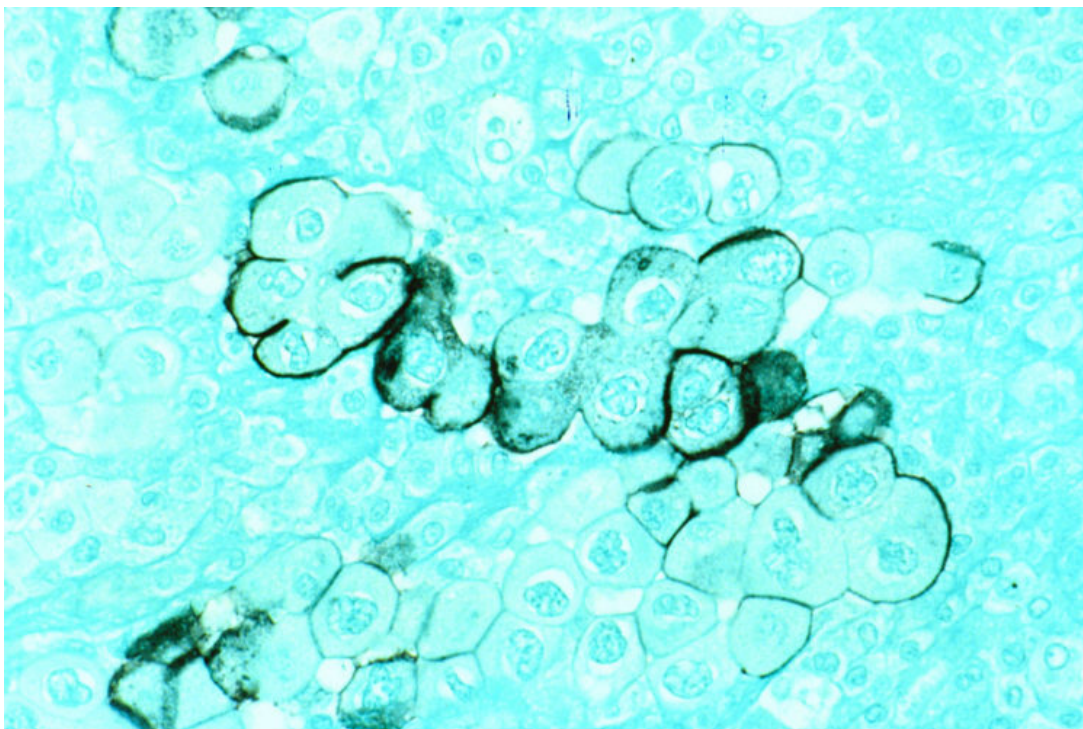


Pancreatic Cancer: Insulinoma and Gastrinoma — Diagnosis and Surgery

[See online here](#)

Pancreatic cancer is one of the most aggressive malignant tumors worldwide. It is considered the 4th cause of overall cancer mortality among cancer patients. The 5-year survival rate for stage 1A pancreatic cancer patients is less than 15%. Patients usually have vague complaints leading to late presentation and early metastasis which contribute to the high mortality rate. Tumors of the pancreas can arise from the exocrine part, mainly the duct system, which is the most common, or arises from the endocrine islet cells (neuroendocrine tumors) which are less common. Most of the pancreatic tumors arise in the head or neck of the pancreas with less frequent tumors arising from the body and tail.



Etiology of Pancreatic Cancer

There is no definite etiologic factor, but many **risk factors** are associated with an increased risk of developing pancreatic cancer, including genetics, smoking, chronic pancreatitis, diet, obesity, and diabetes mellitus.

Genetic susceptibility

Genetic mutations associated with pancreatic cancer include the KRAS2, P53, Smad4,

and CDKN2 genes. The **ABO blood group system** has also been implicated in pancreatic cancer risk. Clinical studies have found a higher correlation between the non-blood group O and pancreatic cancer. This means an increased risk in patients with blood groups A, B, and AB for pancreatic cancer. Another explanation is these patients' susceptibility to **H pylori infection**, which is associated with pancreatic cancer.

Smoking causes almost one-fourth of pancreatic cancer cases. The risk increases proportionally to the smoking index, while smoking cessation can decrease the risk. Ten years after smoking cessation, a former smoker's risk is similar to that of the general population.

Chronic pancreatitis increases the risk of transformation to malignant neoplasm by 2-4%. Pancreatitis prevention has a major positive effect on decreasing pancreatic cancer mortality.

