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Effect of type 2 diabetes mellitus on survival in metastatic pancreatic cancer

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The ethics committee approval was obtained from the Ethics Committee Board of University of Health Sciences Okmeydani Training and Research Hospital (ID:48670771-514.10). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Many epidemiological studies describe a relationship between pancreatic cancer (PC) and Diabetes mellitus (DM). However, there are not enough studies investigating the effect of DM on survival of patients with metastatic PC. The purpose of this retrospective study was to investigate the effect of DM and its treatment on survival of patients with metastatic PC who received chemotherapy (CT) as first line treatment.

Methods: Patients with metastatic PC who were followed up at the department of medical oncology between 2006 and 2018 were enrolled in this retrospective cohort study. Patients aged 18 years and over, who had metastatic disease at diagnosis and were treated with CT were analyzed. Patients with DM were stratified into two groups based on the history of medical treatments used for DM as follows: Oral antidiabetic (OAD) and OAD + insulin combination.

Results: Following results were obtained after analyzing the medical records of 372 patients with metastatic PC, among which 125 (33.6%) had type II DM at the time diagnosis: The median age of the patients was 61 (range: 28-83) years. There were 136 (36.6%) female patients, and the median overall survival (OS) was 9.0 months in patients without DM, and 7.0 months (P=0.023) in those with DM. OS was 8.0 months in diabetic patients using OAD+insulin combination compared to 7.0 months in those receiving OAD (P=0.614) only. Multivariate analysis revealed that the presence of DM [Hazard ratio (HR), 1.43)], Eastern Cooperative Oncology Group Performance Status 3 (HR, 1.62), treatment with gemcitabine+Nab-paclitaxel (HR, 0.29) or folfirinox (HR, 0.46), and CA 19-9 level (HR, 1.01) were factors related to OS.

Conclusion: In our study, we observed that the presence of DM adversely affected survival in metastatic PC patients who received CT as first line treatment; however, whether these patients used OAD or OAD+insulin combination did not affect survival.

Keywords: Pancreas cancer, Diabetes mellitus, Fasting plasma glucose, Survival, Prognosis

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Introduction

Exocrine pancreatic cancer (PC) is an extremely lethal malignancy. It is the fourth leading cause of cancer-related deaths in the United States. Worldwide, it is the eighth leading cause of deaths in both females and males, with incidence and mortality rates varying by gender and race [1-3]. The most common type of PC is pancreatic ductal adenocarcinoma (PDAC). Only 15-20% of patients can be diagnosed at an early stage, with a poor prognosis even after achieving an R0 resection [1, 4].

Type II diabetes mellitus (DM) is a chronic disease characterized by hyperglycemia, insulin resistance, and impairment of insulin secretion. The prevalence of DM has increased dramatically over the past decade due in large part to obesity and sedentary lifestyle [5, 6]. There have been many studies showing that the risk of PC increases in diabetic patients. In a meta-analysis, the risk of PC was approximately 2-fold higher in patients with DM compared to those without DM [7]. In a prospective cohort study, those with a plasma fasting glucose (FPG) level above 200 mg/dl were at least 2 times more likely to die from PC than those with FPG level ≤119 mg/dl [8]. Similarly, another prospective study showed that elevated FPG level, insulin concentration, and insulin resistance were significantly correlated with the risk of PC [9].

Many epidemiological studies describe the relationship between DM and PC [7, 10-13]. However, there are not enough studies investigating the effect DM on survival of patients with metastatic PC. Nakai et al. found that the presence of DM had no prognostic effect on PC in a study including 250 metastatic PC patients [14]. Choi et al. analyzed metastatic PC patients receiving chemotherapy (CT) and reported that patients with PC accompanied by DM tended to survive longer than those without DM [15]. However, in a recent study with 350 metastatic PC patients, presence of long-term DM (≥4 years) negatively affected survival [16].

The present study was designed to assess the effects of DM and its treatment on survival of patients with metastatic PC who received CT as first-line therapy.

