Adverse oncologic impact of new-onset diabetes mellitus on recurrence in resected pancreatic ductal adenocarcinoma: a comparison with long standing diabetic and non-diabetic patients

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Directed by Professor Chang Moo Kang

The Master's Thesis
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ABSTRACT

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Objectives: Diabetes mellitus (DM) is prevalent with pancreatic ductal adenocarcinoma (PDAC). Importantly, new-onset DM is characteristic of the disease and could be an early sign of PDAC. The clinical outcome of PDAC with new-onset DM may differ from that in patients without DM or long-standing DM.

Methods: We retrospectively reviewed medical records of PDAC patients who underwent curative resection between 2006 and 2014. New-onset DM was defined as a diagnosis of DM within 24 months before the diagnosis of PDAC. Survival analysis and Cox regression were performed to evaluate oncologic outcomes.

Results: No significant differences in clinical characteristics were found in three groups. Overall survival (OS) of patients with new-onset DM was worse than non-DM (22 vs. 33 months, p = 0.039). New-onset DM was highly associated with early recurrence (Hazard ratio = 1.451, 95% confidence interval: 1.054-1.999, p = 0.022). Poor oncologic outcome of new-onset DM was more pronounced in low T-stage patients (OS in low vs. high T-stage: 33 vs. 18 months, p = 0.129).

Conclusions: PDAC with new-onset DM have worse oncologic outcomes than non-DM or long-standing DM. These results suggest that new-onset DM represents aggressive tumor biology, especially in the early stage of PDAC.

Key words : DM, new-onset DM; Pancreas cancer; disease-free survival

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I. INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers, with a 5-year survival rate of just 6% [1]. The only potentially curative therapy for PDAC is surgical resection, unfortunately 80%-85% of patients are not candidates for surgical resection at the time of the diagnosis because of the presence of distant metastasis or locally advanced cancer[2]. Early screening and risk factor analysis are therefore essential to increase the chances of successful surgical resection and improve prognosis[3].

Diabetes mellitus (DM), the most common endocrine disease of the pancreas, is widely recognized to be associated with pancreatic cancer.[4,5] The prevalence of DM is higher in pancreatic cancer than in other solid organ malignancies including lung, breast, prostate, and colorectal cancers[6]. Several studies have demonstrated that DM is a risk factor of PDAC[4,5,7-11]. Specifically, diagnosis of DM a few years prior to developing PDAC is more prevalent than in the general

population or in patients with other malignancies[6,12]. There are multiple reports that new-onset DM is a strong risk factor of PDAC[3,4,9,13]. While this unique phenomenon of PDAC is now regarded as an early sign of cancer[14,15], the underlying relationship between new-onset DM and pancreatic cancer remains unclear. Some researchers have suggested that new-onset DM is induced by the cancer itself[15,16].

Therefore, oncologic characteristics including disease-free survival (DFS) and overall survival (OS) of PDAC with new-onset DM might be different than in PDAC patients without DM or long-standing DM. However, the impact of new-onset DM on PDAC outcome has not been properly evaluated[17,18]. In this study, we retrospectively compared the oncologic impact of new-onset DM on resected pancreatic cancer in patients with non-DM or long-standing DM.

II. MATERIALS AND METHODS

1. Patients

We retrospectively reviewed medical records of 288 patients who underwent curative resection for PDAC between 2006 and 2014 (Figure 1). Our study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (4-2017-0462). After excluding patients who were post-operative mortality case, stage IV patients, those who underwent total pancreatectomy, Klatskin tumor, and patients missing DM onset information, 266 patients were finally included. Clinical data including age at the time of

operation, sex, weight, American Society of Anaesthesiologists (ASA) score, tumor location, cell differentiation, tumor size, T-stage, N-stage, lymphovascular invasion, pre-operative carbohydrate antigen 19-9 (CA 19-9) level, neoadjuvant chemoradiation therapy (CCRTx), adjuvant chemotherapy, and pre-operative hemoglobin A1c (HbA1c) level were reviewed. The T- and N-stages of PDAC were classified according to the American Joint Committee on Cancer (AJCC), 8th edition[19].

