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Outcomes in patients with pancreatic cancer as a secondary malignancy: a retrospective single-institution study

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Abstract

Purpose This study aimed to evaluate the clinicopathological features and oncological outcomes of pancreatic cancer (PC) patients with prior malignancies (2nd primary PC) compared with those of patients without any prior malignancies in their history (1st primary PC).

Methods We retrospectively reviewed clinical data from 185 PC patients undergoing surgical resection. Patients were divided into the 1st and 2nd primary PC groups.

Results Forty-three patients (23.2%) had a history of prior malignancy. The 2nd primary PC group was significantly older than the 1st primary PC group (mean, 72.1 vs. 65.9 years, respectively, $P < 0.001$) and was more frequently asymptomatic compared to the 1st primary PC group (67.4 vs. 31.0%, respectively, $P < 0.001$). The tumor size was larger, and extrapancreatic nerve plexus invasion, venous invasion, and lymph node metastasis were more frequently observed in the 1st primary PC group. The rate of adjuvant therapy administration was lower in 2nd primary PC patients (72.5 vs. 51.2%, $P = 0.009$). In the survival analysis, no significant difference in overall or disease-free survival was found between the two groups (16.8 vs. 16.4 months, $P = 0.725$, and 8.7 vs. 9.3 months, $P = 0.284$, respectively).

Conclusion Despite significant surveillance bias, such as earlier detection in 2nd primary PC, the outcomes of patients with 2nd primary PC were comparable to those of patients with 1st primary PC. Further investigation with a larger sample size and matching for patient age and tumor stage in both groups is needed to elucidate the biological features of 2nd primary PC.

Keywords Multiple primary malignancy · Pancreatic cancer · Second primary cancer · Systemic inflammatory response

Introduction

Because of advances in early detection and treatment for cancer patients, the overall cancer-related mortality rate has dropped by 25% during the past 15 years [1], and these improved outcomes have resulted in a growing population of cancer survivors. Consequently, patients survive long enough to develop subsequent primary malignancies, and multiple primary cancers currently account for approximately 18% of all incident cancers [2, 3]. A 2nd primary cancer is a new neoplasm that is biologically independent of preceding malignancies [4] and can develop due to delayed effects of treatment for the 1st primary malignancy, shared lifestyle factors, environmental exposure, and host factors, including hereditary predisposition or immune function, and combinations of these factors [5].

Pancreatic cancer (PC) remains one of the most lethal diseases worldwide and is the 5th- and 3rd-leading cause of cancer-related death in Japan and the USA, respectively [1, 6]. Although surgical resection combined with adjuvant therapy has afforded a significant survival advantage in patients with resectable PC, the 5-year survival rate of PC patients undergoing complete resection remains at 28–44% [7, 8]. However, successful surgical resection offers the only chance for a cure in PC patients, and early detection is essential to reduce the mortality rate associated with PC, particularly in patients without symptoms indicative of PC, such as obstructive jaundice and abdominal pain.

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In recent years, numerous studies focusing on the link between the systemic inflammatory response and cancer and accumulating evidence have demonstrated that several inflammation-based scores have prognostic significance in patients with various types of cancer [9–12]. Earlier studies demonstrated that preoperative inflammation-based prognostic scores or systemic inflammatory indices, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and Glasgow prognostic score (GPS), were independent predictors of survival in PC patients undergoing surgical resection [9, 13, 14]. However, the mechanisms underlying the association between the systemic inflammatory response and poor outcomes in cancer patients are still unknown.

Although the incidence of 2nd primary cancer has risen in recent years and become an increasing concern among cancer survivors, only a few studies have focused on PC development in cancer survivors [15–17], and the clinical characteristics and outcomes of patients with this condition remain unclear. In addition, no studies have evaluated the host inflammatory response in cancer survivors. In this study, we performed a retrospective cohort analysis to evaluate the clinicopathological features, including preoperative hematological inflammatory parameters, and the oncological outcomes of PC patients with a history of prior malignancy (2nd primary PC) compared with those of patients without any prior malignancies in their history (1st primary PC).

