Metformin’s Role In The Overall Survival of Pancreatic Cancer: Is It “Meant For All Men?”

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February 3, 2017

Learning objectives:
1. Identify risk factors, pathophysiology, and treatment for pancreatic cancer
2. Explain the proposed mechanism of action of metformin in pancreatic cancer
3. Evaluate current literature to understand metformin’s role in pancreatic cancer treatment
4. Formulate evidence-based recommendations for use of metformin in pancreatic cancer
I. Disease characteristics
   a. Definitions\textsuperscript{1,2}
      i. Pancreatic ductal adenocarcinoma (PDAC) represents the majority of pancreatic malignancies, with a rate of 90% 
      ii. PDAC begins in exocrine cells that line the ducts of the pancreas, hence the name ductal adenocarcinoma 
      iii. Pancreatic cancer (PC), pancreatic adenocarcinoma (PAC), and PDAC are all commonly used synonymously 
   b. Epidemiology in the United States\textsuperscript{1,4}
      i. Fourth leading cause of cancer death 
      ii. Increase in incidence from 1999-2008 in both men and women 
      iii. Change in mortality trends has been minimal since 2015 
      iv. In the United States in 2016, 53,070 new cases diagnosed and 41,780 deaths 
         ![Five Year Mortality of Pancreatic Cancer](image)
         \textbf{Figure 1. Five Year Mortality of Pancreatic Cancer}
         
         v. High mortality rates have prompted an in-depth investigation into adjunctive methods to improve survival in pancreatic cancer 
   c. Modifiable and non-modifiable risk factors\textsuperscript{2,5,6-9}
      i. Modifiable 
         1. Cigarette smoking, with twice the risk compared to non-smokers 
         2. Obesity 
         3. Type II diabetes mellitus (T2DM) 
         4. Alcohol use 
      ii. Non-Modifiable 
         1. Family history of pancreatic cancer 
         2. Presence of genetic mutations such as BRCA1 and BRCA2, however over 14 genetic mutations have been identified 
         3. Ethnicity, specifically African-American and Caucasian
II. Types of pancreatic cancer
   a. Exocrine
      i. Most common type of solid tumors (95%)
      ii. Pancreatic adenocarcinoma most common exocrine pancreatic cancer
   b. Endocrine
      i. Rarer, neuroendocrine tumor (5%)
      ii. Younger age at diagnosis
      iii. Better prognosis than exocrine tumors

III. Pathophysiology
   a. Activation of oncogenes
      i. Point mutations and abnormal amplification, specifically K-ras mutations
      ii. Amplification of cyclooxygenase (COX) enzymes
   b. Inactivation of tumor suppressor genes
      i. 95% of pancreatic patients have inactivated p16 gene
      ii. Other inactivated tumor suppressor genes include p53, p21, and p27
   c. Deregulation of normal signaling pathways

IV. Signs and symptoms of pancreatic cancer
   a. Signs
      i. Biomarkers may be used for surveillance, but have low specificity for PDAC
      ii. Common biomarkers for detection and surveillance of PDAC include:
         1. Carcinoembryonic antigen (CEA) → used as predictor of survival
         2. Carbohydrate antigen 19-9 (CA 19-9) → utilized in the surveillance of recurrence of disease after surgical resection
   b. Symptoms
      i. Usually non-specific in the earlier stages and may go unnoticed or be mistaken for other diseases such as pancreatitis
      ii. As the tumor grows, symptoms can include:
         1. Jaundice, if tumor develops near the common bile duct
         2. Light-colored stools or dark urine
         3. Pain in the upper/middle abdomen and back
         4. Unintentional weight loss
         5. Loss of appetite
      iii. Severity of symptoms correlates with tumor burden
V. Diagnosis
   
a. Diagnosis often occurs at a late stage
   
i. Major barriers in the treatment of PC include:
      1. Lack of specific symptoms
      2. Nonspecific biomarkers
      3. Anatomy and location of the pancreas, with tumors in the tail associated with worse prognosis and unresectable surgery
   
ii. Difficulty in treating disease due to the presence of metastases when diagnosis is made

| Table 1. Tumor/Node/Metastases (TNM) Staging of Pancreatic Cancer |
|--------------------------|-----------------|-------------------|
| Stage | Primary Tumor (T) | Regional Lymph Node | Distant Metastases |
| Stage 0 | Tis | N0 | M0 |
| Stage IA | T1 | N0 | M0 |
| Stage IB | T2 | N0 | M0 |
| Stage IIA | T3 | N0 | M0 |
| Stage IIB | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| | T3 | N1 | M0 |
| Stage III | T4 | Any N | M0 |
| Stage IV | Any T | Any N | M1 |

