The Impact of Serum Glucose in the Treatment of Locoregionally Advanced Pancreatic Cancer

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Introduction: Studies have consistently identified an increased risk of pancreatic cancer in diabetics, yet the role hyperglycemia may play in predicting prognosis is less clear. This work aims to evaluate the impact of glycemic state and antidiabetics on outcomes after systemic and local treatment for locoregionally advanced pancreatic cancer.

Materials and Methods: This retrospective study consisted of 303 patients with newly diagnosed advanced-stage pancreatic cancer treated from 2004 to 2014. Kaplan-Meier survival analysis method was used to estimate time to event for overall survival, distant metastasis, and locoregional control. Blood glucose values (n = 8599) were assessed both as continuous and categorical variables in univariate and multivariable Cox proportional hazard regression models to estimate hazard ratios (HRs) and identify independent prognostic factors. A 6-month conditional landmark analysis excluding patients with <6 months follow-up or survival was conducted.

Results: Median follow-up and survival was 18.1 and 18.4 months, respectively. On univariate analysis, maximum pretreatment glucose value was associated with reduced overall survival (HR 1.005, $P = 0.023$) and locoregional control (HR 1.001, $P = 0.001$). A pretreatment glucose value ≥ 200 mg/dL was associated with increased mortality in multivariable analysis (adjusted HR 1.01, $P = 0.015$). After conditional analysis, glucose ≥ 200 mg/dL before local treatment was associated with reduced overall survival (adjusted HR 1.562; 95% confidence interval [CI], 1.16-2.11; $P = 0.003$).

Conclusions: Elevated blood glucose before treatment of locoregionally advanced pancreatic cancer was associated with poorer outcomes. These findings should be incorporated in future clinical trial design.

Key Words: pancreatic cancer, glucose, metformin, antidiabetics, Warburg, metabolism

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Pancreatic cancer is recognized as the fourth leading cause of cancer mortality in the United States.[1] Although death rates continue to decline in other major cancer sites, such as colorectum, breast, and prostate, minimal improvements in survival have been achieved for pancreatic cancer patients. Although pancreatic cancer may present with nonspecific symptoms such as malaise, weight loss, and abdominal pain early in the disease course, these are often absent or go unnoticed. Therefore, the dismal 6% 5-year relative survival rate is largely a function of late presentation in patients whose symptoms have remained clinically silent until after locoregional progression.[2] Despite the absence of a clear mechanism, smoking and age have consistently been identified as risk factors for pancreatic cancer.[3] As population longevity and the rate of tobacco use continue to increase in developing countries, the global burden of pancreatic cancer is likely to escalate in the coming years.

Although the initiation of cancer has historically been considered a disease of genetics, the role of metabolism in the process of carcinogenesis has gained popularity in recent literature. In fact, already in the 1920s Nobel prize laureate Otto Warburg described how cancer cells insatiably consume glucose and produce lactate, even in the presence of sufficient oxygen for aerobic phosphorylation.[4] This observation termed the "Warburg Effect," is the biochemical underpinning for the use of [F-18] Fluorodeoxyglucose Positron Emission Tomography scans in the detection and monitoring of tumors. Recent studies have speculated that cancer cells benefit from aerobic glycolysis by a variety of biochemical mechanisms. Namely, enhanced Akt-mediated glucose transporter translocation and hexokinase 2 activity may enable cancer cells to outcompete healthy cells for limited glucose in the tumor microenvironment.[5] Augmented glucose uptake may subsequently enable cancer cells to enhance NADPH production in the oxidative branch of the pentose phosphate pathway, thus increasing available reducing equivalents necessary for de novo biosynthesis in proliferating cells,[6] and to repair oxidative damage from chemotherapy and radiation therapy (RT).[7] This discrepancy in metabolism has sparked interest in the role hyperglycemia and diabetes may play in tumor progression, treatment, and prognosis.