Materials and methods

Patients

From January 2007 to June 2017, 191 patients with a pancreatic exocrine neoplasm underwent surgical resection at our institution. Six patients were excluded from the analysis due to the synchronous occurrence of another primary cancer; therefore, 185 patients were enrolled in this study. This retrospective study was approved by the Institutional Review Board of Tochigi Cancer Center, and informed consent was obtained from all patients included in the study. Patients were divided into two groups: patients without any prior malignancies in their history (1st primary PC group) and patients with one or more prior malignancies (2nd primary PC group). We defined a new PC that was judged to be biologically independent of the original primary cancer and was neither a recurrence nor a metastasis as a 2nd primary PC. Data obtained from reviewing medical records included age, sex, tumor location, tumor size, serum tumor marker levels, including the carbohydrate antigen (CA) 19–9, carcinoembryonic antigen (CEA), and duke pancreatic monoclonal antigen type 2 (DUPAN-2) levels, preoperative hematological inflammatory parameters, including the absolute lymphocyte count, serum

C-reactive protein (CRP) level, serum albumin level, NLR, PLR, and GPS, the presence of pathological venous invasion, extrapancreatic nerve plexus invasion, and lymph node metastasis, tumor stage, resection margin status, administration of adjuvant chemotherapy, primary cancer site, history of chemotherapy, radiation therapy, and endocrine treatment for prior malignancies, time interval to the development of 2nd primary PC, and outcomes. In our study, the GPS was calculated as follows: patients with an elevated serum CRP level (> 10 mg/L) and hypoalbuminemia (< 35 mg/L) were assigned a score of 2, patients with only one of these biochemical abnormalities were assigned a score of 1, and patients with neither of these abnormalities were assigned a score of 0 [18]. The tumor stage of each patient was assigned according to the Union for International Cancer Control (UICC) TNM classification system [19] based on the surgical and pathological findings. The resection margin status of the specimens was defined as R1 when carcinoma was present at the margin (0-mm clearance) according to the criteria of the UICC TNM classification [19]. The time interval to the development of the 2nd primary PC was the duration between completing treatment for the prior malignancy and surgery for the 2nd primary PC.

Statistical analysis

All data were analyzed using SPSS software, version 24 (IBM, Chicago, IL, USA). Fisher's exact test or Pearson's chi-squared test was used to analyze categorical variables. Quantitative variables were compared using the Mann–Whitney test or a paired t test. Survival curves were constructed according to the Kaplan–Meier method. A log-rank test was used to compare survival curves. The overall survival (OS) was calculated as the time from the date of pancreatic surgery to either the date of death or the last follow-up, whichever occurred first. Disease-free survival (DFS) was defined as the time from the date of pancreatic surgery to the date of recurrence, the last follow-up, or death, whichever occurred first. Patients without recurrence at the last follow-up date were censored. OS and DFS were compared using the log-rank test. The factors identified by univariate analysis were further examined by multivariate Cox proportional hazards models to identify significant independent factors for survival. P values less than 0.05 were considered statistically significant.

Results

In total, 185 patients, including 172 patients with ductal adenocarcinoma, seven with adenosquamous carcinoma, and six with invasive intraductal papillary mucinous carcinoma (IPMC), were analyzed. Of them, 102 patients underwent

pancreatoduodenectomy (PD), including pylorus-preserving PD and subtotal stomach-preserving PD, 71 patients underwent distal pancreatectomy, and 12 patients underwent total pancreatectomy. Arterial resection was required in 11 patients (6%), and venous resection including the portal vein and/or superior mesenteric vein was performed in 71 patients (38%). The R0 resection rate was 89%. A total of 125 patients (68%) received adjuvant therapy at our institution, including gemcitabine alone ($n = 35$), S-1 alone ($n = 87$), and gemcitabine plus S-1 ($n = 3$). At a median follow-up of 16.6 months, 130 of the 185 patients had experienced recurrence, and 108 patients had died. Among the 185 patients, 43 (23.2%) had a history of prior malignancies. Of them, seven patients (16.3%) had two malignancies before the PC diagnosis. The preceding primary tumors were most frequently located in the breast (20.0%), followed by the stomach (18.0%), colon and rectum (16.0%), prostate (10.0%), bladder (6.0%), and lung (6.0%) (Table 1). The time interval from the completion of treatment for the prior malignancy to surgery for the 2nd primary PC ranged from 0.5 to 43.0 years (median, 7.8 years). Of the 50 preceding malignancies in 43 patients with 2nd primary PC, 42 lesions (84.0%) were surgically resected (Table 1). Overall, systemic chemotherapy was administered to nine patients (20.9%), radiation therapy was administered to four patients (9.3%), and endocrine therapy was administered to five patients (11.6%).

