PANCREAS – exocrine and endocrine

Systems: Digestive, Endocrine
Causes: Cancer, genetic, infection, ageing, environmental factors

Introduction

The pancreas has an exocrine component of acinar cells and ducts producing 15 different types of digestive enzymes plus an endocrine component within the islets of Langerhans.

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### NEOPLASTIC - endocrine

- Insulinoma
- Gastrinoma
- Glucagonomas
- Somatostatinoma
- VIPoma
- Pancreatic carcinoid tumour

### NON NEOPLASTIC

#### Exocrine Component

**CONGENITAL**

*EMBRYOLOGY*: the pancreas forms from a ventral and dorsal bud. If the proximal portion of the duct serving the dorsal bud persists, one has an accessory pancreatic duct (of Santorini).

The distal portion of that duct merges with that of the ventral bud to form the main pancreatic duct (of Wirsung). This may enter the duodenum as one or separate ducts or may have united with the common bile duct.

Understanding this anatomy helps grasp the basis of pancreatitis related to gall stones.

Size: normal weight = 57 – 120 gms.

80% of the gross weight = exocrine and 20% endocrine tissue.

Agenesis

Total absence of the pancreas is rare and may be associated with other malformations that are usually incompatible with life.

Molecular pathogenesis: Pancreatic and duodenal homeobox-1 gene (PDX1) encodes a transcription factor critical for the development of the pancreas. Homozygous mutations on chromosome 13q12.1 have been reported in pancreatic agenesis.

Pancreas divisum

This is the most common congenital anomaly of the pancreas.

Incidence: 3% - 10%.

Pathophysiology: caused by a failure of fusion of the foetal duct systems of the dorsal and ventral pancreatic primordia. Thus the bulk of the pancreas drains through the dorsal pancreatic duct and the minor papilla. So the usual main pancreatic duct, the duct of Wirsung, is very short and drains only a small portion of the head of the pancreas through the major papilla of Vater.

Clinical presentation: 95% would have no symptoms.

However, chronic abdominal pain and repeated episodes of pancreatitis occurs in some patients.

Macroscopic appearance: can result in the formation of a santoricoele, which is a cystic dilatation of the distal dorsal duct, immediately proximal to the minor papilla. This is the commonest type in 70%.

Diagram courtesy of Dr. Omar Bashir. Radiopaedia.org, rID:17600
A second type – 25% - is when the minor papilla drains all of the pancreas leaving the major papilla of Vater to only drain the bile duct.

**Diagnosis:** by ERCP (*endoscopic retrograde cholangio-pancreatography*), which can demonstrate the presence of two separately draining pancreatic ducts. Injection of contrast into the ampulla of Vater shows no contrast entering the body and tail of pancreas. However, ERCP itself sometimes can cause attacks of pancreatitis, so if available MRI is preferable.

**MRI** (*magnetic resonance imaging*) -

- the dorsal pancreatic duct being in direct continuity with the duct of Santorini, which drains into the minor ampulla
- ventral duct, which does not communicate with the dorsal duct but joins with the distal bile duct to enter the major ampulla

The MRI image below is courtesy of Dr Chris O’Donnell. Radiopaedia.org, Rid:26905
Other tests that can help diagnose pancreas divisum without the risk of causing pancreatitis include endoscopic ultrasound (EUS),

**Treatment:** cutting the minor papilla during ERCT to enlarge its opening, so the contents can drain more freely. Sometimes this may be associated with insertion of a stent.

**Prognosis:** pancreatitis may still recur after surgical treatment.

**Annular pancreas**

**Definition:** it is a band-like ring of normal pancreatic tissue completely or partially encircling the second part of the duodenum.

**Embryology:** due to failure of the two fused ventral buds to rotate with the duodenum from left to right at 7th week of gestation, when fusion would occur with the dorsal bud. The ventral bud forms the inferior part of the uncinate process and inferior portion of the head of the pancreas. The dorsal bud becomes the body and tail of the pancreas.

Annular duct usually joins the main pancreatic duct or accessory duct (duct of Santorini).

**Incidence:** 1 : 250

**Peak age:** can present early in life or later in adults but usually detected in the 3rd to 6th decade.

**Gender:** more frequent in males.

**Other associations:** Down’s syndrome, pancreas divisum, pancreatitis, pancreatic cancer, intraductal papillary mucinous neoplasm (IPMN)

**Clinical presentation:** signs and symptoms of duodenal obstruction with gastric distention and vomiting. Pancreatitis is a common presentation.

**X-ray appearance:** CT scan, courtesy of Dr Bruno Di Muzio. Radiopaedia.org, rID:28905, shows the pancreas encircling the duodenum – yellow arrows.
**Microscopic appearance:** not applicable

**Diagnosis:** ultrasound or CT scan

**Treatment:** is surgery to by-pass the level of obstruction because the pancreatic tissue itself cannot be removed without causing damage to the pancreas. Gastrojejunostomy or duodenojejunostomy are operations of choice in the paediatric population and may be used also in adults.

**Prognosis:** good following surgery.

**ECTOPIC PANCREAS**

**Sites:** stomach, duodenum, jejunum, Meckel diverticulum and ileum.

**Incidence:** found in 2% of routine autopsies.

**Size:** a few mm to cms in size and located in the submucosa.

**Macroscopic:** is an extramucosal broad based lesion along the greater curve of the gastric antrum or in the proximal duodenum.

**Imaging:** **Endoscopy:**
A solid tumour mass can be seen under the mucosal membrane in the gastric antrum.
(Courtesy of World J Gastroenterol 2009; 15(29): 3701-03)
**CT scan:** shows homogeneously enhancing tissue (nodule) like normal pancreas or it may show a cystic area which is an acinar component or pseudocyst. Image courtesy of Dr Jens Christian Fischer, Radiopaedia.org, rID: 31450. The circle shows the nodule.

**Barium studies:** 45% show a central small collection of barium which indicates a central niche or umbilication that is diagnostic of ectopic pancreatic tissue.

**Microscopic:** normal appearing pancreatic acini, glands and sometimes contains islets of Langerhans. In the image below (courtesy of World J Gastroenterol 2009; 15(29):3701-03,) lobules of pancreatic tissue with ducts are located within the smooth muscle of the pylorus.
Clinical Application of Pathology
Clinical Professor Lesley Cala

Clinical features: pain may occur from localized inflammation. Rarely causes mucosal bleeding.

Pathogenesis: unknown

Complications: 2% of islet cell neoplasms arise within ectopic pancreatic tissue. Patients may also have pancreatitis recurrent.

Treatment and Prognosis: laparoscopic wedge resection is often curative.

CONGENITAL CYSTS

Definition: cysts that develop by anomalous development of the pancreatic ducts. Comprise 1% of all pancreatic cysts.

Size: microscopic to 5 cm in diameter.

Incidence: can be sporadic or part of polycystic disease involving the kidneys and liver. Also can be part of Von Hippel - Lindau disease which has vascular neoplasms in the retina, cerebellum and brain stem.

Types:
Duplication (Enterogenous) cysts:
These rare cysts are of foregut derivation and may occur adjacent to the pancreas. They may cause pancreatitis and are often present in childhood.
Site: usually found in the head of the pancreas and some communicate with the pancreatic ducts but do not communicate with the duodenum.

Macroscopic and X-ray appearance: usually unilocular and thin walled, enclosed in a fibrous capsule and filled with a clear serous fluid.
In the CT image, courtesy of J Majeski and J Harmon. South Med J 2000; 93(3), the cyst is in the junction of the body and tail of the pancreas – arrow. It also has calcification in its wall.
Microscopic: Lined by various epithelia including squamous, gastric, small intestinal, respiratory or simple ciliated epithelium. If the internal pressure is high the lining is a flattened cell layer. The wall contains bundles of smooth muscle.

In the image, courtesy of J Majeski and J.Harmon, the cyst has a bilayered muscular wall and its inner surface is lined by ciliated respiratory epithelium, transitional epithelium and gastric mucosa.
Treatment: excise and preserve the pancreas.

**Duodenal Diverticulae**

**Definition:** outpouchings of the duodenum with the lumen of the cyst and the mucosa contiguous with the duodenal lumen. Intramural type, however, is a form of congenital duplication.

**Associated with:** annular pancreas, choledochocele or polysplenia syndrome.

**Site:** most at or near the ampulla of Vater and extend distally into the lumen of the duodenum. The common bile duct and pancreatic duct usually empty into the diverticulum. A second orifice in the diverticulum allows drainage of the duct contents into the intestine.

The intramural type does not communicate with the duodenum.

**Clinical presentation:** intermittent duodenal obstruction, bleeding, abdominal pain and occasionally pancreatitis.

**x-ray appearance:** single contrast upper gastrointestinal study in the AP projection shows narrowing of the true lumen of the duodenum (straight arrow) by the duplicated duodenal segment (curved arrow) giving a smooth mass effect and it does not communicate with the gastrointestinal tract. Image is courtesy of MV Jyaraman, W Mayo-Smith, JS Movson, DE Dupuy, MT Wallach. Radiographics 21 (1), 2001.

The abnormality can also be demonstrated by CT scan and this will show its relationship to the head of the pancreas and the wall of the duodenum.

**Treatment:** the intramural type can be surgically removed from outside the duodenum via an incision in the wall of the duodenum.

The type that resulted from a herniation of the duodenal mucosa through the muscle layer can be surgically removed by severing its stalk.

**Prognosis:** very good.

**Cystic Fibrosis**

**Definition:** it is a disorder of ion transport in epithelial cells that affects fluid secretion in exocrine glands and the epithelial lining of the respiratory, gastrointestinal and reproductive tracts.
Incidence: 1 : 2500 births. Considered to be the most common lethal genetic disease affecting Caucasian populations.

Age: features may appear at birth or much later in adolescence.

Clinical features: chronic lung disease secondary to recurrent infections, pancreatic insufficiency, steatorrhoea, malnutrition, hepatic biliary cirrhosis, intestinal obstruction and male infertility.

Pancreatic abnormalities are present in 90% of patients with cystic fibrosis.

Pathophysiology: abnormally viscous secretions are produced which obstruct organ passages.

Molecular pathogenesis: In normal duct epithelia, chloride is transported by plasma membrane channels (chloride channels).

The primary defect in cystic fibrosis results from abnormal function of an epithelial chloride channel protein, encoded by the cystic fibrosis transmembrane conductance regulator (CFTR) gene on chromosome 7q.31.2

However, the functions of CFTR are tissue specific so the impact of a mutation in CFTR is also tissue-specific. Pancreatic insufficiency, a feature of classic cystic fibrosis, is always present when there are CFTR mutations with abnormal bicarbonate conductance.

Genetics: inherited as an autosomal recessive, so both parents must pass on the defect to the child. If only one parent has the defective gene, and passes it to the child, the child will be a carrier.

Complications: diabetes, malabsorption, pancreatitis.

Macroscopic appearance: -

Mild cases: accumulations of mucous in the small ducts with some dilation of the exocrine glands.

Severe cases: seen in older children or adolescents, ducts are completely plugged, causing atrophy of the exocrine glands and progressive fibrosis. The islets of Langerhans may be left in a fibro-fatty stroma and cystic fibrosis-related diabetes supervenes.


Microscopic appearance: abnormal viscid secretions from exocrine glands are round eosinophilic masses distending and obstructing pancreatic ducts causing destruction of parenchyma and fibrosis.

The loss of pancreatic excretions impairs fat absorption causing avitaminosis A, D and K.

**x-ray appearance:** fatty replacement, acute pancreatitis, calcification of pancreas (7%), multiple cysts 3 mm diameter and pancreatic duct strictures.

CT scan can show complete fat replacement of the pancreas – image courtesy of MB Robertson, KA Choe, PM Joseph. Radiographics 26(3) 2006 – see arrows at the perimeter of the fatty pancreas. Image (a) shows a fatty head of pancreas and image (b) fatty body and tail.
Treatment:

- antibiotics for chest infections
- pancreatic enzyme supplementation needed in 85%
- vitamin supplements
- insulin
- physiotherapy for the lungs
- transplantation of the liver for biliary cirrhosis and portal hypertension and pancreas can be done simultaneously,
  as well as lung transplant if required.

Donor pancreas is given systemic venous drainage and enteric exocrine drainage. Immunosuppression is required. Patients no longer require insulin, and are also independent of supplemental pancreatic enzymes.

Prognosis: life expectancy is 40 – 50 years, with deaths mostly due to lung infections.

OTHER CAUSES of ATROPHY of the Pancreas: main pancreatic obstruction, haemochromatosis, malnutrition, Cushing syndrome, steroid therapy, obesity.

