Elevated Hemoglobin A1c Levels Are Associated with Worse Survival in Advanced Pancreatic Cancer Patients with Diabetes

Young Koog Cheon, Ja Kyung Koo, Yoon Serk Lee, Tae Yoon Lee, and Chan Sup Shim

Digestive Disease Center, Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Korea

Background/Aims: Pre-existing diabetes mellitus (DM) has been identified as an adverse prognostic variable associated with increased mortality in various cancers. Although DM and hyperglycemia are considered risk factors for pancreatic cancer (PC), antidiabetic treatments for patients with advanced PC have been overlooked. This study aimed to evaluate the impact of hemoglobin A1c (HbA1c) levels on PC survival.

Methods: We retrospectively reviewed the medical records of first-diagnosed patients with advanced PC who were admitted to Konkuk University Medical Center from 2005 to 2011.

Results: A total of 127 patients were enrolled, and there were 111 deaths (87.4%) within the 7-year observational period. The most common etiology was disease progression (n=108). DM before PC diagnosis was observed in 65 patients (51.1%), including 28 patients with new-onset DM. The overall median survival times in patients with and without DM were 198 and 263 days, respectively (p=0.091). Survival time according to HbA1c was significantly different between the <7.0% and ≥7.0% groups (362 and 144 days, respectively; p=0.038). In the HbA1c ≥7.0% group, the median overall survival time was 273 days for the metformin group and 145 days for the nonmetformin oral agent group; however, there was no significant difference between the two groups (p=0.058).

Conclusions: A high HbA1c level may be associated with worse survival in patients with advanced PC with DM. Antidiabetic treatment, metformin in particular, was associated with an improved outcome.

Key Words: Pancreatic neoplasms; Diabetes mellitus; Glycosylated hemoglobin A; Metformin

INTRODUCTION

Pancreatic cancer (PC) is a devastating disease that poses significant management challenges. Because of its exceptionally high mortality with an overall survival of <5%, PC ranks as the fifth leading cause of cancer-related death in most developed countries. Currently, there is no effective means to screen for or prevent this cancer.

The association between diabetes mellitus (DM) and PC is well-documented. However, there has been some concern that DM may be a consequence rather than a cause of this neoplasm. The precise prevalence of DM in patients with PC has been difficult to establish because studies relying upon self-reports or registry data for diagnosis of DM have largely underestimated its frequency in patients with PC. Recent studies applying objective biochemical criteria showed that while the prevalence of DM in patients with PC is around 40%, as many as 10% of patients with PC may have abnormalities in glucose metabolism.

Pre-existing DM has been identified as an adverse prognostic variable associated with increased mortality in various cancers, including colorectal, prostate, and breast cancer. Pre-existing DM was also independently associated with reduced survival in patients undergoing resection for PC. Postload plasma glucose concentration and PC mortality were inversely associated in men with a normal glycemic level.

A hyperglycemic state has various indicators; of them, hemoglobin A1c (HbA1c) reflects long-term glycemic control and is a more stable measurement than fasting plasma glucose levels. Although the associations between HbA1c levels and incidence or mortality for malignancies have been shown in two cohort studies, no studies have evaluated the impact of HbA1c levels on the survival of advanced PC.

The diagnosis and treatment of cancer may distract both the
In the present study, we conducted a retrospective analysis of the relationship between HbA1c levels and advanced PC with DM survival, and took into consideration antidiabetic therapy, including metformin.

MATERIALS AND METHODS

1. Patients

Data from the Konkuk University Medical Center were used in this study. Institutional Review Board approved retrospective review. The data was collected between May 2005 and April 2011. One hundred and sixty-five patients with advanced PC were evaluated. Thirty-eight patients were excluded because of missing follow-up data, age of >90 years, lack of evaluation for DM, poor performance status, or gastrointestinal obstruction by cancer. Thus, 127 patients underwent analysis. A total of 65 patients with pre-existing DM and 62 patients without pre-existing DM were recruited. Sixty-five patients with pre-existing DM were divided into a low HbA1c group (group A, <7.0% of HbA1c, n=24) and a high HbA1c group (group B, ≥7.0% of HbA1c, n=41).

