



PANCREATIC NEOPLASMS

M Bernon
PC Bornman
JEJ Krige

INTRODUCTION

Pancreatic tumours are classified according to the various pancreatic cells, which they resemble.

The bulk of the pancreas is made up of pancreatic acini. Acinar cells produce digestive enzymes (e.g. amylase, lipase, trypsin). Tumours arising from these cells are rare and are termed acini cell tumours.

Ducts are responsible for transporting the acinar secretions to the duodenum. The ductal system starts with centroacinar cells through to intralobular and interlobular ducts. The majority of pancreatic cancers arise from the ductal epithelium.

The endocrine cells of the pancreas are arranged in nests of a few hundred cells each termed the Islets of Langerhans. These endocrine cells produce various hormones including insulin, glucagon, somatostatin and pancreatic polypeptide. Pancreatic neuroendocrine tumours may be functional producing some of these hormones resulting in specific clinical syndromes.

PANCREATIC DUCTAL ADENOCARCINOMA

More than 85% of pancreatic cancers are adenocarcinomas arising from the ductal epithelium. It is characterized by an insidious onset in most patients often resulting in advanced disease at the time of presentation.

The incidence of pancreatic adenocarcinomas is increasing. Male and female rates seem to be equivalent with a lifetime risk of about 1 in 95. The incidence increases with age with 80% of cases occurring between 60-80 years.

Pancreatic adenocarcinomas still have a dismal prognosis. Overall five-year survival is less than 5%.

Surgical resection is the only potentially curative treatment. As a result of the late presentation of the disease only about 15-20% of patients are candidates for a potentially curative surgical resection. Even in patients who have surgical resection median survival is only 20 months. This decreases to less than 12 months in patients who have locally advanced disease and less than 6 months if there is metastatic disease.

65% of these cancers are located in the head, 15% in the body, 10% in the tail and 10% are multifocal. Tumours of the body and tail tend to present later and are associated with a worse prognosis

Risk factors

About 5-10% of patients with pancreatic adenocarcinomas have a family history of the disease. Some of these patients may have a well-defined cancer predisposing syndrome such as hereditary non-polyposis colon cancer (HNPCC), Familial Breast cancer (BRCA2 mutation), Familial Syndrome Adenomatous Polyposis (FAP) and Peutz-Jeghers syndrome amongst others. These known cancer predisposing syndromes account for less than 20% of the familial cases. This suggests that other unidentified susceptibility genes exist. Environmental factors have also been implicated as risk factors.

Table 1 Risk factors for pancreatic carcinoma
Predisposing cancer syndrome
Smoking
Chronic Pancreatitis
Possible risk factors
<ul style="list-style-type: none"> • Diabetes mellitus • Obesity

Good evidence of a causative role exists for smoking. The risk increases with greater tobacco use and longer exposure to smoke. Smokers, particularly females have a 2.5% to 3.6% increase in the risk of pancreatic cancer compared to non-smokers.

Chronic pancreatitis is considered a risk factor. Some studies have suggested a 5-15 fold risk compared to normal individuals.

The risk is highest in patients who have hereditary pancreatitis. Hereditary pancreatitis is a rare autosomal dominant condition. It is caused by a mutation in the trypsinogen gene on chromosome 7. The majority of patients with hereditary pancreatitis develop symptoms before the age of 20. These patients have a 40% lifetime risk of developing pancreatic cancer.

It has been suggested that diabetes mellitus is associated with an increase risk of developing pancreatic cancer but diabetes may be a consequence rather than a cause of pancreatic cancer. There is some evidence suggesting that a high fat diet, obesity, previous cholecystectomy, previous distal gastrectomy, caffeine and ethanol may be risk factors.

Clinical Presentation

History

The presenting symptoms depend both on the location of the tumor in the pancreas and the stage of the disease.

Painless obstructive jaundice is common especially with lesions in the head. Tumours arising in the body and tail of the pancreas usually present with vague upper abdominal symptoms mimicking peptic ulcer disease and irritable bowel syndrome. Upper abdominal pain that radiates to the back is common in advanced disease. Pain is thought to be due to involvement of afferent visceral nerves (sympathetic nerves). Severe pain suggests neural involvement and radiates to the back. Patients often present to orthopedic surgeons or chiropractors due to back pain.

Table 2 Clinical Presentation
Painless obstructive jaundice
Upper abdominal pain that radiates to the back
Weight loss
Late onset diabetes
Gastric outlet obstruction
Ascitis
Abdominal mass
Thrombophlebitis migrans
Dyspepsia

Anorexia and weight loss are present in most patients.

Pancreatic cancer is associated with development of diabetes. It should be considered in all patients with late onset diabetes especially if there are no risk factors for diabetes (such as obesity). Vomiting due to gastric outlet obstruction results from infiltration of the duodenum in cases of more advanced disease. Atypical diabetes mellitus (new onset in a thin older adult) precedes the diagnosis of pancreatic cancer in a substantial number of patients. CT screening of all older patients with new onset diabetes mellitus is not cost effective.

Examination

Many patients are emaciated with temporal wasting and other signs of malnutrition. Skin excoriation due to pruritis may be present. This is one of

the most distressing features of biliary obstruction. It is important to check for a Virchow's (left supraclavicular) node, which is associated with upper GIT malignancies. A Sister Mary Joseph nodule is a metastatic umbilical deposit. Both of these signs are a feature of advanced disease.