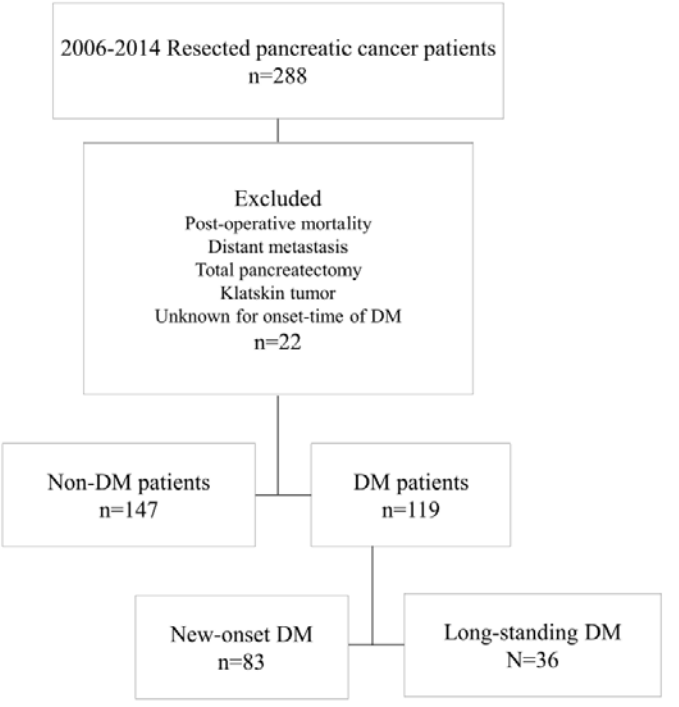

Figure 1. Study design algorism

2. Definition of DM

A history of DM was defined as a diagnosis on the medical record or antidiabetic drug use at the time of PDAC diagnosis. New-onset DM was defined as a diagnosis of DM within 24 months before the diagnosis of PDAC[12,14,18,20]. According to the American Diabetes Association criteria[21], patients with a fasting blood glucose ≥126 mg/dL or HbA1c ≥6.5% without a known history of diabetes at the time of PDAC diagnosis were included in the new-onset DM group. Long-standing DM was defined as a diagnosis of DM made more than 24 months before the diagnosis of PDAC. Accordingly, patients were classified into the following three groups: non-DM, new-onset DM, or long-standing DM.

3. Statistical analysis

Statistical analysis was performed using SPSS 23 software (IBM Corporation, Armonk, NY). Continuous variables are expressed as mean ± standard deviation, and categorical variables are expressed as frequency (percent). The baseline clinical characteristics of the three groups were analyzed using chi-square tests and analyses of variance (ANOVA). Survival was assessed with Kaplan-Meier analyses. Survival outcomes were compared using log-rank tests, and Cox proportional hazards model was applied to calculate hazard ratios (HRs) and 95% confidence interval (CIs) to identify associations between clinical factors and survival rates. Characteristics that demonstrated a univariate association with

survival at a significance level of $p < 0.05$ were entered as covariates into a multivariate proportional hazards regression model, and backward elimination was performed to generate the final model. All p-values <0.05 were considered statistically significant.