2. Definition of diabetes

Diagnosis of pre-existing DM was made based on the documented clinical history and/or biochemical findings, with application of the diagnostic criteria outlined by the American Diabetes Association in January 2010. In brief, patients with a known history of DM, a baseline fasting blood glucose level of ≥126 mg/dL, two or more outpatient random blood glucose levels of ≥200 mg/dL, or an HbA1c level of ≥6.5% were classified into the DM group. Among patients with only inpatient preoperative laboratory results, those with two or more serum measurements of ≥200 mg/dL obtained before 7:00 AM were classified as having DM. The duration of DM before the cancer diagnosis was determined based on the clinical history or first date of documented laboratory abnormalities. New-onset DM was defined as a diagnosis of DM 24 months before the PC diagnosis, and patients with a diagnosis of DM >24 months preceding the cancer diagnosis were classified as having longstanding DM. DM medication profiles were classified into three groups (metformin with/without other agents; other agents with/without insulin; or no treatment).

3. Measurement of HbA1c values

HbA1c levels were measured by high performance liquid chromatography (ADAMS HA-8180; Arkray Inc., Tokyo, Japan) in 65 patients with unresectable PC who were recruited after 2005. Patients without pre-existing DM were not measured because of their normal fasting glucose level. According to the guidelines of the American Diabetes Association, an HbA1c level of 4.0% to 6.0% was considered to be an HbA1c level of <7.0% was the recommended glycemic control level for adults with DM. Therefore, we divided all patients with PC and DM into two groups according to their HbA1c level: <7.0% and ≥7.0%.

4. Data collection

Initial variables were included age, gender, education, body mass index (BMI), smoking, alcohol consumption, performance status (Karnofsky status), family history of PC, and carbohydrate antigen 19-9 (CA 19-9) level. Family history of cancer was restricted to first-degree relatives. The BMI was calculated at admission. According to the World Health Organization standard, BMIs of <24.9, 25 to 29.9, and ≥30 kg/m² were defined as normal, overweight, and obese, respectively. Education was classified as less than high school and high school graduate or more. Chemotherapy history after diagnosis of PC was evaluated.

Because the number of patients who received monotherapy was small, insulin use was not considered for an individual group of glycemic control. In addition, many patients used the drug or the combinations changed over time; thus, the final analysis used the categorical variables of ever or never use of metformin. Oral medications were categorized into two groups: 1) metformin and 2) other drugs (not including metformin), including insulin secretagogues, thiazolidinediones, dipeptidyl peptidase-4, and glucagon-like peptide 1 analogue.

5. Statistical analysis

Patients were classified into DM and non-DM groups. In the DM group, patients were classified according to HbA1c level: <7.0% (group A) and ≥7.0% (group B). Cigarette smoking status was classified as never and ever (past and current).

Numerical data are presented as the median with interquartile range (IQR). Data for patients with PC with DM and without DM were compared with respect to demographic, clinical, and treatment variables using Pearson chi-square test and Fisher exact test for categorical variables. Among patients with DM, data for patients with ≤7.0% and <7.0% HbA1c were compared using the above methods. Estimates of proportions of survival for the follow-up study were calculated using the Kaplan-Meier method with the log-rank test. Data were summarized by the median and 95% confidence intervals (CIs). For survival rates, death unrelated to PC, such as cardiovascular events, were treated as censored patients. Survival was calculated from the day of diagnosis until death or the last follow-up.

Cox regression was used to determine independent predictors of outcome, using survival as the dependent variable and significant factors (p<0.15) by univariate analysis as the independent variables. The p-values ≤0.05 were deemed to indicate statistical significance.
RESULTS

1. Population characteristics

The characteristics of the study population, including risk factors for PC, are shown in Table 1. Baseline clinical and demographic profiles in the DM and non-DM groups were similar with the exception the CA 19-9 level. The median level of CA 19-9 was higher in the DM than in the non-DM group (670.3, IQR=199.4 to 3,955.0 vs 514.4, IQR=99.4 to 3,687.3; p=0.036).

In total, the median age was 69 years (range, 43 to 90 years), with the exception the CA 19-9 level. The median level of CA 19-9 was higher in the DM than in the non-DM group (670.3, IQR=199.4 to 3,955.0 vs 514.4, IQR=99.4 to 3,687.3; p=0.036). In the subgroup analysis of patients with an HbA1c level of ≥7.0%, metformin use also showed a longer survival compared with other antidiabetic medications; however, the difference was not statistically significant (median survival, 273 days vs 145 days; p=0.058) (Fig. 3). The mean value (standard deviation) of HbA1c was 9.2% (3.2) in metformin use and 8.2% (2.4) metformin nonuse in patients with DM (p=0.342).