NON NEOPLASTIC

Exocrine Component

ACQUIRED

Acute Pancreatitis

Definition: is reversible pancreatic parenchymal injury associated with inflammation. The pancreatic enzymes autodigest the gland.

Incidence: 20 cases per 100,000 annually.
Causes: *biliary tract disease and alcoholism* account for 80% of cases, with gallstones being present in 60% of patients with acute pancreatitis. Gallstones pass into the bile duct and lodge at the sphincter of Oddi.

Alcohol leads to intracellular accumulation of digestive enzymes and their premature activation and release at cell level. At duct level, alcohol increases the permeability of ductules, allowing enzymes to reach parenchyma and cause pancreatic damage. Also there is increase in the protein content of pancreatic juice and decrease in bicarbonate levels and trypsin inhibitor concentrations which gives protein plugs that block pancreatic outflow. This situation develops when alcohol ingestion is habitual over 5 – 15 years.

**ERCP** (endoscopic retrograde cholangiopancreatography)– 4% cases

**Trauma** – 1.5% - causes an increase in amylase and lipase levels. Injury is more often in penetrating injuries (eg. knives, bullets) than in blunt abdominal trauma from e.g. steering wheels, horses, bicycles, blunt injury to back crushing the pancreas across the spine with subsequent duct injury.

**Drugs** – 2% - thought probably related to an unknown predisposition. Usually mild. An example is azathioprine which is an immunosuppressive agent used in transplant patients and for auto-immune diseases.

**Other less common causes**: infection (including mumps), hereditary pancreatitis, hypercalcaemia, developmental abnormalities (annular pancreas and pancreas divisum), hypertriglyceridaemia, tumours, toxins surgical procedures, vascular abnormalities, autoimmune pancreatitis.

**Gender**: M : F = 1 : 3 in the group with biliary tract disease and 6 : 1 in those with alcoholism.

**Clinical Presentation**: abdominal pain is the main feature of acute pancreatitis. The pain is severe and constant and is often referred through to the back and left shoulder.

Anorexia, nausea and vomiting are frequent. The patient may go into shock and die during the first week.

**Biochemical**: elevated plasma levels of serum amylase during the first 24 hours followed within 72 hours by a rising serum lipase level.

Glycosuria occurs in 10% of cases.

Hypocalcaemia may occur if there is massive precipitation of calcium into the necrotic fat. If this happens it indicates a poor prognosis.

**Macroscopic appearance**: the pancreas is swollen and contains *multiple focal areas of haemorrhage* (the very dark grey areas). Within the peripancreatic fat and the mesenteric fat are *multiple discrete chalky/white foci* which is typical of fat necrosis. Lipase released by the damaged pancreatic acinar cells attacks the fat cells releasing free fatty acids. The free fatty acids saponify with calcium salts to form soaps. The patient’s serum calcium drops significantly and the lesions of fat necrosis appear. The peritoneal cavity usually contains a slightly turbid brown fluid in which globules of fat can be identified.
Microscopic:

**x-ray appearance:** CT shows focal or diffuse parenchymal enlargement, changes in density due to oedema, indistinct margins to the pancreas due to inflammation and surrounding retropancreatic fat stranding. Image courtesy of Dr Mohammad Taghi Niknejad. Radiopaedia.org, rID: 20829

At the stage of liquefying necrosis, the parenchyma will not enhance and the condition is multifocal. If the necrotic areas have become infected, additionally one may see gas in the organ.
If it is haemorrhagic pancreatitis, there is high attenuation fluid in the retroperitoneal or peripancreatic tissue.

The CT of a case of necrotizing pancreatitis is courtesy of Dr David Cuete. Radiopaedia.org, rID: 23001

Treatment and prognosis:

Treatment is largely supportive, often requiring ICU care in severe cases for respiratory and cardiovascular support and careful management of glucose, calcium and fluid balance.

Ultrasound or CT directed aspiration biopsy may be needed to confirm the presence of pancreatic abscess. Image-directed catheter placement is an alternative to surgical drainage of pancreatic fluid collections.

Prognosis for acute pancreatitis varies according to severity. Overall mortality is 5-10% per attack.

Differential diagnosis:

- pancreatic_ductal adenocarcinoma
- autoimmune pancreatitis
- peptic ulcer disease with posterior perforation
- pancreatic lymphoma (diffuse pattern)

Pseudocyst of the pancreas: this develops as a complication of alcoholic, biliary or traumatic acute pancreatitis, mostly in adult men. Those resulting from biliary disease or trauma occur in younger patients and occur equally in both sexes.

Definition: a lesion that develops when a focus of peri-pancreatic fat necrosis is resorbed, producing a debris-filled space surrounded by granulation tissue that is eventually enclosed within a fibrous capsule but does not have an epithelial lining.

Site: Pancreatic pseudocysts are the most common cystic lesions of the pancreas, accounting for 80% of such masses. A pancreatic pseudocyst is a collection of amylase-rich, lipase-rich, and enterokinase-rich fluid. It is most frequently located in the lesser peritoneal sac in proximity to the pancreas.
It results from pancreatic ductal disruption. The pancreatic secretions incite an intense inflammatory response, which eventually leads to the development of a thick, fibrous capsule surrounding the pancreatic fluid.

**Clinical features:** symptoms may include:

- abdominal pain
- bloating
- nausea
- vomiting
- loss of appetite
- weight loss
- diarrhea
- fever
- a tender mass in abdomen
- jaundice
- fluid buildup in the abdominal cavity

**x-ray appearance:** CT scan is very useful but can encounter difficulty with diagnosis, when separating this condition from cystic mucinous neoplasms. The image below is courtesy of M.Sawyer. Medscape Aug 2015 and shows a pseudocyst abutting the posterior wall of the stomach.

![Image of pseudocyst](image)

**Microscopic:** the cyst wall merges with the cyst contents composed of fibrin, necrotic fat cells, debris, haematoidin pigment and aggregates of histiocytes. Image courtesy of O.Basturk, I Coban and N.Volkan Adsay. Arch Pathol Lab Med 2009, 133 (3) : 423-438.
However, if a mature pseudocyst forms and does not resolve, repeat CT scanning is advised before planned percutaneous, endoscopic, or surgical interventions.

Imaging should also be used liberally in patients recovering from acute pancreatitis who present with persistent abdominal pain or in patients with chronic pancreatitis who have complaints such as nausea, vomiting, early satiety, or a sudden crescendo in the level of abdominal pain.

**Treatment:** Often pseudocysts get better and go away on their own. If a pseudocyst is small and not causing serious symptoms, a doctor may want to monitor it with periodic CT scans. If the pseudocyst persists, gets larger, or causes pain, it will require surgical treatment. If not monitored or treated, a pseudocyst can become infected or rupture, causing severe pain, blood loss and abdominal infection.

For pseudocysts requiring treatment, surgery is usually necessary when a connection is created between the pseudocyst and a nearby digestive organ. The pseudocyst drains through that organ. Depending on the location of the pseudocyst within the pancreas, that connection may be with the stomach, small intestine, or duodenum.

In some cases, this surgery is done laparoscopically. This procedure minimizes hospitalization and recovery time.

**Draining a Pseudocyst**

In other cases, treatment involves draining the pseudocyst without surgery. This can be done by a radiologist or gastroenterologist.

A radiologist will drain it by inserting a needle guided by computed tomography. A gastroenterologist may drain the pseudocyst through the stomach by creating a small opening between the pseudocyst and the stomach, or by placing a stent into the pancreas during endoscopy. If the stent is placed directly into the pseudocyst then the fluid from the pseudocyst is drained into the intestine through this tube.

**Prognosis**

Most pseudocysts resolve without interference, and patients do well without intervention. The outcome is much worse for patients who develop complications or who have the cyst drained. The presence of pancreatic necrosis is a poor prognostic sign. The failure rate for drainage procedures is about 10%, the recurrence rate is about 15%, and the complication rate is 15-20%.

**Chronic Pancreatitis**
Definition: it is a progressive inflammatory disease of the pancreas with irreversible changes and gradual fibrotic replacement of the gland. Exocrine and endocrine functions are lost as a result of the fibrosis.

Incidence: 25 cases per 100,000 population per year.

Clinical features: the main symptoms are abdominal pain (80%) and impaired digestion. The pain is dull in quality and becomes worse after eating. The pain is located in the epigastric area and often radiates through to the back. Patients have nausea and vomiting.

As pancreatic fibrosis increases there is a loss in enzyme output causing steatorrhoea (when 90% of pancreatic function is lost) and weight loss. If steatorrhoea develops suddenly, it suggests main pancreatic duct obstruction by inflammatory strictures, stones or cancer. Endocrine insufficiency does not occur until late in the disease. Pancreatic diabetes requires insulin.

If weight loss is severe or rapid this is a warning pancreatic cancer may have developed.


Toxic metabolic: alcoholic, tobacco smoking, hypercalcaemia, hyperlipidaemia, chronic renal failure

Idiopathic: Tropical, cause unknown - likely genetic.

Genetic: autosomal dominant, cationic trypsinogen, autosomal-recessive/modifier genes, CFTR mutations, SPINK1 mutations, alpha-1-antitrypsin deficiency.

Autoimmune: isolated autoimmune chronic pancreatitis, or Associated with the following conditions – primary sclerosing cholangitis, Sjögren’s syndrome, primary biliary disorder, type 1 diabetes mellitus.

Recurrent and severe acute pancreatitis: postnecrotic, vascular diseases/ischaemia, postradiation exposure.

Obstructive: pancreas divisum. Sphincter of Oddi dysfunction, duct obstruction by tumours or post-traumatic.

Macroscopic appearance: the pancreas may be enlarged or atrophic. It may contain cysts and calcifications. The ducts are dilated, irregular or show strictures. These gross changes are the result of gene mutations, metabolic and environmental factors.

X-ray appearance: CT scan, courtesy of Wikipedia, shows a very shrunken pancreas with numerous calcifications – see arrow.
Complications of chronic pancreatitis:

Pseudocysts – drainage may be endoscopic (transmural or transpapillary) or surgery creating a cyst gastrostomy or cyst jejunostomy. The pseudocyst may cause biliary obstruction or gastric outlet obstruction. Typical clinical symptom is increase in abdominal pain with/without a mild elevation of serum amylase and lipase.

Pancreatic adenocarcinoma – occurs in 4% - surgical resection may be considered or just palliation.

Pancreatic ascites – may require endoscopic stent placement and total parenteral nutrition.

Pleural effusion – can have a therapeutic thoracentesis, endoscopic stent placement and again may need total parenteral nutrition.

Splenic vein thrombosis – will result in bleeding from gastric varices so have a splenectomy.

Diagnosis:

Plain film of the abdomen and CT detect advanced disease. CT features are pancreatic atrophy, calcifications and main pancreatic duct dilatation. CT can also demonstrate pseudocysts, splenic artery pseudoaneurysm and biliary obstruction. Enlargement of the pancreatic head suggests cancer or an inflammatory mass.

Detection of early chronic pancreatitis is more difficult. ERCP with endoscopic injection of contrast into the pancreatic duct via the papilla of Vater can show the duct changes but it does carry a 10% risk of causing acute pancreatitis.

Endoscopic ultrasound can show in the parenchyma – hyperechoic foci and stranding, cysts, and lobularity. It will also show dilation, irregularity, calculi, side branch dilation, hyperechoic walls in the ducts.

MR cholangiopancreatography offers a non-invasive test, instead of ERCP for imaging the pancreatic duct.

MRI or MR cholangiopancreatography and Endoscopic ultrasound, assess the ducts and parenchyma. ERCP detects early ductal changes.
**Hormone-stimulated pancreatic function tests** can help rule out mild exocrine insufficiency in early chronic pancreatitis. The pancreas is stimulated with intravenous cholecystokinin (CCK) or secretin and then fluid is collected from the duodenum. Pancreatic fluid is analyzed for enzyme and bicarbonate production.

**Treatment of chronic pancreatitis**: control the pain, improve the digestion of food stuffs and manage the complications.

Total pancreatectomy may be performed with autoislet cell transplantation.

**TRAUMA**

**Incidence**: pancreatic injury due to blunt trauma occurs in 0.2% - 12%.

**Sites**: commonest in the body of the pancreas.

**Peak age**: commonest in young children and adolescents because of lack of protective abdominal wall fat.

**Mechanism**: the pancreas is injured by compression between the vertebral column posteriorly and the anterior abdominal wall.

*Adults*: motor vehicle accidents

*Adolescent*: bicycle handle-bar injuries

*Infants*: child abuse

**Types**:

1. simple superficial contusion or peripheral laceration in any part of the pancreas, with an intact main pancreatic duct.

2. deep laceration, perforation or transection of the neck, body or tail with or without duct injury.