Additional evidence indicates that hyperglycemia during treatment may confer an unfavorable prognosis. Insulin, an anabolic hormone with mitogenic effects, is elevated in the setting of type 2 diabetes and hyperglycemia. Insulin can bind both to the insulin receptor (IR) and enhance the bioavailability of insulin-like growth factor 1 (IGF-1), further promoting potent antiapoptotic and proproliferative effects through stimulation of the IR and IGF-1 receptor, and subsequent provocation of the PI3K/Akt/mTORC1 and MAPK pathways.[7,8]

The role glycemic state may play as a prognostic factor in pancreatic cancer is unclear, with some studies revealing an increased risk of cancer development with hyperglycemia and an association between type 2 diabetes and pancreatic cancer.[9] However, diabetes has been speculated to be a consequence of pancreatic cancer rather than causative.[10] Interestingly, low serum glucose during the treatment of other cancers (ie, glioblastoma

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multiforme) has been linked to improved clinical outcomes,[11] and trials have attempted to capitalize on this metabolic state.[12] Whether this relationship is true of pancreatic adenocarcinoma remains elusive.

In this study, we investigate the influence glycemic state and antidiabetic medications may have on overall survival, distant metastasis, and locoregional control in a cohort of patients with locally advanced pancreatic adenocarcinoma.

MATERIALS AND METHODS

Patient Population

After Institutional Review Board approval, we conducted a retrospective cohort study consisting of patients with newly diagnosed locoregionally advanced pancreatic adenocarcinoma, initially unresectable and treated at the University of Pittsburgh Medical Center between 2004 and 2014. In accordance with institutional preference, all patients received stereotactic body RT as single or 3-fractions regimens as either monotherapy or in combination with surgery and systemic therapy. In patients receiving multimodality therapy, RT was administered either adjuvantly or neoadjuvantly with surgery and/or systemic therapy at the discretion of the primary oncology team.

Measures

Patient demographics, including age, sex, weight, prescribed medications, body mass index, and comorbidities were collected from the hospital's electronic medical record PowerChart (Cerner). Nonfasting plasma glucose values were inputted into PowerChart by all members of the oncologic team at various time points throughout the treatment process and all available values were initially collected. In many cases, serum glucose was assessed multiple times throughout the day and patients were therefore in differing glycemic states. To account for this, we included all available glucose values (n = 8599) spanning from 90 days pre-radiotherapy to 90 days postradiotherapy. Glucose values were then grouped into time points 1, 2, and 3, defined as 90 days before radiotherapy, during radiotherapy, and 90 days postradiotherapy. However, few serum glucose values were contained by time point 2, during radiotherapy; we therefore excluded this time point from the analysis. At the remaining time points, we analyzed maximum, median, and minimum serum glucose values as continuous variables with respect to overall survival, locoregional control, and distant metastasis.

Furthermore, at both 90 days prior and 90 days post-radiotherapy we stratified the maximum serum glucose value achieved into ≥ 130, ≥ 150, ≥ 175, and ≥ 200 mg/dL. We then conducted Cox regression to evaluate the impact maximum serum glucose values may have on our primary outcomes of interest. Finally, we used a 6-month conditional landmark analysis excluding patients with <6 months of survival or follow-up. Serum glucose values at the preceding time points were considered the primary prognostic factor of interest in this study.

Statistical Analysis

Overall survival, locoregional control, and freedom from distant metastasis were the primary outcome measures evaluated. Given the rapidly progressive nature of locoregionally advanced pancreatic cancer, we found overall survival to be an appropriate measure of cancer mortality. Locoregional control was defined as the absence of both local failure and regional failure during the study period. Kaplan-Meier survival analyses were conducted to estimate the time to event for each of our primary outcomes of interest. In addition to serum glucose values, select variables including patient, disease, and treatment characteristics were subject to univariate survival analysis by log-rank test or unadjusted Cox regression analysis. Multivariable Cox regression modeling was performed using lenient inclusion criteria from univariate analysis ($P < 0.10$) in light of the number of cases and events, in addition to variables felt of relevant clinical value or in question. To limit the impact of immortal time bias, a conditional landmark of follow-up ≥ 6 months was applied for separate multivariable Cox regression survival analysis. All statistical analyses were completed using IBM SPSS Statistics Version 23 (IBM, Armonk, NY).