Materials and methods

Patient enrollment

Patients with PC, who were treated and followed up from 2006 through 2018 at the department of medical oncology, Prof. Dr. Cemil Taşcıoğlu Training and Research hospital, were analyzed retrospectively. The inclusion criteria were defined as follows: Age equal to or greater than 18 years, PC patients with complete medical data, metastatic stage, and those treated with CT. Besides the patients not meeting the eligibility criteria mentioned above, histology other than PDAC and patients with type I DM were excluded from the study. Laboratory data such as FBG, CA19-9, and CEA were obtained before the initiation of CT. A total of 372 patients with PC who met the inclusion criteria were enrolled in the analysis.

Ethics approval

All the stages and related procedures of the present study were performed in accordance with the Declaration of Helsinki. The approval of study was obtained from the Ethics Committee of the Prof. Dr. Cemil Taşcıoğlu Training and Research Hospital (ID: 48670771-514.10).

Data collection

The clinical and demographic features of all patients, such as age, gender, ECOG PS, history of smoking, alcohol use, comorbidities, body mass index (BMI), treatment of DM, the interval between the diagnosis of DM and PC, grade, the site of metastasis, the development or presence of deep venous thrombosis (DVT), FPG at the time of diagnosis, the levels of CEA and CA 19-9 before CT treatment, the first-line CT regimen, and final status were obtained carefully from the hospital medical records.

Stratification

Patients with PC were divided into two groups according to presence of type II DM at the time of diagnosis. Next, pancreatic cancer patients with DM were stratified into two groups based on the history of medical treatments used for DM as follows: Oral antidiabetic (OAD) and OAD + insulin combination.

Statistical analysis

Statistical Package for the Social Sciences 22.0 for Windows (IBM Corp. 2013) was used for analysis. Numerical variables were analyzed using student t-test if normally distributed, and Mann Whitney U test was used otherwise. The comparison of the rates between the groups was carried out with the chi-square test. Survival analyses were conducted using Kaplan-Meier method. Determinant factors were examined with cox regression analysis. Forward stepwise model was performed for the factors with *P*-value <0.200. An overall 5% Type-I error level was used to infer statistical significance. Median overall survival (OS) was defined as the time from the date of diagnosis to the date of death or last follow-up.

Results

A total of 372 PC patients metastatic at diagnosis, 125 (33.6%) of which had type II DM, were included. The median age was 61 (range, 28-83) years. Of the 372 patients, 136 (36.6%) were female. ECOG PS was 3 in 38 (10.2%) patients. Smoking history was present in 208 (55.9%) patients. Among those with DM, 65 (52%) patients received insulin + OAD, while 60 (48%) patients used OAD. The median time from the date of DM diagnosis to the date of PC development was 12 months (Table 1).

At the time of diagnosis, the sites of metastasis in decreasing order were the liver (n: 297, 79.8%), peritoneum (n: 53, 14.2%), lung (n: 50, 13.4%), distant lymph nodes (n: 20, 5.4%), bone (n: 18, 4.8%), and others [spleen, kidney, adrenal (n: 6, 1.6%)] (Table 1).

The treatment regimens used for PC, in decreasing order, were single-agent gemcitabine (37.1%), cisplatin + gemcitabine (32.0%), FOLFIRINOX (19.6%), gemcitabine + Nab-paclitaxel (4.3%), gemcitabine + capecitabine (3.8%), and FOLFOX (3.2%) (Table 1).

The median age of PC patients with DM was 64 years (range, 45-81), which was longer than that of those without DM. In addition, some parameters were more frequent in diabetic group, including female gender, HT, Grade 3 tumor, and increased FPG (Table 1).