III. RESULTS

1. Patient characteristics

Clinical characteristics were similar among the three groups. The only variables that were significantly different were age and ASA score. The new-onset and long-standing DM groups were older than the non-DM group (63.8 ± 9.6, 64.8 ± 8.5, and 61.1 ± 9.7 years, respectively; $p = 0.035$). In addition, there were more patients with an ASA score of 1 in the non-DM group than in the new-onset and long-standing DM groups (32.2%, 19.8%, and 19.4%, respectively; $p = 0.044$). Histopathological characteristics were also similar among the three groups. Tumor sizes in new-onset DM and long-standing DM patients were larger than in non-DM patients, although not significantly ($p = 0.113$). However, members of the long-standing DM group had generally larger tumors than did non-DM patients (2.8 ± 1.4 vs. 2.3 ± 1.3 cm, respectively; $p = 0.046$). The proportions of patients who received CCRTx or adjuvant chemotherapy were similar among all patients. There was no significant

difference in pre-operative HbA1c levels between the new-onset and long-standing DM groups.

Table 1. Patient characteristics

	Non-DM (n = 147)	New-onset DM (n = 83)	Long-standing DM (n = 36)	p value
Age (years)	61.1 ± 9.7	63.8 ± 9.6	64.8 ± 8.5	**0.035**
Sex				0.714
Female	63 (42.9%)	31 (37.3%)	15 (41.7%)	
Male	84 (57.1%)	52 (62.7%)	21 (58.3%)	
Weight (kg)	60.0 ± 9.5	59.7 ± 10.3	56.1 ± 8.0	0.090
ASA				**0.044**
1	47 (32.2%)	16 (19.8%)	7 (19.4%)	
2	80 (54.8%)	44 (54.3%)	18 (50.0%)	
3	19 (13.0%)	20 (24.7%)	10 (27.8%)	
4	0 (0.0%)	1 (1.2%)	1 (2.8%)	
Tumor location				0.659
Head/neck	98 (66.7%)	60 (72.3%)	24 (66.7%)	
Body/tail	49 (33.3%)	23 (27.7%)	12 (33.3%)	

Cell differentiation				0.180
Well	21 (15.7%)	7 (9.7%)	4 (11.4%)	
Moderate	103 (76.9%)	56 (77.8%)	26 (74.3%)	
Poorly	9 (6.7%)	9 (12.5%)	4 (11.4%)	
Undifferentiated	1 (0.7%)	0 (0.0%)	1 (2.9%)	
Tumor size (cm)	2.3 ± 1.3	2.5 ± 1.5	2.8 ± 1.4	0.113
T-stage				0.354
T0	8 (5.4%)	2 (2.4%)	1 (2.8%)	
T1	74 (50.3%)	36(43.9%)	14 (38.9%)	
T2	58 (39.5%)	36 (43.9%)	16 (38.9%)	
T3	7 (4.8%)	8 (9.8%)	5 (13.9%)	
N stage				0.786
N0	74 (50.3%)	39 (47.0%)	18 (50.0%)	
N1	53 (36.1%)	30 (36.1%)	15 (41.7%)	
N2	20 (13.6%)	14 (16.9%)	3 (8.3%)	
Lymphatic invasion				0.937
Yes	44 (21.2%)	24 (30.0%)	12 (33.3%)	
No	97 (68.8%)	56 (70.0%)	24 (66.7%)	

Vascular invasion				0.920
Yes	42 (29.8%)	22 (27.5%)	11 (30.6%)	
No	99 (70.2%)	58 (72.5%)	25 (69.4%)	
Pre-op CA 19-9				0.157
<50 U/mL	75 (51.0%)	38 (45.8%)	12 (33.3%)	
≥50 U/mL	72 (49.0%)	45 (54.2%)	24 (66.7%)	
Neoadjuvant CCRTx				0.080
Yes	46 (31.3%)	37 (44.6%)	10 (27.8%)	
No	101 (68.7%)	46 (55.4%)	26 (72.2%)	
Adjuvant CTx				0.692
Yes	104 (70.7%)	59 (71.1%)	28 (77.8%)	
No	43 (29.3%)	24 (28.9%)	8 (22.2%)	
Pre-op HbA1c				0.525
≥9.0%	-	30 (38.5%)	14 (45.2%)	
<9.0%	-	48 (61.5%)	17 (54.8%)	

ASA, American Society of Anaesthesiologists; CA 19-9, carbohydrate antigen 19-9; CCRTx, concurrent chemoradiation therapy; CTx: chemotherapy; DM, diabetes mellitus; HbA1c; hemoglobin A1c; LN, lymph node; Pre-op, pre-operative.

a: comparing between non-DM and long-standing DM.

