

## PANCREATIC CANCER

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### GENERAL

- Highly lethal cancer
- Very aggressive cancer
- Overall 5 year survival is around 1%
- Discussion in this lecture is limited to exocrine pancreatic cancer. Endocrine tumors of pancreatic origin have better prognosis and are treated differently.

### INCIDENCE

- In United states of America: 2013 SEER estimates
  - Estimated cases 45,220 (22,740 men and 22,480 women)
  - Estimates deaths 38,460
- The incidence of this disease increases with advancing age
- Uncommon in patients younger than 50 years and peaks in the seventh decade of life.
- Men have a 40% higher risk for pancreatic cancer than do women.
- Blacks have a 30% to 40% increased risk of pancreatic cancer compared with whites.

### RISK FACTORS

- Mostly unknown
- Possible link to tobacco – smoking – a consistent risk factor
- Increasing age is a risk factor
- Conflicting data about coffee and alcohol
- Diabetes may be an early manifestation rather than predisposing factor
- Chronic pancreatitis may be a risk factor
- Fruits and vegetable rich diet may reduce risk
- Familial syndrome with increased risk for pancreatic cancer – only a very small number of cases – see below.
- Hereditary breast ovarian syndrome with BRCA 2 mutations increase risk of pancreatic cancer ( along with breast and ovarian cancer)

### PATHOGENESIS

#### Genetic mutations

- KRAS oncogene mutations are common
- Intra ductal proliferative epithelial lesions (PanINs – pancreatic intra-epithelial neoplasms) are considered precursors of invasive ductal pancreatic cancer

#### Familial syndromes with increase risk

- Familial breast cancer (Selective genetic mutations BRCA 2 more strongly associated than BRCA 1)
- Familial pancreatitis syndrome (cationic trypsinogen gene) – pancreatitis
- HNPCC-Hereditary non polyposis colon cancer (DNA mismatch repair gen mutations ) – colon cancer, endometrial cancer
- Familial atypical multiple mole melanoma (p16 mutations – chromosome 9P) – Multiple nevi, atypical nevi and melanoma
- Ataxia telangectasia

- Peutz Jeghers syndrome (STK 11 / LKB 1 mutations) – hamartomatous GI polyps and pigmented skin macules.
- Only 10-20% are thought to have familial pre disposition

#### PREVENTION STRATEGY

- Unknown

#### SCREENING

- No screening is available
- CA 19-9 is not useful for screening
- Optimal screening strategy for patients with strong family history of pancreatic cancer is not known.

#### SYMPTOMS / SIGNS

- Symptoms are influenced by tumor site and extent
- Often vague and nonspecific
- May include upper abdominal discomfort, back pain, anorexia, weight loss, or obstructive jaundice.
- Other symptoms may include nausea, vomiting
- Recent-onset diabetes
- Venous thromboembolism.
- Trousseau’s syndrome: Migratory (superficial) thrombo-phlebitis and visceral malignancy
- Left supra-clavicular lymph adenopathy (Virchow’s node)
- Obstructive jaundice is a presenting symptom in most patients with ductal adenocarcinoma arising in the head of the pancreas; the incidence of jaundice decreases as tumor location shifts towards the pancreatic tail.

#### DIAGNOSIS

- Delay in diagnosis is common
- Biopsy is necessary to confirm diagnosis of cancer (radiological tests cannot replace a biopsy)
- CT scan
- Endoscopic ultrasonography (EUS)
- Diagnostic laparoscopy.
- Although serum concentrations of CA-19-9, a Lewis blood group–related mucin, are frequently elevated in patients with this disease, this tumor marker's role has not been proved in the diagnosis or management of pancreatic cancer.

#### HISTOLOGY

- Primary pancreatic cancer can originate from exocrine (ducts and acini), endocrine (islet cells), or mesenchymal tissue.
- Adenocarcinoma (duct cell) is most common histology
- Approximately 95% of the primary tumors are located in the exocrine pancreas, of which more than 50% occur in the head and 20% in the body or tail. Diffuse involvement of the pancreas is found in the remaining cases.

#### STAGING SYSTEM

- AJCC staging
- Check cancer.gov or cancer.org for complete TNM definitions
- Size is important prognostic factor:

### STAGING WORK UP

- CT scan
- Endoscopic ultrasonography (EUS – accurate test for staging)
- Most patients with pancreatic cancer present with locally advanced or metastatic disease.

### TREATMENT

First step: evaluate patient for possibility of surgical resection

The benefits of therapy are modest at best, so clinical trials remains a sensible option.

For patients with poor performance status, best supportive care is appropriate.

Surgery for resectable tumors

- Surgery is only poetically curative treatment –
- However, most patients present with locally advanced or metastatic disease, and 20% or fewer patients are candidates for potentially curative surgery.
- Diagnostic procedures listed above help determine respectability of pancreatic cancer
- Generally tumors more than 4 cm size are rarely resectable ( less than 10% respectability rate)
- Invasion of superior mesenteric artery or major blood vessels indicates unresectable tumor.
- Even when the tumor appears to be resectable, various studies suggest that as many as 40% of patients will be found to have small metastases to the peritoneum or liver that were not detected on preoperative imaging studies.
- Postoperative mortality rates in patients who undergo pancreaticoduodenectomy (Whipple’s procedure) are influenced by the experience of the surgeon and the treatment center.
- In patients who undergo potentially curative surgery, 5-year survival rates have not exceeded 20% to 24% (generally 5% to 25%).