Table 1: Patient data

Characteristic		Patients (n= 372) n	%	DM (-) (n= 247) n	%	DM (+) (n=125) n	%	*P*-value
Age (year)	Median (min-max)	61 (28-83)		59 (28-83)		64 (45-81)		<0.001
	≥65	134	36.0	73	29.6	61	48.8	0.001
	<65	238	64.0	174	70.4	64	51.2	
Gender	Men	236	63.4	166	67.2	70	56.0	0.034
	Women	136	36.6	81	32.8	55	44.0	
ECOG PS	0-1	231	62.1	157	63.6	74	59.2	0.731
	2	103	27.7	66	26.7	37	29.6	
	3	38	10.2	24	9.7	14	11.2	
Smoking	Yes	164	44.1	101	40.9	63	50.4	0.081
	No	208	55.9	146	59.1	62	49.6	
	Active	146	69.5	100	68.5	46	71.9	0.072
	Ex-smoker	62	29.5	46	31.5	16	25.0	
Alcohol use	yes	18	4.8	13	5.3	5	4.0	0.616
Comorbidity	HT	79	21.2	30	12.1	49	39.2	<0.001
	CIHD	27	7.3	15	6.1	12	9.6	0.216
	COPD	22	5.9	14	5.7	8	6.4	0.777
	CHF	12	3.2	9	3.6	3	2.4	0.521
BMI (Kg/m^2)	Mean (SD)	24.9 (4.9)		24.6 (4.2)		26.0 (4.2)		0.211
DM treatment	Insulin + OAD	65	52.0			65	52.0	
	OAD	60	48.0			60	48.0	
Time interval between DM diagnosis and PC development (year) Median (min-max)		12 (6-46)				12 (6-46)		
grade	I	15	4.0	8	3.2	7	5.6	0.002
	2	269	72.3	193	78.1	76	60.8	
	3	88	23.7	46	18.6	42	33.6	
The site of metastasis at diagnosis	liver	297	79.8	200	81.0	97	77.6	0.444
	Peritoneum	53	14.2	33	13.4	20	16.0	0.491
	Lung	50	13.4	29	11.7	21	16.8	0.177
	Distant LN	20	5.4	12	4.9	8	6.4	0.533
	Bone	18	4.8	13	5.3	5	4.0	0.592
	Other (spleen, kidney, and surrenal)	6	1.6	4	1.6	2	1.6	0.989
DVT	No	333	89.8	224	90.7	109	87.9	0.404
	Yes	38	10.2	23	9.3	15	12.1	
FPG (mg/dL)	Mean (SD)	136.2 (71.8)		108.9 (21.7)		155.4 (71.8)		0.001
CEA (ng/mL)	Mean (SD)	219.1 (2319.6)		256.6 (2852.3)		229.5 (1739.9)		0.484
CA 19-9 (U/mL)	mean (SD)	4352.1 (31295.1)		5514.8 (37985.8)		3671.9 (8195.1)		0.360
First-line regimen	FOLFIRINOX	73	19.6	48	19.4	25	20.0	0.782
	Gemcitabine	138	37.1	91	36.8	47	37.6	
	gemcitabine + Nab-paclitaxel	16	4.3	9	3.6	7	5.6	
	FOLFOX	12	3.2	10	4.0	2	1.6	
	Gemcitabine+ capecitabine	14	3.8	10	4.0	4	3.2	
	Cisplatin ± gemcitabine	119	32.0	79	32.0	40	32.0	
Final status	Dead	347	93.3	228	92.3	119	95.2	0.293
	Alive	25	6.7	19	7.7	6	4.8	

CIHD: Chronic ischemic heart disease, COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, FPG: Fasting plasma glucose, CA19-9: carbohydrate antigen 19-9, CEA: carcinoembryonic antigen, CIHD: Chronic ischemic heart disease, DM: Diabetes mellitus, DVT: deep vein thrombosis, ECOG PS: Eastern Cooperative Oncology Group Performance Status, FOLFIRINOX: Fluorouracil: leucovorin, irinotecan, and oxaliplatin, g/dL, Grams Per Deciliter, HT: hypertension, LN: lymph node, ng/mL, Nano-gram/milliliter, OAD: Oral antidiabetic combination, OS: overall survival, U/mL, Units per milliliter.

During a median 10-month follow up, 347 (93.3%) patients died. Median OS was 9.0 months (95 % CI, 7.7-10.2) in patients without DM vs. 7.0 months (95 % CI, 5.4-8.5) in those with DM (Log rank *P*=0.023) (Figure 1). OS was 8.0 months (95 % CI, 5.7-10.2) in diabetic patients using OAD + insulin combination compared to 7.0 months (95 % CI, 5.1-8.8) in those receiving OAD (Log rank *P*=0.614) (Figure 2).