2. Survival analysis I: Association with DM onset

DFS and OS after surgical resection of PDAC are shown in Figure 2. The new-onset DM group had a significantly shorter DFS than did the non-DM group (median times of 10 and 13 months, p = 0.001). New-onset DM patients also showed reduced DFS than long-standing DM patients (median DFS 15 months, p = 0.039). The median OS of the new-DM group was shorter than in the non-DM group (22 and 33 months, p = 0.039). The median OS of the new-onset group was shorter than in the long-standing DM group, but statistically non-significant (28 and 33 months, p = 0.632). In univariate Cox regression analysis of DFS, variables that were already known as prognostic factors including T-stage, N stage, and CA 19-9 level were associated with significantly shorter DFS (Table 2). In addition, the new-onset DM group has a poorer DFS than did the non-DM group, (HR = 1.593, 95% CI = 1.162-2.185, p = 0.004). In multivariate Cox regression analysis using backward elimination, T-stage (HR = 1.590, 95% CI = 1.267-1.996, p = 0.000), N stage (HR = 1.301, 95% CI = 1.048-1.616, p = 0.017), and new-onset DM (HR = 1.451, 95% CI = 1.054-1.999, p = 0.022) were related to shorter DFS. In univariate Cox regression analysis of OS, T-stage, N stage, lymphatic invasion, vascular invasion, and new-onset DM were associated with shorter OS (Table 3). T-stage was the strongest factor of poor OS in multivariate analysis (HR = 1.547, 95% CI = 1.196-2.002, p = 0.001).

