Pancreatic Cancer

Part 4: Oncology and Hematology · Part 4 – Oncology: Solid Tumors

KEY CLINICAL POINTS

1. Pancreatic cancer is the third leading cause of cancer-related mortality in the U.S., with a 13% overall 5-year survival rate.
2. Cigarette smoking is the primary risk factor, contributing to 25–30% of cases.
3. High BMI (≥30) doubles the risk of pancreatic cancer.
4. Molecular profile: KRAS mutations in 90–95%, TP53 in ~75%, and DPC4/SMAD4 in ~50%.
5. mFOLFIRINOX is the preferred adjuvant therapy for fit patients (median survival 54 months vs. 35 months for gemcitabine).
6. PARP inhibitors are indicated for metastatic disease with BRCA1, BRCA2, or PALB2 germline variants.
7. CA19-9 is a useful marker but is not useful in Lewis antigen non-secretors.
8. Trousseau's syndrome (migratory thrombophlebitis) and Virchow's node are classic signs of advanced disease.
9. Neoadjuvant therapy is the standard for borderline resectable or locally advanced disease to assess biology and downstage.
10. Screening is only indicated for high-risk groups (e.g., BRCA1/2, PALB2, family history).

DEFINITION & CLASSIFICATION

- **Overview:** Third leading cause of cancer mortality in the U.S.; projected to be second leading globally by 2030.
- **Survival Rates:**
  - Localized: 44%
  - Regional: 16%
  - Metastatic: 3.2%

Epidemiology & Survival

- **Incidence:** ~3% of new cases in U.S.; 8.3% of cancer-related deaths.
- **Risk Trends:** Lifetime risk ~1.7%; incidence increasing by 1.1% annually (faster growth in those <55).

EPIDEMIOLOGY

- **Demographics:** Most common in ages 65–79; higher incidence in males and Black individuals.
- **Risk Factors:**
  - **Environmental:** Cigarette smoking (25–30% of cases); high fat/meat diet, low fruit/veg intake.
  - **Hereditary:** 10–16% of cases linked to genetic syndromes (e.g., BRCA2, CDKN2A).
  - **Other:** Obesity (BMI ≥30), physical inactivity, diabetes; Non-O blood type.

Screening & High-Risk Populations

- **Average Risk:** No screening recommended.
- **High Risk:** Screening indicated for BRCA1/2, PALB2, CDKN2A, STK11, or significant family history.
  - Family History: 4.6-fold risk with one first-degree relative; 32-fold with ≥3 affected relatives.
- **Table 88-1:** Lists germline mutations and associated syndromes (e.g., PRSS1/SPIN11b for hereditary pancreatitis, STK11 for Peutz-Jeghers).

ETIOLOGY & PATHOPHYSIOLOGY

- **Precursor Lesions:**
  - PanIN (grades 1–3) → progression to invasive cancer.
  - IPMN: Main duct type more likely malignant; side branch type often benign.
  - Mucinous cystic neoplasms: More common in women, lower malignancy risk.
- **Molecular Characteristics:**
  - KRAS mutations: 90–95% of ductal adenocarcinomas.
  - TP53: ~75%.
  - SMAD4: ~50%.
  - BRCA2: 3.5–10% (Table 88-1).
- **Pathology:**
  - Desmoplastic reaction: Dense fibrotic stroma (Figure 88-1) leads to vessel/nerve compression and poor prognosis.

CLINICAL FEATURES

- **Symptoms:**
  - Painless jaundice (bilirubin >2 mg/dL; common in head of pancreas tumors).
  - Epigastric pain radiating to back.
  - Weight loss, steatorrhea, new-onset diabetes.
  - Pruritus from bile salts.
- **Physical Examination Findings:**
  - **Courvoisier's sign:** Palpable gallbladder with biliary obstruction.
  - **Trousseau's syndrome:** Migratory superficial thrombophlebitis (indicates hypercoagulable state).
  - **Virchow's node:** Left supraclavicular lymphadenopathy.
  - **Sister Mary Joseph's node:** Periumbilical metastasis.

Clinical Significance of Signs

- **Trousseau's syndrome** → strong indicator of occult malignancy.

DIFFERENTIAL DIAGNOSIS

- **Biliary Obstruction:** Distinguish from choledocholithiasis (Charcot's triad: pain, fever, jaundice).
  - Courvoisier's sign → suggests malignancy over stone.
- **Weight Loss & Epigastric Pain:**
  - Chronic pancreatitis vs. cancer: Cancer often presents with steatorrhea and back radiation of pain.

– Other differentials: Gastric malignancy, lymphoma, peptic ulcer disease.

DIAGNOSTIC APPROACH

1. **Imaging:**
   – Dual-phase CT: Evaluate vascular involvement (e.g., SMA, portal vein) and resectability.
   – PET-CT: Identify occult metastases (Figure 88-3).
   – Laparoscopy: Identify metastatic disease preoperatively.
2. **Histologic Confirmation:**
   – Tru-Cut biopsy preferred for tissue sampling.
3. **Molecular & Biomarker Testing:**
   – KRAS, microsatellite status, and BRCA/PALB2 status to guide therapy.
   – CA19-9: Serum marker; note that it is non-detectable in Lewis antigen non-secretors.

