Chronic Pancreatitis: Surveillance

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Genes & Pancreatitis

• Hereditary chronic pancreatitis
  – Mutations: cationic trypsinogen

• Tropical chronic pancreatitis
  – SPINK mutations

• Cystic fibrosis: pancreatic insufficiency

• Idiopathic chronic pancreatitis
  – Disease modifying genes
    • Mutations of CFTR: mild/mild; mild/severe
    • Drug metabolizing enzymes
    • Mutations of protease inhibitors
      – SPINK; alpha-1-antitrypsin, alpha-2-macroglobulin

• Alcohol induced chronic pancreatitis
  – Longilignes ? Polygenetic disease ?
Clinical Problems of Chronic Pancreatitis

• Acute relapses
  – SIRS, MODS
• Pain
• Exocrine insufficiency
• Endocrine insufficiency
• Complications
  – Pseudocysts
  – Ductal obstruction due to scars and / or stones
  – Fistula
  – Bleeding due to arrosion of vessels
  – Pancreatic Cancer
Chronic Pancreatitis: a Disease with Numerous Faces

Steatorrhea
Treatment of chronic Pancreatitis

• Stop alcohol + stop nicotine !!
• Pain therapy
  – analgesics (WHO) versus surgery versus
  – neurolysis (peridural analgesia, splanchnicectomy, ...) versus interventional endoscopy versus inhibition of secretion?
• Therapy of complications
  – interventional endoscopy versus surgery
• Therapy of exocrine insufficiency
  – pancreatin (acid protected pellets < 2mm)
• Therapy of endocrine insufficiency
  – insulin (cave intensified therapy)
Interventional Endoscopy in Chronic Pancreatitis

- Obstructive pancreatitis in pancreas divisum
  - papillotomy of minor papilla
- Stones
  - ESWL + papillotomy + extraction
- Stenosis of the bile duct
  - papillotomy + stent
- Prepapillary stenosis of the main pancreatic duct
  - papillotomy + stent
- Pseudocysts
  - transgastral, transduodenal, transpapillary drainage
  - percutaneous drainage
Interventional Endoscopy

There are almost no controlled trials
Pancreaticolithiasis: ESWL of any Benefit?
Pancreaticolithiasis: ESWL of any Benefit?
Endosonography of a Pancreatic Pseudocyst
Pathogenesis of Pain in Chronic Pancreatitis

- Hypertension of ducts due to obstruction
  - stones, scars, pseudocysts
- Inflammatory infiltration of sensory nerves
- Retroperitoneal effusions
- Ischemia
- Compression / distension of biliary duct, duodenum, pancreatic capsule
  - inflammatory mass, pseudocyst
- Extrapancreatic causes
  - ulcer, meteorism due to steatorrhea
- Psychological disorders due to alcoholism
Palliation of Pain in Chronic Pancreatitis: Use of Enzymes

- Metaanalysis
- 6 randomized, double blind, placebo controlled studies

- Statistical analysis demonstrates no benefit for pancreatic enzymes

pseudocyst

inflammatory mass + duct dilatation

stones + duct dilatation

inflammatory mass
MRCP
distal stenosis of bile duct

ERCP
long stenosis of pancreatic duct without prestenotic dilatation
Risk Factors for Pancreatic Cancer

- No strong risk factors
- Weak risk factors
  - Smoking
  - Chronic pancreatitis
  - Afro-Americans > Caucasians
  - Diabetes in women > 2 years
  - Family history of pancreatic cancer
    - Cameron: Johns Hopkins University, Lustgarten Foundation Conference 2001
Chronic Pancreatitis - Pancreatic Cancer?

- Pancreatic cancer in chronic pancreatitis: more often?
- Which are the risk factors?
- Mechanisms of cancerogenesis in chronic inflammation?
- Prophylactic or therapeutic modalities?
Pancreatitis and the Risk of Pancreatic Cancer
Pancreatitis
Sequence: Chronic Inflammation Cancer?