3. severe crush, perforation or transection of the head of the pancreas with or without duct injury.

4. combined pancreaticoduodenal injury including both minor and severe pancreatic tissue and duct injury.

**Clinical Presentation**: central abdominal pain in the epigastrium, shock. 90% have associated injuries to the liver, spleen, duodenum and kidneys.

**Biochemistry**: the initial serum amylase is normal in 40% of patients, so non-specific.

**X-ray appearance**:

CT is best for examining the patient with blunt trauma to the abdomen. Even single detector CT has a sensitivity of up to 85%. Findings can be very subtle in the first 12 hours. The image below, courtesy of Dr Kenny Sim, Radiopaedia.org, rID:33254 shows – long arrow, the site of laceration of the body of the pancreas. The shorter arrow indicates the non-functioning left kidney which is also included in the trauma.
**X-ray Diagnosis:** one looks for peripancreatic fluid, active extravasation, focal areas of increased size due to contusion. Areas of decreased attenuation post contrast in a normally enhancing pancreas, active haemorrhage, pancreatic haematoma, pancreatic laceration or fracture. The lacerations may be superficial without duct involvement.

*Pancreatic contusion:* image courtesy of Rekhi et al. Emergency Radiology 2009, shows – see arrow – an area in the neck of the pancreas that has not enhanced but would normally do so.

Defects in the pancreas can be missed or show false positives.

For example, a normal variant called *asymmetric fatty atrophy of the pancreas* which is found in the elderly and obese can be confused with contusion.

Another normal variant is the presence of fat surrounding arterial and venous vessels so that this looks like *pancreatic clefts*.

**Treatment:** is medical but some lacerations of the pancreatic duct and also associated injuries will need surgery. Monitoring is by serial CT scans.

**Complications:** disruption of the main pancreatic duct is the main predictor of complications.

Delayed complications include abscesses, fistulae, pseudocysts, sepsis and multi-organ failure.
Pseudocysts may require drainage as in this example, - see asterisk - courtesy of Gupta et al. Radiographics 2004.

Prognosis: Mortality rates range from 10 – 30%. Most deaths occur in the first 48 hours due to severe haemorrhage from traumatized splenic vein, portal vein and inferior vena cava. Long-term, the main complication is the formation of pseudocysts.

Drugs causing pancreatic damage

Incidence: 1.2% of all cases of acute pancreatitis are drug induced.

Mechanism:

The pancreas produces digestive enzymes for release into the gastrointestinal tract. The acinar cells within the pancreas produce the proenzymes, which then are packaged into storage vesicles called zymogens. The zymogens travel through the pancreatic duct and are secreted into the duodenum. Within the duodenum, enterokinase converts trypsinogen to trypsin, and then active trypsin facilitates the conversion of the other pancreatic proenzymes to the active form.

Acute Pancreatitis can occur if there is damage to the acinar cells and/or injury to the pancreatic duct leading to inappropriate accumulation and activation of proenzymes within the pancreas. The activated pancreatic enzymes digest the cell membranes of the pancreas and activate an inflammatory response, which increases the vascular permeability of the pancreas. Hemorrhage, oedema, ischaemia, and necrosis can follow. In severe Acute Pancreatitis, patients progress to systemic inflammatory response syndrome, sepsis, and multiple organ failure. Up to 13% of Acute Pancreatitis cases progress to Chronic Pancreatitis.

Drugs implicated

The World Health Organisation lists 525 drugs which could cause pancreatic damage. Of these only 30 are conclusively responsible. However, Proc (Bayl Univ Med Cent) 2008 Jan; 21(1): 77-81 list 115 from within the list of 525 as suspect.

The drugs fall into the following groups:

- Antibiotics
- Immunosuppressant
- Anti-hypertensive
- Aminosalicylates
- Diuretics
- Corticosteroids
- Oestrogen
- Diabetic drugs
- Valproate
- Some general anaesthetic drugs
- Anti-depressants.

Clinical presentation: symptoms and signs of acute pancreatitis

Macroscopic and radiological appearance: as for acute pancreatitis

Diagnosis: suspicious linkage if symptoms improve with withdrawal of the drug and relapse with re-entry of the drug.

Prognosis: as for any case of acute pancreatitis.

NON NEOPLASTIC

Endocrine component

Congenital

Cystic fibrosis-related diabetes (CFRD)

Cystic fibrosis-related diabetes (CFRD) is diabetes specifically caused by cystic fibrosis, a genetic condition.

Age: Cystic fibrosis related diabetes mellitus (CFRD) develops with age, the median age at diagnosis is 21 years

Incidence: one in two middle-aged patients with cystic fibrosis, have CFRD.

Clinical features: It is different from either type 1 or type 2 diabetes mellitus, but shares features of both.

The primary cause is a relative insulin deficiency related to destruction of pancreatic islets. Insulin resistance also may play a role, especially in association with acute exacerbations or chronic progression of pulmonary disease.

Pathogenesis:

Development of CFRD is associated with worse lung function, poorer nutritional status, and more chest infections. In addition, longitudinal studies have demonstrated decreased survival (sixfold) in individuals with CFRD as compared with non-diabetic CF patients, with females at particularly high risk in some studies. Insulin treatment improves lung function and nutritional status.
Microscopic appearance:

The CFTR mutation (cystic fibrosis transmembrane conductance regulator) causes thick secretions to obstruct the pancreatic duct with resultant pancreatic fibrosis and loss of β cells.

Image courtesy of Department Pathology, University of Iowa.

Treatment: administer insulin supplements.

Prognosis:

In those who presented fasting hyperglycemia, microvascular complications are rare with less than 10 years of diabetes progression. In patients with over 10 years with the disease, 14% had microalbuminuria, 16% retinopathy, 55% neuropathy and 50% gastropathy.


NON NEOPLASTIC

Endocrine component

Acquired

Diabetes Mellitus

Definition: Diabetes mellitus is a condition in which the pancreas no longer produces enough insulin or cells stop responding to the insulin that is produced, so that glucose in the blood cannot be absorbed into the cells of the body.

Clinical features: Symptoms include frequent urination, lethargy, excessive thirst, and hunger.
**Incidence:** 1 in 20 of the Australian population. Nearly one million people with diabetes 2011-2012

**Peak age:** Type 1 diabetes – 22 yrs. Type 2 diabetes – middle aged and older.

**Gender:** the prevalence of diabetes appears to be greater in women and this is thought related to obesity.

**Clinical presentation:** frequent urination, excessive thirst

**Composition of Endocrine Pancreas:** this consists of the islets of Langerhans which number 1 million clusters, which together weigh 1.0 gms. There are 4 major and 2 minor types of cells.

- β cells which produce insulin
- α cells which produce glucagon
- δ cells contain somatostatin which inhibits insulin and glucagon release from the β and α cells.
- PP cells stimulate secretion of gastric and intestinal enzymes and inhibits intestinal motility.
- Rare – DI cells produce:
  - (a) Vasoactive intestinal polypeptide
  - (b) A hormone inducing glycogenolysis and hyperglycaemia
  - (c) Stimulates GI fluid secretion producing secretory diarrhoea
- Rare – enterochromaffin cells synthesize serotonin. The pancreatic tumours causing carcinoid syndrome arise from these enterochromaffin cells.

**Pathogenesis:**

Hyperglycaemia is the result of defect in insulin secretion, defect in insulin action or defects in both. Skeletal muscle is the major insulin-responsive site for postprandial glucose utilization and thus prevents hyperglycaemia and maintains glucose homeostasis. Insulin synthesis and release is triggered by glucose itself.

**Action of Insulin** – it increases the rate of glucose transport into certain cells in the body such as skeletal muscle cells (including heart) and adipocytes. Glucose uptake by the brain is independent of insulin.

In muscle, glucose is stored as glycogen, in fat it is stored as lipid and also inhibits lipid degradation. Lastly insulin promotes protein synthesis.

**Types of Diabetes**

- **Type 1** – immune-mediated absolute deficiency of insulin – accounts for 10% of cases. It is an auto-immune disease caused primarily by T lymphocytes reacting against β cell antigens. Both genetic susceptibility and environmental factors are important. Clinical onset is abrupt when 90% of the β cells are destroyed.
- **Type 2** – relative insulin deficiency plus peripheral resistance to insulin action – 80% of cases. Genetic factors are more important than in Type 1. Occurs in 5% of the population. There is a decreased ability of peripheral tissues to respond to insulin (insulin resistance). The β cell dysfunction is manifested as inadequate insulin secretion in the face of insulin-resistance and hyperglycaemia. Obesity, especially central obesity is linked to insulin resistance. The islet amyloid protein (amylin) is found in 90% of Type 2 diabetics.
- **Secondary causes:** 10% - due to drugs like glucocorticoids, thiazides, phenytoin and to infections such as cytomegalovirus, congenital rubella.
- **Gestational diabetes** – 1% of cases.
- **Monogenic forms of diabetes: 3 types** –
  (a) MODY – Mature Onset Diabetes of the Young. 50% of carriers of glucokinase mutations develop gestational diabetes.
  (b) Mitochondrial inherited from the maternal gene.
  (c) Rarely mutations in the insulin gene or receptor.

**Macroscopic appearance of Pancreas:** Type 1 diabetes of long duration is associated with loss of pancreatic weight, due to atrophy of exocrine tissue. This is believed to result from loss of the trophic effects of locally produced insulin upon the surrounding acinar tissue.

**Microscopic appearance of Pancreas in Type 1**

The majority of insulin-staining beta cells have disappeared, and the resulting pseudo-atrophic islets are characterised by abundant glucagon-secreting alpha cells and minor fibrosis of the islet interstitium. Up to 50% of patients may however retain some residual beta cells. The ducts, ductules and acini are normal. Fibrosis in interlobular and intralobular areas.

There are 3 types of islets: pseudopancreatic islets, hyperactive islets and PP islets and the majority look atrophic. They are not found in well- knit nests and the margins are not distinct. The islet cells are small with a small and dense nucleus and scanty cytoplasm.

Some islets show hyperplasia and are large and more cellular.

**Type 2 diabetics:** Recent research from the University of Newcastle, UK has identified the presence of fat in the β cells which causes the cell to function poorly. Dieting to lose weight over the whole body does cause loss of fat from the islet cells in the pancreas, with restoration of normal production of insulin.

**Complications:** Diabetes is a leading cause of end-stage kidney disease, adult-onset blindness, non-traumatic lower extremity amputations. Diagram courtesy of Robbins. Pathology. 7th ed
Kidney: when diabetic kidneys were transplanted into normal recipients, the kidney lesions reverse. When normal kidneys are transplanted to diabetics lesions appear 3 – 5 years later.

Diabetic nephropathy: death from renal failure is the second commonest cause of death of diabetics. There are 3 types of glomerular lesions: capillary basement thickening occurs in a few years, diffuse mesangial sclerosis occurs after 10 years and nodular glomerulosclerosis is found in 15-30% of long-term diabetics – Kimmelstein-Wilson kidney – see image below.

Diabetic pyelonephritis – acute and chronic and begins in the interstitial tissue then spreads to the tubules. Necrotizing papillitis (or papillary necrosis) occurs. This is more prevalent in diabetics than in non-diabetics. It is a severe form of acute pyelonephritis. See image below.
Cardiovascular system: atherosclerosis of the arteries, especially of the coronary arteries causing myocardial infarction which is the commonest cause of death in diabetics – see image below showing an almost occluded lumen to a coronary artery.

The image below is an almost full thickness myocardial infarction. Arrows point to necrotic area.
Atherosclerosis will also lead to gangrene of the extremities, especially the lower limbs.

**Gangrene lower limb** due to atherosclerosis and also smoking:

Hyaline arteriolosclerosis narrows the lumen of the vessels and so increases peripheral resistance and this will cause a rise in blood pressure – viz. hypertension.

**Diabetic microangiopathy** is due to thickening of the basement membrane of capillaries. It actually causes increased leakage of plasma proteins causing nephropathy, retinopathy and neuropathy.

**Ocular complications:** retinopathy, cataract and glaucoma.

The image below is fundoscopy showing retinopathy, text and image courtesy of Robbins and Cotran. Atlas of Pathology. The arrow on the upper image is pointing to hard exudates. The arrow on the lower image is pointing to the proliferation of small vessels near the optic disc. The delicate new vessels grow toward the vitreous humour. These are prone to bleed, producing vitreal haemorrhages obscuring vision. A proliferation of fibrovascular and glial tissue ensues and when the abnormal tissue contracts, there is a risk for retinal detachment. As the macula is involved in the process vision is very reduced. The condition may appear after more than 10 years of poorly controlled hyperglycaemia.
Peripheral neuropathy is nerve damage caused by chronically high blood sugar and diabetes. It leads to numbness, loss of sensation, and sometimes pain in the feet, legs, or hands. It is the most common complication of diabetes.