RESULTS

Patient Characteristics

We identified 308 patients with locoregionally advanced pancreatic cancer, treated between 2004 and 2014. Patients with nonadenocarcinoma histology (n = 5) were excluded and the remaining 303 patients were included for analysis (Table 1). The study cohort was composed of 152 (50.2%) male individuals and

TABLE 1. Patient, Disease, and Treatment Characteristics (N = 303)

Characteristics	n (%)
Patient characteristics	
Age (y)	
Median (range)	70 (33-90)
Sex	
Male	152 (50.2)
Female	151 (49.8)
Race	
White	277 (91.4)
Other	12 (4.0)
Unknown	14 (4.6)
Body mass index	
Median (range)	24.8 (14.5-45.8)
Comorbidities	
Diabetes	176 (58.1)
Coronary artery disease	37 (12.2)
Hyperlipidemia	73 (24.1)
Hypertension	207 (68.3)
Medications	
Metformin	41 (13.5)
Pancreatic enzymes	130 (42.9)
Sulfonylurea	23 (7.6)
Insulin	158 (52.1)
Statin (before or at diagnosis)	59 (19.5)
Glucocorticoid	91 (30.0)
β-blocker (before or at diagnosis)	53 (17.5)
β-blocker (active use)	107 (35.3)
Disease characteristics	
Histology	
Adenocarcinoma	303 (100)
Lymph node status	
cN0	127 (41.9)
cN+	164 (54.1)
Not reported	12 (4.0)
Resectability	
Unresectable	149 (49.2)
Borderline resectable	40 (13.2)
Resectable	111 (36.6)
Unknown	3 (1.0)
Treatment characteristics	
Surgery	136 (44.9)
Immunotherapy	12 (4.0)
Chemotherapy	248 (81.8)

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TABLE 2. Glucose Values (n = 8599) Measured Before, During, and After Radiation

	Within 90 d Before Radiation	Within 90 d After Radiation
No. glucose measurements per patient		
Median (range) (mg/dL)	5 (1-150)	1 (1-222)
Median glucose measurement per patient		
Median (range) (mg/dL)	128.0 (72.5-268.0)	134.5 (59.0-324.0)
Minimum glucose measurement per patient		
Median (range) (mg/dL)	96.0 (34.0-267.0)	93.5 (25.0-286.0)
Maximum glucose measurement per patient		
Median (range) (mg/dL)	177.5 (73.0-639.0)	175.5 (59.0-561.0)
No. patients with any glucose value (mg/dL), n (%)		
≥ 130	185 (61.1)	125 (41.3)
≥ 150	157 (51.8)	107 (35.3)
≥ 175	129 (42.6)	82 (27.1)
≥ 200	94 (31.0)	65 (21.5)

151 (49.8%) female individuals. The median age was 70 years (range, 33 to 90) with a median preradiotherapy body mass index of 24.8 (range, 14.5 to 45.8). A considerable proportion of our study cohort received surgical management (44.9%) and/or chemotherapy (81.8%), whereas the minority received immunotherapy (4.0%). As alluded to, our database in its entirety consisted of 8599 glucose values measure before, during, and after RT. Primary tumor locations were as follows: body 11.9% (n = 36), head 62.4% (n = 189), tail 2.6% (n = 8), uncinate 7.3% (n = 22), 5.0% (n = 15), genu 0.3% (n = 1), and multiple areas 10.5% (n = 32).

