PROBLEMS IN PANCREAS PATHOLOGY

Frozen Section Diagnosis and Mucinous Neoplasms

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Overview

• Pancreas carcinoma

• Problem areas in the diagnosis of pancreatic neoplasms
  – Frozen section
  – Cystic lesions
    • Mucinous tumors
Pancreas Carcinoma

- Ductal adenocarcinoma 90%
- 2nd most common GI (colon 1st)
- 30,000 new cases per year
- Risk factors- cig, CP, DM, hereditary
- 4th cause cancer deaths
- At diagnosis up to 80% metastatic
Pancreas Carcinoma

• Overall 5-yr survival < 5%
• Potentially “curative” surgery 10-15%
• Mean survival unresectable 4-5 months
• 5-yr survival after surgical resection for cure, 20%; mean survival 10-20 months
• Only hope “long-term” survival is complete tumor resection
WHO Classification Epithelial Pancreas Tumors

• Benign
  – Serous cystadenoma
  – Mucinous cystic neoplasm (MCN) / intraductal papillary mucinous neoplasm (IPMN)

• Borderline
  – MCN / IPMN (mod dysplasia)
  – Solid pseudopapillary

• Malignant
  – Ductal adenocarcinoma
  – MCN / IPMN with carcinoma
  – Acinar

• Endocrine
Frozen Sections
Surgeon’s Perspective

• Biopsy/FNA if unresectable or non-operative
• If resectable, resection without tissue diagnosis (controversial; bx, FNA, FS)
• “not typical” - FS for diagnosis pancreas
• FS assess resectability / tissue confirmation
• FS margins
• 10% resection for presumed malignancy, benign

EC Ellison, Chair, Dept Surg, OSU
Suspected Pancreatic Malignancy

Laparotomy/scopy → Resectable

Resectable

Resection with or without FS

Prob Resect → Resect + -

Tissue Confirmation

FS

Tissue Confirmation

FS

Bypass + -

More Tissue Bypass
Frozen Section

- Malignant vs. benign
- Straight forward on large well fixed section
- Frozen – small and artifact
- Ductal adenocarcinoma
- Chronic pancreatitis
Pancreas Frozen Sections

- Criteria for cancer
- Major and minor
  - Major - identified in all cancer and no benign cases
    - Disorganized duct distribution

Frozen Section
Major Criteria

• Nuclear size variation ≥ 4:1
• Incomplete ductal lumen
  – Nests
  – Single file
  – Gaps
  – Cribriforming
Frozen Section
Minor Criteria

Helpful when present, but less common

Perineural invasion

Mitoses, necrotic debris, nucleoli
Disorganized Ducts and Stroma

Chronic pancreatitis

Adenocarcinoma
Nuclear Variation
Nucleoli and Necrosis

Chronic pancreatitis

Adenocarcinoma
FS - Approach

• Low power
  – Stroma and duct organization

• Higher power
  – Cytology
  – Mitosis, nucleoli, perineural
  – Hyperchromasia not helpful
DIAGNOSIS – NO MALIGNANCY
FS - Approach

- Haphazard ducts and stroma
- Nests and single cells
DIAGNOSIS - ADENOCARCINOMA
FS- Approach

• The difficult case
  – Stroma and duct organization
  – Cytology
  – Mitosis, necrosis, perineural invasion not found in many
FS- Approach

ATYPICAL REQUEST MORE TISSUE
Pitfalls

Chronic Pancreatitis

• Irregular ducts and stroma
• Atrophic acini and ducts and “pseudo” partial ductal lumen
• Reactive epithelial atypia
Pitfalls Ductal Adenocarcinoma Variants

FOAM CELL

HIGH GRADE
Pitfall - Cystic Pseudocyst or Neoplasm?
Pitfalls - Other

- Artifact
- Normal anatomy at ampulla
- Changes adjacent to tumor
- Sampling error
Frozen Section– Tumor Type

- Tumor type may alter surgical procedure
- Adenocarcinoma vs.
  - Neuroendocrine
  - Lymphoma
- Clues
  - Trabecular, organoid
  - Diffuse
- Neoplasm, defer type
FS Tumor Type

Neuroendocrine Carcinoma (Nests)

Lymphoma (Diffuse)
Low Grade Neoplasm
Neuroendocrine vs. SPT
Solid Pseudopapillary Tumor

E-Cadherin membranous loss

Cytokeratin/Chromogranin -

A1AT +
Metastasis and Resectability

• Tumor involving SMA - Stop
• Liver lesions
  – Bile duct hamartoma (von Meyenburg complex) - Pancreas resection
  – Bile duct adenoma - Pancreas resection
  – Neuroendocrine carcinoma - ? Pancreas resection
  – Adenocarcinoma - Stop
Summary - Frozen Section

- Chronic pancreatitis can form a mass and may surround adenocarcinoma
- Chronic pancreatitis vs. adenocarcinoma
  - Lobular organization
  - Cytology - 4 fold variation and partial ducts
  - Mitoses and perineural invasion - If you are lucky
- Pitfalls
- Tumor type
- Metastasis and resectability
Pancreas Cystic Tumors

• Diagnosis, management
• Nonneoplastic cysts common
• Cystic neoplasms <10% tumors but low grade
• Neoplastic cysts
  – Serous cystadenoma
  – Mucinous cystic neoplasm
• Cystically dilated ducts
  – Intraductal papillary mucinous vs. Pancreatic intraepithelial neoplasia
• Cyst - degenerative change
Pancreatic Cystic Lesions