Microvascular injury to small blood vessels supplying nerves – vasa nervorum can affect all peripheral nerves including pain fibres, motor neurones and the autonomic nervous system.

The main risk factor for diabetic neuropathy is hyperglycemia. In the DCCT (Diabetes Control and Complications Trial, 1995) study, the annual incidence of neuropathy was 2% per year, but dropped to 0.56% with intensive treatment of Type 1 diabetics. The progression of neuropathy is dependent on the degree of glycemic control in both Type 1 and Type 2 diabetes. Duration of diabetes, age, cigarette smoking, hypertension, height and hyperlipidemia are also risk factors for diabetic neuropathy.

Note in the brain the presence of hyperglycaemia will result in hyperosmolar coma. Patient becomes dehydrated, confused, stupor, coma. Fluid balance must be corrected very slowly to avoid severe cerebral oedema.

Treatment: is medical control of weight and hyperglycaemia but surgery is needed for complications of the disease.
Surgical treatment: (a) Whole pancreas transplantation, usually combined with renal transplantation has been used for the treatment of Type 1 diabetes but the patients have to be immune-suppressed long-term.

Pancreatic-kidney transplant accounts for 90% of cases. Organs are taken from a deceased donor. The organs are transplanted into the patient’s pelvic region.

(b) Islet cell transplantation is thought will result in a cure. 40% of patients are off insulin within one year of the last infusion but only 17% at 3 years. A number of patients need less insulin and also suffer fewer hypoglycaemic attacks. Patients have to take immunosuppressive drugs.

Image courtesy of Mayo Foundation for Medical Education and Research, illustrating a pancreas-kidney transplant.

Prognosis: Causes of death in diabetes:

- Myocardial infarction – 50% cases
- Cerebrovascular accident – 12%
- Renal failure – 12%
- Various cancers – 10%
- Bronchopneumonia, pyelonephritis – 6%
- Congestive heart failure is common
- Gangrene – common
- Diabetic coma – rare
- Hypoglycaemic coma – rare.
NEOPLASTIC

Exocrine component of Pancreas

BENIGN TUMOURS

Serous Cystadenoma

Site: Usually found in the head of the pancreas. May be associated with von Hippel Lindau syndrome.

Gender: Males: females = 1 : 4
Age: usually presents in middle age to elderly patients (> 60 years of age).

Clinical presentation: often asymptomatic but some present with pain, weight loss, jaundice or a palpable mass.

Macroscopic appearance: these are benign neoplasms composed of many small cysts, usually <10 mm in size (locules 1 – 20 mm) arranged in a honeycomb-like formation.

3 types:-

- polycystic: 70%
- honeycomb: 20%
- oligocystic (macrocystic variant): <10% (cysts can be larger than 20 mm)
**Microscopic appearance:**

The cysts are lined by glycogen-rich flat or cuboidal epithelium separated by fibrous septa that radiate from a central scar, which may be calcified. Lesions can be rather large at presentation (~5 cm).

![Microscopic appearance](image)

**X-ray appearance:**  there may be amorphous central calcification overlying the pancreas on a *plain film*

*Ultrasound:* nonspecific hypoechoic mass in the pancreatic head region, with internal echoes indicating microcysts. The oligocystic subtype may demonstrate individually identifiable cysts

*CT:* typically demonstrates a multicystic, lobulated mass in the pancreatic head described as a 'bunch of grapes'

- the individual cysts are <20 mm in size and more than six in number (except for the oligocystic variety)
- an enhancing central scar may be present which can show associated stellate calcification in 20% of cases

*MRI*  Serous cystadenomas usually appear as a cluster of small cysts within the pancreas. There is no visible communication between the cysts and the pancreatic duct.

*Angiography:* as there are hypervascular components, the mass may show enhancement.

CT, courtesy of Dr Patrick Felipe Catricala, Radiopaedia.org, rID22974, demonstrates the tumour in the head of the pancreas.
Treatment and Prognosis:

Most lesions are observed without treatment. They are benign lesions and do not recur once resected.

Differential diagnosis on imaging:

- intraductal papillary mucinous tumour (IPMN) of pancreas: - communicates with pancreatic ducts
- pancreatic pseudocyst
- mucinous cystadenoma – calcification tends to be peripheral, usually unilocular and if multilocular type, individual cysts tend to be >20 mm in size.

Mucinous cystadenoma

**Definition:** it is a large unilocular or multilocular cystic epithelial pancreatic neoplasm lined by columnar mucinous epithelium and which *do not communicate with the pancreatic ductal system*.

**Classification:** as benign, borderline, or malignant, based on histomorphologic features which predict their behaviour.

**Sites:** body or tail of the pancreas but occasionally (20%) in the head of the pancreas.

**Age:** middle age

**Gender:** previously thought exclusive to females, it has occasionally been described in males.

**Clinical presentation:** One third of cases are asymptomatic. Symptoms include epigastric heaviness, a palpable abdominal mass, nausea, vomiting and back pain.

While mucinous cyst adenomas very infrequently communicate with the pancreatic duct, they can cause partial pancreatic ductal obstruction. They are considered premalignant or malignant lesions with usually elevated CEA (carcinoembryonic antigen) and CA 19-9 (cancer antigen 19-9) serum levels.
Macroscopic appearance: mucinous cystadenoma

x-ray appearance: 

CT

- the tumour contour tends to be rounded or ovoid
- associated calcification when present tends to be more peripheral
- contents of the lesion may be heterogenous attenuation
- internal septations may be present and tend to be linear or curvilinear

However, sometimes it is impossible to distinguish cystadenoma from cystadenocarcinoma.

Microscopic appearance: are composed of columnar, mucin-producing epithelium, supported by ovarian-type stroma. These tumours make mucin (a thick sticky fluid), they do not arise in the larger pancreatic ducts, and they have a peculiar ovarian-type supporting stroma.

x-ray appearance: 

CT image courtesy of Dr Hani Al Salam, Radiopaedia.org, rID 14583.

Arrow is pointing to the cystic mass in the body of the pancreas.
An MRI of a *cystadenocarcinoma*, courtesy of Christopher O’Donnell Radiopaedia.org, rID 16960. Arrow is pointing to the cystic tumour in the head of the pancreas.

**Treatment:** The treatment of choice is surgical removal of the tumour since if left untreated almost all of these tumours may progress towards the development of invasive pancreatic cancer.

The surgical procedure depends on the location of the tumour. The vast majority of these tumours are precancerous. Because it is a precancerous tumour, it is preferable to avoid radical surgery, therefore techniques of organ preservation for removal of these tumours are used. For very small tumours in the head of the pancreas a pancreatic head resection preserving the duodenum and the bile duct may be done.
A Whipple operation is only occasionally indicated for tumours in the head of the pancreas and a distal pancreatectomy is performed for the tumours in the tail of the pancreas. The spleen is preserved in patients that undergo distal pancreatectomy for these tumours. For tumours in the neck of the pancreas a central pancreatectomy to preserve pancreatic tissue can be performed. Laparoscopic surgical approaches for distal pancreatectomy and central pancreatectomy are sometimes used.

Prognosis:

Patients with resected benign mucinous cystic neoplasms (MCN) do not need follow-up because these do not recur in the remaining pancreas after resection. The risk for new mucinous cystic neoplasms following resection is zero. In contrast, patients with resected malignant MCNs should be followed every 6 months for local recurrence and distant metastasis (mainly haematogenous) using either CT or MRI.

**Acinar cell cystadenoma**

**Definition:** a rare benign cystic lesion of the pancreas lined by cells exhibiting acinar differentiation. First described in 2002.

**Sites:** may involve the head or the entire pancreas.

**Size:** range in size from 2 – 15 cm, mean 7 cm.

**Age:** range is 16 – 66 yrs.

**Gender:** 70 % female.

**Clinical Presentation:** most are incidental findings but may present with abdominal pain.

**Macroscopic appearance:** Mean size 6 cm, unilocular or multilocular cysts with watery fluid and have a smooth lining and the cysts rarely connect with the ductal system.

Some cases are multicentric and others diffusely involve the entire gland, with islands of parenchyma between the cysts – see image below, courtesy of Deepali Jain, PathologyOutlines 2012.

*Incidentally detected acinar cell cystadenomas are usually < 1.0 cm and unilocular, and some are not apparent grossly.*
**Microscopic:** most of the cysts are lined by well-differentiated cells with acinar differentiation, as a single layer or clusters of cells around the lumen. Residual pancreatic tissue is present between the larger cysts. Some acini may be dilated. The cells of the lesion have uniform nuclei, apical granular eosinophilic cytoplasm. The lumen of the cyst may contain inspissated eosinophilic enzymatic secretions. The surrounding pancreatic tissue is fibrotic and atrophic.

– see image below, courtesy of Deepali Jain, PathologyOutlines 2012.

**Differential diagnosis:** from the acinar cell cystadenocarcinoma which has more complex epithelium, nuclear atypia, prominent nucleoli, necrotic areas, solid nests of tumour cells, mitotic figures and evidence of infiltration into the surrounding stroma.

**x-ray:** Imaging is nonspecific because of its macrocystic, multilocular or unilocular structure that is similar to other cystic pancreatic masses.

**Treatment:** complete resections are curative. Surgical resection is warranted to treat abdominal pain and prevent local extension or malignant transformation to acinar cell cystadenocarcinoma.

**Prognosis:** no patients have had documented disease recurrence or progression, even in the setting of an incomplete resection.

**NEOPLASTIC**

**Exocrine Component of Pancreas**

**MALIGNANT TUMOURS**

**Infiltrating Ductal Adenocarcinoma**

This tumour accounts for 90% of the tumours in this group.

**Definition:** Infiltrating ductal adenocarcinoma of the pancreas is an invasive malignant epithelial neoplasm with glandular (ductal) differentiation and without a predominant component of any other type of carcinoma. Referred to as Pancreatic ductal adenocarcinoma (PDAC)

**Site:** the majority occur in the head of the pancreas but a small number do occur in the body and tail.
Incidence: 6 per 100,000. 4th leading cause of death in the U.S. Accounts for 3% of all new cancer patients, at 50,000 cases per year in the United States.

Peak Age: seen between 60 years and 80 years, mean age at diagnosis 70 years but occasionally patients under the age of 40 years have been reported.

Gender: slightly more common in men than women

Clinical Presentation: Most patients do not develop symptoms until after the cancer has metastasized, and many patients are not correctly diagnosed until many months or even years after they first develop symptoms.

As a result, only 20% of patients are surgical candidates at the time of diagnosis. Common presenting symptoms include epigastric pain that radiates to the back, unexplained weight loss, painless jaundice, light clay-colored stools, dark urine, pruritus, nausea, and 10% develop spontaneously appearing and disappearing thromboses. New onset diabetes mellitus in an older patient is an early sign of the disease in some patients. Unfortunately, there are no effective screening tests for early asymptomatic disease.

Risk factors: Cigarette smoking, a family history of pancreatic cancer, diabetes mellitus, obesity, chronic pancreatitis, cirrhosis, Helicobacter pylori infection, HIV infection, hepatitis B, cystic fibrosis, Black, Ashkenazi-Jewish descent, heavy tobacco use, alcohol use, high fat/cholesterol diet and hereditary conditions. The latter includes a family history of pancreatic cancer, Lynch syndrome, Li-Fraumeni syndrome, multiple endocrine neoplasia 1, hereditary breast and ovarian cancer, familial multiple mole melanoma syndrome, von-Hippel Lindau syndrome and the Peutz-Jegher syndrome.

Genetic: A mutation in the K-ras oncogene is one of the most common and earliest found in PDAC, occurring in 90% of cases. Other common genetic mutations commonly found in PDAC include activation of oncogenic Her-2/neu, and loss of function in tumor suppressor genes such as p16, p53, and SMAD4. Advanced PanIN lesions develop increasing genetic variability, proliferate, and eventually acquire the means to invade and metastasize.

Macro: Extrapancreatic invasion occurs (75%), and perineural invasion (80%). Invasion of duodenum, ampulla of Vater, and/or common bile duct and the portal vein. Lymph node involvement (40%). Infiltrating ductal adenocarcinomas form poorly defined firm fibrotic masses. They are white–yellow, and they obscure the normal lobular architecture of the pancreas. This latter feature can distinguish between chronic pancreatitis and infiltrating ductal adenocarcinoma. Some cancers undergo central necrosis and these cancers can form gross cysts. Cysts may also be found adjacent to the carcinoma due to localized dilatation of obstructed ducts (retention cysts).