Serum glucose values showed a minor increasing trend throughout the course of treatment. The median glucose value within 90 days before radiation, during, and within 90 days postradiation were 128.0, 130.0, and 134.5 mg/dL. A detailed summary of serum glucose values is presented in Table 2. The mean (and SD) maximum pre-RT glucose values were 199.6 ± 90.0, 192.5 ± 108.4, and 197.9 ± 92.3, respectively, for unresectable, borderline resectable, and resectable patients ($P = 0.931$).

Univariate Analysis

The median survival of our pancreatic cancer study population was 18.4 months (95% confidence interval [CI], 16.3-20.5). With a median follow-up time of 18.1 months (range, 2.0 to 112.1) the 1 and 2-year Kaplan-Meier estimates were as follows: overall survival 69.4% (95% CI, 64.1%-74.4%) and 35.9% (95% CI, 30.4%-41.4%), locoregional control 69.2% (95% CI, 58.0%-80.4%) and 28.0% (95% CI, 16.8%-39.2%), freedom from distant metastasis 52.9% (95% CI, 45.3%-62.5%) and 22.7% (95% CI, 15.4%-30.0%).

Univariate analysis was performed using the variables in Table 3. Increasing age was associated with both diminished overall survival (unadjusted HR 1.017, $P = 0.003$) and freedom from distant metastasis (unadjusted HR 1.018, $P = 0.024$) when assessed continuously. Pancreatic enzyme usage was associated with improved freedom from distant metastasis rates (2-year estimate 17.9% vs. 27.9%, $P = 0.050$) and overall survival (2-year estimate 26.2% vs. 46.2%, $P = 0.001$), whereas insulin usage correlated with improved 2-year overall survival (31.2% vs. 39.0%, $P = 0.030$). Metformin and sulfonylurea usage were not associated with any assessed outcomes. Surgical management (15.0% vs. 61.3%, $P < 0.001$), chemotherapy (9.8% vs. 41.3%, $P < 0.001$), and immunotherapy (33.5% vs. 91.7%, $P = 0.012$) were all identified as significant positive parameters for 2-year overall survival.

When evaluated as a continuous variable, maximum pretreatment glucose was correlated with reduced locoregional control (unadjusted HR 1.005, $P = 0.023$) and overall survival (unadjusted HR 1.001, $P = 0.053$). Further, reduced 2-year locoregional control was observed in patients achieving a pretreatment glucose value ≥ 150 mg/dL (46.8% vs. 13.2%, $P = 0.024$) or ≥ 175 mg/dL (38.7% vs. 8.5%, $P = 0.069$). Finally, pretreatment glucose value ≥ 200 mg/dL was identified as a consistent negative parameter for 2-year overall survival (42.5% vs. 24.2%, $P = 0.001$).

Multivariable Analysis

Variables achieving or approaching significance at the $P \leq 0.10$ level were considered for multivariable Cox regression. In this model surgery remained a significant independent positive predictor of survival (adjusted HR 0.32; 95% CI, 0.23-0.45; $P < 0.001$), distant metastasis (adjusted HR 0.335; 95% CI, 0.209-0.536; $P < 0.001$), and locoregional control (adjusted HR 0.48; 95% CI, 0.26-0.90; $P = 0.022$) (Table 4). Furthermore, maximum pretreatment glucose value was associated with reduced survival (adjusted HR 1.01; 95% CI, 1.00-1.01; $P = 0.015$). To reduce the risk of immortal time bias, a condition landmark analysis was conducted with a 6-month follow-up cutoff.

In our 6-month conditional landmark analysis, a trend toward diminished 2-year overall survival was noted as maximum pretreatment glucose value achieved progressed from 130 to 200 mg/dL (Fig. 1). Finally, maximum pretreatment glucose value ≥ 200 mg/dL was found to be a significant independent negative predictor of survival (adjusted HR 1.562; 95% CI, 1.16-2.11; $P = 0.003$) (Fig. 2).

