SnapShot: Pancreatic Cancer

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Cancer Cell

PATHOLOGY

Exocrine Pancreatic Cancer (95%)
- Ductal adenocarcinoma (90%)
  Premalignant: Carcinoma in situ (*PanIN-3)
- Mucinous cystadenocarcinoma (5%)
  (Acinar cell, pancreatoblastoma)
  Premalignant: **IPMN or mucinous cystadenoma

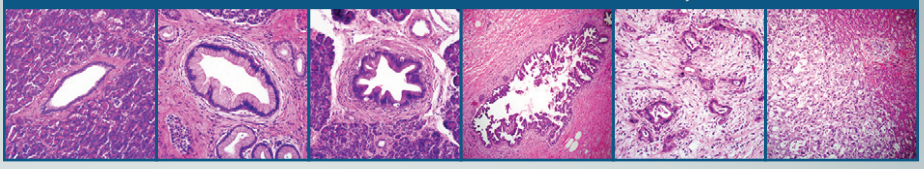
Endocrine Pancreatic Cancer (5%)
- Islet cell
- Carcinoid

*PanIN (Pancreatic intraepithelial neoplasia)

**IPMN (Intraductal papillary mucinous neoplasm)

HISTOPATHOLOGY

Photos by Christine Iacobuzio-Donahue



Normal | PanIN-1 | PanIN-2 | PanIN-3 | Cancer | Metastasis

ASSOCIATION WITH INHERITED CANCER SYNDROMES

- Mutation of *BRCA2* – Chromosome 13q12
- Peutz-Jeghers syndrome – autosomal dominant mutations in *LKB1/STK11* on chromosome 19p13
- Familial atypical multiple mole melanoma (FAMMM) syndrome – autosomal dominant mutation in *CDKN2A* tumor suppressor gene on 9p21
- Hereditary nonpolyposis colorectal cancer (HNPCC) – autosomal dominant mutations in DNA mismatch repair genes
- Familial kindreds - 2 or more first degree relatives
- *PALB2* mutation

GENOMIC VULNERABILITIES

Mutations
KRAS, BRCA2, PALB2, TP53,
other DNA repair genes

Amplifications
ERBB2 (HER2/neu)

Deletions (synthetic lethal possibility)
SMAD4 (DPC4)
CDKN2A (p16)

Hypermethylation
Inhibitors of DNMTs

CLINICAL AND MOLECULAR PROGNOSTIC FACTORS

Poor clinical prognostic factors
- Later stage
- R1 resection (tumor at margin, lymph node positive)
- Perineural invasion or vascular invasion
- Poor performance status
- Low serum albumin
- Liver metastasis
- Marker CA19-9 ≥ 59x ULN

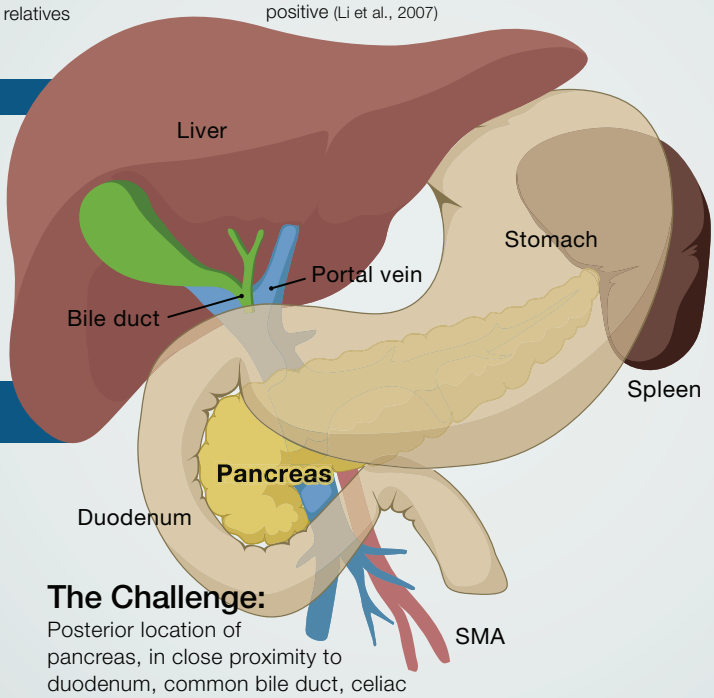
Poor molecular prognostic factors
- Mutated *SMAD4*
- Mutated *TP53*

ORIGIN/EVOLUTION

Exact cell of origin not clear
(candidates include epithelium, acinar cell, islet cell)

Possible total time to evolve: 21-28 years
- 11.7 years: original gene mutation -> primary cancer
- 6.8 years primary -> metastasis
- 2.7 years appearance of metastases -> death.
  (Yachida et al., 2010)

Stem cell hypothesis
CD44, CD24, and epithelial-specific antigen (ESA) positive (Li et al., 2007)



The Challenge:

Posterior location of pancreas, in close proximity to duodenum, common bile duct, celiac plexus, superior mesenteric artery (SMA), and portal vein, leads to late diagnosis as well as very bothersome symptoms of obstruction of biliary drainage, with infection, pain, and unresectability.