See image below courtesy of Dr RH Hruban and N.Fukushima Modern Pathology 2007, 20: 561-570.
**x-ray:** Best imaging is CT scan but the diagnosis can be suggested with a barium meal. In the image below, courtesy of J.R.Ballinger, Radiopaedia.org, rID23672, the duodenal loop is widened considerably by the mass in the head and neck of the pancreas.

![CT scan of pancreas carcinoma](image)


**Microscopic:** Pancreatic intraepithelial neoplasia (PanIN) is the presumed precursor lesion to infiltrating ductal adenocarcinoma, and PanIN lesions can mimic infiltrating cancer. Also it can be extremely difficult, if not impossible, to distinguish histologically between a benign reactive gland of chronic pancreatitis and an infiltrating gland of well-differentiated pancreatic cancer.

Clearly the treatment and life expectancy of the two conditions is very different.

Infiltrating ductal adenocarcinoma of the pancreas is an invasive malignant epithelial neoplasm with glandular (ductal) differentiation and without a predominant component of any of the other carcinoma types. The degree of gland formation can vary from well-formed glands, to partially formed glands, to focal intracellular mucin production by poorly oriented cells infiltrating singly, to solid sheets of neoplastic cells.
Several features can be used to distinguish between benign reactive glands and infiltrating ductal adenocarcinoma, and most of these are related to location. In evaluating the location of a duct, note that non-neoplastic glands, even when there is severe chronic pancreatitis, form *predictable lobular* units. The ducts are towards the center of the lobular unit and are surrounded by grape-like clusters of acini.

The neoplasm has *a haphazard growth pattern* – see image below courtesy of Dr RH Hruban and N. Fukushima, *Modern Pathology* 2007, 20: 561-570.

![Image](image1.png)

The glands are adjacent to vessels and intravascular invasion occurs – see image below courtesy of RH Hruban and N Fukushima. *Modern Pathology* 2007, 20:561-570 - which can then mimic Pan IN, the precursor.

![Image](image2.png)

Perineural invasion is a diagnostic feature of this tumour. Image again courtesy of Hruban and Fukushima.

![Image](image3.png)
**Treatment:** Surgery if the tumour has not spread and the patient is without metastases. The only curative treatment option is surgical resection.

Out of every hundred patients with pancreatic carcinoma only 20 patients will be scheduled for explorative laparotomy.

Out of these 20, only about 13-14 patients will undergo resection of the tumor, but only half of these resections will finally prove to be radical at pathologic examination of the resected specimen. The resection consists of a partial Whipple or the modern variant, the so-called 'pylorus-preserving' pancreaticoduodenectomy.

**Palliation**

When the tumor proves to be unresectable during exploratory laparotomy, a so-called 'double bypass' (gastro-enterostomy en hepaticojejunostomy) is usually performed for palliative reasons.

When curative resection is not considered an option, based on preoperative imaging and cytology or histology, palliation consists of endoscopic or percutaneous biliary stenting and celiac plexus block for relief of pain.

Patients with extensive hepatic metastases, are probably best served by palliation by means of endoscopic bile duct stenting.

In patients with a longer life expectancy with a small, but locally unresectable tumor and without distant metastatic disease, a double bypass is generally also considered acceptable palliation.

At the time of diagnosis a pancreatic head carcinoma is usually a little larger than 3 cm. When tumours of the pancreatic body and tail are diagnosed, they are usually much larger, because they present late with nonspecific symptoms.

These tumours are usually unable to be resected. Tumours originating in the distal common bile duct or ampulla may also grow into the pancreatic head and with pancreatic head carcinoma these tumours are grouped together under the name periampullary tumours. This is of practical value as diagnostic imaging, staging and treatment of all these periampullary tumours is the same.

**Prognosis:** median survival is 14 months with surgery, compared with 5 months without surgery.

However, 10% may survive 5 years with surgery.

**Precursor of Ductal adenocarcinoma is:-**

*Pancreatic intraepithelial neoplasia - 3 grades.* These do not involve the main pancreatic duct and are small so cannot be seen grossly or by radiology imaging.

*Normal* ductal and ductular epithelium is cuboidal to low-columnar epithelium with amphophilic cytoplasm. Mucinous cytoplasm, nuclear crowding and atypia are absent.

However, *PanIN* – 1A (pancreatic intraepithelial neoplasia) has flat epithelial lesions composed of tall columnar cells with basally located nuclei which are small and round or oval in shape, and abundant supranuclear mucin.

*PanIN-1B* are epithelial lesions with a papillary, micropapillary or basally pseudostratified architecture but are otherwise identical to PanIn-1A
**PanIN-2** – these mucinous epithelial lesions may be flat but are mostly papillary.

Cytologically, these lesions must have some nuclear abnormalities which may include some loss of polarity, nuclear crowding, enlarged nuclei, pseudo-stratification, and hyperchromatism. These nuclear abnormalities fall short of those seen in PanIN-3. Mitoses are rare, but when present are nonluminal (not apical) and are not atypical. True cribiform structures with luminal necrosis and marked cytologic abnormalities are generally not seen and, when present, should suggest the diagnosis of PanIN-3.

**PanIN-3** - is really carcinoma in situ.

**Lesions mimicking PaIN-3** –

(a) intraductal papillary mucinous neoplasm which does involve the main pancreatic duct and its branches.

(b) mucinous cystic neoplasm. Its feature is the presence of ovarian-type stroma and absence of any connection to the duct system. These are large in size.

**Acinar cell cystadenocarcinoma**

This accounts for 1 – 2% of pancreas neoplasms and is a rare neoplasm.

This is not of ductal origin. The cells look like acinar cells.

**Age:** median age is 50 years.

**Gender:** Females : males = 3 : 2

**Demographic:** all racial and ethnic backgrounds affected.

**Etiology:** is unknown but believed due to genetic mutations.

**Clinical features:** very slow growing. Eventually it may cause abdominal pain, nausea and vomiting, and lead to weight loss. If significant numbers of Islet cells are destroyed as well, diabetes will occur. Metastasizes to the lymph nodes and liver.

**Diagnosis:** serum amylase, complete blood count with differential, and blood tests that may involve tumours markers, such as:

- Carcinoembryonic antigen (CEA)
- CA 19.9
- CA 15.3
- Alpha fetoprotein

**Imaging:** ultrasound, CT and MRI. The CT is useful to detect recurrence or metastasis.

**Ultrasound:** can demonstrate a hypoechoic mass in the head of the pancreas and show if the bile duct and/or main pancreatic duct are occluded. Image courtesy of Otto van Delden and R. Smithuis, Medscape Sep 17, 2014. For a mass in the body or tail, endoscopic ultrasound is needed as it can avoid bowel gas interference.
**CT scan** - Evaluation of the adjacent vasculature is important, including the superior mesenteric artery (SMA) and vein (SMV) and the portal and splenic veins, because pancreatic tumours are unresectable if metastases are present, if there is vessel involvement in which the SMV is completely occluded and reconstruction is not possible, or when there is more than 180° involvement of the celiac artery or SMA. Involvement of the splenic artery does not preclude resection. If the tumours are resectable, preoperative evaluation of normal vascular variants is crucial to avoid complications of intraoperative vascular injury. This coronal CT scan demonstrates narrowing and encasement of the portal vein by a pancreatic mass. Courtesy of Dr Zahir Amin, Medscape Sept 17, 2004.

Also see below coronal CT showing obstructed common bile duct by a tumour in the head of the pancreas with dilatation of the intrahepatic ducts.
MR may be used as MR cholangio-pancreatography and also MR angiography.

PET scan (positron emission tomography) is good to demonstrate spread and metastasis.

**Macroscopically:** the tumour consists of a large multilocular cystic mass with a pseudocapsule and a spongy appearance on the cut surface. Image courtesy of Deepali Jain. PathologyOutlines.com. August 2012. The tumour can grow up to 20 cms in size.

**Microscopically:** the cysts are lined by a single layer of cuboid/columnar cells. The cytoplasm is the same as acinar cells with eosinophilic granules in the apex and prominent nucleoli. Image shows multiple small cysts – courtesy of Deepali Jain. PathologyOutlines.com. Aug 2012.
Risk factors: smokers are at the highest risk and so are patients with long-standing, poorly controlled diabetes. Also chronic pancreatitis and obesity.

Complications if untreated:

- Gastrointestinal obstruction
- Biliary tract obstruction causing jaundiced
- Compress adjoining organs if the tumour size is large, affecting their function
- Invasion of surrounding tissue and organs
- If the cyst destroys enough islet cells of the pancreas, it can result in diabetes
- The tumour can metastasize to the liver and lymph nodes

Treatment: surgical excision is preferred but if the imaging indicates spread and metastasis, a combination of surgery, radiotherapy and chemotherapy may be used.

Prognosis: if surgical excision is done before spread to adjacent organs or metastasis has occurred, the outlook is quite good with acinar cell adenocarcinoma.

Mucinous Cystic Neoplasm

Definition:

Mucinous pancreatic tumors can be subdivided into peripheral and ductal tumors according to the site of origin.

The peripheral type of mucinous cystic tumors includes mucin-producing cystadenoma and cystadenocarcinoma.

This tumour has ovarian-type stroma and does not communicate with the main pancreatic duct (WHO classification 2000).

Imaging: peripheral type - CT shows a large septate mass with a smooth external contour – see image courtesy of Dr A Nawaz Khan. Medscape Nov 11, 2015.
The *ductal types* originate from the main pancreatic duct (MPD) or its branches.

[Intraductal tumors are referred to as *intraductal papillary mucinous tumor (IPMT)*] – discussed further on.

**Sites of MCN:** 97% develop in the tail of the pancreas.

**Prevalence of cancer in MCN:** 18%

**Gender:** 95% occur in women.

**Clinical presentation:** Symptomatic patients present with mild abdominal pain but 10% present with acute pancreatitis.

**Pathology on histological classification:** 75% have adenoma, 10.0% borderline tumours, 5.0% are carcinoma in situ, 10.0% invasive carcinoma.

**Age:** Patients with invasive cancer are much older – 55 years – than those with noninvasive cancer – 44 years. Suggests progression from adenoma to cancer.

**Macroscopic appearance:** Findings associated with malignancy are the presence of nodules and for these to be >60 mm. The tumour consists of large septated thick walled mucinous cysts that lack communication with the ductal system and occur almost exclusively in the body and tail of the pancreas in middle aged women.

**Microscopic appearance:** They are characterized by two distinct histologic components: an inner epithelial layer composed of tall mucin-secreting cells, and a dense cellular ovarian-type stroma.
The latter distinguishes this tumour from intraductal papillary mucinous tumour (IPMT), with which it can be confused.

The IPMT has different biologic behavior and pathologic features, including prevalence of invasive cancer, recurrence rate after radical resection, and presence of multifocal lesions.

**Treatment:** resection would be considered for all cases but in low-risk MCNs (≤4 cm/no nodules), nonradical resections are thought appropriate.

**Prognosis:** only patients with invasive carcinoma have recurrence. The 5-year disease-specific survival for non-invasive MCN is 100% but for invasive MCN only 60%.

**Intraductal papillary Mucinous Tumour (IPMT)**

Described in 1982.

**Definition:** is a type of tumor that grows within the pancreatic ducts (intraductal) and is characterized by the production of thick mucin and some of these tumours progress to invasive cancer.

**Site:** branch-type in the head and uncinate process, main duct type more diffuse like chronic pancreatitis.

**Peak Age:** main duct type appears 10 years earlier than side-branch type.

**Gender:** slight female predilection.

**Clinical presentation:** abdominal pain, nausea and vomiting and sometimes jaundice if the tumour is in the head of the pancreas.

**Molecular pathology:** In July 20 2011, report from Bert Vogelstein at Johns Hopkins in Science Translational Medicine discovered that all intraductal papillary mucinous neoplasms had mutations in GNAS, KRAS or both genes. Benign serous cystadenomas did not have these mutations. When the test has been used on a larger number of patients, it could avoid unnecessary surgery for those with the benign tumour.
Macroscopic:

- **main duct**
  - reminiscent of chronic pancreatitis
  - segmental or diffuse distribution
  - ~60% are malignant
- **branch duct type**
  - mostly seen in the head and uncinate process
  - more localised and mass-like
  - may be macro or microcystic in appearance
  - typically indolent behaviour ~5% (range 2-10%) are malignant
- **mixed type lesions** - Solid components are suspicious of malignant transformation.

**Imaging:** the image below, courtesy of Dr A Nawaz Khan, shows a tumour in the head of the pancreas - see white arrow. The black arrow in the lower left image indicates a dilated main pancreatic duct.