Definitions
- Tis = carcinoma in situ
- T1 = tumor limited to pancreas ≤ 2 cm
- T2 = tumor limited to pancreas, > 2 cm
- T3 = tumor extends beyond the pancreas but without involvement of celiac axis or superior mesenteric artery
- T4 = tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
- N0 = no regional lymph node metastasis
- N1 = regional lymph node metastasis
- M0 = no distant metastases
- M1 = distant metastasis

b. Imaging
   
i. Helical computed tomographic scan, specifically pancreatic protocol CT scan
   
ii. Magnetic resonance imaging scan, specifically a pancreatic MRI scan
   
iii. Magnetic resonance cholangiopancreatography, to clearly identify pancreas and bile ducts
   
iv. Endoscopic ultrasound
VI. Treatment of pancreatic cancer \(^2\^-5,7\^-10,12\)
   a. Surgery
      i. One of the few treatment options that may extend survival and the only curative treatment
      ii. Only 10-20% of patients are candidates for surgery due to metastasis identified at diagnosis
      iii. Factors involved in the decision for surgery include patient’s age, comorbidities, performance status, location of the tumor, with the body and the tail being affected late in the disease state and rendering them rarely resectable
      iv. Surgical definitions \(^3\)
         1. Resectable: imaging results show surgery to be beneficial
         2. Borderline resectable
            a. Tumors involved with nearby structures
            b. Not clearly resectable, nor clearly unresectable
            c. Higher likelihood of incomplete resection
         3. Unresectable
            a. Locally advanced: tumors involved with nearby structures to an extent that renders them unresectable, despite non-metastatic nature
            b. Metastatic: disseminated disease
   v. Surgical procedures \(^3\)
      1. Whipple procedure
         a. Also known as a pancreatoduodenectomy
         b. Removes the head of the pancreas, gallbladder, duodenum, part of the bile duct, and often part of the stomach

Figure 3. Pancreatic cancer testing \(^3\)
2. Distal pancreatectomy  
   a. Surgery removes the body, tail of the pancreas, nearby lymph nodes, and at times, the spleen

3. Total pancreatectomy  
   a. Removal of the entire pancreas  
   b. Also involves removal of the gallbladder, duodenum, part of the bile duct and stomach, adjacent lymph nodes, and at times, the spleen  
   c. Uncommon surgery

b. Chemoradiation used in the adjuvant setting in specific patient populations

c. Chemotherapy regimens for pancreatic cancer

i. Most beneficial chemotherapeutic regimen identified by considering:  
   1. Resectability status, identified by the potential to attain negative surgical margins  
   2. Performance status measured by Eastern Cooperative Oncology Group  
   3. Previous treatments, including surgery and radiation

ii. FOLFIRINOX  
   1. Combination of chemotherapeutic agents including folinic acid, 5-fluorouracil (5-FU), irinotecan hydrochloride, and oxaliplatin  
   2. Associated with severe toxicities such as neutropenia, diarrhea, thrombocytopenia, nausea, vomiting, and sensory neuropathy  
   3. Survival rates of approximately 11 months

iii. Gemcitabine-based therapies  
   1. Gemcitabine as monotherapy  
   2. Combination therapies such as with capecitabine and cisplatin  
   3. Combination with EGFR inhibitor, erlotinib, used as targeted treatment  
      a. Most recent data shows a slight increase in survival of gemcitabine/erlotinib combination therapy compared to gemcitabine monotherapy  
      b. Median overall survival of 6.2 months  
   4. Combination with albumin-bound paclitaxel (Abraxane®)
a. Regimen often used first line when FOLFIRINOX is not an option
b. Associated with less toxicities than FOLFIRINOX regimen
c. Median overall survival of 12.2 months

VII. Prognosis and survival\textsuperscript{2,12,14}
   a. Dependent on the following:
      i. If the cancer is localized to the pancreas
      ii. Potential for the tumor to be resected
      iii. Metastasis of cancer to the lymph nodes or elsewhere in the body
b. Highest cure rates for cancer localized to the pancreas
c. FOLFIRINOX and gemcitabine combination therapy regimens have mortality benefit
d. Dismal survival rates and late diagnosis contribute to the need for additional therapies

\textbf{METFORMIN}\textsuperscript{1-4,8,12}

I. Why metformin?
   a. T2DM has long been identified as a risk factor and a determinant of poor outcomes in patients with pancreatic cancer
   b. In-vitro studies have proposed an associated benefit in cancer cells treated with metformin
   c. Evans et al, 2005\textsuperscript{15}
      i. First experimental study to hypothesize metformin and cancer association
      ii. Pilot case-control study in Scotland that hypothesized a possible dose-dependent response with metformin
      iii. Authors concluded that there may be a possible benefit with metformin use in reducing cancer risk; however, conclusions not specific to any cancer