The patient characteristics of the two groups are summarized in Table 2. Patients in the 2nd primary PC group were significantly older than those in the 1st primary PC group (mean, 72.1 vs. 65.9 years, respectively, $P < 0.001$). The age distribution at pancreatic resection revealed that only 0% and 4.7% of the 2nd primary PC patients were in their 40s and 50s, respectively, whereas the corresponding proportions were

4.2% and 21.8%, respectively, for the 1st primary PC patients (Fig. 1). On the other hand, 65.1% of the 2nd primary PC patients were 70 years or older at the time of pancreatic resection, whereas only 38.7% of the 1st primary PC patients fell into this category. No significant differences were observed between the two groups regarding the history of smoking, alcohol consumption, and diabetes mellitus. Patients in the 2nd primary PC group were more frequently asymptomatic than those in the 1st primary PC group (67.4 vs. 31.0%, respectively, $P < 0.001$). Of the 43 patients with 2nd primary PC, at least 32 patients received regular follow-up examinations for a prior malignancy. PCs were incidentally found in 11 of 12 patients followed by abdominal computed tomography (CT) every 6 months, in one patient followed by abdominal ultrasonography (US) every 6 months, in five of six patients followed by abdominal CT every year, and in two patients followed by abdominal CT every 2 years. Three patients with a history of breast cancer who were followed by annual mammography and one patient with a history of lung cancer followed by annual chest CT were diagnosed with PC after the development of symptoms. The tumor was more frequently located in the pancreatic body and/or tail in the 2nd primary PC group (55.8 vs. 35.9%, $P = 0.043$). The combined resection of major vessels was more frequently performed in the 1st primary PC group (50.7 vs. 16.3%, $P < 0.001$). Histopathologically, the presence of extrapancreatic nerve plexus invasion, venous invasion, and lymph node metastasis was frequently observed in the 1st primary PC group ($P = 0.008, 0.009,$ and 0.007, respectively). Consequently, the tumor stage was significantly higher in the 1st primary PC group ($P = 0.001$). However, no difference in the R0 resection rate was observed between the two groups. According to the Clavien–Dindo [20] classification system and postoperative

Table 1 Origin of prior malignancies in patients with 2nd primary pancreatic cancer

Prior malignancy	Number of lesions ($n = 50$)	Median interval to develop pancreatic cancer (years, range)	Surgery ($n = 43$)	Adjuvant therapy following surgery for 1st primary malignancies				Chemotherapy ($n = 5$)	Radiation ($n = 2$)	Endocrine therapy ($n = 1$)
				Chemotherapy ($n = 7$)	Radiation ($n = 2$)	Endocrine therapy ($n = 4$)	Unknown ($n = 6$)			
Breast	10 (20%)	16.4 (1.8–39.0)	10	2	2	4	1	1	0	0
Stomach	9 (18%)	6.0 (1.3–17.0)	8	1	0	0	1	0	0	0
Colorectal	8 (16%)	2.8 (0.5–8.6)	8	1	0	0	1	0	0	0
Prostate	5 (10%)	2.8 (1.2–8.2)	3	0	0	0	0	0	1	1
Lung	3 (6%)	11.6 (0.8–12.4)	3	1	0	0	0	0	0	0
Bladder	3 (6%)	4.7 (2.2–9.5)	3	0	0	0	1	0	0	0
Esophagus	2 (4%)	6.3 (2.2–10.4)	1	0	0	0	0	1	1	0
Non-Hodgkin lymphoma	2 (4%)	7.3 (7.1–7.5)	0	0	0	0	0	2	0	0
Cervical	2 (4%)	19.0 (10.0–28.0)	2	0	0	0	1	0	0	0
Others	6 (12%)	10.8 (1.5–43.0)	5	2	0	0	1	1	0	0