A separate subset analysis on resectable patients was performed because of the large improvement in survival generally seen with surgery. Analysis of maximum pre-RT glucose value produced the same relationship with overall survival (HR 1.01, $P = 0.034$). Furthermore, the results were identical with the 6-month conditional landmark multivariable model.

DISCUSSION

In this retrospective cohort study, we evaluated the role glycemic state may play as a prognostic factor before, during, and after the treatment of locoregionally advanced pancreatic adenocarcinoma. Using a robust data set with an extensive number of glucose values (n = 8599), we found evidence that elevated serum glucose is associated with a reduction in overall survival in this study population. To our knowledge, this is the first study to report on the association between glycemia and overall survival, distant metastasis, and locoregional control in a strict cohort of locoregionally advanced pancreatic adenocarcinoma patients.

In our conditional landmark analysis, we excluded patients with <6 months of survival as patients with such a poor prognosis were less likely to be affected by glycemia. Pretreatment glucose values ≥ 150 or ≥ 175 mg/dL were associated with a statistically significant and drastic reduction in 2-year locoregional control. On multivariable analysis in this population, we report significantly diminished overall survival in patients achieving a pretreatment glucose value ≥ 200 mg/dL. Furthermore, our data suggest that there may be a glycemic threshold value before which perturbations in oncologic outcomes are not apparent.

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TABLE 3. Univariate Survival Analysis for Locoregional Control, Distant Metastasis-free Rate, and Overall Survival

	Locoregional Control *P* (2 y Estimate/HR*)	Distant Metastasis-free *P* (2 y Estimate/HR*)	Overall Survival *P* (2 y Estimate/HR*)
Age (continuous)	0.949	**0.024 (HR 1.018)**	**0.003 (HR 1.017)**
Sex	0.363	0.203	0.908
Race	0.986	0.144	0.144
BMI (continuous)	0.149	0.545	0.753
Comorbidities			
Diabetes	0.570	0.759	0.122
Coronary artery disease	0.762	0.203	0.236
Hyperlipidemia	0.361	0.556	0.579
Hypertension	0.621	0.300	0.726
Medications			
Metformin	0.501	0.644	0.473
Pancreatic enzymes	0.525	**0.050 (17.9% vs. 27.9%)**	**0.001 (26.2% vs. 46.2%)**
Sulfonylurea	0.549	0.518	0.978
Insulin	0.308	0.592	**0.021 (34.0% vs. 41.1%)**
Glucocorticoid	0.160	0.449	0.139
β-blocker (before or at diagnosis)	**0.043 (27.8% vs. 0.0%)**	0.615	0.288
β-blocker (active use)	0.142	0.662	0.206
Lymph node status	0.209	0.577	0.915
Resectability			
Unresectable	**0.034 (20.8%)**	**< 0.001 (6.4%)**	**< 0.001 (16.2%)**
Borderline resectable	**0.034 (11.1%)**	**< 0.001 (23.1%)**	**< 0.001 (42.5%)**
Resectable	**0.034 (40.4%)**	**< 0.001 (36.4%)**	**< 0.001 (58.8%)**
Surgery	**0.030 (13.2% vs. 47.1%)**	**< 0.001 (5.2% vs. 37.1%)**	**< 0.001 (15.0% vs. 61.3%)**
Chemotherapy	0.617	**0.003 (0.0% vs. 24.4%)**	**< 0.001 (9.8% vs. 41.3%)**
Immunotherapy	0.212	0.115	**0.012 (33.5% vs. 91.7%)**
Median glucose value (continuous)			
Pretreatment	0.139	0.890	0.637
Posttreatment	0.923	0.863	0.563
Minimum glucose value (continuous)			
Pretreatment	0.526	0.308	0.519
Posttreatment	0.451	0.377	0.247
Maximum glucose value (continuous)			
Pretreatment	**0.023 (HR 1.005)**	0.285	**0.053 (HR 1.001)**
Posttreatment	0.182	0.756	0.585
Any pretreatment glucose value (mg/dL)			
≥ 130	0.158 (40.0% vs. 22.9%)	0.723 (29.2% vs. 23.4%)	0.612 (40.0% vs. 34.5%)
≥ 150	**0.024 (46.8% vs. 13.2%)**	0.502 (29.7% vs. 21.9%)	0.495 (38.5% vs. 33.7%)
≥ 175	**0.069 (38.7% vs. 8.5%)**	0.247 (29.6% vs. 19.1%)	0.258 (39.9% vs. 31.4%)
≥ 200	0.200 (33.5% vs. 12.5%)	0.287 (27.7% vs. 19.4%)	**0.001 (42.5% vs. 24.2%)**
Any posttreatment glucose value (mg/dL)			
≥ 130	0.103	0.648	0.289
≥ 150	0.124	0.877	0.836
≥ 175	0.437	0.501	0.922
≥ 200	0.227	0.669	0.214