2. Influence of HbA1c level and antidiabetic treatment on survival of patients with PC and DM

The demographic characteristics of group A (HbA1c of <7.0%) and group B (HbA1c of ≥7.0%) in advanced PC with DM were summarized in Table 2. There was no significant difference in age, sex, BMI, smoking, alcohol consumption, education, tumor location, chemotherapy, or type of antidiabetic therapy between groups A and B. The median level of HbA1c was 6.9% (range, 5.7% to 6.9%) in group A and 8.1% (range, 7.0% to 20.0%) in group B (p=0.003).

Kaplan-Meier survival analysis showed a slightly longer survival time in patients without DM than in patients with DM (95% CI, 114.1 to 372.0) and 198 days in patients with DM (95% CI, 125.4 to 283.5; p=0.091). Among patients with DM, Kaplan-Meier survival analysis showed a significantly longer survival time in group A (HbA1c level of <7.0%) than in group B (HbA1c level of ≥7.0%) (Fig. 2). The median survival was 362 days (95% CI, 246.2 to 461.8) in patients with DM (95% CI, 109.0 to 179.0) in group B (p=0.014).

Metformin use showed a longer survival than metformin nonuse in patients with PC, however, it did not show a statistically significant difference (median survival, 264 days vs 195 days, respectively; p=0.058). In the subgroup analysis of patients with DM (hazard ratio [HR], 1.28; 95% CI, 0.89 to 2.49; p=0.091), the difference was not statistically significant (median survival, 273 days vs 145 days; p=0.058) (Fig. 3). The mean value (standard deviation) of HbA1c was 9.2% (3.2) in metformin use and 8.2% (2.4) metformin nonuse in patients with DM (p=0.342).

3. Impact of other potential variables on survival

The median survival was 284 days (95% CI, 209.6 to 372.4) in stage IIIb and 119 days (95% CI, 93.5 to 144.5) in stage IV (p<0.001). The 1- and 2-year survival rates were 43% and 20% in stage IIIb and 21% and 3% in stage IV, respectively. The median survival was 294 days (95% CI, 226.4 to 355.2) in patients with chemotherapy and 166 days (95% CI, 92.0 to 254.0) in patients without chemotherapy (p=0.005). The 1- and 2-year survival rates were 45% and 18% in patients with chemotherapy and 22% and 9% in patients without chemotherapy, respectively.

Table 3 shows the results of univariate and multivariate analyses of all variables associated with survival in all patients. DM (hazard ratio [HR], 1.28; 95% CI, 0.89 to 2.49; p=0.091), CA 19-9 level of >150 U/L (HR, 1.98; 95% CI, 1.08 to 3.95; p=0.033) and a high level of HbA1c (HR, 2.55; 95% CI, 1.22 to 4.08; p=0.003) were statistically significant predictors of survival in the univariate analysis.

In the multivariate analysis using the Cox regression model in all patients, chemotherapy (HR, 2.77; 95% CI, 1.13 to 2.80; p=0.014) and stage III (HR, 2.34; 95% CI, 1.43 to 3.85) were the significant predictors of longer survival in advanced PC.

In subgroup analysis in patients with DM (Table 4), an HbA1c level of ≥7.0% (HR, 2.12; 95% CI, 1.15 to 3.92; p=0.014), CA 19-9 level of >150 U/L (HR, 1.98; 95% CI, 1.08 to 3.95; p=0.043), metformin nonuse (HR, 1.53; 95% CI, 0.93 to 2.94; p=0.058), and no chemotherapy (HR, 2.23; 95% CI, 1.22 to 4.08; p=0.003) were statistically significant predictors of survival in the univariate analysis. Multivariate analysis using the Cox regression model showed that no chemotherapy (HR, 1.91; 95% CI, 1.04 to 3.22; p=0.047) and high level of HbA1c (HR, 2.55; 95% CI, 1.01 to 6.04; p=0.033) were significantly associated
Table 1. Clinicopathological Characteristics of Diabetes and Nondiabetes in Advanced Pancreatic Cancer Patients