Table 2 Comparison of clinicopathological variables between patients with 1st primary pancreatic cancer and those with 2nd primary pancreatic cancer

		1st primary PC ($n = 142$)	2nd primary PC ($n = 43$)	P value
Mean age, years (range)		65.9 (range, 41 to 85)	72.1 (range, 50 to 84)	< 0.001
Sex	M: F	67 (47.2%): 75 (52.8%)	22 (51.2%): 21 (48.8%)	0.728
Smoking				
	Never ($n = 97$)	76 (53.5%)	21 (48.8%)	0.804
	Former ($n = 57$)	42 (29.6%)	15 (34.9%)	
	Current ($n = 30$)	23 (16.2%)	7 (16.3%)	
Alcohol consumption				
	< 20 g/day ($n = 136$)	106 (74.6%)	30 (69.8%)	0.692
	≥ 20 g/day ($n = 48$)	36 (25.4%)	12 (27.9%)	
Diabetes mellitus				
	No ($n = 143$)	111 (78.2%)	31 (72.1%)	0.678
	Yes ($n = 42$)	31 (21.8%)	11 (25.6%)	
Symptom				
	Asymptomatic ($n = 73$)	44 (31.0%)	29 (67.4%)	< 0.001
	Symptomatic ($n = 112$)	98 (69.0%)	14 (32.6%)	
Tumor location				
	Ph ($n = 105$)	86 (60.0%)	19 (44.2%)	0.043
	Pb and/or Pt ($n = 75$)	51 (35.9%)	24 (55.8%)	
	Phbt ($n = 5$)	5 (3.5%)	0 (0%)	
Tumor size (median, mm)		40 (range, 10 to 163)	31 (range, 8 to 80)	< 0.001
CA19–9 (≤ 37 U/mL)				
	Normal ($n = 53$)	37 (26.1%)	16 (37.2%)	0.181
	High ($n = 131$)	104 (73.2%)	27 (67.8%)	
CEA (≤ 5 ng/mL)				
	Normal ($n = 134$)	99 (69.7%)	35 (83.3%)	0.237
	High ($n = 49$)	41 (28.9%)	8 (18.6%)	
DUPAN-2 (≤ 150 U/mL)				
	Normal ($n = 83$)	60 (42.3%)	23 (53.5%)	0.042
	High ($n = 60$)	52 (36.6%)	8 (18.6%)	
Neoadjuvant therapy				
	No ($n = 175$)	133 (93.7%)	42 (97.7%)	0.688
	Yes ($n = 9$)	8 (5.6%)	1 (2.3%)	
Combined resection of major vessels				
	No ($n = 106$)	70 (49.3%)	36 (83.7%)	<0.001
	Yes ($n = 79$)	72 (50.7%)	7 (16.3%)	
Extrapancreatic nerve plexus invasion				
	No ($n = 77$)	51 (35.9%)	26 (60.5%)	0.008
	Yes ($n = 107$)	90 (63.4%)	17 (39.5%)	
Venous invasion				
	No ($n = 95$)	65 (45.8%)	30 (69.8%)	0.009
	Yes ($n = 90$)	77 (54.2%)	13 (30.2%)	
Lymph node metastasis				
	N0 ($n = 43$)	26 (18.3%)	17 (39.5%)	0.007
	N1 ($n = 142$)	116 (81.7%)	26 (60.5%)	
Histological grade				
	G1/G2/G3	6/112/10	2/33/6	0.426
UICC tumor stage				
	IA/IB/IIA/IIB/III/IV	1/0/24/106/4/7	4/2/11/26/0/0	0.001

(continued)