II. Metformin for use in T2DM
   a. Mechanism
      i. Oral hypoglycemic agent in the biguanide class
      ii. Decreases hepatic glucose production and increases insulin sensitivity

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{mechanisms_of_metformin.png}
\caption{Mechanisms of metformin in T2DM\textsuperscript{16}}
\end{figure}
b. Indications\(^\text{17}\)
   i. Mainstay of treatment in T2DM
   ii. Other indications include polycystic ovary syndrome and non-alcoholic steatohepatitis

c. Doses and max dose\(^\text{17}\)
   i. Typical dose in T2DM initiated at 500 mg daily, up to 1000 mg twice daily
   ii. Max dose per FDA labeling is 2550 mg daily

III. Mechanisms of metformin in pancreatic cancer\(^2,18-23\)
   a. Inhibition of mammalian target of rapamycin (mTOR) and 5’ adenosine monophosphate-activated protein kinase (AMPK) activation
      i. Under instances of energetic stress in the body AMPK is activated
      ii. AMPK then shuts down synthesis of DNA by inhibiting mTOR and fatty acid synthesis by inhibiting acetyl-CoA carboxylases-1 (ACC1)
      iii. By inhibiting both DNA and fatty acid synthesis, the rates of cancer cell proliferation are markedly reduced
      iv. Metformin acts by disrupting mTOR communication in the signaling pathways specific to pancreatic cancer cells that are responsible for DNA synthesis and proliferation

![Proposed mechanism of metformin in PC\(^\text{17}\)](image)

b. Mitochondrial action
   i. Organic Cation Transporter (OCT’-s)
      1. Pancreatic cancer cells express OCT1, OCT2, and OCT 3 unlike normal cells
      2. Metformin is able to be transported into the mitochondria of cancer cells by means of the OCT’-s
   ii. Inhibition of Complex I
      1. Complex I normally functions to increase membrane potential to allow the electron transport chain (ETC) to continue and produce adenosine triphosphate (ATP)
2. Once metformin is inside the mitochondria, it inhibits complex I and decreases membrane potential.
3. With membrane potential decreased, the ETC is inhibited, proton pump excretion is decreased, and apoptosis ensues.
   c. Decreased expression of insulin-like growth factor-1 receptor (IGF-1R)
   d. Decreased expression of hypoxia-inducible factor (1α)

**LITERATURE REVIEW**

**Table 2: Previous studies evaluating the association between anti-diabetic medications and pancreatic cancer**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Study type</th>
<th>Patient Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currie, et al. 2009</td>
<td>Retrospective cohort study</td>
<td>DM patients with pancreatic cancer</td>
<td>Significant risk reduction in metformin users compared with sulfonylurea users (HR, 0.20; 95% CI, 0.11-0.36)</td>
</tr>
<tr>
<td>DeCensi, et al. 2010</td>
<td>Meta-analysis</td>
<td>11 studies reporting 4,042 cancer events and 529 cancer deaths</td>
<td>31% reduction in overall relative risk (0.69; 95% CI, 0.61-0.79)</td>
</tr>
<tr>
<td>Sadeghi, et al. 2012</td>
<td>Case-control study</td>
<td>PDAC patients with DM</td>
<td>Metformin decreases the risk of pancreatic cancer (OR, 0.38; 95% CI, 0.22-0.69)</td>
</tr>
<tr>
<td>Singh, et al. 2013</td>
<td>Meta-analysis</td>
<td>11 studies consisting of 1770 cases of pancreatic cancer with metformin, sulfonylurea’s (SU), thiazolidinediones (TZD’s), and insulin</td>
<td>No significant association between metformin (OR 0.76, 95% CI, 0.57-1.03, p = 0.073), insulin (OR 1.59, 95% CI, 0.85-2.96, p = 0.144) or TZD (OR 1.02, 95% CI, 0.81-1.3, p = 0.844) in their use and developing pancreatic cancer</td>
</tr>
<tr>
<td>Wang, et al. 2014</td>
<td>Meta-analysis</td>
<td>13 studies evaluating the risk of pancreatic cancer in patients on metformin therapy</td>
<td>Use of metformin is associated with a lower risk of pancreatic cancer in patients with DM (RR 0.63, 95% CI (0.46-0.86, p = 0.003)</td>
</tr>
<tr>
<td>Cerullo, et al. 2016</td>
<td>Retrospective cohort study</td>
<td>Diabetic patients who received metformin therapy following surgical resection</td>
<td>Patients on metformin after surgery had an improved overall survival at 18 months and 3 years following surgery; decreased risk of mortality in this patient population (HR = 0.79; 95% CI, 0.67-0.93, p = 0.005)</td>
</tr>
</tbody>
</table>
Does metformin provide overall survival benefit in patients with pancreatic cancer?