*Univariate survival testing performed using log-rank (categorical variables) and unadjusted Cox regression analysis (continuous variables).
Significant values are Bold.
BMI indicates body mass index; HR, hazard ratio.

These results are biologically plausible. The PI3K/Akt/mTORC1 pathway, which is upregulated by the activation of the IR by glucose and insulin binding, seems to be a monumental regulator of survival during periods of cellular stress.[13] Properties of the tumor microenvironment, including limited oxygen and nutrients, and reduced pH, contribute to intrinsically stressful conditions.[14] Enhanced PI3K/Akt/mTORC1 activity may confer a survival advantage to malignant cells. Indeed, preclinical data examining the effects of these pathways has confirmed that augmented activation is associated with altered cellular function consistent with antiapoptotic and procellular proliferative states.[15] By both directly and indirectly increasing IGF-1 bioavailability, insulin possesses additional mitogenic effects. Furthermore, glucose can alter the expression of RET and glial cell line-derived neurotrophic factor in a concentration-dependent manner in pancreatic cancer cell lines,[16] suggesting that hyperglycemia may promote pancreatic cancer progression and increase resistance to chemotherapy.[17] Although preclinical data suggest that molecular antagonists of key proteins in downstream pathways may exert potent anticancer effects, downregulation by intense lifestyle and dietary alterations is being attempted at other cancer sites to potentially offset these glucose-fueled pathways.[12,18] This represents an appealing possible mechanism that may account for the cancer-specific outcomes affected by glycemia in our study population.

A review of recent literature yields evidence for an association between hyperinsulinemia, as would be observed in insulin-resistant diabetics, and the risk of pancreatic cancer development.[19]

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TABLE 4. Multivariable Cox Regression Overall Survival Models With and Without 6-month Conditional Landmark Analysis

