Pancreatic Cancer: Current Understanding and Future Challenges

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Pancreatic Cancer: Incidence and Mortality

Pancreatic Cancer Incidence and Mortality

Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Siegel R et. al., CA Cancer J Clin, 64, 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>86,930</td>
<td>72,330</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>29,480</td>
<td>40,000</td>
<td></td>
</tr>
<tr>
<td>Colorectum</td>
<td>26,270</td>
<td>24,040</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>20,170</td>
<td>19,420</td>
<td></td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>15,870</td>
<td>14,270</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,040</td>
<td>10,050</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,450</td>
<td>8,590</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>11,170</td>
<td>8,520</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>10,470</td>
<td>7,130</td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,900</td>
<td>6,230</td>
<td></td>
</tr>
<tr>
<td>All Sites</td>
<td>310,010</td>
<td>275,710</td>
<td></td>
</tr>
</tbody>
</table>

- 4th Leading Cause of Cancer Deaths in the United States.
- Median Survival < 6 Months.
- No Effective Treatment.
Pancreatic Cancer and 2030

Pancreatic Cancer: Second Leading Cause of Cancer-related Death by 2030

Rahib, L., et. al., Cancer Res., 74, 2913-21, 2014
# Risk Factors and Inherited Syndromes

## Table 1. Risk Factors and Inherited Syndromes Associated with Pancreatic Cancer.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Approximate Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factor</strong></td>
<td></td>
</tr>
<tr>
<td>Smoking (^3)</td>
<td>2–3</td>
</tr>
<tr>
<td>Long-standing diabetes mellitus (^4)</td>
<td>2</td>
</tr>
<tr>
<td>Nonhereditary and chronic pancreatitis (^5)</td>
<td>2–6</td>
</tr>
<tr>
<td>Obesity, inactivity, or both (^6)</td>
<td>2</td>
</tr>
<tr>
<td>Non-O blood group (^7)</td>
<td>1–2</td>
</tr>
<tr>
<td><strong>Genetic syndrome and associated gene or genes — %</strong></td>
<td></td>
</tr>
<tr>
<td>Hereditary pancreatitis (PRSS1, SPINK1) (^8)</td>
<td>50</td>
</tr>
<tr>
<td>Familial atypical multiple mole and melanoma syndrome (p16) (^9)</td>
<td>10–20</td>
</tr>
<tr>
<td>Hereditary breast and ovarian cancer syndromes (BRCA1, BRCA2, PALB2) (^10,11)</td>
<td>1–2</td>
</tr>
<tr>
<td>Peutz–Jeghers syndrome (STK11 [LKB1]) (^12)</td>
<td>30–40</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colon cancer (Lynch syndrome) (MLH1, MSH2, MSH6)(^13)</td>
<td>4</td>
</tr>
<tr>
<td>Ataxia–telangiectasia (ATM) (^14)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Li–Fraumeni syndrome (P53) (^15)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

* Values associated with risk factors are expressed as relative risks, and values associated with genetic syndromes are expressed as lifetime risks, as compared with the risk in the general population.

Ryan, Hong and Bardeesy, NEJM, 371, 2014
Pancreatic Cancer Treatment

Disappointing Progress in the Treatment of Pancreatic Cancer

1997

- Median survival
  - GEM: 5.65 months
  - 5-FU: 4.41 months
  - Log-Rank Test: p=0.0025
- Comparison: 5-FU vs. GEM

2007

- Survival Probability (%)
  - HR = 0.81
  - 95% CI (0.67 to 0.98)
  - 2.13 months longer median survival
- Comparison: Erlotinib vs. Placebo
  - Erlotinib (n = 261): Median = 6.37 months
  - Placebo (n = 260): Median = 5.96 months

2011

- Survival Probability (%)
  - Hazard ratio, 0.57 (95% CI, 0.45–0.73)
  - P<0.001 by stratified log-rank test
- Comparison: FOLFIRINOX vs. Gemcitabine
  - FOLFIRINOX: 11.1 months
  - Gemcitabine: 6.6 months