**Objective**
To determine if metformin has a survival benefit in diabetic patients with pancreatic cancer

**Design**
Single-centered, retrospective cohort study

**Methods**
Medication history collected via questionnaire, and clinical information was collected via medical record

**Intervention**
Patients who had ever received metformin were compared to those who had never received metformin, regardless of the dose and duration

**Patient Population**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed and pathologically confirmed pancreatic ductal adenocarcinoma</td>
<td>Patients who had a prior or concurrent malignancy</td>
</tr>
<tr>
<td>Patients were confirmed to have a pre-cancer diagnosis of diabetes mellitus</td>
<td>Patients who were not treated at MD Anderson for pancreatic cancer</td>
</tr>
<tr>
<td>Patients who were on metformin and other anti-diabetic combinations</td>
<td>Patients who did not have diabetes</td>
</tr>
</tbody>
</table>

**Endpoints**
Survival benefit for newly diagnosed patients with pancreatic cancer and diabetes, who received antidiabetic therapy prior to cancer diagnosis

**Statistics**
Baseline characteristics of the study population were compared using Student t-test for continuous variables and Pearson X² for categorical variables

Kaplan-Meier plot was used to estimate overall survival curves

Log-rank test was used to compare the survival curves of the 2 groups

Univariate and multivariate Cox proportional hazards regression models were used to evaluate potential predictors of survival

**Baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients, n (%)</th>
<th>Metformin, n (%)</th>
<th>Non-metformin, n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61-70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>139 (46)</td>
<td>52 (44.4)</td>
<td>87 (47)</td>
<td>0.655</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>198 (65.6)</td>
<td>75 (64.1)</td>
<td>123 (66.5)</td>
<td>0.671</td>
</tr>
<tr>
<td>Diabetes duration, y</td>
<td>0-2</td>
<td>&gt;2-5</td>
<td>&gt;5-10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>148 (49)</td>
<td>55 (18.2)</td>
<td>39 (12.9)</td>
<td>60 (19.9)</td>
<td>54 (46.2)</td>
</tr>
</tbody>
</table>
### Antidiabetics (ever used)

<table>
<thead>
<tr>
<th></th>
<th>Insulin</th>
<th>Sulfonylurea</th>
<th>Metformin</th>
<th>Thiazolidinedione</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>118 (39.1)</td>
<td>109 (36.1)</td>
<td>117 (38.7)</td>
<td>61 (20.2)</td>
</tr>
<tr>
<td></td>
<td>29 (24.8)</td>
<td>44 (37.6)</td>
<td>117 (100)</td>
<td>24 (20.5)</td>
</tr>
<tr>
<td></td>
<td>89 (48.1)</td>
<td>65 (35.1)</td>
<td>0</td>
<td>37 (20)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>0.663</td>
<td>0.914</td>
<td></td>
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### Tumor size, cm<sup>a</sup>

<p>| | | | |</p>
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<tr>
<td></td>
<td>3.9 ± 1.6</td>
<td>4.0 ± 1.8</td>
<td>3.9 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>0.412</td>
<td>0.663</td>
<td>0.914</td>
</tr>
</tbody>
</table>

### Tail involved

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<tbody>
<tr>
<td></td>
<td>46 (15.2)</td>
<td>24 (20.5)</td>
<td>22 (11.9)</td>
</tr>
<tr>
<td></td>
<td>0.042</td>
<td>0.763</td>
<td></td>
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</tbody>
</table>

### Stage

<p>| | | | |</p>
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<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>67 (22.2)</td>
<td>27 (23.1)</td>
<td>40 (21.6)</td>
</tr>
<tr>
<td>Unresectable</td>
<td>124 (41.1)</td>
<td>50 (42.7)</td>
<td>74 (40)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>111 (36.7)</td>
<td>40 (34.2)</td>
<td>71 (38.4)</td>
</tr>
<tr>
<td></td>
<td>0.412</td>
<td>0.763</td>
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</tr>
</tbody>
</table>

<sup>a</sup> = numbers are in mean ± SD.

### Results

#### Median survival in months (95%) CI for patients with different stages of disease and use of metformin

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=302)</th>
<th>Metformin (n=117)</th>
<th>Non-metformin (n=185)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>12.8 (11-14.7)</td>
<td>15.2 (12.6-17.8)</td>
<td>11.1 (8.9-13.3)</td>
<td>0.009</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resectable</td>
<td>28.2 (19.7-36.8)</td>
<td>31.0 (15.2-46.8)</td>
<td>21.4 (14.4-28.3)</td>
<td>0.293</td>
</tr>
<tr>
<td>Unresectable</td>
<td>13.8 (11.2-16.5)</td>
<td>15.5 (13.4-17.7)</td>
<td>11.0 (8.7-13.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Metastatic</td>
<td>8.3 (6.9-9.7)</td>
<td>8.8 (7.0-10.6)</td>
<td>7.3 (5.5-9.1)</td>
<td>0.482</td>
</tr>
<tr>
<td>Nonmetastatic</td>
<td>16.6 (14.3-18.9)</td>
<td>20.8 (15.7-26.0)</td>
<td>14.8 (12.5-17.2)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