• ↑Use & sensitivity of imaging has ↑detection
• Most frequent pseudocysts
• Intraductal papillary mucinous neoplasms most common neoplasm
• Workup pseudocyst vs. neoplasm- Hx, XR, ERCP, Tumor markers, EUS FNA
• Observe or operate (drain or resect)
Pancreatic Cysts - Management

• Patient age and symptoms
  – If young patient with large cyst → surgery
  – If symptomatic and op candidate → surgery
  – If asymptomatic → CT, EUS, ?FNA/Bx
    • Mucinous → Surgery

• Not all cysts need evaluation –elderly with incidentally found small cysts

• Follow-up with serial CT scans

• Natural history of mucinous cysts unknown
Non-Neoplastic Cyst
Pancreatic Pseudocyst
Neoplastic Cysts
Mucinous Cystic Neoplasm

- Women 30-50 yo
- Body/tail
- No continuity duct
- Survival nearly 100% if noninvasive
Mucinous Cystic Neoplasm
Mucinous Cystic Neoplasm

- Mucinous epithelium
- Ovarian type stroma
Mucinous Cystic Neoplasm Classification

- Classification by dysplasia
  - MCN with low grade dysplasia (mucinous cystadenoma)
  - MCN with moderate dysplasia (borderline)
  - MCN with
    - High grade dysplasia (CIS)
    - Invasive carcinoma
Mucinous Cystic Neoplasm with Moderate Dysplasia

(Borderline, Uncertain Malignant Potential)
Mucinous Cystic Neoplasm with High Grade Dysplasia
MCN with Invasive Adenocarcinoma
Mucinous Cystic Neoplasm - Pitfall

- Extensive denudation
- Pseudocyst
- Ovarian stroma?
- Sample well
  - Denudation (frozen section pitfall)
  - Variation
Neoplastic Cysts

Serous Microcystic Adenoma

- Older women
- Most body/tail, single
- Well circumscribed, microcystic, scar
- Benign
Serous Microcystic Adenoma - Microscopic
Serous Microcystic Adenoma - Microscopic

- Variably sized cysts lined by cuboidal to flattened epithelium
- Clear to eosinophilic cytoplasm
- Distinct cell borders
- Central round nuclei
Serous Microcystic Adenoma

PAS positive

Diastase sensitive
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Dilated Ducts
Intraductal Papillary Mucinous Neoplasm

- 6th to 7th decade, men and women
- Head > tail
- Involvement main duct, branch duct or combination
- Continuity with duct system
- Mucin seen at ERCP
- 5 year survival nearly 100% if noninvasive and margin negative
Intraductal Papillary Mucinous Neoplasm (IPMN)
IPMN– Whole Pancreas
IPMN – Classification

- Grade dysplasia
  - IPMN with low grade dysplasia (adenoma)
  - IPMN with moderate dysplasia (borderline)
  - IPMN with high grade dysplasia (CIS)
  - Invasive

- Differentiation
  - Intestinal
  - Gastric foveolar
  - Pancreatobiliary
IPMN- Carcinoma

High Grade Dysplasia (CIS)  Invasive (colloid)
IPMN with Invasive Carcinoma
Pancreatic Intraepithelial Neoplasia (PanIN)

- Mucinous epithelial hyperplasia, metaplasia or dysplasia; micro < 5 mm
- Nomenclature for precursor lesions- “Pancreatic cancer think tank” US 1999; Forum Japan 2002
- Frequent in malignant cases and PanIN 1 present in benign cases
- Clinical significance- Precursor, high risk, understanding biology and progression

Takaori, Pancreas, 2004
PanIN 1A and 1B
PanIN 1A
Mucinous Metaplasia
PanIN 1B
Papillary Hyperplasia
PanIN 2, 3
Moderate, Severe Dysplasia
PanIN - Molecular

- Normal
- PanIN-1A
- PanIN-1B
- PanIN-2
- PanIN-3

Genes involved:
- Her-2
- K-ras
- p16
- p53
- DPC4
- BRCA2
Mucinous Tumor
Frozen Section

• Denudation and pseudocyst

• Margin
  – IPMN
  – PanIN
  – If low grade - stop
  – If CIS/invasion - resect more?
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Pancreatic Cysts

• Degenerative change
  – Solid pseudopapillary
  – Neuroendocrine
  – Adenocarcinoma

• Congenital

• Enterogenous cyst

• Other (endometriosis…)
Solid-Pseudopapillary Tumor

- Benign or low grade
- Young women
- Gross-cystic solid
- Monomorphous cells
- Pseudopapillary, fibrovascular stalks
- A1AT, CD10
- B-Catenin nuclear
- E-Cadherin nuclear and loss membranous
Cystic Neuroendocrine Tumor
Lymphoepithelial Cyst
Lymphangiomatosis
Ciliated Foregut Cyst
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*Includes ductal adeno, MCN and IPMT
** BCatenin & ECadherin (nuclear), CD10
Pancreas Cystic Tumors
Summary

• Important to recognize suggested by XR
• Must distinguish from pseudocyst
• Mucinous vs. serous
• Epithelial type and dysplasia
• Sample well to exclude invasion
• Tumors not typically cystic, can be
• H&E diagnosis (IHC may help)