Conroy et. al., NEJM, 36, 2011
Pancreatic cancer treatment

Disappointing Progress in the Treatment of Pancreatic Cancer

- A Combination of nab-Paclitaxel and Gemcitabine Improved Survival in Advanced Pancreatic cancer

2013

Improved Survival

Improved Survival in Resected Pancreatic Cancer Cases

Late Diagnosis

Dismal Outcome
(Median Survival < 6 mo)

(18-20%)

Resectable Cases
(Median Survival < 2 yrs)

(~12%)

5 yr Survival

Molecular Differences in Tumors Determine Patient Outcome?
Progression Model of Pancreatic Carcinogenesis

Iacobuzio-Donahue, C.A., Gut, 61, 2012
Desmoplastic stroma

Prominent, Desmoplastic Stroma in Pancreatic Cancer

Pancreatic cancer heterogeneity

Pancreatic Cancer is Highly Heterogenous

PDAC subtypes

Are There Different Molecular Subtypes of PDAC?

Collison et. al., Nat. Med., 17, 2011
Metabolic Reprogramming in Pancreatic Cancer

Sousa and Kimmelman, Carcinogenesis, 35, 2014
Stromal networks

Complex Stromal Networks Supporting Pancreatic Cancer Progression and Therapeutic Resistance

Stromnes, I.M., et. al., Carcinogenesis, 35, 2014
Disease outcome

Treatment Strategies to Improve Disease Outcome

Drug Delivery and Effectiveness of Systemic Therapy

Targeting Stroma
Mouse model

Pancreatic Cancer Mouse Model (KPC)

*LSL-Kras-G12D  X  p53 LSL R172H  X Pdx-Cre 1

\[ \downarrow \]

Pancreatic Ductal Adenocarcinoma (PDAC)

(Median Survival = 4-5 months)

*Hingorani, S. et. al., Cancer Cell, 2005
Inhibition of Hedgehog signaling

Inhibition of Hedgehog Signaling Depleted Stroma, Enhanced Drug Delivery and Improved Survival in Mice

V=Vehicle
G=Gemcitabine
I= IPI-926 (Hedgehog Inhibitor)
I/G= IPI-926/Gem

Olive KP et. al., Science, 324, 2009
Enzymatic targeting

Enzymatic Targeting of Stroma Enhances Therapeutic Response

Provenzano et. al., Cancer Cell, 21, 2012
Enzymatic targeting

Enzymatic Targeting of Stroma Enhances Therapeutic Response

Proenzano et. al., Cancer Cell, 21, 2012
Two faces of anti-stromal therapy. Stromal-targeting may not (always) have beneficial therapeutic response.
Sonic Hedgehog as a tumor suppressor

Sonic Hedgehog as a Tumor Suppressor in PDAC

Genetically Engineered Mouse Model

C

Percent survival

Time (months)

PKCY (n=26)
Shh-PKCY (n=23)

p=0.0049, Log Rank

D

Survival from Palpation of Tumor (days)

PKCY
ShhPKCY

p < 0.001

E

Macrometastasis (Percent)

p = 0.039

F

Number / 80 hpf

PKCY (8 weeks)
ShhPKCY (8 weeks)

A 1 2 3

A 1 2 3
Myofibroblast depletion

Myofibroblast Depletion Enhances PDAC

A. Time course of GCV treatment.

B. Histological images showing early and late control and depleted samples.

C. Bar graphs showing early and late PDAC pathological scores.

D. Bar graphs showing early and late PDAC tumor necrosis.
Myofibroblast depletion

Myofibroblast Depletion Reduces Overall Survival

GCV = genciclovir (Depletes Myofibroblasts in PKT;αSMA-tk+ Mice)
Complex tumor-stromal interaction in PDAC. Tumor-stromal interaction is complex and therapeutic approaches targeting stroma may require new molecular taxonomy in pancreatic cancer.
Inflammation and pancreatic cancer