- Median follow-up time was 11.4 months
- Metformin was associated with a 32% decrease in the risk of death (HR, 0.68; 95% CI, 0.52-0.89, p = 0.004), and this remained significant after excluding insulin users (HR, 0.62; 95% CI, 0.44-0.87; p = 0.006)
- Overall survival duration was 4.1 months longer in patients treated with metformin than in those not treated with metformin

### Author’s Conclusion

Metformin, used before cancer diagnosis and throughout treatment, could potentially be used as a supportive agent in the treatment of pancreatic cancer in diabetic patients

### Critique

#### Strengths

- Relatively large sample size of patients with diabetes and pancreatic cancer
- Tumor specific factors such as location, size, as well as CA 19-9 levels taken into account
- Multivariate analysis conducted
- Metformin arm with more tail involvement

#### Limitations

- Retrospective study
- More insulin use in non-metformin arm
- No specified metformin dose
- Did not consider combined effect of metformin and other antidiabetic agents or glycemic control status
- No information on cancer treatment regimens
**Take Home Points**

- There is a clinical association between diabetic patients treated with metformin and increase in survival.
- Beneficial effects of metformin were seen across all stages of pancreatic cancer, however only statistically significant in nonmetastatic.
- Metformin use improved survival in the nonmetastatic cancer stage by 6 months.

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**Objective**

To investigate whether metformin use before PDAC diagnosis affected survival of patients with known T2DM.

**Design**

Retrospective cohort study.

**Methods**

- Using the Surveillance, Epidemiology, and End Results (SEER) registry, patient and Medicare claims information were obtained.

**Population**

**Inclusion**

- Patients > 65 years of age
- Patients identified to have pancreatic adenocarcinoma through the use of ICD-9 codes
- T2DM cohort included either one hospital claim or two outpatient claims >1 year, but <2 years before PDAC diagnosis.

**Exclusion**

- Patients with >1 primary cancer
- Patients without Medicare Part B coverage (outpatient visits) or Medicare Part D coverage
- Patients who were diagnosed with T2DM in the year before PDAC diagnosis
- Patients who did not have a diabetic medication claim in the 6 months prior to cancer diagnosis.

**Endpoints**

Overall survival measured as the period from PDAC diagnosis to the date of death.

**Statistics**

- Kaplan-Meier analysis performed to determine difference in survival benefit among patients prescribed metformin vs. other anti-diabetic medications.
- Logistic regression model used to calculate propensity scores based on patient characteristics and concomitant medications.
- Cox proportional model used to adjust for confounders and specific disease characteristics such as stage and treatment modality (chemotherapy, surgery, radiation).

**Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Metformin n= 1,098, (%)</th>
<th>Non-metformin n = 818, (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>76.2 (6.8)</td>
<td>78 (7.2)</td>
<td>0.97</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>876 (80.1)</td>
<td>618 (75.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>African-American</td>
<td>106 (9.7)</td>
<td>128 (15.7)</td>
<td></td>
</tr>
<tr>
<td>Sex-male</td>
<td>433 (39.4)</td>
<td>319 (39)</td>
<td>0.85</td>
</tr>
<tr>
<td>Diabetic</td>
<td></td>
<td></td>
<td>0.94</td>
</tr>
<tr>
<td>comorbidity severity index (DCSI)</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
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</tr>
<tr>
<td>16 (1.5)</td>
<td>19 (2.3)</td>
<td>246 (22.4)</td>
<td>362 (44.3)</td>
</tr>
<tr>
<td>562 (51.2)</td>
<td>245 (30)</td>
<td>191 (23.4)</td>
<td></td>
</tr>
<tr>
<td>273 (24.9)</td>
<td></td>
<td></td>
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<tr>
<td>246 (22.4)</td>
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</table>

<table>
<thead>
<tr>
<th>Tumor/treatment characteristic</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>81 (8.3)</td>
<td>60 (8.8)</td>
<td>171 (25.1)</td>
<td>382 (56.1)</td>
<td></td>
</tr>
<tr>
<td>241 (24.8)</td>
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<tr>
<td>82 (8.4)</td>
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<tr>
<td>567 (58.3)</td>
<td></td>
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</tr>
</tbody>
</table>

| Cancer-directed surgery        | 145 (13.3) | 74 (9.2) | <0.01 |
| Radiatoin                      | 148 (13.6) | 72 (9)   | <0.01 |
| Chemotherapy                    | 342 (31.2) | 185 (22.6) | <0.01 |

| Other medications              |           |          |        |
| Sulfonylurea                    | 448 (40.8) | 279 (34.1) | <0.01 |
| Insulin                         | 328 (29.9) | 494 (60.4) | <0.01 |
| TZD                             | 288 (26.2) | 198 (24.2) | 0.31  |
| Meglitinide                     | 45 (4.1)   | 56 (6.9)  | <0.01 |
| DPP4 inhibitor                  | 152 (13.8) | 87 (10.6) | 0.04  |