Microscopic: They are histologically divided into

- adenoma
- borderline malignant
- intraductal papillary mucinous adenocarcinoma

Biochemistry: In patients without pancreatitis, abnormal (either elevated or depressed) pancreatic enzyme markers (amylase/lipase) are associated with malignant IPMN, with elevation of these a marker of invasiveness.

**Imaging:** The characteristic feature is that these tumours communicate with the pancreatic duct or its branches, which helps to distinguish these tumours from mucinous cystadenoma / cystadenocarcinoma which do not.

- **CT - main duct IPMN** (with dilatation of main duct >5 mm)
  - either segments of the pancreatic duct (or the entire duct) are dilated and filled with low density (mucin) material
overlying pancreatic parenchyma may be thinned
- if proximal, the distal pancreatic duct may be dilated without direct involvement (cystic neoplasms can have a similar appearance)
- solid mural nodules are suspicious for malignant transformation—appear as hyperdense nodules protruding into the mucin-filled dilated ducts
- enhancing nodules following administration of contrast are very suspicious of malignancy.
- occasionally mucinous material can be seen to bulge out of a dilated ampulla of Vater (essentially pathognomonic)

- **branch duct IPMN**
  - the majority of the gland is normal in appearance, except for a single or multiple side branches demonstrating marked dilatation
  - cystic mass-like appearance which often mimicks cystic tumours of the pancreas
  - its appearance has been termed a bunch of grapes due to its appearance
  - microcystic variety has appearances similar to serous cystadenomas, but again communication with the main pancreatic duct is the key to correct diagnosis

- **MRI** appearances are similar to those seen on CT. Mural nodules appear hypointense compared to surrounding fluid / mucin and enhance following administration of contrast. Mucin globules do not enhance and lie dependently within the duct.

- **Ultrasound** Ultrasound demonstrates dilated ducts which appear hypoechoic. Mural nodules and mucin globules may appear hyperechoic, and difficult to separate from adjacent pancreatic parenchyma. Diffuse main duct type has appearances essentially indistinguishable from chronic pancreatitis, with duct dilatation and parenchymal atrophy.

- **ERCP** Direct imaging of the pancreatic duct demonstrates variable dilatation (segmental or diffuse or branch) depending on the type. Polypoid mural tumour or amorphous mucinous luminal filling defects may be identified. Mucinous material may be seen protruding from the Ampulla of Vater.

**Pathogenesis:** direct invasion into adjacent organs or more frequently dissemination in the peritoneal cavity (pseudomyxoma peritonei) can occur.

**Treatment:**

Although generally indolent, malignant degeneration does occur. Current consensus criteria recommend resection for main duct IPMNs and varying treatment of branch duct IPMNs, ranging from resection to surveillance, depending on high risk stigmata and worrisome features.

The treatment of choice for main-duct IPMNs is resection due to a 60% chance of malignancy.

**Side-branch IPMNs** are occasionally monitored with regular CT or MRIs, but most are eventually resected, with a 30% finding of malignancy. Surgery can include the removal of the head of the pancreas (a pancreaticoduodenectomy), removal of the body and tail of the pancreas (a distal pancreatectomy), or rarely removal of the entire pancreas (a total pancreatectomy). In selected cases the surgery can be performed using minimally invasive techniques such as laparoscopy or robotic surgery.

**Prognosis:**

Survival 5 years after resection of an IPMN without malignancy is approximately 80%, 85% with malignancy but no lymph node spread and 0% with malignancy spreading to lymph nodes.
Intraductal papillary mucinous neoplasms (IPMNs) are classified into two broad groups - those that are associated with an invasive cancer and those that are not associated with an invasive cancer. This separation has critical prognostic significance. Patients with a surgically resected intraductal papillary mucinous neoplasm without an associated invasive cancer have an excellent prognosis (>95% will be cured), while patients with a surgically resected intraductal papillary mucinous neoplasm with an associated invasive cancer have a worse prognosis.

Intraductal papillary mucinous neoplasms without an associated invasive cancer can be further subcategorized into three groups. They are IPMN with low-grade dysplasia, IPMN with moderate dysplasia, and IPMN with high-grade dysplasia. This categorization is useful as IPMNs are believed to progress from low-grade dysplasia to moderate dysplasia to high-grade dysplasia to an IPMN with an associated invasive cancer.

**Pancreatoblastoma**

This is the most common pancreatic tumour in infancy and early childhood but is rare and characterised by acinar differentiation, squamoid corpuscles, stromal bands.

**Clinical presentation:** abdominal pain, vomiting and jaundice. Rarely presents early. Usually locally advanced or metastatic.

**Macroscopic:** solid, soft masses, partially encapsulated, often lobulated and nodular, 2 - 20 cm in size.

Images of gross appearance, ultrasound and CT scan of an 8 year old girl, are courtesy of H. Montemarano, G J Loneragan, D I Boulas, DM Selby. Radiology 2000; 214: 476-482.

**Imaging:**

**Ultrasound:**

They are usually large, well defined, heterogeneous mass with solid and multilocular cystic areas that contain hyperechoic septae. Dilatation of biliary duct is not common as the tumors themselves are soft, though they are frequently large at presentation.

In the image, the curved arrows indicate the heterogeneous mass and the straight arrows show where it is arising from the body and tail of the pancreas.
CT – below – white arrows are on the perimeter of the tumour.

- usually relatively well defined and heterogeneous due to solid and multilocular cystic components with enhancing septae
- may demonstrate fine calcifications
- most often occurs in the head of the pancreas and tend to be large and solitary, though dilatation of bile duct is uncommon
- hepatic metastases: hypodense
- less frequently, invasion of adjacent structures and biliary tree may be noted
Microscopic: mainly two cell types; those with acini differentiation and look like normal acinar cells of the pancreas plus squamoid nests. Less commonly endocrine or ductal features.

- Very cellular, uniform epithelial cells in sheets and nests with acini/ducts
- Squamoid corpuscles (circumscribed whorled nests of plump spindle cells with a squamous appearance and occasional keratinization) are common and specific
- Pediatric cases often have hypercellular stroma, occasionally with bone/cartilage

Electron microscopy may show acinar cell features, so the differential diagnosis has to be made from acinar cell adenocarcinoma.

Micro image courtesy of E M Chung, M D Travis, R M Conran Radiographics 2006; 26(4). Note the small rosette-like glandular structures (arrows) intermixed with solid sheets of uniform epithelial cells – arrowheads.

Treatment: surgical excision plus chemotherapy if advanced disease.

Prognosis: Children: 50% cured after excision; most survive and do well with chemotherapy if no metastases, but those with metastases often die. 35% metastasize to lymph nodes and liver.

- Children: higher survival if complete resection; 5 year overall survival is 79%
- Adults: mean survival 18 months

Pancreatic lymphoma

Definition: Pancreatic lymphoma is most commonly a B-cell sub-type of non-Hodgkin lymphoma and is classified as either primary or secondary:
primary pancreatic lymphoma is a rare extranodal manifestation of any histopathologic subtype of B-cell non-Hodgkin's lymphoma, representing < 2% of extranodal lymphomas and 0.5% of pancreatic tumours.

secondary lymphoma: found in 30% of non-Hodgkin lymphoma patients with widespread disease, it is the dominant form and is the result of direct extension from peripancreatic lymphadenopathy.

Age: mean age of 55 years; range 35-75.

Etiology: found in immunocompromised patients.

Clinical presentation:

- abdominal pain: ~ 85%
- mass: ~ 60%
- weight loss: ~ 50%
- obstructive jaundice: ~ 40% of cases
- acute pancreatitis: ~ 10%

Fever, chills, night sweats are present in only 2% of cases.

Site:

- focal form: occurs in the pancreatic head in 80% of cases and has a mean size of 8 cm
- diffuse form: infiltrative, leading to glandular enlargement and poor definition so simulate the appearance of acute pancreatitis

Imaging:

CT:

- minimal enhancement
- peri-pancreatic lymph node enlargement
- uniform low attenuation
- diffuse form may simulate acute pancreatitis
- encasement of the peri-pancreatic vessels may occur; vascular invasion is less common in lymphoma than in adenocarcinoma
Image courtesy of Dr Andrew Dixon, Radiopaedia.org, rID 16513

MRI

- **focal form**: low signal intensity on T1-weighted images and intermediate signal intensity on T2-weighted images (slightly higher signal intensity than the pancreas but lower signal intensity than fluid), and *shows faint contrast enhancement*.
- **diffuse form**: low signal intensity on T1- and T2-weighted MR images and *shows homogeneous contrast enhancement*, although small foci of reduced or absent enhancement are sometimes seen.

**Ultrasound:** may reveal a homogeneous, lucent, or complex mass. These masses are usually echo-poor and may mimic cystic lesions

**Microscopic appearance:**

As the prognosis of a pancreatic lymphoma is favorable, its differentiation from a carcinoma is crucial. The correlation of sonographic, CT, and angiographic findings may result in a correct diagnosis. However, if doubt exists, sonography-guided biopsy may reveal the true nature of the mass.

There are many small round cells with moderate anisonucleosis.

Immunohistochemical studies - LCA, Ki67 (in 5 % of tumor cells) and CD20 is strongly positive.

**Treatment:** first-line treatment is chemotherapy. A few cases do need surgery.

**Prognosis:** long-term regression or even remission is frequent. Cure rates of 30% have been reported. There is only a 5% 5-year survival with pancreatic adenocarcinoma, with which it can be confused.

**NEOPLASTIC**

**ENDOCRINE Tumours of the Pancreas**

The Islets of Langerhans form the endocrine pancreas and the different cell types are associated with different tumours responsible for individual clinical syndromes. All types combined form 5% of pancreatic tumours.

Some pancreatic and extra-pancreatic endocrine tumours produce two or more hormones e.g. insulin, glucagon, gastrin, ACTH, melanocyte-stimulating hormone, vasopressin, serotonin and nor-epinephrine. This is not the same as MEN-1 and MEN-2 where several glands produce an excess of different hormones.

The syndromes associated with islet cell tumours are summarised in the figure below.

Insulinoma – accounts for 90% of this group

Definition: insulinoma is a rare form of a neuroendocrine tumour derived from beta cells and continually secretes insulin.

Sites: 99% of insulinomas originate in the pancreas and the remainder within ectopic pancreatic tissue elsewhere. In addition 5% of the insulinoma may co-exist with tumours of the parathyroids and pituitary (Multiple Endocrine neoplasia type 1). In that situation the insulinomas are more likely to be multiple and malignant.

Size: most are less than 2 cm but can grow very large.

Incidence: 1 – 4 new cases per million population per year.

Peak age: between 30 and 60 years – usually average is 45 years except those patients who have the insulinoma with multiple endocrine neoplasm MEN – type 1 when it will be seen in the 20’s.

Gender: Male : female = 2 : 3

Clinical presentation:

Patients with insulinomas usually develop neuroglycopenic symptoms. These include recurrent headache, lethargy, diplopia, and blurred vision, particularly with exercise or fasting. Severe hypoglycemia may result in seizures, coma, and permanent neurological damage. Symptoms resulting from the catecholaminergic response to hypoglycemia (i.e. tremulousness, palpitations, tachycardia, sweating, hunger, anxiety, nausea) are not as common. Sudden weight gain is sometimes seen.

Molecular pathology and Genetic:

90% are benign so grow only at their origin. The other 10% are malignant so metastasize.

Heterozygous mutations have been found of the MEN-1 gene on 11q. Aneuploidy of chromosome 11 is common in both MEN-1 and non-MEN-1 insulinomas. K-ras mutation is found in 25% of insulinomas.

Pathophysiology: beta cells secrete insulin when the blood glucose rises. Insulin causes the blood glucose to drop back to normal resting levels. However, insulin produced by this tumour is not correctly controlled by glucose so the continuation of secretion will drop the blood glucose to dangerously low levels – hypoglycaemia.

Biochemistry: the finding of low blood glucose, elevated insulin, proinsulin and C-peptide levels can make the diagnosis of insulinoma. Imaging is used to confirm its location within the pancreas.

For the diagnosis of true hypoglycemia to be made the following triad should be satisfied:

1. symptoms and signs of hypoglycemia,
2. concomitant plasma glucose level of 45 mg/dL (2.5 mmol/L) or less, and
3. reversibility of symptoms with administration of glucose.
A Suppression Test over 72 hours may be undertaken as an in-patient. If insulin levels fail to drop in the presence of hypoglycaemia this strongly suggests an insulinoma. The test is stopped when the blood glucose reaches 2.7 mmol/L

**Imaging**: CT (90% success). Image courtesy of Dr Z A Ali, Medscape Feb 21, 2016 – arrow indicates the insulinoma.

![](image1)

or MRI (85% success).