Inflammation and Pancreatic Cancer

Chronic Pancreatitis

Desmoplastic Stroma

NF-κB Signaling

Inflammatory Cytokines

COX2, NOS2
Inflammatory changes

Inflammatory Changes During Development and Progression of Pancreatic Cancer
**Kras in pancreatic cancer**

Inflammation Enhances and Maintains a Pathologic Level of Oncogenic KRAS in Pancreatic Cancer
Macrophage inhibitory factor (MIF)

Macrophage Migration Inhibitory Factor (MIF)

Increased Expression in Tumors

- NF-κB
- ERK1/2
- Akt
- COX2
- p53
- NOS2

- Proinflammatory Cytokine
- Expressed in Epithelial and inflammatory Cells
MIF, Inflammation and Cancer

At the Crossroads of Inflammation and Tumorigenesis
By Carlos Cordon-Cardo* and Carol Prives†

From the *Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York 10021; and the †Department of Biological Sciences, Columbia University, New York, New York 10027

Macrophage Migration Inhibitory Factor MIF Interferes with the Rb-E2F Pathway
Oleksii Petrenko* and Ute M. Moll*

Macrophage Migration Inhibitory Factor: Perspective
Increased Expression of MIF in Tumors from Pancreatic Carcinoma Cases
A Higher Expression of MIF is Associated with Poor Survival in Human Pancreatic Carcinoma Cases

Human Pancreatic Carcinoma Cases

A higher expression of MIF is associated with poor survival in human pancreatic carcinoma cases.

A Higher Expression of MIF is Associated with Poor Survival in Human Pancreatic Carcinoma Cases

Validation in Independent Cohorts

Human Pancreatic Carcinoma Cases

Validation Cohort 1

Validation Cohort 2

P = 0.0075

P = 0.0201

High MIF (N=11)

Low MIF (N=11)

High MIF (N=13)

Low MIF (N=13)
EMT Enhances Malignant Progression

EMT Enhances Malignant Progression in Pancreatic cancer

Wang et. al., Nat. Rev. Gastroenterology & Hepatol., 2011
* Rhim et. al., Cell, 2012.
MIF Induces EMT

MIF induces EMT in Pancreatic Cancer Cells
MIF Induces EMT in Pancreatic Cancer Cells
MIF accelerates tumor growth

MIF Accelerates Tumor Growth and Metastasis in Orthotopic Xenografts in Mice
MIF alters Global Gene Expression Profile

MIF Induces a Marked Change in Global Gene Expression Profile including EMT-related Genes in Orthotopic Tumors

- MIF over-expressing tumors are poorly differentiated.
- MIF induces a change in global gene expression profile.
- MIF over-expressing tumors showed expression of EMT-related genes.
MIF Enhances Cancer Progression

Ongoing Study

HYPOTHESIS: MIF Enhances Pancreatic Cancer Progression

Pancreatic Tumors in KPC Mice Express a High Level of MIF

(KPC: KRAS$^{G12D}$, P53$^{R172H}$, Pdx-1-Cre)

MIF Immunostaining

KPC

KPC

KPC/MIF$^{-/-}$
MIF and cancer progression

Ongoing Study
HYPOTHESIS: MIF Enhances Pancreatic Cancer Progression

MIF-Deficient KPC Mice Show Longer Survival

![Graph showing survival rates for KPC (N=31) and KPC/MIF-/- (N=48). The graph indicates a statistically significant difference in survival rates, with P < 0.001.]
A higher MIF expression is associated with poor outcome in PDAC patients.
MIF induces EMT in pancreatic cancer cell lines.
MIF enhances growth and metastasis of tumor xenografts in mice.
MIF-deficiency increases survival in KPC mice with lethal PDAC.
MIF may be a candidate target for designing improved treatment.
Pancreatic Tumor Biology

Understanding Pancreatic Tumor Biology is Key to Improving Disease Outcome

Late Diagnosis
(Pancreatic Cancer
(Median Survival < 6 mo)

Early Detection
Tumor Biology
Effective Therapy
• Novel Targets

Poor Therapeutic Response