In univariate analysis, presence of DM (HR, 1.277, 95% CI, 1.020-1.598), ECOG PS 3 (HR, 1.629, 95% CI, 1.133-2.341), and treatments with gemcitabine + Nab-paclitaxel (HR, 0.412, 95% CI, 0.227-0.746) or FOLFIRINOX (HR, 0.450, 95% CI, 0.331-0.610) were determined as factors affecting survival. Multivariate analysis indicated that presence of DM (HR, 1.433, 95% CI, 1.109-1.852), ECOG PS 3 (HR, 1.628, 95% CI, 1.081-2.241), treatments with gemcitabine + Nab-paclitaxel (HR, 0.293, 95% CI, 0.146-0.586) or FOLFIRINOX (HR, 0.465, 95% CI, 0.327-0.661), and elevated CA 19-9 (HR, 1.001, 95% CI, 1.000-1.002) were the independent predictors of OS (Table 2).

Table 2: Univariate and multivariate analysis for OS

Characteristic		Univariate analysis for OS HR	95 % CI for HR	*P*-value	Multivariate analysis for OS HR	95 % CI for HR	*P*-value
Age (Year)	>65 vs. ≤65	1.014	0.814-1.262	0.903			
Gender	Female vs. Male	0.891	0.713-1.112	0.306			
Smoking	Yes vs. No	0.890	0.718-1.102	0.286			
DM	Yes vs. No	1.277	1.020-1.598	0.032	1.433	1.109-1.852	0.006
HT	Yes vs. No	0.831	0.640-1.079	0.165			
CIHD	Yes vs. No	0.851	0.566-1.280	0.439			
COPD	Yes vs. No	1.008	0.654-1.544	0.970			
CHF	Yes vs. No	0.893	0.501-1.590	0.701			
BMI	kg/m^2	1.000	0.958-1.045	0.993			
ECOG PS	0-1	Ref.		0.001	Ref.		0.036
	2	1.509	1.185-1.922	0.001	1.269	0.956-1.683	0.099
	3	1.629	1.133-2.341	0.008	1.628	1.081-2.241	0.020
Grade	3 vs. 1-2	1.078	0.843-1.376	0.547			
Liver metastasis	Yes vs. No	0.845	0.636-1.121	0.242			
Peritoneum metastasis	Yes vs. No	0.900	0.669-1.209	0.483			
Lung metastasis	Yes vs. No	1.211	0.891-1.643	0.220			
Distant LN metastasis	Yes vs. No	0.856	0.531-1.379	0.523			
Bone metastasis	Yes vs. No	0.763	0.467-1.245	0.280			
Other	Yes vs. No	1.209	0.538--2.713	0.646			
DVT	Yes vs. No	1.180	0.833-1.669	0.350			
First-line regimen	Gemcitabine	Ref.		<0.001	Ref.		<0.001
	Gemcitabine + Nab-paclitaxel	0.412	0.227-0.746	0.003	0.293	0.146-0.586	0.001
	FOLFOX	0.893	0.493-1.616	0.707	1.270	0.653-2.456	0.481
	Gemcitabine + capecitabine	0.632	0.356-1.120	0.116	0.576	0.250-1.321	0.193
	Gemcitabine + cisplatin	0.836	0.650-1.074	0.161	0.865	0.651-1.150	0.320
	FOLFIRINOX	0.450	0.331--0.610	<0.001	0.465	0.327-0.661	<0.001
Glucose	mg/dL	0.999	0.996-1.002	0.540			
CEA	ng/mL	0.999	0.999-0.1001	0.388	0.999	0.999-1.001	0.053
CA 19-9	U/mL	0.999	0.999-1002	0.105	1.001	1.000-1.002	0.044

Figure 1: Overall survival in all patients according to the presence of diabetes mellitus

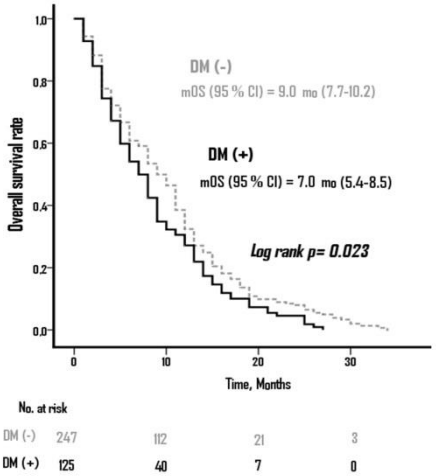
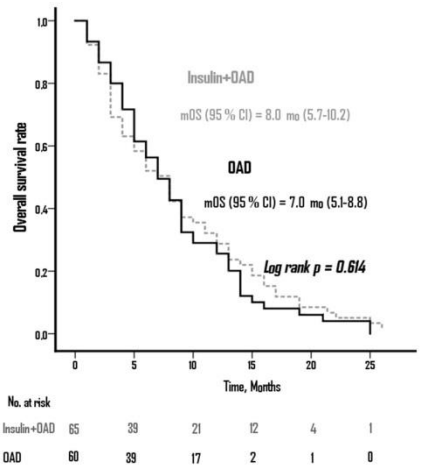