Diabetes mellitus, diet, and obesity

There is a correlation between obesity/diet and pancreatic cancer. Higher BMI is a risk factor; while diabetes mellitus increases the risk of pancreatic cancer. In rare instances, pancreatic cancer can cause diabetes since it destroys insulin-producing cells.

Epidemiology

Pancreatic cancer is rare, but it has a high mortality rate and is one of the most common causes of mortality due to cancer. Its incidence varies greatly across the region, suggesting the influence of diet and other environmental factors, such as smoking, vitamin D deficiency, alcohol consumption, and history of diabetes.

Clinical Presentation of Pancreatic Cancer

Patients commonly present with **epigastric or back pain**, general constitutional symptoms of **fatigue, anorexia, and weight loss, GI symptoms** due to duodenal obstruction; nausea, and vomiting. Late manifestation with **jaundice, steatorrhea, pruritus** (intolerable itching), and **dark urine** due to biliary obstruction.

A physical examination will be remarkable for **cachexia, jaundice, ascites, epigastric or right upper quadrant mass, and palpable gallbladder** at the right costal margin, which is known as **Courvoisier's sign**.

Other findings at physical examination

- Ascites, hepatomegaly, and palpable abdominal mass.
- **Blumer's Shelf**- a mass in the rectal pouch, found during a rectal examination, due to metastasis.
- **Sister Mary Joseph nodule**- a subcutaneous metastasis in the paraumbilical area (found in advanced cases).
- **Virchow's Nodes**- metastatic nodes found behind the medial aspect of the left clavicle.
- Other cervical lymph nodes may be enlarged as well.

Trousseau sign is migratory thrombophlebitis and venous thrombosis, which can be a common initial presentation indicating a hypercoagulable state. **Pancreatic panniculitis**

is nodular erythematous subcutaneous fat necrosis, thought to be due to pancreatic enzyme digestion of the subcutaneous fat. It can occur in pancreatitis, cancer, and neuroendocrine tumors.

Pain associated with pancreatic cancer is a dull, visceral **pain** of insidious onset and intermittent course. It is located in the epigastrium and radiates to the back and sides. The pain improves slightly by leaning forward and is worse with eating and lying supine. Pancreatic head tumors give rise to **early cholestatic jaundice, dark urine, steatorrhea, itching, and pale, greasy stools.**

Diagnosis of Pancreatic Cancer

Laboratory evaluation of patients with jaundice and abdominal pain includes **serum aminotransferase enzymes, alkaline phosphatase, total and direct bilirubin, and serum lipase.**

CA 19-9 is a tumor marker that is more sensitive in large tumors and positive Lewis blood group antigens. High marker levels are associated with higher specificity. It can be used as a prognostic marker for the follow-up of disease response to treatment and recurrence.

Imaging with an **abdominal ultrasound** is used initially to evaluate jaundice and visualize the biliary tract. A **CT scan** is used to evaluate patients with abdominal pain. It allows visualization of the pancreas and the entire abdomen to detect small tumors and help with staging in case of metastases. **ERCP** is used to evaluate jaundice due to biliary obstruction and allow decompression intervention by inserting a stent to relieve the biliary obstruction.

MRCP is an alternative means of biliary tract assessment but lacks any therapeutic intervention. **Endoscopic ultrasound (EUS)** allows visualization of small tumors and lymph node metastasis for better staging and percutaneous guided biopsy. **PET scanning** is mainly beneficial for detecting occult distant metastasis. **Fine needle aspiration** of the tumor can be guided percutaneously by ultrasound or endoscopic US and CT scan.

Staging of Pancreatic Cancer

Staging is the first step in evaluating pancreatic cancer for **resectability**. Resectable tumors are confined to the pancreas without distant metastasis to the liver, peritoneum, or distant organs. Invasion of the major blood vessels in the abdomen, e.g. aorta, superior mesenteric, and celiac arteries is not a contraindication to surgery unless the tumor is unresectable.

For tumor staging, TNM classification is considered

Tx: The primary tumor can't be assessed. **T0:** No evidence of primary tumor in the pancreas. **Tis:** Carcinoma in situ. **T1:** Tumor is less than 2 cm and limited to the pancreas. **T2:** The tumor is larger than 2 cm. **T3:** The tumor extends beyond the pancreas to adjacent structures. **T4:** The tumor invades the celiac or superior mesenteric arteries.

Lymph nodes N; Nx: LNs cannot be assessed. **N0:** No LN metastasis. **N1:** Positive LN metastasis.