| Characteristic                      | Diabetes (n=65) | No diabetes (n=62) | p-value |
|-------------------------------------|----------------|--------------------|---------|
| Age, yr                             | 69 (46-89)     | 67.5 (43-90)       | 0.857   |
| Male                                | 27 (41.5)      | 33 (52.1)          | 0.421   |
| Body mass index, kg/m²              |                |                    |         |
| <25                                 | 41 (62.1)      | 32 (52.1)          | 0.259   |
| 25-29.9                             | 16 (24.6)      | 14 (22.6)          |         |
| ≥30                                 | 0              | 5 (8.1)            |         |
| Unknown                             | 8 (12.3)       | 10 (16.1)          |         |
| Stage*                             |                |                    |         |
| IIIa vs IV                          | 34 (52.3)      | 33 (53.2)          | 0.393   |
| IIIb vs IV                          | 31 (47.7)      | 29 (46.8)          |         |
| CA 19-9, U/L                        | 670.3 (0.5-19,623.9) | 514.4 (8.0-694,290.0) | 0.006   |
| Nodal metastasis                    |                |                    |         |
| Yes                                 | 54 (83.1)      | 48 (77.4)          | 0.605   |
| Location of tumor                   |                |                    |         |
| Head                                | 37 (56.9)      | 29 (46.8)          | 0.249   |
| Body                                | 8 (12.2)       | 14 (22.6)          |         |
| Tail                                | 20 (30.8)      | 19 (30.6)          |         |
| Method of histologic diagnosis     |                |                    |         |
| Endoscopic ultrasound-guided       | 6 (9.2)        | 6 (9.7)            | 0.238   |
| Ultrasonography-guided             | 34 (52.3)      | 34 (54.8)          |         |
| Ascites cytology                    | 2 (3.1)        | 2 (3.8)            |         |
| Not performed                       | 23 (35.4)      | 19 (30.6)          |         |
| Level of HbA1c, %                   |                |                    |         |
| <7                                  | 24 (36.9)      | 21 (34.0)          |         |
| ≥7                                  | 41 (63.1)      | 38 (66.0)          |         |
| Pancreas parenchymal atrophy by CT  |                |                    |         |
| Yes                                 | 19 (22.2)      | 9 (17.6)           | 0.050   |
| Treatment of diabetes               |                |                    |         |
| Metformin                           | 28 (42.1)      | 23 (37.1)          | 0.600   |
| Others                              | 27 (41.5)      | 29 (46.8)          |         |
| No treatment                        | 10 (15.4)      | 14 (22.6)          |         |
| Family history of cancer†           |                |                    |         |
| No                                  | 60 (95.2)      | 59 (96.7)          | 0.929   |
| Yes                                 | 3 (4.8)        | 3 (3.3)            |         |
| Smoking                             |                |                    |         |
| Yes                                 | 18 (27.7)      | 26 (41.9)          | 0.408   |
| Alcohol                             |                |                    |         |
| Yes                                 | 20 (30.8)      | 27 (43.5)          | 0.443   |
| Chemotherapy                        |                |                    |         |
| Yes                                 | 27 (41.5)      | 31 (50.0)          | 0.113   |
| Education                           |                |                    |         |
| <High school                        | 28 (43.1)      | 32 (51.6)          | 0.108   |
| ≥University                         | 17 (26.2)      | 15 (24.2)          |         |
| Unknown                             | 10 (15.4)      | 15 (24.2)          |         |

Data are presented as median (range) or number (%).
CA 19-9, carbohydrate antigen 19-9; HbA1c, hemoglobin A1c; CT, computed tomography.
*American Joint Committee Cancer staging 7th edition; †Information on family history was missing for five cases.
Table 2. Clinicopathological Characteristics according to Hemoglobin A1c Levels in Advanced Pancreatic Cancer with Diabetes