	All Patients (n = 303)		Patients With ≥ 6 mo Follow-up (n = 277)	
Variables	**Adjusted HR (95% CI)**	***P***	**Adjusted HR (95% CI)**	***P***
Locoregional control				
β-blocker (before or at diagnosis)	1.80 (0.61-5.31)	0.287	1.60 (0.54-4.71)	0.396
Surgery	**0.48 (0.26-0.90)**	**0.022**	**0.41 (0.21-0.79)**	**0.008**
Maximum pretreatment glucose value	1.00 (1.00-1.01)	0.253	1.00 (1.00-1.01)	0.352
Distant metastasis				
Age (continuous)	1.004 (0.987-1.022)	0.613	1.004 (0.987-1.022)	0.630
Use of pancreatic enzymes	1.123 (0.744-1.695)	0.580	1.099 (0.726-1.663)	0.656
Surgery	**0.335 (0.209-0.536)**	**< 0.001**	**0.342 (0.213-0.549)**	**< 0.001**
Chemotherapy	0.515 (0.226-1.176)	0.115	0.612 (0.248-1.509)	0.286
Immunotherapy	0.603 (0.252-1.443)	0.256	0.595 (0.249-1.425)	0.244
Overall survival				
Age	1.01 (0.99-1.02)	0.383	1.01 (1.00-1.03)	0.158
Pancreatic enzyme use	1.22 (0.90-1.66)	0.203	1.26 (0.91-1.73)	0.159
Insulin use	0.99 (0.73-1.33)	0.935	0.92 (0.67-1.25)	0.584
Surgery	**0.32 (0.23-0.45)**	**< 0.001**	**0.32 (0.23-0.46)**	**< 0.001**
Chemotherapy	**0.50 (0.32-0.77)**	**0.001**	0.72 (0.44-1.18)	0.191
Immunotherapy	0.63 (0.30-1.32)	0.221	0.68 (0.32-1.42)	0.301
Maximum pretreatment glucose value	**1.01 (1.00-1.01)**	**0.015**	**1.01 (1.00-1.01)**	**0.015**

Bold values indicate statistically significant.
CI indicates confidence interval; HR, hazard ratio.

Despite this, data examining glycemic state as a prognostic factor for pancreatic cancer is severely lacking. However, a recent retrospective analysis of 302 patients found increased 2-year survival rates in pancreatic cancer patients using metformin (30.1% vs. 15.4%, $P = 0.004$).[20] Metformin is a widely used type 2 diabetes medication known to lower serum glucose by activating adenosine monophosphate-activated protein kinase. These findings indirectly indicate that glycemic control during the treatment of pancreatic cancer may reinforce standard oncologic treatment modalities and improve cancer-specific outcomes. This effect, however, was not seen in our patient group, possibly because of the small number of patients taking metformin at the time of treatment (13.5%). Furthermore, Cheon et al[21] reported increased median overall survival time in diabetic advanced-stage pancreatic cancer patients with HbA1c <7.0% versus ≥7.0% (362 vs. 144 d, $P = 0.038$). In this 127-patient cohort metformin usage also trended with diminished mortality (273 vs. 145 d, $P = 0.058$). Our glycemia findings are consistent with these previous reports and indicates that hyperglycemia may confer a poor prognosis in patients with locoregionally advanced pancreatic cancer.

Several limitations are present in this study. Patient serum glucose values were often assessed numerous times throughout the day and patients were therefore in differing glycemic states. This represents a potential source of variability in our data that we attempted to mitigate by including all 8599 glucose values spanning from 90 days pre-RT to 90 days post-RT for analysis. Patient data were acquired retrospectively, and unavoidable confounding is possible. Although the patient population did have some inherent treatment heterogeneity (ie, resectability status), no significant difference was noted among maximum glucose values on the basis of resectability subgroups and a subset analysis performed among resectable patients still retained comparable findings. Nevertheless, to our knowledge, this represents the greatest number of glucose data points per patient in a study of this kind, whereas assessing the impact of glucose and antidiabetic agents with survival endpoints and locoregional control.

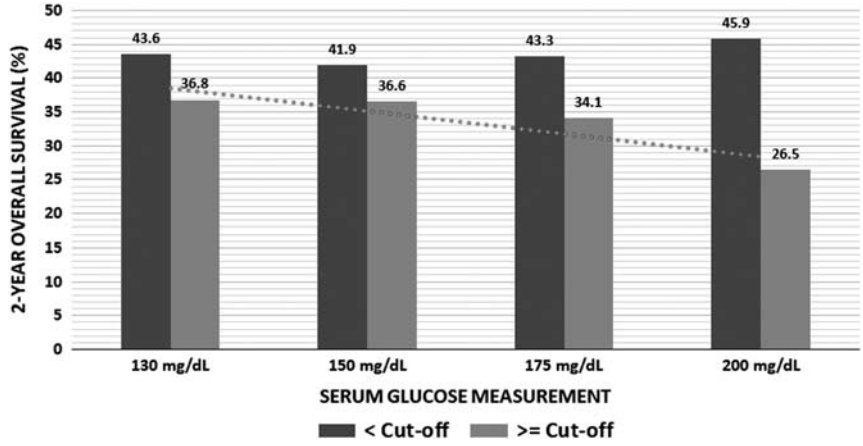

FIGURE 1. Two-year overall survival estimates on the basis of maximum pretreatment (within 90 d of radiation) glucose values following conditional landmark analysis.