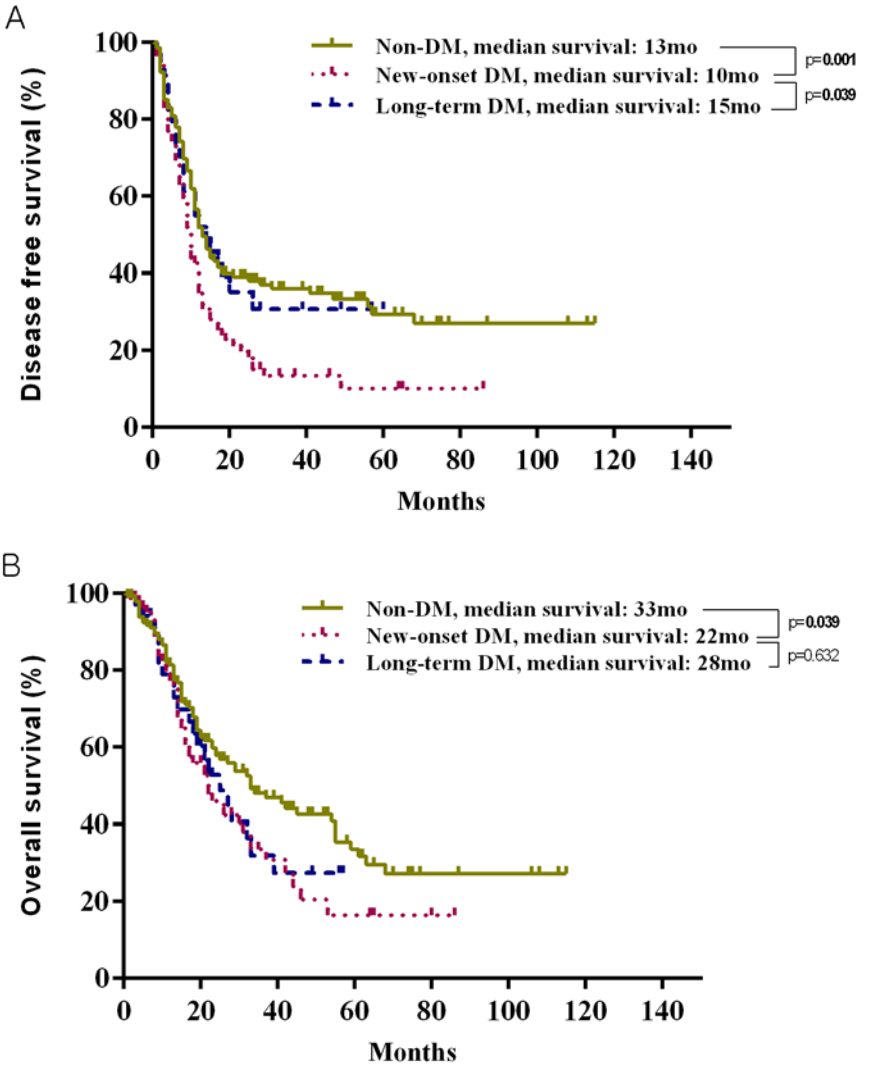

Figure 2. Kaplan-Meier survival analysis for non-DM, new-onset DM, and long-standing DM after surgical resection of pancreatic ductal adenocarcinoma. Disease-free survival (A) and (B) overall survival rates of non-DM, new-onset DM, and long-standing DM after surgical resection of pancreatic ductal adenocarcinoma.

Table 2. Cox proportional hazards analysis for disease-free survival

Clinical factor	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
T-stage	1.741	1.413-2.146	**0.000**	1.590	1.267-1.996	**0.000**
N stage	1.517	1.249-1.856	**0.000**	1.301	1.048-1.616	**0.017**
Lymphatic invasion	1.255	0.917-1.716	0.155			
Vascular invasion	1.352	0.984-1.858	0.063			
Neoadjuvant CCRTx	1.097	0.812-1.483	0.547			
Adjuvant CTx	0.885	0.640-1.223	0.459			
Onset time of DM						
New-onset DM/ non-DM	1.593	1.162-2.185	**0.004**	1.451	1.054-1.999	**0.022**
Long-standing DM / non-DM	0.986	0.619-1.571	0.953			
CA 19-9 ≥50 U/mL	1.361	1.013-1.827	**0.041**			

CA 19-9, carbohydrate antigen 19-9; CCRTx, concurrent chemoradiation therapy; CI, confidence interval; CTx, chemotherapy; DM, diabetes mellitus.

Table 3. Cox proportional hazards analysis for overall survival

Clinical factor	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
T-stage	1.825	1.442-2.310	**0.000**	1.547	1.196-2.002	**0.001**
N stage	1.677	1.336-2.104	**0.000**	1.439	1.126-1.837	**0.004**
Lymphatics invasion	1.489	1.057-2.097	**0.023**			
Vascular invasion	1.470	1.036-2.085	**0.031**			
Neoadjuvant CCRTx	0.966	0.689-1.355	0.842			
Adjuvant CTx	0.772	0.541-1.101	0.153			
Onset time of DM						
New-onset DM/ non-DM	1.452	1.012-2.085	**0.043**			
Long-standing DM/ non-DM	1.345	0.827-2.189	0.233			
CA 19-9 ≥50 U/mL	1.366	0.984-1.897	0.063			

CA 19-9, carbohydrate antigen 19-9; CCRTx, concurrent chemoradiation therapy; CI, confidence interval; CTx, chemotherapy; DM, diabetes mellitus.