| Characteristic                          | HbA1c <7.0 (group A, n=24) | HbA1c ≥7.0 (group B, n=41) | p-value |
|----------------------------------------|----------------------------|---------------------------|---------|
| Age, yr                                | 69.5 (54-92)               | 69 (46-90)                | 0.972   |
| Male                                   | 10 (41.7)                  | 17 (41.5)                 | 0.561   |
| Body mass index, kg/m²                 |                            |                           |         |
| <25                                    | 14 (58.3)                  | 27 (65.9)                 | 0.477   |
| 25-29.9                                | 6 (26.6)                   | 10 (24.4)                 |         |
| ≥30                                    | 0                          | 0                         |         |
| Unknown                                | 4 (19.1)                   | 4 (9.8)                   |         |
| HbA1c, %                               | 6.5 (5.7-6.9)              | 8.1 (7.0-10.0)            | 0.002   |
| Stage*                                 |                            |                           |         |
| III/b                                  | 12 (50.0)                  | 22 (52.7)                 | 0.548   |
| IV                                     | 12 (50.0)                  | 19 (46.3)                 |         |
| CA 19-9, U/L                           | 8752 (130-19,543)          | 6409 (0.50-103,470.0)     | 0.163   |
| Nodal metastasis                       |                            |                           |         |
| Yes                                    | 19 (79.2)                  | 22 (78.0)                 | 0.259   |
| Location of tumor                      |                            |                           |         |
| Head                                   | 14 (58.3)                  | 21 (51.2)                 | 0.631   |
| Body                                   | 4 (16.7)                   | 5 (12.2)                  |         |
| Tail                                   | 6 (25.0)                   | 15 (36.6)                 |         |
| Pancreas parenchymal atrophy by CT     |                            |                           |         |
| Yes                                    | 6/16 (37.5)                | 11/20 (55.0)              | 0.378   |
| Method of histologic diagnosis         |                            |                           |         |
| Endoscopic ultrasound-guided           | 3 (12.5)                   | 3 (7.3)                   | 0.199   |
| Ultrasonography-guided                 | 14 (58.3)                  | 22 (53.7)                 |         |
| Ascites cytology                       | 0                          | 1 (2.4)                   |         |
| Not performed                          | 7 (29.2)                   | 15 (36.6)                 |         |
| Treatment of diabetes                  |                            |                           |         |
| Metformin                              | 11 (45.8)                  | 18 (43.9)                 | 0.603   |
| Others                                 | 9 (37.5)                   | 17 (41.5)                 |         |
| No treatment                           | 4 (16.7)                   | 6 (14.6)                  |         |
| Chemotherapy                           |                            |                           |         |
| Yes                                    | 12 (50.0)                  | 17 (41.5)                 | 0.262   |
| Family history of cancer               |                            |                           |         |
| No                                     | 23 (95.8)                  | 28 (92.6)                 | 0.118   |
| Yes                                    | 1 (4.2)                    | 1 (2.4)                   |         |
| Unknown                                | 0                          | 2 (4.9)                   |         |
| Smoking                                |                            |                           |         |
| Yes                                    | 7 (29.2)                   | 11 (26.8)                 | 0.996   |
| Alcohol                                |                            |                           |         |
| Yes                                    | 9 (37.5)                   | 12 (29.2)                 | 0.562   |
| Education                              |                            |                           |         |
| <High school                           | 16 (66.7)                  | 25 (61.0)                 | 0.125   |
| ≥High school graduate                  | 4 (16.7)                   | 6 (14.6)                  |         |
| Unknown                                | 4 (16.7)                   | 6 (14.6)                  |         |

Data are presented as median (range) or number (%).
HbA1c, hemoglobin A1c; CA 19-9, carbohydrate antigen 19-9; CT, computed tomography.
*American Joint Committee Cancer staging 7th edition.
with poor survival compared with patients with chemotherapy and low level of HbA1c in advanced PC with DM. At the end of the observation period, 56 patients (86.2%) with DM and 55 patients (88.7%) without DM died. The causes of death in patients with DM were tumor progression (94.6%, n=53) and non-PC-related causes (5.4%, n=3 with heart disease). The causes of death in patients without DM were tumor progression (98.2%, n=54) and biliary sepsis (1.8%, n=1).

DISCUSSION

DM and impaired glucose tolerance are thought to be risk factors for not only cardiovascular events, but also malignancies. Comorbid DM has been implicated as an adverse prognostic factor for cancer in general. A recent meta-analysis of 23 studies reported that pre-existing DM was associated with increased all-cause mortality relative to non-DM cancer patients (HR, 1.41; 95% CI, 1.28 to 1.55). Two large cohort studies examined the association of DM for ≥10 years with subsequent PC risk. In both studies, DM was positively associated with PC risk. Another prospective cohort study reported a 2.5-fold greater risk of PC mortality among men with DM compared with those without DM.