Figure 2: Overall survival in patients with diabetes mellitus according to the anti-diabetic treatment



Discussion

The present study investigated the impact of DM and its treatment on the survival of metastatic pancreatic cancer patients treated with CT, concluding that DM adversely affected survival in pancreatic cancer patients, but treatment for DM was not associated with it.

Undoubtedly, DM is a major and growing health problem which is related to significant comorbidities. Epidemiological data revealed an increased risk of PC with DM. There are also several studies showing that anti-diabetic drugs may significantly reduce the risk of PC and therefore increase the survival of affected patients [17-19]. Most studies examining the effect of DM on PC prognosis have been performed with patients who underwent surgery for PC and the results are therefore conflicting. In a study of 74 surgically resected PC patients, uncontrolled severe hyperglycemia rather than the presence of DM negatively affected survival after pancreatic cancer resection [20]. However, in a study by Lee et al. [21] including patients who underwent resection for PC, the presence of DM at diagnosis significantly reduced both disease-free survival and OS; with a median OS of 28 months in diabetic patients compared to 33 months in those without DM. The median time from DM diagnosis to PC development was shorter than 2 years. More recently, another study reported that patients with DM have more aggressive tumors and higher surgical morbidity, concluding that they have significantly shorter survival than those without DM and this effect is more pronounced in patients undergoing neoadjuvant CT [22]. Similarly, in a meta-analysis involving 6 studies, survival was significantly shorter in PC patients with DM who received adjuvant CT, compared those without DM [23].

Choi et al. [15] performed a study enrolling 183 advanced-stage PC patients, of which 160 had DM, reporting the median OS as 8.4 months in patients with DM vs. 7.5 months in those without DM. Authors also showed that median OS was 11.0 months in patients using metformin compared to 7.9 months in those not receiving metformin, suggesting that patients with DM tended to have longer OS than those without DM. In addition, metformin treatment was associated with longer OS. Likewise, in another study, OS was 13.3 months in advanced-stage PC patients with DM, while it was 10.0 months in those without DM. However, neither DM nor anti-diabetic therapy had a prognostic effect on disease survival [14].

In a meta-analysis by Ma et al. [23] analyzing both early- and advanced-stage PC patients, the risk of mortality was high in patients treated with CT. Another meta-analysis performed by Mao et al. [24] found that the effect of DM on OS was associated with the tumor stages and the duration of DM. Recently, Lizumi et al. [16] conducted a study with metastatic PC patients who had DM and received a single-agent gemcitabine. When patients were divided into 2 groups based on the duration of PC development after DM diagnosis as short-term DM (n: 87, <4 years) and long-term DM (n: 45, ≥4 years), long-term DM was associated with shorter PFS and OS. Similarly, in our study, median OS was significantly shorter in PC patients with DM. Only in 9 (7.2%) patients, the time between DM and PC diagnosis was ≤ 4 years. However, no significant relationship between treatments used for DM and survival was found in our study.

Previous studies have shown that DM is associated with some poor prognostic factors, including a higher tumor stage, a more aggressive clinical behavior, greater rates of lymph node metastasis, and increased perineural invasion [21, 25-27]. In our study, shorter survival in patients with DM is likely due to the more aggressive nature of tumor.

Our study included relatively greater sample size compared to the previous studies, providing a real-life data. In addition, we could analyze the effect of using OAD or insulin treatment on survival.

Limitations

Due to its retrospective nature, the results of our study might be inherently flawed by selection bias. Moreover, HbA1C levels of the patients were missing. The data regarding the OAD or insulin medication could not be given in detail.

Conclusion

Summing up, we observed that the presence of DM adversely affected disease survival in metastatic PC patients who received CT as first line treatment, however, whether these patients used OAD or insulin + OAD did not affect survival. Our findings need to be confirmed by larger studies.

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