3. Survival analysis II: comparison of DM onset by T-stage

For low T-stage tumors including T0 and T1 (Figure 3), the DFS and OS of new-onset DM group were shorter than those of the non-DM group (DFS: 12 vs. 47 months, p=0.001, OS: 31 vs. 54 months, p=0.045). However, there was no statistically difference in oncologic outcomes between the new-onset DM and long-standing DM groups (DFS of long-standing DM group: 20 months, p=0.097, OS of long-standing DM group could not be calculated). In contrast to low T-stage, the DFS and OS rates of high T-stage (T2 and T3) PDAC were similar among the three groups (DFS of non-DM and new-onset groups: 9 months, long-standing DM group: 8 months; OS of non-DM group: 20 months, new-onset and long-standing DM groups: 18 months, all $p > 0.05$). Oncologic outcome by T-stage of PDAC was also analyzed (Figure 4). In the non-DM group, OS was highly influenced by T-stage (low vs. high T-stage $p < 0.001$). In the long-standing DM group, OS was also significantly shorter for high T-stage tumors ($p = 0.003$). In the new-onset DM group, OS was not influenced by tumor stage (low vs. high T-stage $p = 0.129$), suggesting aggressive tumor behavior even in low T-stages.

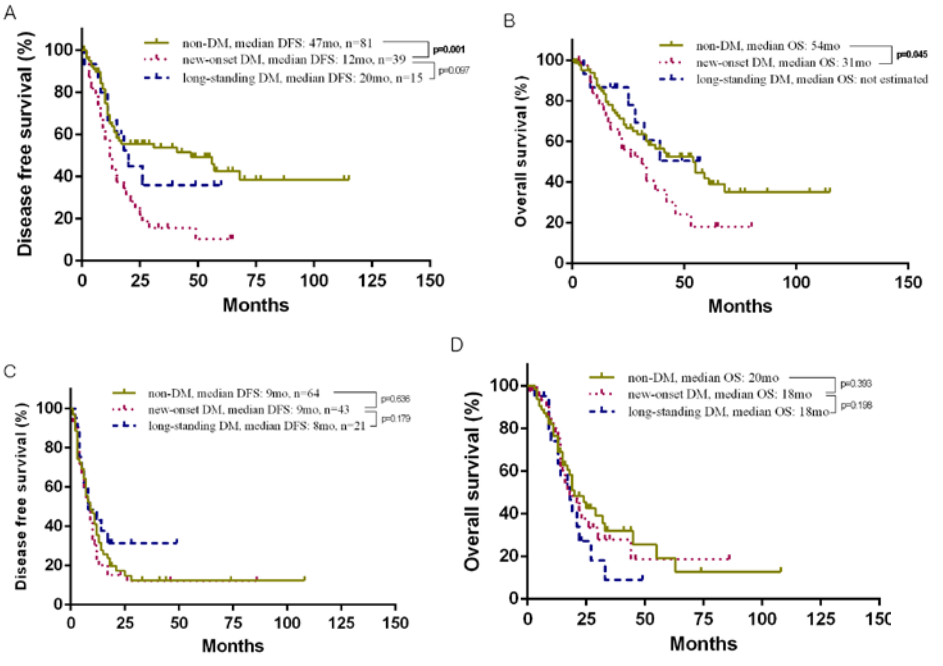

Figure 3. Kaplan-Meier survival analysis for DM onset according to tumor stage. Disease-free survival (A) and overall survival (B) rates by DM onset for low tumor stages including T0 and T1. Disease-free survival (C) and overall survival (D) rates by DM onset for advanced tumor stages including T2 and T3. DM, diabetes mellitus.