Distant metastasis M: **Mx:** cannot be assessed; **M0:** no distant metastases; **M1:** positive

for distant metastasis.

Treatment of Pancreatic Cancer

Surgical resection is the only curative treatment for pancreatic cancer; however, the long-term survival rate is low, even with resectable tumors. **Pancreaticoduodenectomy (Whipple's operation)** is the most appropriate procedure for head tumors and cholangiocarcinoma. The procedure includes removing the head of the pancreas, duodenum, gall bladder, and gastric antrum. Surgical complications include **high mortality rates, delayed gastric emptying, or pancreatic leak.**

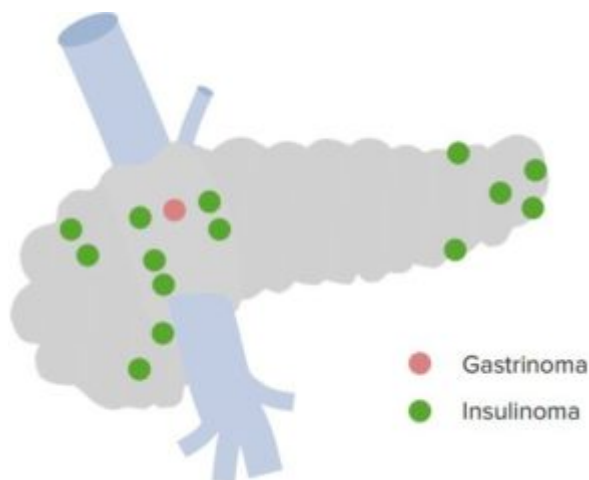
Distal pancreatectomy is optimal for body and tail tumors, which usually present late. The main complication of distal pancreatectomy is a pancreatic leak. Surgical intervention may be used with unresectable tumors for palliation, e.g., decompression and relief of the obstruction and biliary drainage.

Celiac ganglion neurolysis is another intervention for pain control in patients with unresectable tumors. **Gastrojejunostomy** is performed in patients with duodenal obstruction.

Gemcitabine-based chemotherapy regimens are approved for metastatic cancer. They offer a one-year survival benefit and may be combined with erlotinib for better results. Neoadjuvant and adjuvant chemotherapy treatment is controversial. A FOLFIRINOX regimen, which combines leucovorin, fluorouracil, irinotecan, and oxaliplatin, was approved recently. It offers a slightly better survival benefit in patients who can tolerate multiple chemotherapeutic agents.

Palliative therapy: Jaundice improves with endoscopic stent placement and decompression surgery, which are indicated to relieve biliary obstruction, malabsorption, pruritus, and guard against cholangitis. Pain control with opiates and radiation therapy should be considered in all patients with resectable tumor and palliative therapy.

Pancreatic Neuroendocrine Tumors



“Distribution of Functioning Neuroendocrine Tumors of Pancreas”
Image created by Lecturio

Neuroendocrine tumors arise from the islet cells of the pancreas that secrete insulin, glucagon, gastrin, and vasoactive intestinal polypeptide. However, most of these tumors are non-functioning and do not secrete hormones. These are rare tumors that constitute

less than 5% of primary pancreatic tumors. They can be sporadic or associated with other syndromes, e.g., **multiple endocrine neoplasia I**, **Von Hippel Lindau disease**, and **neurofibromatosis I**.

Localization of neuroendocrine tumors

A **CT scan** is the best initial diagnostic modality with high sensitivity and specificity for pancreatic neuroendocrine tumors. The sensitivity increases with tumor size and contrast enhancement.

MRI with gadolinium enhancement has excellent sensitivity and specificity. It is preferable for the detection and evaluation of liver metastasis.

Endoscopic ultrasound (EUS) is useful for detecting small micro tumors that cannot be detected with CT or MRI, as well as duodenal wall gastrinoma and lymph node metastases. It allows US-guided fine-needle aspiration for tumor cytology.

The **Octreotide scan** uses a radiolabelled somatostatin analog for visualizing tumors with high somatostatin receptor expression. It is accurate for localizing even non-functioning and poorly differentiated tumors.

The **Pet scan** accurately localizes and stages NETs with high resolution, especially with functional tracers, e.g., gallium.

Venous sampling is sometimes used to localize functioning tumors that are not visualized by conventional imaging. A sampling of the portal vein or hepatic vein with an assessment of hormonal levels, especially after injecting the stimulating agent, e.g., secretin. Intraoperative palpation of the duodenum and pancreas, and intraoperative ultrasound, are used for accurate localization and staging of the tumors that cannot be detected by conventional imaging.