**Transabdominal ultrasound** (50%),

**Endoscopic ultrasound** has up to 90% sensitivity, depending upon location in the pancreas.

Selective **arteriography** has 82% accuracy with a 5% false-positive rate. Arteriography with catheterization of small arterial branches of the coeliac system combined with calcium injections and simultaneous measurements of hepatic vein insulin during each selective calcium injection localizes tumors in 50% of patients.

During surgery to remove an insulinoma, an **intra-operative ultrasound** can sometimes localize the tumour if it has eluded detection on pre-op imaging. Finds 90% of insulinomas.

**Macroscopic**: Gross appearance of insulinoma shows a typical red-brown appearance.

Images courtesy of Wikipedia.

Microscopic: courtesy of library of University of Utah. Normal islet on the right and the mass of tumour cells on the left.
The identity of the islet tumour can be confirmed by immunoperoxidase stains, using antibody for insulin to show the uptake (brown) by the β cells. (Courtesy University of Utah). Insulinoma cells contain less insulin and secretory granules than normal β cells but more pro-insulin.

**Treatment:**

*Is surgical removal* of the insulinoma. This may involve removing part of the pancreas as well (Whipple procedure and distal pancreatectomy). First surgical cure reported in 1929.

*Medications* such as diazoxide and somatostatin can be used to block the release of insulin for patients who are not surgical candidates or who otherwise have inoperable tumours.

Streptozotocin is used in *islet cell carcinomas* which also produce excessive insulin. Combination chemotherapy is used: either doxorubicin + streptozotocin, or fluorouracil + streptotozocin in patients where doxorubicin is contraindicated.
In metastasizing tumours with intrahepatic growth, hepatic arterial occlusion or embolization can be used.

**Prognosis**

Most patients with benign insulinomas can be cured with surgery. Persistent or recurrent hypoglycemia after surgery tends to occur in patients with multiple tumours. About 2% of patients develop diabetes mellitus after their surgery.

However, if it is a malignant insulinoma – accounts for 10% - and there is pre-operative spread to the liver, survival is 16 – 26 months.

**Gastrinoma**

**Definition:** it is a functioning pancreatic neuroendocrine tumour composed of G cells which produce gastrin; a hormonal stimulus for gastric acid secretion.

**Incidence:** 0.5 – 2.0 per million and second in frequency to insulinoma. The most common functioning tumour in MEN-1 patients and found in 25%.

**Site:** Only 30% are found in the pancreas, the remainder in the duodenum and stomach.

90% of the pancreatic ones are found in the head of the pancreas.

**Age:** 30 – 50 years

**Gender:** M : F = 2:1.

**Pathogenesis:** 50% are aggressive and metastasize to the liver. Gastrinomas in the duodenum tend to remain localized.

**Clinical Presentation:** referred to as the Zollinger-Ellison Syndrome (ZES). Enormous secretion of gastrin from the tumor cells leads to hyperplasia of the fundic parietal cells and increased basal acid secretion causing severe ulcer disease. Ulceration might even extend into the small intestine. The acidic content of the small intestine causes the release of secretin, which is responsible for the **diarrhoea**, in part, caused by the outpouring of water and bicarbonate from the pancreas and small intestine.

Abdominal pain is present in 75% of patients. Typically, it is located in the upper abdomen and mimics that of peptic ulcer disease. This symptom is reported more frequently by men and patients with the sporadic form of ZES.

73% have diarrhea; this is the most common symptom in patients who have multiple endocrine neoplasia-type 1 and ZES (MEN 1/ZES) as well as in female patients. The combination of diarrhea and abdominal pain is present in more than half the patients.

Heartburn is the third most common symptom, and mimics gastroesophageal reflux disease (GERD).

Also nausea, vomiting, gastrointestinal bleeding, and weight loss. Gastrointestinal bleeding frequently is due to ulceration in the duodenum and is the presenting symptom in 25% of patients.
In patients in whom MEN 1/ZES is suspected, a history indicative of nephrolithiasis, hypercalcemia, and pituitary disorders should be sought. A family history of nephrolithiasis, hyperparathyroidism, and gastrinoma also may be present.

Suspect Zollinger-Ellison syndrome when there are peptic ulcers that persist or recur, despite treatment for H. pylori infection.

**Macroscopic:** usually more than 2 cms in the pancreas but in the duodenum may be only a few mms.

Photograph courtesy of R B Lewis, G E Lattin, E Paal. Radiographics 2010, 30(6) shows a circumscribed yellow mass.

**Microscopic:** well-differentiated and show a trabecular and pseudoglandular pattern.

Histological examination on HE-stained sections must be accompanied by immunostaining for chromogranin A, synaptophysin, gastrin and Ki-67.

Cytology is generally not useful except in an intraoperative setting for tumour confirmation.

**Imaging:** studies are necessary in all patients with biochemically confirmed Zollinger-Ellison Syndrome to determine:

- whether surgical resection is indicated
- to localize the primary tumour
- to determine the extent of the disease
- to determine whether metastatic disease to the liver and beyond is present
- to assess changes in tumour extent with treatment

Recommended procedure is to initially do an upper gastro-intestinal endoscopy to inspect the duodenum for tumours. This is followed by a CT scan of the abdomen and somatostatin-receptor scintigraphy (SRS). The latter is the best study to initially stage the disease and detect liver and distant metastases. Note that bone metastases occur in one-third of patients with liver metastases so an MRI of the spine is important.

If these studies are negative and surgery is being considered, selective angiography with secretin stimulation and hepatic venous sampling could follow.

Endoscopic ultrasound is particularly useful to locate pancreatic lesions.
Imaging findings that result from high levels of gastric acid include thickened gastric folds, ulcers, and those related to complications of ulcer disease. Elevated gastrin levels also may lead to formation of multiple carcinoid tumors within the stomach. These tumors may regress after surgical resection of the gastrinoma.

The CT below, courtesy of R B Lewis, G E Lattin and E Paal. Radiographics 2010 30(6) shows grossly thickened stomach folds due to the high level of gastric acid.

The CT below from the same patient shows a 5 cm heterogeneous mass in the pancreas (arrows) with hyper and hypoattenuation.

**Treatment:** surgery to remove the tumour as soon as possible as 50% become malignant.

**Prognosis:** with liver metastases, patients live less than one year. 5-year survival is 25%.

With localised disease or metastases to lymph nodes but no liver metastases, 5-year survival is 90%. Surgical resection will lead to complete cure without any recurrence in 25% of patients.
GLUCAGONOMA

**Definition:** is a rare tumour of the alpha-2 cells producing excessive glucagon, a hormone which works with insulin to control the level of blood sugar.

**Sites:** tumour of the alpha cells of the pancreas and almost always found in the pancreas.

**Incidence:** 1 in 20,000,000. Account for 8 – 13% of functioning pancreatic neuroendocrine tumours.

**Peak age:** seen between 40 and 70 years

**Gender:** slight female preponderance.

**Clinical presentation:**

- mild diabetes – occurs in 90%,
- necrotising migratory erythematous (NME) rash – occurs in 70%,
- Anaemia
- diarrhoea,
- deep vein thromboses and
- psychiatric disturbances.

Photo of NME rash, courtesy of S Wu, J Bai, J Xu, Q Ma,, Z Wu. 2014, World Journal of Surgical Oncology, 12: 220. **Skin biopsies** may also be taken to confirm the presence of NME.

There are well demarcated erythematous plaques, with fragile vesicles on the buttock.

**Biochemistry:** plasma glucagon can be 30 times normal. A **blood serum glucagon concentration of 1000 pg/mL** or greater is indicative of glucagonoma (the normal range is 50–200 pg/mL).

Increased levels have been reported in cases of decreased kidney function, acute pancreatitis, hypercorticism, liver diseases, severe stress, extended fasting, and familial hyperglucagonemia. Rarely do these cases result in levels over 500 pg/mL, except in the case of patients with liver diseases.
Abnormally low concentrations of amino acids, zinc, and essential fatty acids may be found, which are thought to play a role in the development of NME. The haemoglobin level may also be low showing anaemia.

Glucagonomas may overproduce multiple hormones, each of which can have clinical manifestations. Insulin is the second-most common hormone secreted by these tumors. Others include (in order of frequency) adrenocorticotropic hormone (ACTH), pancreatic polypeptide, and parathyroid hormone (PTH) or substances with activity similar to PTH, such as gastrin, serotonin, vasoactive intestinal polypeptide (VIP), and melanocyte-stimulating hormone (MSH).

**Molecular pathogenesis:** In 75-80% of cases, the glucagonoma starts in malignant form, and in 50% of these cases, metastasis exists at diagnosis.

Three forms of glucagon exist. The pancreatic form contains 29 amino acids and has a molecular weight of 3485 daltons, the gastric form contains 29 amino acids and has a molecular weight of 3500 daltons, and the enteric form, or enteroglucagon, contains a polypeptidic chain, has a high molecular weight, and is biologically and chemically different from other hormones, although it cross-reacts with them.

**Genetic:** A family history of the syndrome multiple endocrine neoplasia type I (MEN I) is a risk factor.

**Macroscopic appearance:** Glucagonomas that are not associated with glucagonoma syndrome are diagnosed in various ways. The tumor may appear as a malignant pancreatic tumor discovered because of local growth, with or without metastases, or the tumor may be associated with insulinoma or gastrinoma. Glucagonoma may also occur as a single microadenoma found incidentally at autopsy in elderly patients. Glucagonoma very rarely is part of multiple endocrine neoplasia (MEN) type 1 syndrome (also called Wermer syndrome). In such cases, the glucagonoma appears as a single, biologically inactive lesion. Similar to other islet cell tumors, the primary and metastatic lesions are slow growing.

**Imaging:** The tumor itself may be localized by any number of radiographic modalities, including angiography, CT, MRI, PET, and endoscopic ultrasound. Laparotomy is useful for obtaining histologic samples for analysis and confirmation of the glucagonoma.

Note on the abdominal CT there is a 5-7 cm vascular, nodular mass in the tail of the pancreas.
Microscopic appearance: immunostaining shows numerous glucagon-positive cells on the right – brown staining.

Diagnosis: Tests that may be done include:

- CT scan of the abdomen
- Glucagon level in the blood
- Glucose level in the blood

Treatment:

Heightened glucagon secretion can be treated with the administration of octreotide, a somatostatin analog, which inhibits the release of glucagon. Doxorubicin and streptozotocin have also been used successfully to selectively damage alpha cells of the pancreatic islets. These do not destroy the tumour, but help to minimize progression of symptoms.

The only curative therapy for glucagonoma is surgical resection, where the tumour is removed. Resection has been known to reverse symptoms in some patients.

Prognosis: As only 250 cases have been described since Becker in 1942, long term survival is not fully known. Approximately 60% of these tumors are cancerous. It is common for this cancer to spread to the liver, but if absent may have 85% 5-year survival. Only about 20% of people can be cured with surgery.
Somatostatinoma

**Definition:** rare tumour of the δ delta cells of the islets of Langerhans, that produces somatostatin. It is the rarest of the pancreatic neuroendocrine tumours.

**Sites:** commonly found in the head of the pancreas but 40% occur in the duodenum. Rarely found to arise in lungs, liver and kidneys.

**Incidence:** 1 in 40,000,000 persons

**Peak age:** 40 – 60 years

**Gender:** equal

**Race:** no predilection.

**Clinical presentation:** syndrome of mild diabetes, gallstones, steatorrhoea, hypochlorhydria, anaemia and weight loss. This is due to the inhibitory actions of somatostatin on other pancreatic islet cells and on neuroendocrine cells of the gastro-intestinal tract. Hence blood levels of insulin and glucagon are low.

Symptoms of somatostatinoma due to hormone excess only occur with very high hormone levels, and, therefore, with large tumors.

About 50% of patients with somatostatinoma have other endocrine disorders, particularly those presenting with duodenal tumours. Neurofibromatosis type-1 (NF-1), and less frequently, MEN-1, von Hippel-Lindau disease, tuberous sclerosis, and gastrointestinal stromal tumours (GIST) have presented with somatostatinoma as well. Tumour markers, with the exception of somatostatin, are nonspecific, and include pancreatic polypeptide, ghrelin, andrenomedulin, neuron-specific enolase, and chromogranin A.

**Pathophysiology:** actions of somatostatin include:

- In the anterior pituitary gland, the effects of somatostatin are:
  - Inhibit the release of growth hormone thus opposing the effects of growth hormone releasing hormone (GHRH)
  - Inhibit the release of thyroid-stimulating hormone (TSH)

  Somatostatin suppresses the release of gastrointestinal hormones
  - Gastrin
  - Cholecystokinin(CCK)
  - Secretin
  - Motilin
  - Vasoactive intestinal peptide (VIP)
  - Gastric inhibitory polypeptide (GIP)
  - Enteroglucagon
Lowers the rate of **gastric emptying**, and reduces smooth muscle contractions and blood flow within the intestine

Suppresses the release of **pancreatic hormones**

- Inhibits the release of insulin
- Inhibits the release of glucagon
- Suppresses the **exocrine secretory action** of pancreas.