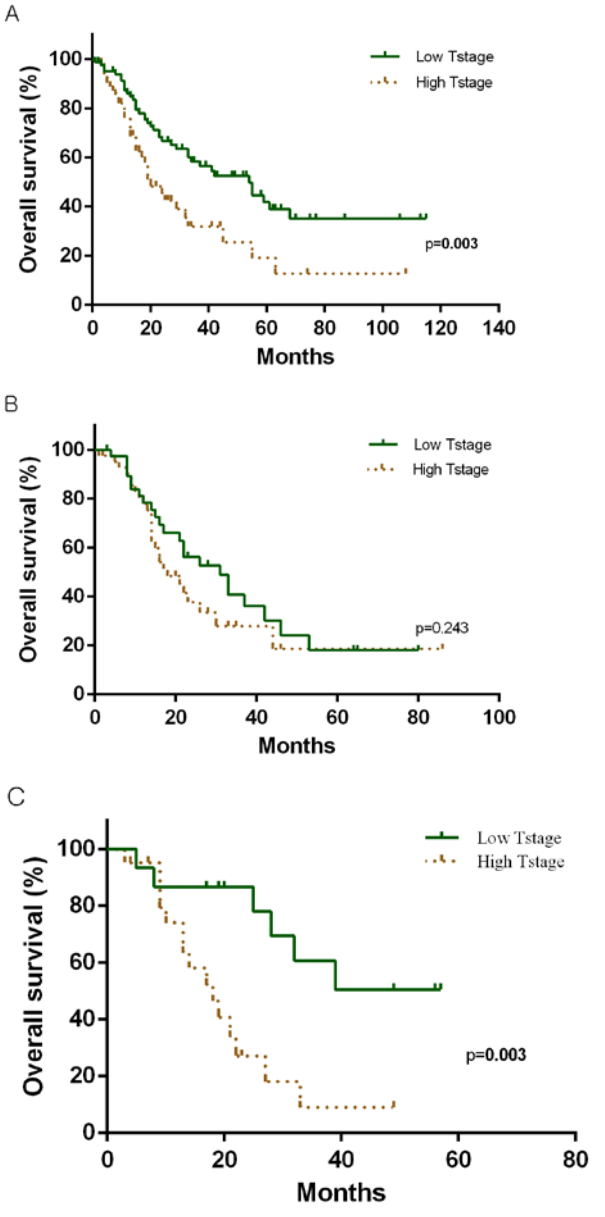

Figure 4. Kaplan-Meier survival analysis of PDAC by tumor stage according to DM onset. Overall PDAC survival rates of PDAC by tumor stage in the (A) non-DM, (B) new-onset DM and (C) long-standing DM groups. DM, diabetes mellitus; PDAC, pancreatic ductal adenocarcinoma.

IV. DISCUSSION

DM is prevalent in patients with PDAC[6,10,11]. Moreover, new-onset DM is a unique phenomenon in this disease[3,6,14,22]. Although the mechanism of new-onset DM in pancreatic cancer is still unclear, several studies have suggested that DM develops as a result of the malignancy[14,23,24]. Pelaez-Luna et al demonstrated that DM occurred before the tumor was radiologically detectable[23]. Permert and colleagues reported improved glucose tolerance following pancreatic resection in six patients[24]. Pannela et al found that DM resolved in 17 of 30 patients who underwent pancreaticoduodenectomy, but DM prevalence was unchanged in long-standing DM patients[14]. In this regard, pancreatic cancer in new-onset DM may be different from that in non-DM or long-standing DM patients. Several studies have investigated this difference by performing risk analysis or assessing the oncologic outcomes of PDAC in patients with new-onset DM[4,5,9,18,25,26].

Several studies have reported aggressive oncologic behavior of PDAC in patients with new-onset DM[20,25-27]. Chu et al concluded that new-onset DM was associated with increased tumor size and shorter OS[20]. Balzano et al showed that new-onset DM was independently associated with early recurrence after surgical resection of PDAC[27]. A meta-analysis also found poor oncologic outcomes in patients with new-onset DM[25]. However, others reported that new-onset DM did not have clinical impact on PDAC, but long-standing DM did[17], or there was no difference in oncologic outcomes between new-onset and