Post operative adjuvant therapy

- Controversial – best option is unclear.
- There has been interest in the use of adjuvant therapy in an attempt to improve outcome.
- Options include adjuvant chemotherapy alone OR adjuvant chemo-RT.
  - A small, randomized trial suggested an improvement in median and long-term survival in patients who received postoperative 5-fluorouracil and radiation. This has long been considered standard of care in USA.
  - However, the benefit of postoperative chemo radiation has not been confirmed in subsequent randomized trials.
  - CONKO-1 trial from Germany reported benefit of adjuvant Gemcitabine compared to surgery alone (3 year survival of 36% versus 19%). Considered European standard.
  - A US trial (RTOG 9704) suggested improved outcome in pancreatic head tumors with post operative Gemcitabine →FU-RT→ Gemcitabine versus FU-RT (3 year survival of 31% versus 22%).
  - A recent trial in Europe (ESPAC) indicated similar median survival (23 months) between adjuvant Gemcitabine versus FU-LV. Either of regimen can be considered.

Unresectable tumors

- For patients with locally advanced but unresectable disease, chemo - radiation, palliative chemotherapy, and participation in clinical trials are reasonable options.
- Chemotherapy and radiation for unresectable tumors
  - FU with RT is considered standard in USA

- Newer agents such as Gemcitabine, Capecitabine and targeted agents are under study
- Might be better in patients with uncontrolled pain since RT may help pain.
- Chemotherapy alone for unresectable tumors
  - Reasonable choice
  - European trial indicated that Induction chemo-RT with maintenance Gemcitabine was no better than Gemcitabine alone.
- Neoadjuvant Chemotherapy and radiation followed by surgery
  - The use of preoperative radiation therapy combined with various chemotherapeutic drugs, radiation-sensitizing agents, or both, is currently being investigated. Initial preliminary feasibility data – no randomized trials are available.

Chemotherapy for metastatic tumors (stage 4 cancer)

- Therapy is palliative.
- Single agent:
  - Gemcitabine is currently the first-line therapy of choice for patients with metastatic disease and good performance status.
  - Mild to moderate activity seen with Gemcitabine, FU, Taxanes, Platinum and Irinotecan
  - Gemcitabine was superior to FU in randomized trial (better pain control and improved appetite and weight – Clinical benefit) . Clinical benefit 24%, response rates less than 10%, 1 year surgical 18%.
- Combination regimens:
  - Most of the trials of combination have failed to show survival advantage over Gemcitabine alone.
  - Recent data:
    - Gemcitabine + oral Erlotinib was slightly better than Gemcitabine alone in Progression free survival and survival (median survival 6.2 vs. 5.9 months, 1 year survival 23% versus 17% - statistically significant).
    - Gemcitabine + oral Capecitabine was slightly better than Gemcitabine alone in Progression free survival and survival.
    - FOLFIRINOX has shown improved responses compared to Gemcitabine alone (median overall survival 11.1 vs. 6.8 months).
  - Combination may provide slight benefit in good performance status patients only.
  - Combination therapy may not provide any advantage in poor performance status patients.
- A recent German trial (CONKO 3) reported benefit of second line FU-LV-Oxaliplatin over FU-LV (26 weeks versus 13 weeks) in patient failing first line Gemcitabine.
- Summary of chemotherapy for stage 4:
  - Gemcitabine alone or Gemcitabine containing combination is considered standard of care. Gemcitabine containing combination should be used in good PS patients.

Poor PS patients:

- Best supportive care and hospice are appropriate for patients with poor PS or patients failing initial therapy with progressive metastatic disease

**Treatment summary table:**

Stage	Treatment	Comment
Stage I and II	Surgery Post operative adjuvant chemo-RT or Chemo	
Stage III	Chemo-RT or Chemo	Palliative care
Stage IV	Chemotherapy	Palliative care
Palliative care , pain control, biliary stent etc for all appropriate patients		

**PALLIATIVE CARE IN SPECIAL SITUATIONS**

Palliative measures to alleviate pain in patients with unresectable or metastatic disease:

- Optimal analgesic medications including Narcotics
- Radiation therapy with or without chemotherapy
- Chemical splanchnicectomy with 50% ethanol at the time of surgical exploration
- Celiac nerve blocks or similar local neurosurgical procedures.

Obstructive jaundice ( Biliary obstruction): Palliation may be achieved by

- Endoscopic biliary stent placement (ERCP)
- Percutaneous biliary stent placement (Radiology procedure)
- Surgical biliary bypass
- Duodenal stent for gastric outlet obstruction

**FOLLOW UP**

- Individualized

**PROGNOSIS**

The prognosis of patients with pancreatic cancer is directly related to tumor stage.

Overall 1 year survival rate is 20%

Stage	5 year survival	Comment
I	12%-14%	
II	5%-7%	
III	3%	
IV	1%	
ACS data		

**SAMPLE QUESTIONS**