Most studies that have investigated the association between DM and the cancer morbidity or mortality used the fasting plasma glucose level or postload plasma glucose level. On the other hand, HbA1c is a good time-integrated indicator of blood glucose concentrations over the preceding 1 to 3 months. It is also a particularly convenient screening or monitoring tool for DM because it does not require subjects to fast. However, no studies to date have investigated the association between HbA1c levels and the mortality of advanced PC. Because PC has a very rapid clinical course and is almost uniformly fatal, it may distract both the patient and the health care team from the diagnosis of DM and appropriate management of hyperglycemia. Our findings indicate that an elevated HbA1c level (≥7.0%) was associated with decreased survival in patients with advanced PC with DM.

Another possibility is that DM and hyperglycemia affect tumor behavior by increasing proliferation and dissemination. There are several potential explanations for the observed association between increased all-cause mortality and pre-existing DM in patients with cancer. First, patients with both cancer and DM may have increased tumor cell proliferation and metastasis in a physiologic environment of hyperinsulinemia and hyperglycemia. Insulin has been shown to have a direct, dose-

Fig. 1. Kaplan-Meier estimated survival probability curve for patients with advanced pancreatic cancer with and without diabetes. The median survival of patients with diabetes was 198 days (95% confidence interval [CI], 125.4 to 263.5) compared with 263 days (95% CI, 114.1 to 372.0) in the non-diabetic group (p=0.091).

Fig. 2. Kaplan-Meier estimated survival probability curve for patients with advanced pancreatic cancer with diabetes according to the level of hemoglobin A1c (HbA1c; <7.0%, group A) and according to the median survival was 362 days (95% confidence interval [CI], 246.2 to 461.8) in group A and 145 days (95% CI, 109.0 to 179.0) in group B (p=0.014).

Fig. 3. Kaplan-Meier estimated survival probability curve for patients with hemoglobin A1c levels ≥7.0% according to the antidiabetic treatment (metformin use or metformin nonuse). The median survival time was 273 days (95% confidence interval [CI], 123.2 to 359.8) in the metformin use group and 145 days (95% CI, 39.5 to 256.3) in the metformin nonuse group (p=0.058).
dependent, growth-promoting effect on PC cell lines in vitro. Moreover, high concentrations of insulin are able to bind to and activate the insulin-like growth factor 1 (IGF-1) receptor. Activation of this receptor is known to have growth-promoting effects, including modulation of cell cycle progression. Excess insulin could also indirectly affect the development of PC through down-regulation of IGF-binding protein 1.

Second, patients with preexisting DM may have a poor response to cancer treatment, including increased risk and intraoperative mortality. In this study, subgroup analysis of the patients with chemotherapy showed that survival was shorter in patients with an HbA1c level of ≥7.0% than in patients with an HbA1c level of <7.0%, although the difference was not statistically significant (median survival, 394 days, 95% CI, 271.7 to 516.4 vs 227 days, 95% CI, 80.8 to 373.2; p=0.093). Finally, DM is a well-established risk factor for cardiovascular mortality in adults without cancer, and the microvascular and macrovascular damage it causes likely accumulates to some extent regardless of cancer status. In this study, while three patients (7.3%) died of cardiovascular events in the high HbA1c group, there was no death related to cardiovascular events in the low HbA1c group.

Because PC has a very rapid clinical course and is almost uniformly fatal, many physicians are not concerned with either DM itself or glycemic control. There are no studies of the impact of DM or high levels of glucose on mortality in patients with advanced PC with DM. Our findings revealed that DM does not have an impact on the prognosis of advanced PC compared with previous studies, which showed an association between DM and cancer mortality. However, in patients with DM, a high HbA1c level was associated with poor survival compared with a low level of HbA1c in PC with DM. The median survival was 362 days (95% CI, 246.2 to 461.8) in group A and 145 days (95% CI, 109.0 to 179.0) in group B (p=0.014). Appropriate antidiabetic treatment is required in advanced PC if the patients do not have a poor performance status or advanced stage. Among antidiabetic therapeutic agents, metformin was associated with a longer survival of PC in this study (p=0.058). However, the statistical power was limited because this observation was made

