Molecular Characterization of Neoplasms of the Pancreas

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Disclosure

• Dr. Hruban has the potential to receive milestone payments and royalties from Anza Therapeutics as a result of the mesothelin invention
“If you've seen one Redwood, you've seen them all”

Ronald Reagan
(3/12/1966)
As paraphrased by Jerry Brown
“If you’ve seen one pancreatic cancer, you’ve seen them all”

5-year relative survival by period
Pancreas, total, females

http://www.kreftregisteret.no
Examples

1. Medullary carcinoma and microsatellite instability
2. Undifferentiated carcinomas and E-cadherin loss
3. Beta-catenin gene mutations in solid-pseudopapillary neoplasms
4. KRAS2 gene mutations in undifferentiated carcinomas with osteoclast-like giant cells
5. Chromosome 11p loss in pancreatoblastoma
6. PIK3CA and STK11 gene mutations in Intraductal Papillary Mucinous Neoplasms
Medullary Carcinoma

Poorly differentiated, Syncytial growth pattern, Pushing boarders
Microsatellite Instability (MSI)

1. MSI status has prognostic value- median survival for MSI cases of 62 months, versus 10 months (hazard ratio = 5.6; P = 0.007)

2. MSI status may have therapeutic implications- Fluorouracil (5FU)-based adjuvant chemotherapy benefits patients with stage II or stage III colon cancer with microsatellite-stable tumors but not those with tumors exhibiting high-frequency microsatellite instability

Nakata et al., Clin Cancer Res. 2002; 8: 2536-40.

Microsatellite Stable

Microsatellite Unstable

Microsatellite Instability (MSI)

3. Has implications for other family members

- The medullary phenotype is highly associated with a family history of cancer in first-degree relatives (P < 0.001).


Medullary Carcinoma

Microsatellite Instability  \(\leftrightarrow\)  Medullary

Good Prognosis,
Not 5-FU,
Family Hx
Undifferentiated Carcinoma

- A malignant epithelial neoplasm with a significant component showing no glandular structures or other features to indicate a definite direction of differentiation
- Mean survival of 5.2 months after diagnosis
Undifferentiated Carcinoma
E-cadherin Expression

Proportion of cancers with E-cadherin loss

Noncohesive carcinoma
Undifferentiated carcinoma
- Anaplastic 14/15 (93%)
  - UCOCGC 6/6 (100%)
Signet ring 2/7 (29%)
Overall 22/28 (79%)*

Cohesive carcinoma
Ductal adenocarcinoma
- Moderate 0/24 (0%)
  - Poor 0/13 (0%)
Colloid carcinoma
- Moderate 0/1 (0%)
  - Poor 0/1 (0%)
Overall 0/39 (0%)

p<0.001

Winter and Iacobuzio, Clinical Cancer Research
E-cadherin
Survival in Relation to E-cadherin Status in Resection Specimens

Winter and Iacobuzio, Clinical Cancer Research

Proportion Surviving

E-cadherin loss

Historical reference, n=1252

p=0.01
Undifferentiated Carcinomas

Loss of E-cadherin $\leftrightarrow$ Non-cohesive

$\Rightarrow$ Poor Prognosis
Undifferentiated Carcinoma with Osteoclast-like Giant Cells

- Malignant epithelial neoplasm composed of large benign appearing multinucleated giant cells admixed with atypical neoplastic mononuclear cells
- Highly aggressive neoplasms with a mean survival of <12 months
p53
KRAS2 Gene Mutations in the Components of an UCOCGC

Osteoclast-like Giant Cell Tumors are undifferentiated carcinomas that arise directly from intraductal epithelial precursors – "Undifferentiated Carcinomas with Osteoclast-like Giant Cells"
Middle-aged Male with FAMMM Syndrome caused by a p16-Leiden deletion, Jaundice and Weight Loss
Biopsy of an ampullary lesion was initially interpreted as reactive, but KRAS2 gene sequencing revealed a codon 12 mutation. A resection was performed revealing an UCOCGC of the pancreas.
Immunolabeling for p16 Showed Loss of Expression in the Mononuclear Cells and Retained Expression in the Giant Cells
Undifferentiated Carcinoma with Osteoclast-Like Giant Cells

KRAS2 gene mutation

Epithelial with Reactive Giant Cells

Poor Prognosis
Solid-Pseudopapillary Neoplasm
Solid-Pseudopapillary Neoplasms

- Clinically, the vast majority occur in young women (20’s), with a female to male ratio of 10-20:1
- Grossly well demarcated masses. On cross section, they are cystic and solid with areas of hemorrhage and necrosis
Solid-pseudopapillary Neoplasm
Solid-Pseudopapillary Neoplasms

- >90% have β-catenin mutations
- KRAS2 wild-type
- 15% TP53 mutations
- 0% DPC4, p16

Abraham et al., American Journal of Pathology. 2002;160:1361-1369
Solid-pseudopapillary or Pancreatic Endocrine Neoplasm?
Solid-Pseudopapillary Neoplasm

• Has therapeutic implications - Surgical resection, even the surgical resection of metastases is the treatment of choice
Solid-Pseudopapillary Neoplasm

Loss of β-catenin  Non-cohesive

Great Prognosis
Pancreatoblastoma
Pancreatoblastoma

- Malignant neoplasms showing multiple lines of differentiation including acinar differentiation and squamoid nests
- Endocrine and ductal differentiation may also be seen
- Occur primarily in children (1-15 years)- Previously called infantile pancreatic carcinoma
Abraham et al., American Journal of Pathology. 2001;159:1619-1627
Genetic Alteration in Pancreatoblastomas

• Associated with Beckwith-Wiedemann Syndrome
• 86% LOH on 11p*

Similar to other infantile embryonal tumors such as hepatoblastomas
• Hepatoblastoma
• Nephroblastoma
• Pleuropulmonary blastoma

Am J Pathol
159:1619
Pancreatoblastoma

LOH on 11p

Squamoid nests and acinar cells

Unified with other Primitive Neoplasms
Intraductal Papillary Mucinous Neoplasms
Unique Genetic Changes

- **PIK3CA**: Four mis-sense PIK3CA gene mutations in 36 IPMNs (11%)
- **STK11/LKB1**: Sequence analysis of a pancreatic cancer from a patient with PJS revealed loss of the wild-type allele of the STK11/LKB1 gene
- **STK11/LKB1**: Inactivation of STK11/LKB1, by homozygous deletions or somatic sequence mutations coupled with loss of heterozygosity, was also demonstrated in 4-6% of 127 sporadic pancreatic and biliary adenocarcinomas.


Peutz-Jeghers Syndrome - 132 fold increased risk of pancreatic cancer
Screening implications
ENDOSCOPIC ULTRASONOGRAPHY (EUS)

- High frequency US + endoscopy
- Screened 109 patients with PJS or a strong family history of pancreatic cancer

Canto et al, Clin Gastroenterol Hepatol. 2004 Jul;2(7):606-21
Canto et al, Clin Gastroenterol Hepatol. 2006; 4:766-81
Peutz-Jeghers Syndrome

47 y.o. W/F with 1.5 cm lesion

CT

EUS
IPMN with Carcinoma-In-Situ

Canto et al, Clin Gastroenterol Hepatol. 2004 Jul;2(7):606-21
Canto et al, Clin Gastroenterol Hepatol. 2006; 4:766-81
Almost half of the reduction in breast cancer mortality over the last 25 years has come from mammography

MOLECULAR ↔ MORPHOLOGY

PROGNOSIS

TREATMENT
Selected References