		1st primary PC ($n = 142$)	2nd primary PC ($n = 43$)	P value
Resection status				
	R0 ($n = 165$)	127 (89.4%)	38 (88.4%)	0.785
	R1 ($n = 20$)	15 (10.6%)	5 (11.6%)	
Adjuvant therapy				
	No ($n = 59$)	38 (26.8%)	21 (48.8%)	0.009
	Yes ($n = 125$)	103 (72.5%)	22 (51.2%)	
Clavien-Dindo classification				
	$\leq$ grade 2	114 (80.2%)	34 (79.1%)	0.831
	$\geq$ grade 3	28 (19.8)	9 (20.9%)	
Pancreatic fistula according to the ISGPS				
	$\leq$ grade A	126 (88.7%)	37 (86.0%)	0.600
	grade B/C	16 (11.3%)	6 (14.0%)	
Lymphocyte count, /μL (median, range)		1360 (350–3970)	1420 (670–2350)	0.944
Serum CRP level, mg/L (median, range)		1.3 (0.1–55.3)	1.5 (0.1–60.5)	0.825
Serum albumin level, g/L (median, range)		41 (26–53)	40 (24–49)	0.431
NLR (median, range)		2.41 (0.67–12.83)	1.96 (0.94–6.66)	0.308
PLR (median, range)		150.0 (34.0–1194.3)	136.0 (74.6–414.9)	0.698
GPS				
	Score of 0 ($n = 140$)	106 (74.6%)	34 (82.9%)	1.000
	Score of 1/2 ($n = 32$)	25 (17.6%)	7 (17.1%)	

CA19–9, carbohydrate antigen 19–9; *CEA*, carcinoembryonic antigen; *CRP*, C-reactive protein; *DUPAN-2*, duke pancreatic monoclonal antigen type 2; *GPS*, Glasgow prognostic score; *ISGPS*, International Study Group for Pancreatic Surgery; *NLR*, neutrophil-lymphocyte ratio; *Pb*, pancreatic body; *PC*, pancreatic cancer; *Ph*, pancreatic head; *PLR*, platelet-lymphocyte ratio; *Pt*, pancreatic tail

pancreatic fistula (POPF) definition of the International Study Group for Pancreatic Surgery (ISGPS) [21], no significant difference in the overall incidence of postoperative complications (higher than Clavien–Dindo grade 2 or POPF grade B/C) was found between the two groups. There were no
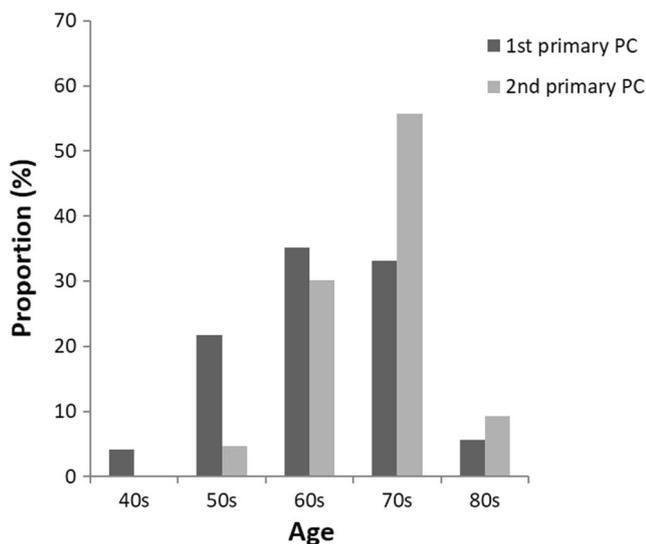

Fig. 1 Age distribution of patients with PC as their only tumor (1st primary PC) and those with a history of prior malignancy (2nd primary PC) at the time of pancreatic resection

perioperative or in-hospital deaths related to the surgical procedure in either group. The rate of adjuvant therapy administration in the 2nd primary PC group was significantly lower than that in the 1st primary PC group ($P = 0.009$). The main reasons for withholding adjuvant chemotherapy in the 2nd primary PC group were older age ($n = 5$, 24%), poor performance status ($n = 5$, 24%), patient refusal of therapy ($n = 3$, 14%), early failure of therapy ($n = 2$, 10%), protracted postoperative complications ($n = 2$, 10%), and associated comorbidities ($n = 2$, 10%). No significant difference was found regarding the preoperative hematological inflammatory parameters, including the absolute lymphocyte count, serum albumin level, serum CRP level, NLR, PLR, and GPS, between the two groups.