| Variable | Median survival, day | Univariate* | p-value | Multivariate† | p-value |
|----------|---------------------|-------------|---------|---------------|---------|
| Diabetic/Nondiabetes | 198/263 | 1.28 (0.89-2.49) | 0.091 | 1.43 (0.85-2.42) | 0.046 |
| Age, yr | <65 vs ≥65 | 250/201 | 1.19 (0.79-1.79) | 0.404 | |
| CA 19-9 | <150 vs ≥150 | 394/208 | 2.11 (1.27-3.49) | 0.003 | 1.68 (0.97-2.90) | 0.065 |
| T stage | ≤T3 vs T4 | 299/273 | 1.22 (0.74-2.29) | 0.245 | |
| Lymph node involvement | Yes vs No | 284/154 | 1.46 (1.27-2.65) | 0.030 | 1.02 (0.54-1.91) | 0.691 |
| TNM stage‡ | Yes vs No | 284/119 | 2.12 (1.42-3.14) | <0.001 | 2.34 (1.43-3.85) | 0.001 |
| Smoking | Yes vs No | 174/243 | 1.25 (0.89-2.02) | 0.159 | |
| Alcohol | Yes vs No | 243/208 | 1.06 (0.70-1.61) | 0.787 | |
| Body mass index, kg/m² | <25 | 190 | | | |
| | 25-29.9 | 242 | | | |
| | ≥30 | 248 | 0.83 (0.52-1.32) | 0.403 | |
| Chemotherapy | Yes vs No | 298/166 | 1.81 (1.19-2.77) | 0.005 | 2.77 (1.12-2.80) | 0.014 |
| Pancreas parenchymal atrophy | Yes vs No | 201/247 | 1.06 (0.66-1.78) | 0.828 | |

HR, hazard ratio; CI, confidence interval; CA 19-9, carbohydrate antigen 19-9; TNM, tumor, node, metastasis.
*Kaplan-Meier and log rank test; †Cox proportional hazards model; ‡American Joint Committee Cancer staging 7th edition.
Two recent epidemiologic studies reported that patients with DM treated with metformin were less likely to develop cancer, but those treated with insulin or sulfonylurea were more likely to die of cancer.\(^\text{31,32}\) The molecular target of metformin is unknown, but it acts to inhibit complex I of the mitochondrial electron transport chain to block oxidative respiration.\(^\text{33}\) This results in increased cellular adenosine monophosphate (AMP) to adenosine triphosphate ratios and activates AMP-activated protein kinase (AMPK).\(^\text{34}\) AMPK coordinates the activity of a plethora of key metabolic and growth pathways that together act to restore the cellular energy balance.\(^\text{35}\) Furthermore, AMPK has been found to play a role in cell polarity and cell division.\(^\text{36}\) Therefore, in addition to amelioration of hyperglycemia and hyperinsulinemia, which are factors that mediate the adverse impact of type 2 DM on cancer, metformin has direct effects on cancer cells, blocking the mitogenic effects of insulin and IGF-1.

This study has several major limitations. First, it was retrospective in design and included a single tertiary referral center. Second, the statistical power was limited because these observations were made from a small number of study subjects. The association between high HbA1c levels and shorter survival of advanced PC must be further investigated in larger studies. However, this cannot be investigated in a prospective randomized controlled study due to ethical and moral issues. Third, the change in the HbA1c level after antidiabetic treatment was not evaluated.

In conclusion, high HbA1c is associated with poor survival in patients with PC. Antidiabetic treatment, metformin in particular, use is associated with an improved outcome.

### Table 4. Results of Univariate and Multivariate Analysis of All Prognostic Factors Associated with Survival in Diabetes