Staging (AJCC)

- **T Category:**
  – TX: Not assessable.
  – Tis: Carcinoma in situ (PanIN-3, IPMN with high-grade dysplasia).
  – T1: ≤2 cm.
  – T4: Involves celiac axis, SMA, or common hepatic artery.
- **N Category:**
  – NX: Not assessable; N0: No regional nodes; N1: 1–3 nodes.
- **M Category:**
  – M0: No distant metastasis; M1: Distant metastasis.
- **Prognostic Stage Groups (Table 88-4):**
  – Stage 0: Tis, N0, M0.
  – Stage IA: T1, N0, M0.
  – Stage IB: T2, N0, M0.
  – Stage IIA: T3, N0, M0.
  – Stage IIB: T1/T2/T3 with N1; or T4 with any N and M0.
  – Stage III: T1/T2/T3 with N2; or T4 with any N and M0.
  – Stage IV: Any T, Any N, M1.

MANAGEMENT & TREATMENT

1. **Resectable Disease (Table 88-3):**
   • Criteria: No solid tumor contact with celiac axis, hepatic artery, or SMA; contact with superior mesenteric–portal veins <180°; patent superior mesenteric–portal veins; no extrapancreatic disease.
   • Action: Surgery (pancreaticoduodenectomy or distal pancreatectomy) → followed by adjuvant therapy.
   • Adjuvant Options: mFOLFIRINOX or gemcitabine ± capecitabine or nab-paclitaxel.
2. **Locally Advanced Disease:**
   • Action: Neoadjuvant chemotherapy to assess tumor biology and attempt downstaging for margin-negative resection.

- Comparison: mFOLFIRINOX (median survival 54 months) vs. gemcitabine alone (35 months).

3. **Metastatic Disease:**
   - Systemic Therapy: PARP inhibitors for patients with BRCA1, BRCA2, or PALB2 mutations.
   - Supportive Care:
     - Anticoagulation (DOACs or LMWH) for Trousseau's syndrome.
     - PERT for malabsorption symptoms.
     - Opioids/nerve blocks for pain management.

Supportive Care

- **Nutrition:** PERT for exocrine insufficiency; nutritional support for weight loss.

COMPLICATIONS & PROGNOSIS

- **Prognosis by Stage:**
  - Localized: 44% 5-year survival.
  - Regional: 16%.
  - Metastatic: 3.2%.
- **Complications:**
  - Hypercoagulable states (Trousseau's syndrome).
  - Malabsorption and weight loss from exocrine insufficiency.
  - Peritoneal carcinomatosis (Sister Mary Joseph's node).

SPECIAL POPULATIONS

- **Genetic Screening:**
  - BRCA1/2, PALB2, CDKN2A, STK11 carriers require specific surveillance.
- **Molecular Profiling:**
  - KRAS wildtype tumors may respond to novel therapies.
  - Microsatellite instability (MSI) guides immunotherapy eligibility.

KEY PEARLS & HIGH-YIELD POINTS

- **Trousseau's Syndrome:** A critical clinical sign of occult malignancy and hypercoagulability.
- **CA19-9 Limitation:** Not useful in Lewis antigen non-secretors; do not rely solely on it for monitoring in these patients.
- **Resectability Rule:** Surgery is only indicated if the tumor does not involve major vessels (SMA, celiac axis) or has limited involvement of portal veins (<180°).
- **Neoadjuvant Strategy:** Standard for borderline resectable/locally advanced to assess response and downstage.

REFERENCE TABLES

TABLE 88-1

Germline Mutations, Familial Cancer Syndromes, and Fold Risk of Pancreatic Cancer

GERMLINE MUTATION	FAMILIAL CANCER SYNDROME	ESTIMATED INCREASED RISK (FOLD) OF PANCREATIC CANCER
BRCA2a	Familial breast/ovarian cancer and others	3.5–10
	Familial breast cancer and others	
p16/CDKN2A	Familial atypical multiple mole melanoma (FAMMM)	15–22
	Peutz-Jeghers syndrome	
PRSS1 or SPIN11b	Hereditary (familial) pancreatitis	53
	Ataxia-telangiectasia	
MLH1, MSH2, MSH6, PMS2	Heredity nonpolyposis colorectal syndrome or Lynch syndromed	9–36

TABLE 88-2

Definition of Primary Tumor (T) T CATEGORY TX T0 Tis

T CATEGORY	T CRITERIA
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T4	Tumor involves celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size

N CATEGORY	N CRITERIA
NX	Regional lymph nodes cannot be assessed
N1	Metastasis in one to three regional lymph nodes

M CATEGORY	M CRITERIA
M0	No distant metastasis

AJCC Prognostic Stage Groups

WHEN T IS...	AND N IS...	AND M IS...	THEN THE STAGE GROUP IS....
Tis	N0	M0	0
	N0	M0	
T1	N1	M0	IIB
	N2	M0	
T2	N0	M0	IB
	N1	M0	
T2	N2	M0	III
	N0	M0	
T3	N1	M0	IIB
	N2	M0	
T4	Any N	M0	III
	Any N	M1	

TABLE 88-3

Extent of Disease and Therapeutic Approach

DESIGNATION (MEDIAN SURVIVAL)	THERAPEUTIC APPROACHES
1. Resectable (localized): (18–23 mo) **• No solid tumor contact with celiac axis, hepatic artery, or superior mesenteric artery (SMA), contact with superior mesenteric–portal veins of <180°** **• Patent superior mesenteric–portal veins** **• No extrapancreatic disease**	Surgery followed by adjuvant therapy • mFOLFIRINOX or gemcitabine +/– capecitabine or nab-paclitaxel Neoadjuvant chemotherapy followed by surgery