long-standing DM patients[18,20]. In this study, new-onset DM was associated with aggressive oncologic behavior. In addition, new-onset DM was identified as significant prognostic factor more than well-known factors including lymphovascular invasion, perineural invasion, or CA 19-9 level[28-32]. Although the oncologic impact of new-onset DM on OS was not verified by comparing T- and N-stages, new-onset DM was shown to be one of the strongest prognostic factor to predict early recurrence of PDAC in multivariate Cox regression analysis. When comparing oncologic outcomes between patients with new-onset and long-standing DM, the DFS of new-onset DM was statistically shorter, but the OS rates of the new-onset and long-standing DM groups were not statistically different. This result may have been due to the increased tumor size of the long-standing DM group. Indeed, tumor stage was found to be the most important prognostic factor (HR for OS = 1.547, 95% CI = 1.126-1.837, p = 0.001), resulting in the shorter OS of long-standing DM.

T- and N-stages are generally considered the most important prognostic factors of most solid organ malignancies. According to a study validating the AJCC 8th staging system for PDAC, the OS of patients with T1, T2, and T3 stage tumors were 24, 19, and 14 months, respectively[19]. Therefore, we defined low T-stage cancer as T0 and T1 and high T-stage as T2 and T3. For low T-stages, the oncologic outcomes of the non-DM and long-standing DM groups were superior to that of new-onset DM group. However, the DFS and OS of the three groups were similar for high T-stage cancer. Therefore, DM onset appears to

influence low but not high T-stage cancer. One interesting result of this study was that new-onset DM attenuated the DFS and OS of low T-stage cancer. Although T-stage was the most important prognostic factor for OS in the Cox regression analysis, OS of low T- and high T-stages did not reveal a significant difference. In other words, new-onset DM could attenuate the favorable oncologic outcome of low T-stage PDAC.

This study has some limitations. First, it was retrospective in design, and most of the data were extracted from the medical records. Second, confounding factors were not adjusted, which may lead to bias. For these reasons, the results should be validated using large-scale prospective clinical data.

V. CONCLUSION

Patients with new-onset DM have a shorter DFS and OS than PDAC patients without DM or with long-standing DM. Moreover, only patients with low T-stage PDAC new-onset DM reduced OS, at a rate similar to that observed for high T-stage PDAC. Our results suggest that new-onset DM is associated with aggressive PDAC tumor biology. Further research is needed to elucidate the mechanisms of new-onset DM in pancreatic cancer.

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ABSTRACT (IN KOREAN)

췌장암 환자에서 새롭게 진단된 당뇨병이 췌장암의 수술 후 재발에 미치는 영향

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목적: 당뇨병은 췌장암에서 호발하는 질병이다. 특히, 췌장암이 진단 되기 전에 새롭게 진단된 당뇨병은 췌장암 증상 중 하나로 여겨지며, 다른 췌장암과는 다른 예후를 보일 것이다.

방법: 2006년에서 2014년까지 췌장암으로 완치를 위한 수술적 절제를 받은 환자들의 의무 기록을 검토 하였으며, 새롭게 진단된 당뇨병은 췌장암 진단 24개월 이전에 진단된 당뇨병으로 정의 하였다. 당뇨병이 없는 환자, 당뇨병을 24개월 이후에 진단 받은 환자, 새롭게 진단된 당뇨병을 가지고 있는 환자에서 발생한 췌장암의 생존 분석 및 위험 요인 분석을 시행 하였다.

결과: 세 군 간의 임상 요인의 차이는 없으며, 새롭게 진단된 당뇨병을 가진 환자에서 췌장암 재발이 더 증가되었다. ($p=0.039$) 특히 새롭게 진단된 당뇨병은 낮은 T 병기 환자에서 예후를 더 나쁘게 하는 결과를 보여 주었다.

결론: 새롭게 진단된 당뇨병이 있는 경우에, 췌장암은 더 불량한 예후를 보이며, 특히 재발에 중요한 위험인자로 확인 되었다.

핵심되는 말 : 당뇨병, 췌장암, 새롭게 진단된 당뇨병, 재발