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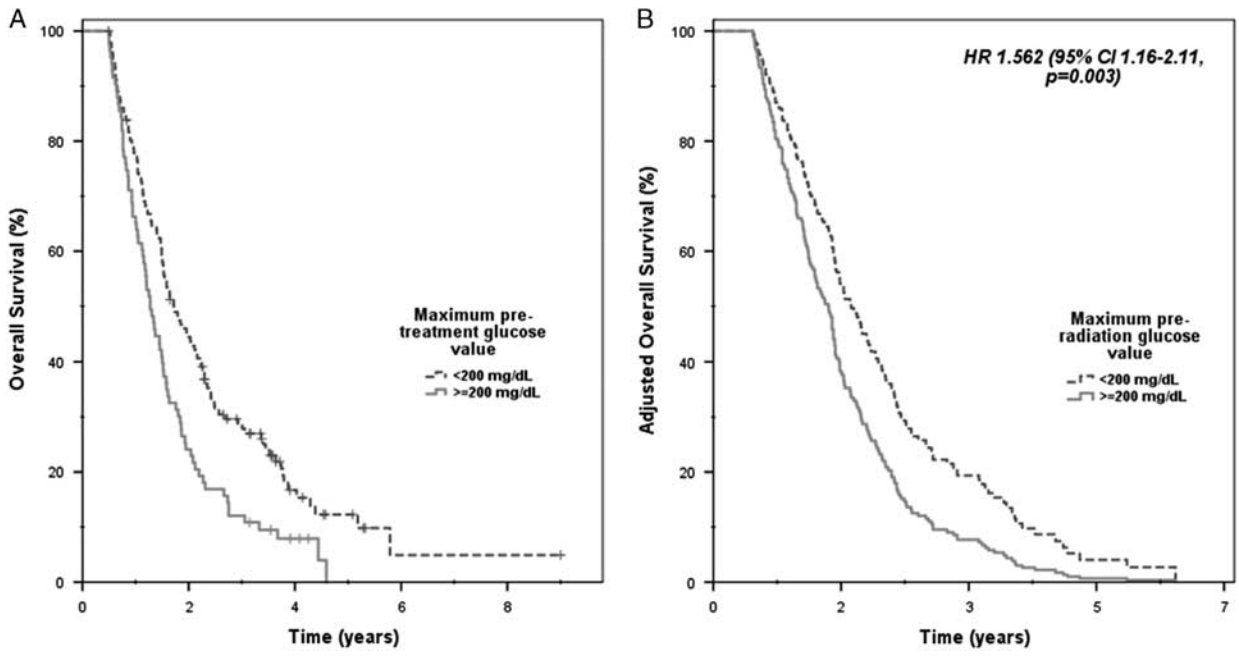

FIGURE 2. Unadjusted (A) and adjusted (B) overall survival estimate on the basis of maximum recorded pretreatment (within 90 d of radiation) glucose value with the exclusion of patients with <6 months of survival and/or follow-up. CI indicates confidence interval; HR, hazard ratio.

CONCLUSIONS

Hyperglycemia was associated with reduced overall survival in patients with locoregionally advanced pancreatic cancer after robust statistical analysis. High-quality prospective studies are needed to further elucidate the relationship between the glycemic state and pancreatic cancer prognosis, and these results can be included in future clinical trial design.

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