In the survival analysis, the median OS of patients with 2nd primary PC was 16.4 months, which was similar to that of patients with 1st primary PC (16.8 months, $P = 0.725$) (Fig. 2a, Supplementary Table 1). The median DFS of patients with 2nd primary PC (9.3 months) was also similar to that of patients with 1st primary PC (8.8 months, $P = 0.284$) (Fig. 2b, Supplementary Table 1). Among patients who received adjuvant chemotherapy after pancreatectomy, no difference in OS or DFS was found between patients with 1st primary PC who received adjuvant chemotherapy ($n = 104$) and those with 2nd
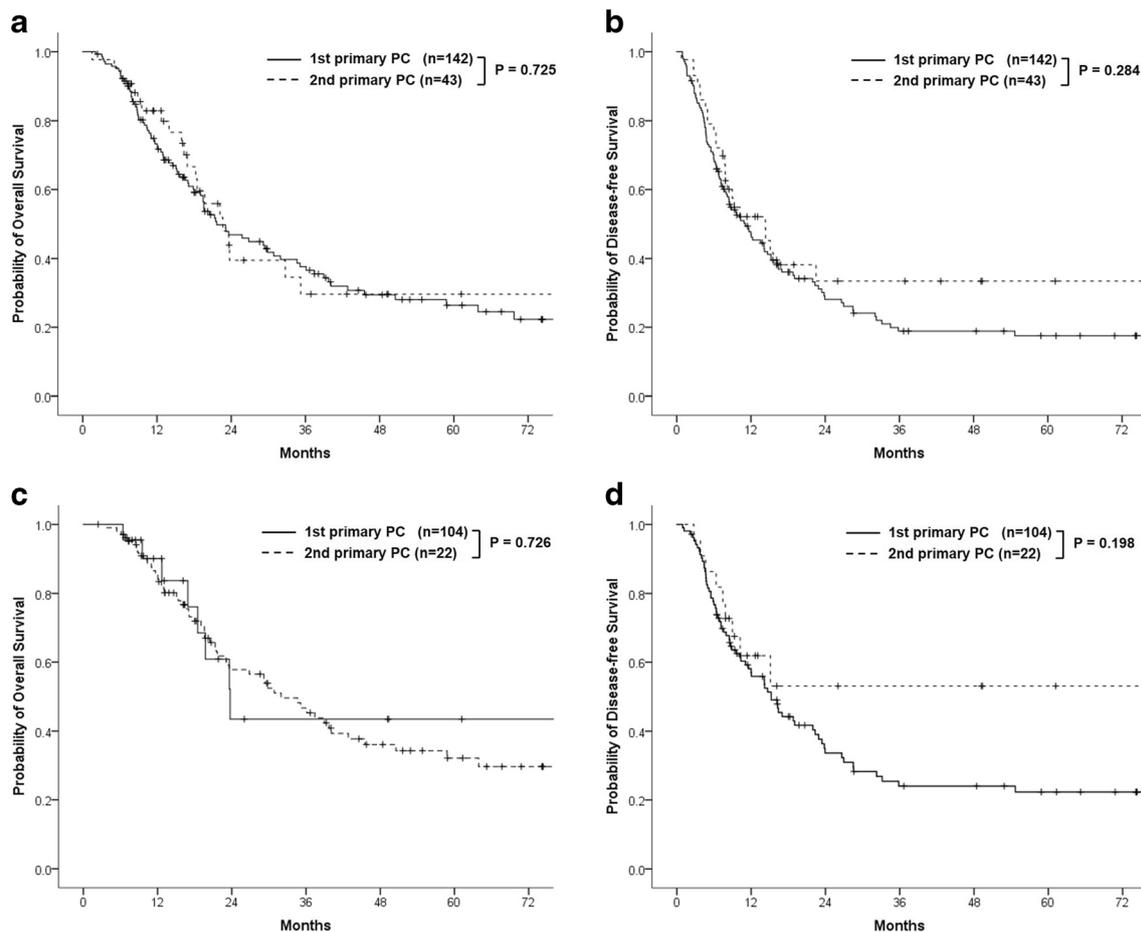
Fig. 2 Kaplan–Meier survival curves based on history of prior malignancy. No significant difference was observed in overall survival (OS) (**a**) or disease-free survival (DFS) (**b**) between patients with PC as their only tumor (1st primary PC) and those with a history of prior