**Macroscopic:** in the pancreas are greater than 4 cm but in the duodenum are less than 2 cm. Are round, well demarcated masses.

**Imaging:** **CT scan** – done usually for the work-up of unexplained abdominal pain.

In the images below, courtesy of B Zhang, Q Xie, S Gao, Y Fu, Y Wu, J Zhejiang Univ Sci B 2010 Jan; 11(1): 22-26, the non contrast scan on the left shows the tumour – T – in the body and tail of the pancreas and the post contrast on the right shows the mass enhanced earlier than normal pancreatic tissue.

**Endoscopic** evaluation of the upper gastrointestinal tract is useful for excluding other conditions that can produce similar constellations of symptoms. **Gastric pH should be measured** at the time of endoscopy to evaluate for hypochlorhydria.

**Intraoperative endoscopic transduodenal** illumination may help localize small endocrine tumors that reside within the wall of the duodenum or within the pancreatic parenchyma.

**Real-time intraoperative ultrasonography** (IOUS) can provide additional information about the location and number of pancreatic endocrine tumors. It also can be used to detect small lymph node and hepatic metastases. This technique should always be used in patients who undergo exploration for tumours that could not be definitively localized preoperatively.
**Somatostatin scintigraphy** – uses Indium-111-pentetreotide and can detect primary and metastatic tumour.

**Selective transhepatic portal venous sampling** - blood is sampled from different locations within the portal venous drainage of the pancreas and pancreatic bed. Serum levels of somatostatin are determined from the blood samples to help localize the tumour based on anatomic venous drainage. The sample with the highest serum hormone level is presumed to have been drawn from the main venous drainage of the tumour.

**Microscopic:** Somatostatinomas can be associated with calcium deposits called psammoma bodies.

There is a medullary pattern and no significant cellular atypia. Immunohistochemical test positive for somatostatin. See the brown-stained cells in the image below (courtesy of Deepali Jain, 2015 PathologyOutlines.com). Locally invasive.

![Image of brown-stained cells](image.png)

Routine histologic examination does not predict the biologic behavior of these neoplasms, and malignancy is typically determined by the presence of tumour spread to regional lymph nodes or by the existence of hepatic or distant metastases.

**Biochemistry:** Fasting blood somatostatin levels >10ng/ml is abnormal.

Somatostatinomas often simultaneously produce other hormone products, including insulin, gastrin, VIP, glucagon, corticotropin (previously adrenocorticotropic hormone [ACTH]), calcitonin, pancreatic polypeptide, and others. If these products are secreted into the bloodstream in significant quantities, they affect the clinical presentation and diagnosis.

**Diagnosis:** Metastasis occurs most typically to the liver. Regional lymph nodes and bone are involved sites less often. Metastases are present at initial diagnosis in 80% with a pancreatic primary and in nearly 50% of patients whose primary tumour is duodenal. Late diagnosis is thought to play a significant role.

**Treatment:** Treatment is by chemotherapy with streptozocin, dacarbazine, doxorubicin or by regular monitoring and surgical debulking via Whipple procedure and other resections of the gastrointestinal organs affected. If the patient already has metastases, the surgeon may resect the primary tumour and debulk the liver metastases. In addition, the gallbladder is usually removed to avoid the development of gallstones.
Small (<2 cm) benign lesions that are remote from the main pancreatic duct may be enucleated. Regional pancreatectomy is usually necessary for tumours that are deep in the substance of the pancreatic gland near the main duct, have ill-defined capsules, or are large (>2 cm). Tumours in the body or tail of the pancreas can be managed with distal pancreatectomy, whereas lesions in the head or uncinate process of the gland can be resected via pancreaticoduodenectomy. Tumours in the neck of the pancreas can be managed with middle segment pancreatectomy (oversewing the proximal pancreatic stump and draining the distal pancreatic duct via pancreaticogastrostomy or pancreaticojejunostomy).

**Prognosis:** Postoperative 5-year survival rates of patients with metastatic somatostatinoma is 30-60%, but patients without metastases have a 5-year survival rate approaching 100%. Prognosis is primarily based on the presence or absence of liver metastases. The presence of regional lymph node spread does not necessarily connote decreased patient survival. The *standard tumour/node/metastasis (TNM)* classification scheme is not used to stage somatostatinomas.

**VIPoma (vasoactive intestinal peptide)**

**Definition:** VIP is normally made in the ganglion cells and nerve fibres of the pancreas, gut and the brain. The VIPoma tumour arises from the D1 cells of the islets.

**Sites:** 90% occur in the pancreas. 10% are in extra-pancreatic sites especially in children, occurring in colon, liver and neural tissue.

**Incidence:** 1 in 10,000,000. 3 – 8% of all pancreatic neuroendocrine tumours.

**Peak age:** can occur at any age but mean is in the 5th decade.

**Gender:** slight female preponderance.

**Clinical Presentation:** the tumour induces the Verner-Morrison syndrome so causes diarrhoea. Lethargy, muscle weakness, nausea, vomiting and crampy abdominal pain are frequent symptoms.

Associated with the VIP Syndrome are neural crest tumours e.g. neuroblastomas, ganglioneuroblastomas, gangioneuromas, phaeochromocytomas.

**Macroscopic:** are usually large and solitary and can be locally invasive and have usually metastasized by time of presentation. 5% occur in association with multiple endocrine neoplasia type 1.

**Imaging:** CT scan (courtesy of A. Abu-Zaid, A Azzam, Z Abudan, A Algouli, A Almana, T Amin) shows a circumscribed enhancing lesion in the tail of the pancreas with a cystic component – red arrow. There is a metastasis in the liver, also with a cystic component – yellow arrow.
Microscopic: again courtesy of above authors for the CT image – tumour cells are uniform, intermediate size cuboidal cells with centrally located nuclei, stippled chromatin outline and delicately granular eosinophilic cytoplasm.

Biochemistry: have impaired glucose tolerance, hypokalaemia and achlorhydria.

Also fasting VIP plasma level of 75 pg/lt is suggestive but if elevated above 200 pg/ml is diagnostic.

Diagnosis: 80–90% of all VIPomas are somatostatin receptorpositive, so octreoscan scintigraphy is an extremely helpful radiological procedure.
**Treatment:** The first goal of treatment is to correct dehydration. Fluids are often given to replace fluids lost in diarrhea.

The next goal is to slow the diarrhea. Some medications can help control diarrhea. Octreotide, which is a human-made form of the natural hormone somatostatin, blocks the action of VIP.

The best chance for a cure is surgery to remove the tumor. If the tumor has not spread to other organs, surgery can often cure the condition.

For metastatic disease, peptide receptor radionuclide therapy (PRRT) can be highly effective. This treatment involves attaching a radionuclide (Lutetium-177 or Yttrium-90) to a somatostatin analogue (octreotate or octreotide). This delivers high doses of beta radiation to kill tumors.

**Prognosis:** Surgery can usually cure VIPomas. However, in 30 – 50% of patients, the tumour has spread by the time of diagnosis and cannot be cured.

**Pancreatic carcinoid tumour**

**Definition:** *Carcinoid* is the term used to describe well to moderately-differentiated neuroendocrine tumours, found in the stomach, intestine, pancreas, appendix, rectum, and lung.

It is the commonest of the neuroendocrine tumours and its enterochromaffin cells produce 5-hydroxytryptamine - 5-HT (serotonin) to excess, producing the symptoms of the carcinoid syndrome, especially when it has metastasized to the liver.

**Sites:** the gut is the commonest site, especially appendix and rectum, followed by bronchus. In the ileum are often multiple and more aggressive. Also found in the kidney, ovary and testes.

Only 0.55% of carcinoids are found in the pancreas. There is an association with multiple endocrine neoplasia type 1 in 10% of gastrointestinal carcinoids.

**Incidence:** 1.5 per 100,000 population

**Peak age:** 55 – 65 yrs

**Gender:** no difference between men and women in white races but in black people, more common in men.

**Pathophysiology and biochemistry:** the neuroendocrine system is made up of both nerve and gland cells and makes hormones which are released into the circulation. The other non-hormone function of these cells is for example, regulating the speed at which food passes through the gut, or in the lung regulating air and blood flow. Carcinoid tumours develop when changes occur in the enterochromaffin cells so that they grow out of normal control. As a result the tumour cells can also produce the usual hormone, serotonin (5-HT) to excess and chromogranin-A, particularly when the tumour has metastasized to the liver, lymph nodes and bone. These substances can be measured in the blood.

The carcinoid can also produce 5-hydroxyindole acetic acid (5-HIAA) which is a product of serotonin breakdown and this can be measured in the urine.
However, if the carcinoid tumour only produces small amounts of the hormone, it means the patient may not have symptoms for years, even though the tumour is increasing in size. Pressure on adjacent structures may occur late and also it may have metastasized to the liver. At that point in time, the patient has symptoms of the Carcinoid Syndrome.

**Pathological behaviour:** is determined by tumour size, depth of invasion, hormonal responsiveness, and presence or absence of function.

**Clinical presentation:** is usually when the patient has the Carcinoid Syndrome, with severe diarrhoea being the most troubling symptom. Other features are flushing of the face, bronchospasm, cyanosis, telangiectasia, and skin lesions. Examination finds 50% have right heart valve disease due to the high concentration of 5-HIAA in liver metastases causing endocardial fibrosis. Finding 5-HIAA in the urine is diagnostic for the syndrome. Serotonin is metabolised to 5-HIAA by monamine oxidase from within the tumour or elsewhere.

**Macroscopic:** the cut surface is white to yellow and when over 2 cm size start to exhibit malignant behaviour. It metastasizes to regional lymph nodes and the liver. The photo below, courtesy of World J Surg Oncol. 2004; 2:3, shows a well demarcated tumour from the surrounding parenchyma and it is near but not stenosing the pancreatic duct.

![Macroscopic Image](image-url)

**Imaging:** CT scan of Chest, Abdomen and Pelvis. A CT typically shows a relatively large pancreatic mass indistinguishable from other pancreatic tumours.

MRI can be useful – see image below courtesy of AF Scarsbrook, A Ganeshan, J Statham, RV Thacker, A Weaver, D Talbot et al. Radiographics 2007, 37 (2). The gadolinium-enhanced T1 image shows a mass in the head of the pancreas – arrow – that is indistinguishable from pancreatic adenocarcinoma. It needed biopsy to obtain a histological diagnosis.
Microscopic: the cell arrangement is compatible with any neuroendocrine tumour. The argentaffin reaction of Fontana-Masson is negative while argentophil reaction of Grimelius is positive. Immunohistochemistry demonstrates 100% tumour cell staining with chromogranine, anti-NSE and anti-synaptophysine antibodies. Tumour cells display strong immuno-reactivity to anti-serotonine antibodies.

Treatment:

Surgery remains the cornerstone of treatment of localized tumours. However, many patients develop metastases and require a multidisciplinary approach for optimal management. Patients with liver metastases have various treatment options, such as surgical resection, radiofrequency ablation, arterial embolization, chemotherapy, long-acting somatostatin analogs, peptide receptor radionuclide therapy with $^{111}$In-, $^{90}$Y-, or $^{177}$Lu-labeled octreotide analogs are used routinely or in clinical trials to improve quality of life or survival. Systemic targeted therapies with mammalian target of rapamycin inhibitors (everolimus), tyrosine kinase inhibitors (sunitinib, sorafenib) and VEGF monoclonal antibodies (bevacizumab) are also currently being evaluated in metastatic carcinoid tumors for improving survival.

Follow-up Imaging

CT of the abdomen and pelvis is recommended every 6–12 months along with chest radiography in patients who have undergone complete surgical resection, but CT of the chest, abdomen, and pelvis may be more appropriate in patients with metastatic disease undergoing nonsurgical therapy. The role of octreotide scanning in routine follow-up is unclear, but octreotide may be used on an annual basis or could be used to resolve diagnostic problems, particularly in those patients with somatostatin receptor–positive tumors on initial staging. MRI may be appropriate in slow-growing tumors to reduce radiation exposure, particularly in younger patients. Echocardiography is recommended in all patients with cardiac symptoms. These subsets of patients are more prone to develop carcinoid heart syndrome, the development of which is associated with a significantly poorer prognosis.

Prognosis: 5 year survival rate is 35%. 