS and YK collected the clinical data, which included postoperative course data. HH, TK, SK, AH and TTs performed statistical analysis. HH, MK and KMa interpreted patient data. HH and MK confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board of Toyama Prefectural Central Hospital (approved no. 57-52). Written informed consent was obtained from all individual participants included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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