

PANCREATIC CANCER

Epidemiology:

- 4th leading cause of cancer-related death in the US. 2nd to colorectal cancer in GI cancer-related deaths.
- Incidence of new cases anticipated in 2004: 31,860 Expected deaths: 31,270
- Rare before the age of 45, but the incidence rises sharply after 45 years old
- M: F=1.3:1, more common in black males (14.8 per 100,000 vs. 8.8 general population)
- Only potential cure is surgery. Due to late presentation only 15 - 20 % of patients are surgical candidates.
 - 80-85% inoperable when diagnosed.
- Prognosis is poor even in those with potentially resectable disease.
 - 5 year survival after pancreaticoduodenectomy is 25-30 % for node negative vs. 10 % for node positive
- Inoperable median survival: 8 -12 months with locally advanced tumors vs. 3-6 months for metastatic disease.

Risk Factors: chronic pancreatitis, smoking, diabetes mellitus, and family history pancreatic cancer

- increased in hereditary nonpolyposis colorectal cancer (HNPCC), familial breast cancer (BRCA2), Peutz-Jeghers, ataxia-telangiectasia, familial atypical multiple mole melanoma (FAMMM), and hereditary pancreatitis.
- Tumor suppressor genes: p16 (inactivated in 95%), p53 (75%), DPC4 (20%) Oncogene: k-ras (> 90%)

Clinical Presentation:

- **History:** pain upper abdomen, dull ache that radiates to back. +/- intermittent and worse with eating, weight loss, anorexia, early satiety, diarrhea, or steatorrhea, pruritis, jaundice, recent onset of atypical DM, unexplained thrombophlebitis, or previous pancreatitis.
- **PE:** abdominal mass or ascites noted in 20%, Courvoisier's sign (nontender palpable gallbladder with jaundice), Metastases: left supraclavicular lymphadenopathy (Virchow's node), periumbilical lymphadenopathy (Sister Mary Joseph nodes), and perirectal metastases (Blumer shelf), rarely pancreatic panniculitis (subcutaneous nodular fat necrosis).
- Body/Tail tumors present with pain and weight loss, tumors in head present with steatorrhea, weight loss, and painless jaundice.
- **Labs:** ↑ Bili, Alk Phos, GGT, mild LFT's. (Body/tail labs may be normal). Amylase/Lipase usually normal.

Diagnostic Imaging:

Diagnostic Studies for Pancreatic Cancer			
Test	Sensitivity	Specificity	Useful in staging
Ultrasound	80 percent	90 percent	No
Endoscopic ultrasound	90 percent	90 percent	Yes
CT scan	90 percent	95 percent	Yes
Endoscopic retrograde choangiopancreatography	90 percent	90 percent	No
MRI scan	90 percent	90 percent	No
Fine needle aspirate	90 percent	98 percent	No

- CT scan has a better sensitivity than, and similar specificity to US
- ERCP used for patients where CT or US does not reveal a mass within the pancreas, and if differential diagnosis includes chronic pancreatitis. MRCP has been reported to be comparable ERCP.
- MRI can visualize both the bile and pancreatic ducts, useful in patients in whom attempted ERCP is either unsuccessful or provides incomplete information due to pancreatic duct obstruction.
- Endoscopic ultrasound-guided FNA is controversial.
 - Risks: hemorrhage, pancreatitis, fistula, abscess, perforation, death, dissemination.
 - Dx: sensitivity of 92%, specificity of 100%, and diagnostic accuracy of 95% for
 - LN: sensitivity of 83%, specificity of 100%, and diagnostic accuracy of 88%
 - Less likely to cause intraperitoneal spread of the tumor since the biopsy is obtained through the bowel wall rather than percutaneously.
- Laparoscopy or Lap US: new staging modality for periampullary tumors
 - Small occult metastases (<1 cm in diameter) on surface of the liver, peritoneum rarely visible by CT, MRI, or US may be visualized. If the tumor appears to be resectable following lap visualization, lap US may be performed to eval liver and portal, peripancreatic, periaortic, and celiac axis lymph nodes, and vascular involvement.
 - Major benefit of staging laparoscopy: reduces the number of apparently operable cases that are found to be unresectable at laparotomy.
- CA 19-9 reported sensitivity and specificity of 80 to 90% -but related to tumor size
 - Surgically unresectable >1000U/mL, Benign disease <37 U/mL

Staging of Pancreatic Exocrine Cancer[†]

Definition of TNM

Primary tumor (T)

TX Primary tumor cannot be assessed
 T0 No evidence of primary tumor
 Tis In situ carcinoma
 T1 Tumor limited to the pancreas, 2 cm or less in greatest dimension
 T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension
 T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
 T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed
 N0 No regional lymph node metastasis
 N1 Regional lymph node metastasis

Distant metastasis (M)