### Results

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mean survival (metformin vs. no metformin)</th>
<th>Log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>9.2 vs. 6.5 months</td>
<td>0.08</td>
</tr>
<tr>
<td>Stage II</td>
<td>9.3 vs. 7.6 months</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stage III</td>
<td>7.4 vs. 4.5 months</td>
<td>0.02</td>
</tr>
<tr>
<td>Stage IV</td>
<td>2.9 vs. 2.4 months</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Overall</td>
<td>5.5 vs. 4.2 months</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Propensity score adjusted Cox-proportional hazards model for metformin

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>0.88 (0.81-0.96)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stage I (ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>1.19 (1.01-1.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stage III</td>
<td>1.43 (1.18-1.73)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stage IV</td>
<td>2.4 (2.07-2.78)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Surgery</td>
<td>0.41 (0.34-0.49)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Radiation</td>
<td>0.56 (0.48-0.65)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.39 (0.35-0.43)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
### Univariate survival among diabetics by class of medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mean survival (medication vs. none)</th>
<th>Log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>5.5 vs. 4.2 months</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>5.1 vs. 4.9 months</td>
<td>0.81</td>
</tr>
<tr>
<td>Insulin</td>
<td>4.3 vs. 5.5 months</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TZD</td>
<td>5.3 vs. 4.8 months</td>
<td>0.66</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>6.1 vs. 4.9 months</td>
<td>0.44</td>
</tr>
<tr>
<td>DPP4 inhibitor</td>
<td>3.4 vs. 5 months</td>
<td>0.26</td>
</tr>
<tr>
<td>Alpha glucosidase inhibitor</td>
<td>3.5 vs. 5 months</td>
<td>0.41</td>
</tr>
</tbody>
</table>

### Author’s Conclusion
- Diabetic patients with both metastatic and non-metastatic disease have survival benefit when treated with metformin compared to other anti-diabetic medications

### Critique
**Strengths**
- Stratified disease by stage and treatment modality
- Large population size
- Included comparison with other anti-diabetic medications
- Attempted to identify diabetes severity with diabetes comorbidity index
- Several statistical analyses to account for confounders and differences among treatment groups

**Limitations**
- No target metformin dose, and did not account for varying metformin doses
- Retrospective study
- Patients in metformin arm received more cancer-directed therapies, attempted to control for this with statistical analyses
- Physician order-entry data
- Unknown patient adherence as ICD-9 codes utilized to assess medication administration
- Did not aim to separate metformin monotherapy vs. combination with other antidiabetic medications

### Take Home Points
- In patients with diabetes and both metastatic and non-metastatic PDAC, metformin usage at the time of diagnosis have improved overall survival compared with patients on other anti-diabetic medications

---

**Objective**
To determine the effect of metformin exposure on survival in patients with advanced pancreatic adenocarcinoma (PAC)

**Design**
Retrospective cohort study

**Methods**
- The Health Improvement Network (THIN) in the United Kingdom used to conduct this retrospective cohort study

**Intervention**
- Metformin initiation during the peri-diagnosis phase in “exposed” patients vs. non-metformin in “unexposed” patient population
### Population

**Inclusion**
- Diagnosis of pancreatic adenocarcinoma with a prior diagnosis of type II diabetes mellitus
- Patients who were prescribed metformin in the “peri” diagnosis phase, defined as 6 months prior to diagnosis and 1 month post-diagnosis

**Exclusion**
- Diagnosis of PAC other than adenocarcinoma
- Discontinuation of metformin prior to the diagnosis of PAC
- Renal failure
- History of pancreatic cancer resection
- Age <40 at the time of incident PAC diagnosis

### Endpoints
Overall survival after exposure to metformin, specifically time between 1 month after metformin initiation and death

### Statistics
- Pearson’s $X^2$ test used for categorical variables and Student’s t-test used for continuous variable
- To assess primary analysis using univariate and multivariate Cox proportional-hazards model was used