Insulinomas are benign tumors that secrete insulin, causing hypoglycemia. Patients present with symptoms of hypoglycemia and adrenergic stimulation, including palpitations, weakness, diaphoresis, amnesia, abnormal behavior, tremors, and blurring of vision. Severe cases may present with seizures and coma. Symptoms improve dramatically with glucose administration.

Laboratory diagnosis depends on elevated serum insulin in patients with induced hypoglycemia for 72 hours or postprandial hypoglycemia. Elevated serum insulin more than 10 $\mu\text{U/mL}$ with hypoglycemia below 40 mg/dL and C-peptide levels of more than 2.5ng/mL are considered for diagnosis.

Pancreatic Insulinoma

Management

Surgical resection: After accurate localization of the tumor site, surgical resection carries the most favorable prognosis. Surgical resection of the tumor varies according to the location. Enucleation of solitary tumors, distal pancreatectomy, total pancreatectomy, and Whipple procedure are all used for resection. Resection, cryotherapy, radiofrequency ablation or embolization are all used for metastatic disease to the liver.

Laparoscopic surgery is less invasive than open surgery and can use endoscopic ultrasound for better localization of the tumor.

Medical therapy: Diazoxide is used to inhibit insulin secretion. Side effects include edema and hirsutism.

Octreotide: second line after diazoxide and can inhibit secretion of insulin, glucagon, and gastrin.

Verapamil has also been tried with positive results.

Glucagonoma originates from alpha cells of the islets of the pancreas. The tumor secretes glucagon hormone, responsible for hyperglycemic symptoms and necrolytic migratory erythema. It is mostly malignant and metastasizes early.

Clinical presentation

Patients present with diabetes mellitus, anemia, weight loss, diarrhea, hypercoagulability with thrombosis, cheilitis, stomatitis, and necrolytic migratory erythema. Necrolytic migratory erythema consists of painful, pruritic lesions, which are common in most patients, in friction areas and range from maculopapular rash, blisters, and pustular infective lesions. Early diagnosis of these lesions will help avoid complications of thrombosis and neurological involvement.

Laboratory evaluation: CBC, serum glucose, and hepatic function tests are important to assess for diabetes mellitus and liver metastases. Radioimmunoassay (RIA) of glucagon level of more than 500 pg/mL is diagnostic.

Medical treatment: Nutritional support for patients with weight loss and nutritional deficiency is the first step. Octreotide can be used to inhibit glucagon secretion. Evorolimus and sunitinib are approved for unresectable malignant tumors.

Surgical intervention: Similar to insulinoma after tumor localization and assessment of resectability. Liver metastases can be treated with surgical resection, radiofrequency ablation, or arterial embolization.

Gastrinomas are tumors that secrete gastrin hormone responsible for what is known clinically as Zollinger-Ellison Syndrome. The tumor arises from the pancreas, stomach, duodenum, jejunum, and even lymph nodes. They can be malignant with metastases to the liver and regional lymph nodes.

Clinical presentation: Hyperacidity, as a result of the gastrin hormone, leads to multiple peptic ulcers that are resistant to medical treatment. The most frequent symptoms are abdominal pain and diarrhea. Patients may present with complications of peptic ulceration, including perforation, pyloric stenosis, GI bleeding, and complications of acid reflux, including oesophagitis and stricture. Diarrhea and weight loss develop due to irritation of the small intestine with acidic content.

Laboratory evaluation: Gastric PH and basal acid output are used to assess gastric hyperacidity, while a fasting serum gastrin level of more than 1000 pg/mL is a sensitive screening test. Measurement of serum or venous sample gastrin, and gastric acid secretion following secretin or calcium injection, is more sensitive to localize gastrinoma.

Proton pump inhibitors are used to control the symptoms, while chemotherapy is used for malignant metastatic disease. Surgical intervention is the definitive cure for resectable tumors.

VIPoma is a rare tumor characterized by hypersecretion of a vasoactive intestinal polypeptide, leading to diarrhea and hypokalemia.

Prognosis

Though the pancreatic cancer survival rate has improved, it is still considered incurable. For all stages of pancreatic cancer, the one-year survival rate is 20%; the five-year survival rate is 7%. The low survival rate is attributed to the fact that malignancy has metastasized at the time of diagnosis, and surgery is impossible at every metastatic point.

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