2,015 patients with chronic pancreatitis
Diagnosis: 1946 - 1989, follow up: 7 years
56 Pancreatic cancer

373 patients with chronic pancreatitis,
median follow up: 9 years
4 x pancreatic cancer
= 26-times elevated risk

Malka et al: Gut 2002; 51: 849
Chronic Pancreatitis and Pancreatic Cancer

Different causes of death:
11 x liver disease, 11 x sepsis
13 x malignancies (ENT-, esophagus)
16 x „various“
Malka et al: Gut 2002; 51: 849

Collected statistics:
2,166 patients with chronic pancreatitis
40 patients with pancreatic cancer
124 patients with other malignancies
Thuluvath et al: J Clin Gastroenterol 2003; 36: 159
### How often is Pancreatic Cancer in Chronic Pancreatitis in Reality?

<table>
<thead>
<tr>
<th>Count</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>10,000</td>
<td>Patients with pancreatic cancer</td>
</tr>
<tr>
<td>300</td>
<td>Patients with malignancies and chronic pancreatitis</td>
</tr>
<tr>
<td>100</td>
<td>Patients with pancreatic cancer in chronic pancreatitis</td>
</tr>
<tr>
<td>1</td>
<td>Patient with pancreatic cancer in hereditary pancreatitis</td>
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Progression of Chronic Pancreatitis

Prospective studies:

Ammann et al: Gastroenterology 1999 200 patients

Malka et al: Gastroenterology 2000 500 patients

follow-up (years)

Years after the onset of chronic pancreatitis

Diabetes
Pancreatitis in Patients with PRSS1 Mutations

80 patients with PRSS1 mutations (21 N29I, 59 R122H)
Follow-up 14 ± 10 years
Keim, Witt et al: 2003
Pancreatitis in Patients with PRSS1 Mutations

Severe first attack
Treatment in a hospital

Similar probability of calcifications, duct dilatation and first surgery

Late appearance of diabetes
Progression of Different Forms of Chronic Pancreatitis

- **Hereditary pancreatitis**: Layer et al: 1994
- **Idiopathic pancreatitis**: Keim, Witt et al: 2003
Smoking and manifestation of hereditary pancreatitis

Smoking & manifestation of pancreatic cancer in hereditary pancreatitis.
Lowenfels et al: JAMA 2001
Pancreatic Cancer & Hereditary Pancreatitis

72 patients no pancreatic cancer
mild course in the majority of patients
Sibert et al: J Med Genetics 1978

42 patients, no pancreatic cancer, no deaths from pancreatitis
excellent or good: 78%

85 patients, one patient with pancreatic cancer
Keim et al: 2003
Time to Pancreatic Cancer by Mutation Status

Howes et al: 2004
Is Pancreatic Cancer a Preventable Disease?

Smoking
No exercise

Obesity, Diabetes (Nutrition)
Pancreatic cancer in family
Known genetic factors
Chronic pancreatitis
Helicobacter
Hereditary pancreatitis
CFTR

30%
10-15%
10%
1-2%
??
Natural Course of Inherited Pancreatitis

• Early onset in the majority of patients
• Severe first attack leading to treatment in a hospital
• Progression to diabetes or calcification slower than in alcoholic chronic pancreatitis
• No major difference between PRSS1 (N29I, R122H) and SPINK1 (N34S)
• No sufficient data in patients with CFTR mutations
• Pancreatic cancer a consequence of long-lasting pancreatitis
• NOT ENOUGH PROSPECTIVE DATA
Early Diagnosis of Pancreatic Cancer?

According to Stefan Rosewicz +, Berlin, 2003

Diagram shows various imaging techniques:
- CT
- MRT
- ERCP
- US
- EUS
- FDG-PET
Early Diagnosis of Pancreatic Cancer?

- Regular check ups:
- Tumor markers (CA 19-9) & Sonography?
- Endosonography?
- PET?
- MR?
- Evaluation of pancreatic secretions: Ki-ras, p53 ...?
Summary

• Abstain from smoking
• Diagnostic evaluations according to the underlying clinical problem
• Treatment and surveillance of endocrine insufficiency according to compliance
• Early diagnosis of pancreatic cancer in chronic pancreatitis still not possible