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Metformin n=247, (%)</th>
<th>Non-metformin n=269, (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex-male</td>
<td>140 (57)</td>
<td>136 (51)</td>
<td>0.164</td>
</tr>
<tr>
<td>Diabetic complication</td>
<td>30 (12)</td>
<td>14 (5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>7 (3)</td>
<td>30 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>162 (66)</td>
<td>183 (68)</td>
<td>0.556</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>113 (46)</td>
<td>110 (41)</td>
<td>0.266</td>
</tr>
<tr>
<td>Duration of DM, d</td>
<td>1920 (137)</td>
<td>1225 (159)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>71.5</td>
<td>72</td>
<td>0.529</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.63</td>
<td>7.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>27.5</td>
<td>25.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GFR (mL/min)</td>
<td>76.7</td>
<td>72.8</td>
<td>0.055</td>
</tr>
<tr>
<td>Insulin use</td>
<td>105 (43)</td>
<td>85 (32)</td>
<td>0.01</td>
</tr>
<tr>
<td>Sulfonylurea use</td>
<td>186 (75)</td>
<td>110 (41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TZD</td>
<td>44 (18)</td>
<td>6 (2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Results

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Number of subjects</th>
<th>Adjusted HR*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin unexposed</td>
<td>269</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Metformin Exposed</td>
<td>247</td>
<td>1.11 (0.89, 1.38)</td>
<td>0.367</td>
</tr>
<tr>
<td><strong>Secondary analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin unexposed</td>
<td>269</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Metformin exposed</td>
<td>101</td>
<td>1.09 (0.80, 1.47)</td>
<td>0.585</td>
</tr>
</tbody>
</table>

- Exposed subjects: 247
- Unexposed subjects: 26
- Total patients which survived past 30 days (first day of follow-up): 516
- Primary analysis: performed on patients who were exposed 6 months prior to 1 month after PAC diagnosis
- Secondary analysis: performed only on exposed patients with exposure to metformin in the 6 months prior to PAC diagnosis, i.e. “new starters”
  *adjusted for age, sex, duration of diabetes, presence of diabetic complications, history of pancreatitis, Charlson index, BMI, GFR, smoking at the time of diagnosis, history of insulin use, history of sulfonylurea use, HbA1c

<table>
<thead>
<tr>
<th>Author’s Conclusion</th>
<th>• There is no survival benefit seen in diabetic patients with advanced PAC who were on metformin therapy prior to diagnosis</th>
</tr>
</thead>
</table>
| Critique            | **Strengths**  
• Controlled for prior metformin exposure by looking at a secondary analysis of “new starters”  
• Utilized “initial treatment carried forward” approach, similar to “intent to treat” in clinical trials  
• Considered eGFR and renal status as inclusion/exclusion for metformin use  
**Limitations**  
• Retrospective study design  
• Unknown cancer stage  
• Unknown cancer treatment  
• Combination medications with metformin not adjusted  
• Incomplete data for certain variables such as HbA1c, BMI, and eGFR  
• Did not take into consideration glycemic control |

| Take Home Points | • Diabetic patients treated with metformin therapy prior to diagnosis with advanced pancreatic cancer disease may not see a survival benefit |


**Objective**  
To assess the efficacy of the addition of metformin to a standard systemic therapy in patients with advanced pancreatic cancer

**Design**  
Double-blind, randomized, multicenter, placebo-controlled phase 2 trial

**Methods**  
Site of the study: four hospitals in the Netherlands. Patients randomized in 1:1 ratio by computer-generated algorithm to receive one of two interventions

**Intervention**  
Standard chemotherapy regimen: IV gemcitabine (1000 mg/m^2) on days 1, 8, and 15 every 4 weeks + oral erlotinib (100mg) + either metformin 500mg, which was increased to 1000mg twice daily in the second week, or placebo twice daily

**Population**  
- **Inclusion**  
  • Patients with confirmed metastatic or unresectable locally advanced pancreatic adenocarcinoma  
  • Patients 18 years or older  
  • Estimated survival of at least 2 months  
  • Adequate bone marrow, hepatic and renal function  
- **Exclusion**  
  • Patients with borderline resectable disease  
  • Hypersensitive to metformin or had any systemic disorder that would allow unsafe drug therapy  
  • Previous treatment with metformin within 6 months before enrollment or with erlotinib was not allowed
Endpoints

- Primary: overall survival at 6 months in the intent-to-treat population
- Secondary: progression-free survival, overall survival (death due to any cause), proportion of patients achieving an objective partial response

Statistics

- To detect an increase in 6 month overall survival from 50% to 75%, a sample size of 120 patients was required with a power of 80%, two-sided alpha of 5%
- Kaplan-Meier method was used to estimate overall survival at 6 months and the time-to-event endpoints
- $X^2$ and Fisher's exact tests were used to detect differences in overall response and baseline characteristics
- All outcome analysis was in the intention-to-treat population

Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Metformin group, n (%) n=60</th>
<th>Placebo group, n (%) n=61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y, range)</td>
<td>65 (44-79)</td>
<td>64 (45-78)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27 (44%)</td>
<td>34 (57%)</td>
</tr>
<tr>
<td>Female</td>
<td>34 (56%)</td>
<td>26 (43%)</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>16 (26%)</td>
<td>16 (27%)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>45 (74%)</td>
<td>44 (73%)</td>
</tr>
<tr>
<td>Primary tumor location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>39 (64%)</td>
<td>40 (67%)</td>
</tr>
<tr>
<td>Body</td>
<td>20 (33%)</td>
<td>18 (30%)</td>
</tr>
<tr>
<td>Previous surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>45 (74%)</td>
<td>51 (85%)</td>
</tr>
<tr>
<td>Whipple procedure</td>
<td>6 (10%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Palliative hepaticojejunostomy</td>
<td>10 (16%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (13%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>CA 19.9 kU/l</td>
<td>245 (21-2118)</td>
<td>561 (112-6319)</td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Metformin arm, (95% CI)</th>
<th>Placebo arm, (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>56.7% (44.1-69.2)</td>
<td>63.9% (51.9-75.9)</td>
<td>0.41</td>
</tr>
<tr>
<td>Median overall survival, months</td>
<td>6.8 (5.1-8.5)</td>
<td>7.6 (6.1-9.1)</td>
<td>0.78</td>
</tr>
<tr>
<td>Median progression-free survival, months</td>
<td>4.1 (1.8-6.5)</td>
<td>5.4 (5-5.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>Deaths, n, (%)</td>
<td>52 (87)</td>
<td>54 (89)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Overall survival at 6 months was 63.9% (95% CI 51.9-75.9) in the placebo group and 56.7% (95% CI 44.1-69.2) in the metformin group

Author’s Conclusion

The addition of metformin to gemcitabine and erlotinib does not improve the clinical outcome of patients with advanced pancreatic cancer
<table>
<thead>
<tr>
<th>Critique</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• First randomized, placebo controlled trial specific to metformin use in pancreatic cancer population</td>
<td>• No characterization of the tumor</td>
<td>• Unknown if patients diabetic prior to diagnosis, or developed diabetes from the cancer itself</td>
</tr>
<tr>
<td>• Periodic monitoring of tumor response and progression every two weeks</td>
<td>• Small proportion of patients who were diabetic</td>
<td>• Patients in placebo group received more treatment cycles than in metformin group</td>
</tr>
<tr>
<td></td>
<td>• Metformin arm had higher CA 19-9 levels that were unadjusted</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Take Home Points</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anti-diabetic doses of metformin are unable to achieve concentrations necessary to have an anti-neoplastic effect and cause energetic stress in these cells</td>
<td></td>
</tr>
<tr>
<td>• When added to conventional treatment, there was no benefit seen in patients with metformin instead of placebo</td>
<td></td>
</tr>
</tbody>
</table>

**CONCLUSION AND RECOMMENDATIONS**

I. Conclusions
   a. Pancreatic cancer remains a lethal disease
   b. Plausible biological mechanism for the role of metformin in antineoplastic therapies

II. Recommendations
   a. Does metformin provide overall survival benefit in patients with pancreatic cancer?
      i. For diabetic patients who have metastatic or non-metastatic PC, an increase in overall survival may be seen in patients already receiving metformin therapy prior to diagnosis with pancreatic cancer
         1. Though an unknown dose was studied in the patient population in which benefit was seen, the maximum dose allowed by the United States Food and Drug Administration (FDA) is 2,550 mg/day
         2. Until safer daily limits are approved specifically in pancreatic cancer patients under a different indication, metformin should be continued based on patient specific characteristics and FDA regulations
         3. Patient renal status, including eGFR, as well as overall toxicity profile should be monitored
      ii. For diabetic patients who have metastatic or non-metastatic PC and were not receiving metformin prior to diagnosis, evidence is not sufficient to support metformin initiation for survival benefit in this population if not clinically indicated for T2DM
      iii. For diabetic or non-diabetic patients with metastatic disease initiated on metformin with concurrent chemotherapy after PDAC diagnosis, current data suggests no benefit in overall survival, however further prospective studies are needed
      iv. Future studies needed to evaluate the benefit of metformin in patients diagnosed with diabetes after PDAC and in non-diabetic patients with PDAC
III. Future directions\textsuperscript{13, 28}

a. To date, there are over 38 clinical research trials underway to investigate the use of metformin combination therapy in the treatment of 14 different cancers
b. Of these trials, seven focus on pancreatic cancer treatment modalities with metformin
c. Other upcoming research include trials to synthesize metformin analogues which can penetrate the mitochondria more effectively, specifically in pancreatic cancer cells
d. Studies are also underway to identify new biomarkers with improved diagnostic value

**REFERENCES**