malignancy (2nd primary PC). There was no difference in OS (**c**) or DFS (**d**) between patients with 1st primary PC who received adjuvant chemotherapy and those with 2nd primary PC who received adjuvant chemotherapy

primary PC who received adjuvant chemotherapy ($n = 22$) (20.3 vs. 16.5 months, $P = 0.726$ and 11.8 vs. 10.3 months, $P = 0.198$, respectively) (Fig. 2c, d). The multivariate analysis identified larger tumor size (HR = 2.169; 95% CI = 1.439–3.270; $P < 0.001$), combined resection of major vessels (HR = 1.582; 95% CI = 1.018–2.459; $P = 0.041$), lymph node metastasis (HR = 2.195; 95% CI = 1.277–3.773; $P = 0.004$), resection status (HR = 2.256; 95% CI = 1.274–3.995; $P = 0.005$), and adjuvant chemotherapy (HR = 0.354; 95% CI = 0.221–0.567; $P < 0.001$) as independent prognostic factors for OS and the CA19–9 level (HR = 1.571; 95% CI = 1.028–2.399; $P = 0.037$), larger tumor size (HR = 1.924; 95% CI = 1.329–2.786; $P = 0.001$), extrapancreatic nerve plexus invasion (HR = 1.623; 95% CI = 1.051–2.507; $P = 0.029$), lymph node metastasis (HR = 1.939; 95% CI = 1.175–3.201; $P = 0.010$), resection status (HR = 2.149; 95% CI = 1.250–3.694; $P = 0.006$), and adjuvant chemotherapy (HR = 0.440; 95% CI = 0.290–0.667; $P < 0.001$) as independent prognostic factors for DFS (Supplementary Table 2).

Discussion

Cancer survivors have been reported to be at a high risk for developing 2nd primary cancers [22, 23]. Several population-based studies have demonstrated that specific cancers are associated with an elevated risk for subsequent 2nd primary PC [14, 15]. A recent study revealed that colorectal cancer survivors have a significantly higher risk of developing 2nd primary PC than the general population [24]. Although several studies have reported an increased risk of 2nd primary PC in cancer survivors, only a few studies have focused on the characteristics and outcomes of patients with 2nd primary PC compared with those of patients with PC as their only tumor [16, 17].

The reported prevalence of 2nd primary PC among overall PC patients ranges from 6 to 14% [4, 16, 17], whereas the prevalence was 23.2% in the present cohort. The high prevalence of 2nd primary PC in the present study can be explained by the fact that more than half of the patients who developed

2nd primary PC had visited our cancer center for regular follow-up examinations for prior malignancies and were diagnosed with PC without symptoms. The smaller tumor size and lower rate of lymph node metastasis, as well as the more frequent location in the pancreatic body and/or tail, of 2nd primary PC, are also likely to be due to this surveillance bias. In the present study, the most common prior malignancies of patients with 2nd primary PC were breast cancer (20%), gastric cancer (18%), colorectal cancer (16%), and prostate cancer (10%). According to nationwide cancer statistics in Japan [25], the most common cancer for males is gastric cancer, followed by colorectal cancer, lung cancer, and prostate cancer. In females, breast cancer, colorectal cancer, and gastric cancer are the 3 most prevalent cancers. Therefore, our results seem to be consistent with the prevalence of these cancers in Japan rather than demonstrate an increased risk of developing 2nd primary pancreatic cancer. The clinical outcomes of the 2nd primary PC patients were comparable to those of the 1st primary PC patients despite earlier stages in the 2nd primary PC patients. The most likely reason for this discrepancy is that the 2nd primary PC group consisted of older patients, and the rate of adjuvant therapy administration in this group was lower than that in the 1st primary PC group (51.2 vs. 72.5%, respectively). Earlier studies also demonstrated that patients with 2nd primary PC were older than those with 1st primary PC [16, 17]. Although the influence of genetic predisposition was not considered in the present study, only 4.7% of the 2nd primary PC patients were below the age of 60 at pancreatic resection. Hereditary PC is known to show a trend toward earlier onset than sporadic PC [26]. In addition, an earlier study demonstrated that PC patients younger than 60 years old had a significantly higher prevalence of germline mutations [27]. The present results indicate that the development of 2nd primary PC in the present cohort may be attributed to lifestyle factors or environmental factors shared with prior malignancies rather than genetic predisposition. Because of the small number of patients who underwent radiation and/or chemotherapy, the impact of treatment-related factors on the incidence of 2nd primary PC could not be determined in this study. In addition, differences in patient backgrounds, including age, tumor progression, and the rate of adjuvant chemotherapy administration due to surveillance bias, make it difficult to accurately compare clinical outcomes between the 1st and 2nd primary PC patients. Further investigation in a multicenter clinical setting with a larger sample size and patient matching in both groups is needed to evaluate the pathological and biological features of 2nd primary PC.