IN VIVO MODELS

- Genetically engineered mouse models (e.g., the KPC model by Hingorani et al., 2005)
- Primary patient-derived tumor xenografts (e.g., the PancXenoBank by Jimeno et al., 2009)

BREAKING TOLERANCE

- Anti-CTLA-4
- Anti-PD1
- Anti-PD-L1
- Anti-macrophage approaches

STROMA TARGETS

- Hypoxia
- Extracellular matrix
- Stellate cells - Vitamin D signaling
- SPARC
  (Secreted Protein Acidic, Rich in Cysteine)
- Collagen
- Hyaluronan
- Hedgehog signaling
- TGF-β signaling
- Inflammation:
  NF-κB, IL-6, JAK1/2, COX2
- High interstitial fluid pressure, growth induced solid stress

FUEL UTILIZATION

- Glucose (Aerobic glycolysis)
  PI3K, AKT, LDHA, PKM2
- Glutamine (Glutaminolysis)
  MYC, ASCT2, GLS, POL I
- Cellular constituents (Autophagy)
  AMPK
- Extracellular constituents (Macropinocytosis)
  RAS, SRC

CLINICAL STAGING AND USEFUL TREATMENTS

Resectable (localized): Surgical resection with possible follow-up XRT plus 5-FU or gemcitabine or with 6 cycles of gemcitabine, median survival = 12-19 months
- No encasement of celiac axis or superior mesenteric artery (SMA)
- Patent superior mesenteric – portal veins
- No extra pancreatic disease

Locally advanced: XRT plus 5-FU or gemcitabine, or chemotherapy alone, median survival = 6-10 months
- Encasement of arteries
- Venous occlusion (SMV or portal)
- No extra-pancreatic disease

Metastatic disease: Chemotherapy – See treatment regimens in the table to the right, median survival with treatment = 6-11 months

CLINICAL REGIMENS PROVEN TO INCREASE SURVIVAL FOR PATIENTS WITH ADVANCED METASTATIC PANCREATIC CANCER

Regimen	Control	Median Survival (Months)		p Value	Reference
		Regimen	Control		
gemcitabine	5-FU	5.6	4.4	0.0025	Burris, et al., 1997
gemcitabine + erlotinib	*GEM	6.24	5.91	0.038	Moore, et al., 2007
FOLFIRINOX**	*GEM	11.1	6.8	<0.001	Conroy, et al., 2011
nab-paclitaxel + gemcitabine	*GEM	8.5	6.7	0.000015	Von Hoff, et al., 2012

*GEM: gemcitabine **FOLFIRINOX: Folinic acid + 5-FU + Irinotecan + Oxaliplatin

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Pancreatic cancer can basically be divided into two major subtypes: adenocarcinoma, which is thought to arise in the exocrine portion of the pancreas (95% of cases), and rare endocrine tumors, which arise from islet cells (often designated as neuroendocrine tumors). This Snapshot concentrates on the most common and lethal type of adenocarcinoma of the pancreas: infiltrating ductal adenocarcinoma (designated here as pancreatic ductal adenocarcinoma or PDA).

Pancreatic cancer kills more than 37,000 people each year in the United States and more than 213,000 people worldwide. It has the worst 1 and 5 year survival rates of all cancers and, unfortunately, it is increasing in incidence. The highest rates of pancreatic cancer incidence are seen in industrialized and Western countries. In Europe, Nordic countries have the highest incidence rates (perhaps suggesting a role for Vitamin D). In the United States, the incidence is particularly high in Native Hawaiians, African Americans, and Korean Americans. The incidence of pancreatic cancer also increases sharply after age 50. Pancreatic cancer in young patients is frequently familial; there is a 40% increase in risk for pancreatic cancer if there is familial pancreatitis. Other risk factors include diabetes, metabolic syndrome, pancreatitis, cigarette smoking, heavy alcohol consumption, infectious agents (*H. pylori*, hepatitis B), and gastric resection. Diets low in fruits and vegetables and involving high intake of meat (particularly barbequed) are also associated with increased risk.

This Snapshot is designed to outline the pathology of PDA, its association with inherited cancer syndromes, information regarding the origin and evolution of the disease, clinical and molecular prognostic factors, and clinical staging along with common treatment regimens that have been proven to increase survival. Clearly, new ways to attack pancreatic cancer are needed. Also outlined in the SnapShot are four possible ways to attack the disease via genomic vulnerabilities, PDA's fuel utilization pathways, stroma targets, and breaking immune tolerance. These include some already discovered targets as well as some additional therapeutic possibilities. We hope that this cataloging of possibilities alongside the clinical aspects of the disease will help drive new approaches and ideas for development of new therapies and new methods for early detection of this awful disease.

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