MX Distant metastasis cannot be assessed
 M0 No distant metastasis
 M1 Distant metastasis

Stage grouping

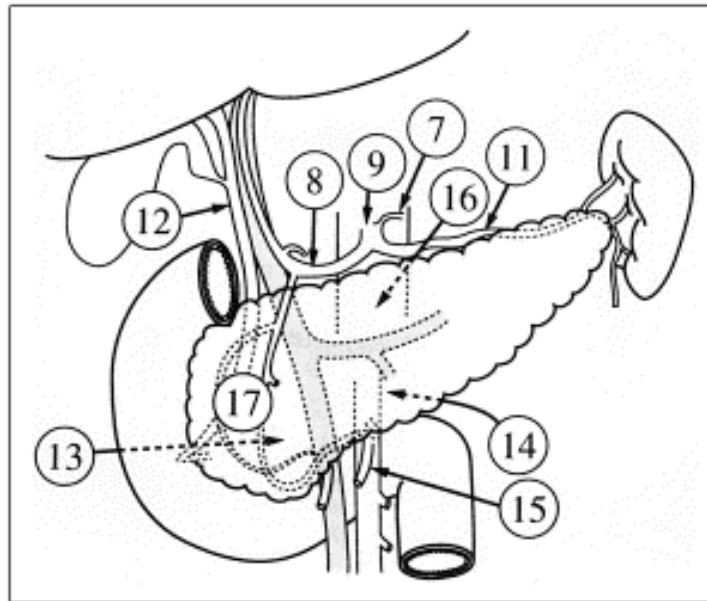
Stage 0	Tis N0 M0
Stage IA	T1 N0 M0
Stage IB	T2 N0 M0
Stage IIA	T3 N0 M0
Stage IIB	T1-3 N1 M0
Stage III	T4 Any N M0
Stage IV	Any T Any N M1

[†] Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York, Inc.

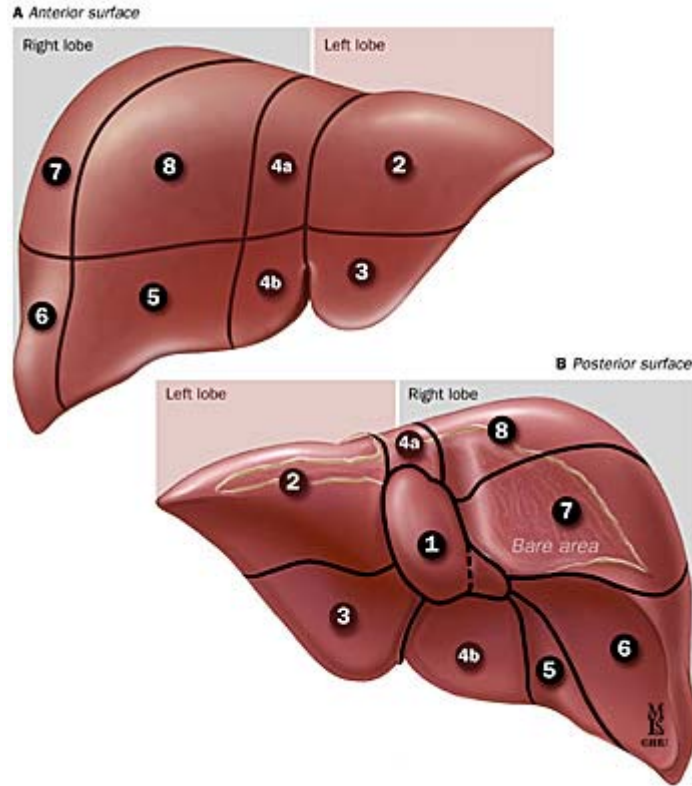
Stage Grouping	5-Year Survival
Stage I	20-40%
Stage II	10-25%
Stage III	10-15%
Stage IV	0-8%

Pathology:

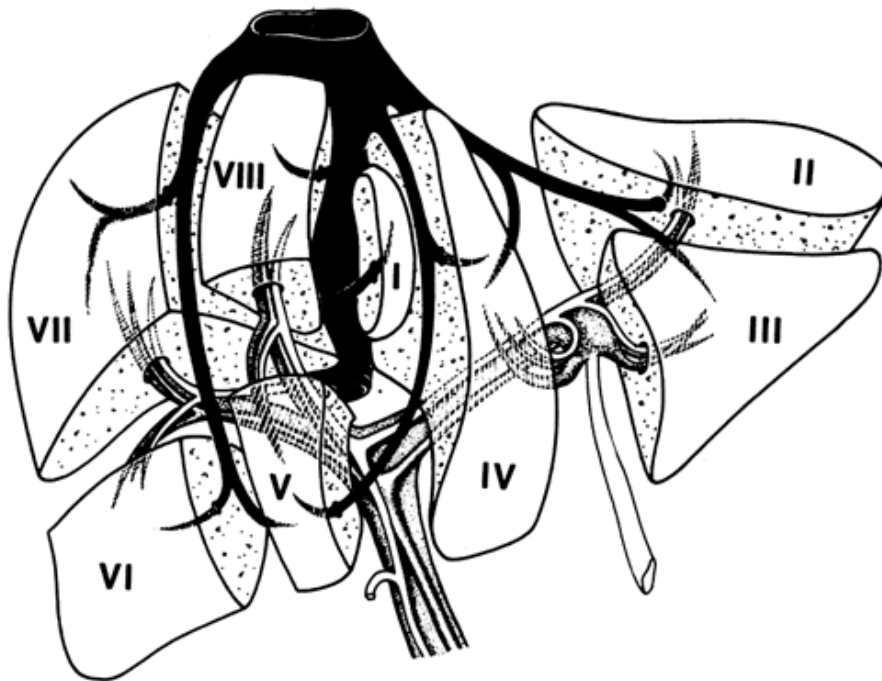
- Ductal adenocarcinoma >80% of all primary pancreatic cancer. Remainder: Adenosquamous, cystadeno, acinar.
 - 65% ductal arise in the head, neck, or uncinete process of the pancreas.
 - 15% originate in the body and tail, and 20% diffusely involve the entire gland.
- Ductal adenocarcinoma can infiltrate into vascular spaces, lymphatic spaces, and perineural spaces.
- At the time of discovery, most have metastasized to peripancreatic lymph nodes.
- Metastases to the liver (up to 80%), peritoneum (60%), lungs and pleura (50 to 70%), and adrenal glands (25%).



Classification of lymph node groups in the management of periampullary adenocarcinoma. They are as follows: 7 = left gastric artery; 8 = common hepatic artery; 9 = celiac trunk; 11 = splenic artery; 12 = hepatoduodenal ligament; 13 = posterior pancreaticoduodenal; 14 = superior mesenteric artery; 15 = middle colic artery; 16 = paraortic; and 17 = anterior pancreaticoduodenal lymph nodes.



- The liver is divided into eight segments, based on vascular inflow and bile duct drainage. Branches of the hepatic artery and portal vein supply each segment. Plane from GB fossa through vena cava (Cantlie's line) divides L/R lobes. Each Lobe has 4 segments. Caudate lobe (seg I) drains both R and L ductal systems.

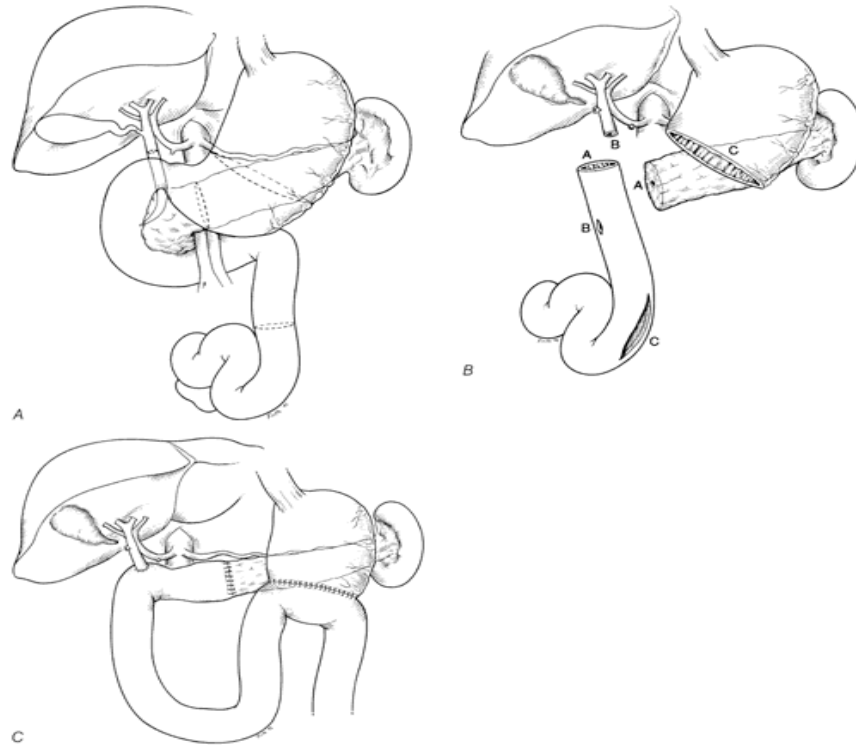


Surgery:

- If mass in pancreas is detected, and the patient is a surgical candidate: taken to OR.
- Preoperative staging can be done with: CT, angiography, endoscopic ultrasound, and laparoscopy
- Disease that is limited to the pancreas and peripancreatic nodes (stage I-IIB) is most likely to be cured by radical resection.
- Absolute contra-indication for resection: metastases in the liver, peritoneum, omentum, or any extraabdominal site.
- Relative contra-indications are involvement of the bowel mesentery, porto-mesenteric vasculature, and celiac axis.
- Tumors that involve the major peripancreatic vessels such as the SMV, portal vein, or SMA may be technically resectable, their curability is controversial.
 - Lack of major vascular involvement resectability rate: over 90 %
 - Partial involvement of the SMV and/or SMA on CT angio resectability rate of 10 to 50%

Pancreaticoduodenectomy for Tumors of the Head, Neck, or Uncinate Process

- Controversial use of preoperative transhepatic and endoscopic stents to improve surgery-related morbidity and mortality. Some report harmful sepsis, increased M &M.
- Pylorus-preserving pancreaticoduodenectomy, which decreases the incidence of postoperative dumping, marginal ulceration, and bile reflux gastritis that can occur in many patients undergoing partial gastrectomy. The procedure preserves the gastric antrum, pylorus, and the proximal 3 to 6 cm of the duodenum, which is anastomosed to the jejunum to restore gastrointestinal continuity. The available data suggest that long-term survival is not adversely affected, and there are no additional complications. This is favored in most patients.
- Perioperative mortality 4%.
- Prognostic factors: nodal status in resected patients.
 - Five-year survival is 10% for node+ and 25-30 % for node negative
 - Other predictors of a favorable outcome include tumor size <3 cm, negative margins, well-differentiated tumors, and small intraoperative blood loss (<750 mL).



Whipple pancreaticoduodenectomy. *A*. The dashed lines indicate the lines of transection. *B*. Includes pancreaticoduodenectomy, cholecystectomy, truncal vagotomy, antrectomy, proximal jejunectomy. Gastrointestinal continuity will be restored by choledocjejunostomy, pancreaticojejunostomy, gastrojejunostomy as indicated by the letters *A*, *B*, and *C*. *C*. The completed reconstruction.

- Ultraradical surgery with portal vein resection, total pancreatectomy, and retroperitoneal lymphadenectomy has been performed primarily in Japan. An initial report by Manabe et al. suggested a superior outcome compared with the standard Whipple. Proponents argue that the more extensive
- resection allows removal of multifocal disease and additional potentially involved peripancreatic nodes. It also eliminates the need for pancreaticoenteric anastomosis, thereby removing the risk of a postoperative leak or pancreatic fistula. However, since then most reports failed to demonstrate improved survival and, as with total pancreatectomy, patients who underwent this procedure developed diabetes, which was often difficult to control.
- Ishikawa et al. reviewed 59 pts. Group R1 panc head LN dissection. Group R2 wide LN and soft tissue dissection including para-aortic nodes. Operative mortality same in R1&2. 3 year survival R1 13% vs. 38% R2.

Distal Pancreatectomy for Tumors of the Body and Tail

- Distal subtotal pancreatectomy, usually combined with splenectomy.
- Limited data available regarding the outcome of surgical resection suggest a short survival, high perioperative mortality rate and poor prognosis compared to those with cancers involving the head of the pancreas

Chemotherapy:

- **Adjuvant Therapy (Postoperative):** 5-FU based chemoradiation

GITSG study: Gastrointestinal Tumor Study Group (GITSG) demonstrated improved survival with a combo of external beam radiation and 5-fluorouracil regimen was subsequently applied to patients who had undergone complete surgical resection. Postoperative combined modality treatment was associated with a significant prolongation in median survival (20 versus 11 mo) and a doubling of 2-year survival (20 vs. 10 %).

EORTC study: European Organization for Research and Treatment of Cancer (EORTC) postoperative chemoradiotherapy was not associated with a significant improvement in median survival or two-year survival (26 vs. 34% for control and treated patients.)

ESPAC-1 trial: 2nd trial by European investigators pooled analysis included 541 patients three parallel studies: Chemoradiotherapy vs. no chemoradiotherapy, Adjuvant chemo vs. no chemo, a 2x2 factorial design trial with four groups: chemoradiotherapy, chemotherapy, both, or observation. In the initial report, there was no survival difference between postop chemoradiotherapy compared to none. In contrast, there was significant survival benefit for adjuvant chemotherapy compared to none.

- **Neoadjuvant Therapy (Preoperative):** 5-fluorouracil-based chemoradiation
- **Advanced Pancreatic CA:** unresectable locoregional or metastatic disease: standard treatment for patients with unresectable locoregional disease is radiation and concomitant 5-fluorouracil or gemcitabine alone.

Surgical Palliative Procedures

- Biliary decompression can be achieved either by endoscopic or percutaneous transhepatic stenting.
- To relieve obstruction of the duodenum by tumor lap gastric bypass can be done
- Pain can be controlled intraoperative splanchnicectomy, percutaneous celiac block

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