| Variable                        | Median survival, day | Uniivariate* HR (95% CI) p-value | Multivariate† HR (95% CI) p-value |
|---------------------------------|----------------------|----------------------------------|----------------------------------|
| HbA1c %                         | 362/145              | 2.12 (1.15-3.92) 0.014           | 2.55 (1.08-6.04) 0.023           |
| Age, yr                         | 248/201              | 1.18 (0.67-2.07) 0.563           |
| CA 19-9                         | 424/201              | 1.98 (1.08-3.95) 0.042           | 1.28 (0.54-3.06) 0.129           |
| T stage                         | 227/190              | 1.21 (0.76-2.25) 0.322           |
| Pancreas parenchymal atrophy    | 145/248              | 1.21 (0.64-2.29) 0.500           |
| Lymph node involvement          | 248/190              | 1.10 (0.58-2.24) 0.622           |
| T/NM stage\(^\text{‡}\)         | 312/174              | 1.77 (0.82-3.81) 0.147           |
| Smoking                         | 174/208              | 1.16 (0.64-2.11) 0.628           |
| Alcohol                         | 169/208              | 1.08 (0.59-1.98) 0.818           |
| Body mass index, kg/m\(^2\)    |                      |                                 |
| <25                             | 190                  |                                 |
| 25-29.9                         | 248                  |                                 |
| ≥30                             | 195                  | 0.70 (0.35-1.39) 0.301           |
| Chemotherapy                    |                      |                                 |
| Yes vs No                       | 298/128              | 2.23 (1.22-4.08) 0.009           | 1.98 (1.04-3.82) 0.047           |
| Antidiabetic treatment          |                      |                                 |
| Metformin vs Others             | 273/145              | 1.53 (0.92-2.54) 0.058           | 1.83 (0.84-4.07) 0.129           |

HR, hazard ratio; CI, confidence interval; HbA1c, hemoglobin A1c; CA 19-9, carbohydrate antigen 19-9; T/NM, tumor, node, metastasis.

*Kaplan-Meier and log rank test; †Cox proportional hazards model; ‡American Joint Committee Cancer staging 7th edition.
CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Hidalgo M. Pancreatic cancer. N Engl J Med 2010;362:1605-1617.
2. Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an update. Dig Dis 2010;28:645-656.
3. Evensart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA 1995;273:1605-1609.
4. Pannala R, Leimert JB, Bamlet WR, Jr. A, Petersen GM, Chari ST. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. Gastroenterology 2008;134:981-987.
5. Wang E, Gupta S, Holle EA. Diabetes mellitus and pancreatic cancer in a population-based case-control study in the San Francisco Bay Area, California. Cancer Epidemiol Biomarkers Prev 2006;15:1458-1462.
6. Hoy A, Bilezkinjan PA. Clinical review 63: diabetes and pancreatic cancer: clues to the early diagnosis of pancreatic malignancy. J Clin Endocrinol Metab 1994;79:1213-1221.
7. Chari ST, Leibson CL, Rabe KG, et al. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. Gastroenterology 2008;134:95-101.
8. Barone BB, Yeh HC, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA 2008;300:2754-2764.
9. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Derks F, van der Kwast TH. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus: a population-based analysis. Int J Cancer 2007;120:1986-1992.
10. Chu CK, Mazo AE, Goodman M, et al. Prevalence of diabetes mellitus and long-term survival after resection of pancreatic adenocarcinoma. Ann Surg Oncol 2010;17:502-513.
11. Cannon RM, LeGrand R, Chagpar RB, et al. Multi-institutional analysis of pancreatic adenocarcinoma demonstrating the effect of diabetes status on survival after resection. HPB (Oxford) 2012;14:228-235.
12. Smith GD, Egger M, Skipley MJ, Marmot MG. Post-challenge glucose concentration, impaired glucose tolerance, diabetes, and cancer mortality in men. Am J Epidemiol 1992;136:1110-1114.
13. Rohlfing CI, Little RR, Wiesner HJ, et al. Use of glycated hemoglobin (HbA1c) in screening for undiagnosed diabetes in the U.S. population. Diabetes Care 2000;23:187-191.
14. Nakashima S, Yamada M, Hatton M, Suzuki G. Relationship between HbA1c and mortality in a Japanese population. Diabetologia 2005;48:230-234.
15. Khaw KT, Wareham NJ, Bingham S, Luben R, Welch A, Day N. Preliminary communication: glycated hemoglobin, diabetes, and incident colorectal cancer in men and women: a prospective analysis from the European prospective investigation into cancer...
cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care 2006;29:254-258.

33. El-Mir MY, Nogueira V, Fontaine E, Averet N, Rigoulet M, Leverve X. Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. J Biol Chem 2000;275:223-228.

34. Zhou G, Myers R, Li Y, et al. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 2001;108:1167-1174.

35. Martin M, Manis P. Metformin: a diabetes drug for cancer, or a cancer drug for diabetics? J Clin Oncol 2012;30:2698-2700.

36. Williams T, Brennan JE. LKB1 and AMPK in cell polarity and division. Trends Cell Biol 2008;18:193-198.