To date, differences between the host systemic inflammatory response of cancer survivors and that of patients without prior malignancy have not been investigated. In the tumor microenvironment, the effects of tumor-infiltrating lymphocytes (TILs) have been studied in various types of solid tumors, and a high TIL density has been reported to correlate with better survival [28]. In PC patients, higher levels of tumor-infiltrating CD4$^+$ and CD8$^+$ T cells have been reported to be associated with prolonged survival [29]. Although the link between the systemic inflammatory response and inflammation in the tumor microenvironment in cancer patients has remained unclear, previous studies demonstrated that the peripheral blood levels of CD4$^+$ and CD8$^+$ T cells were lower in PC patients than in healthy controls [30]. In addition, an increased level of regulatory T cells (Tregs) in the peripheral blood was associated with a poorer prognosis in unresectable PC patients [31]. These previous studies suggest that the host immune/inflammatory response in the peripheral blood may represent the tumor inflammatory microenvironment and clinical outcome. In the present study, our results indicate that the host systemic inflammatory response in PC patients may be similar regardless of the presence or absence of preceding malignancies. However, age, a history of smoking, and comorbidities, such as cardiovascular diseases, have been reported to be associated with systemic inflammatory parameters [32–34]. These factors might exert greater effects on these systemic inflammatory parameters in patients with 2nd primary PC who are older than in those with 1st primary PC. In addition, systemic inflammatory parameters may not be sufficient to assess the host immune/inflammatory response. In future studies, evaluations of TIL frequencies in tumor specimens and profiles of peripheral blood T cell subsets will be necessary for comparisons of pre-existing immune/inflammatory responses between patients with 1st primary PC and those with 2nd primary PC.

The present study has several limitations. First, this study involved a relatively small number of patients with 2nd primary PC and was therefore insufficiently powered to yield reliable results. Second, only patients who had undergone surgery for PC were selected; however, surgical resection may be utilized more frequently in patients with 2nd primary PC than in those with 1st primary PC, indicating that our results may not accurately reflect the overall population of PC patients. Third, information pertaining to the pathological staging of prior malignancies and the treatment history was lacking. Despite these limitations, this study represents the first attempt to compare various systemic inflammatory parameters between PC patients who survived prior malignancies and those without any prior malignancies in their history.

The time interval to the development of 2nd primary PC is important for establishing an optimal surveillance program for cancer survivors to ensure the early detection of 2nd primary PC. Jo et al. [17] reported that the cumulative rate of 2nd primary PC diagnosis in cancer survivors has been steadily increasing for 20 years, with a current rate of 90.9%. In the present study, PC was found in an asymptomatic state in 19 of 21 patients with 2nd primary PC who were followed by abdominal imaging tests, such as contrast-enhanced abdominal CT, within at least 2 years for a prior malignancy, while all

four patients who were followed by nonabdominal imaging tests were diagnosed with PC after the development of symptoms. Our results suggest that biennial contrast-enhanced abdominal CT should be included in the surveillance program for cancer survivors regardless of the primary origin.

Conclusion

Second primary PC is frequently detected as an incidental finding during follow-up examinations for prior malignancies and at an earlier stage than 1st primary PC. However, the oncological outcomes of patients with 2nd primary PC were comparable to those of patients with 1st primary PC. Further investigation, including multicenter studies with larger sample sizes and matching for patient age and tumor stage in both groups, is essential to elucidate the clinicopathological features and clinical outcomes of 2nd primary PC.

Compliance with ethical standards

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