Courvoisier's Law states that a palpable non-tender gallbladder in the setting of jaundice is usually not due to stones. Many patients who present with these signs have a pancreatic tumour that is obstructing the common bile duct. Ascites indicates peritoneal metastasis and irresectable disease. Deep and superficial venous thrombosis occurs in a minority of patients (thrombophlebitis migrans is a paraneoplastic phenomenon and is referred to as Trousseau's syndrome). It is important to have a high index of suspicion, as many of the symptoms and signs of pancreatic cancer are non-specific.

Investigations

The role of investigations in a patient with suspected pancreatic cancer includes confirmation of the diagnosis, staging of disease and assessment of resectability.

Laboratory studies

Routine blood tests may reveal a rise in serum bilirubin as well as ALP and GGT.

A high CA 19-9 is the most useful tumour marker for pancreatic cancer.

Radiological Investigations

Trans-abdominal ultrasound, CT and MRI/MRCP, ERCP and endoscopic ultrasound all have a role in the diagnosis and staging of pancreatic cancer.

Trans-abdominal ultrasound is a useful initial first investigation in patients presenting with jaundice. It is good at detecting biliary and pancreatic duct

dilation (double duct sign), liver metastasis and ascites. It is not good at detecting pancreatic masses less than 2cm in size or assessment of vascular invasion.

Multiphase (IV contrast) helical computed tomography is the imaging procedure of choice. It allows visualisation of the primary tumour and its relation to the superior mesenteric artery, the superior mesenteric and portal veins as well as distant metastasis. Contrast enhanced CT predicts resectability with 80-90% accuracy.

MRCP is not routinely done but it is useful if there is doubt about the level of biliary obstruction.

ERCP is now reserved in the main for palliative biliary stenting or when there is a suspicion of a periampullary tumour. Endoscopic ultrasound is a useful adjunct to obtain a pre-operative tissue diagnosis and to help with assessment of resectability.

A pre-operative tissue diagnosis is not generally required before surgery but is preferable before commencement of chemo or radiotherapy.

CT PIC — showing double duct sign

Staging laparoscopy

Staging laparoscopy is used selectively in patients with equivocal CT findings, marked weight loss, severe pain or markedly elevated CA19-9 levels. It is used to detect as yet undiagnosed peritoneal deposits or liver metastasis.

Treatment

Surgical Resection Surgical resection is the only potentially curative therapy. Unfortunately less than 20% of patients present with resectable disease.

Factors contraindicating resection are:

- Presence of metastatic disease

- Lymph node involvement (out of the resection margin)
- Major vessel involvement (Superior mesenteric artery, celiac artery, hepatic artery, portal or superior mesenteric veins)
- Co morbid disease.

Approaches for resection are determined largely by the tumor location. Resection of tumours in the head and uncinate process require a pancreaticoduodenectomy (Whipple's procedure) while tumours in the body and tail are managed with a distal pancreatectomy.

Pancreaticoduodenectomy involves resection of the head of the pancreas, duodenum and bile duct. Reconstruction requires three anastomosis to the jejunum; hepaticojejunostomy (hepatic duct), pancreaticojejunostomy (pancreatic duct) and gastrojejunostomy (stomach).

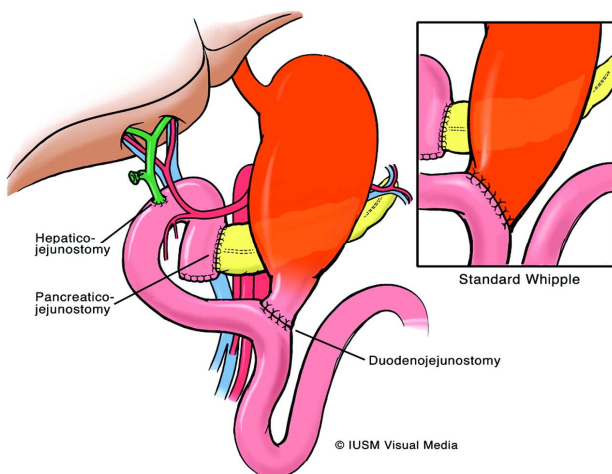


Figure 1 Pylorus preserving pancreaticoduodenectomy (Classic whipple shown in the insert) Note the 3 anastomosis American journal of Roentgenology 2007; 189:1044-1050

Pancreatic resection remains one of the most technically challenging surgical procedures. Pancreaticoduodenectomy carries a 5% perioperative mortality rate in the best centers in the world. Complication rates are reported to be between 30-

60%. The most common surgical related complications are pancreatic fistula, intra-abdominal collections, hemorrhage and delayed gastric emptying.

Five-year survival after a potentially curative resection is less than 15%. The most important good prognostic factors include small tumour size (< 3cm), clear resection margins and no lymph node involvement.

Routine preoperative biliary decompression should only be considered for specific indications such as cholangitis, advanced malnutrition and significant time delay before surgery. This is usually achieved with an endoscopically (ERCP) placed plastic stent. Percutaneous drainage [PTC] is an alternative if this fails.

Palliative Treatment

The majority of patients with pancreatic adenocarcinomas present with advanced disease and palliation of symptoms is the main focus in these patients. The symptoms that most commonly need treatment are obstructive jaundice, gastric outlet obstruction and pain.

- **Obstructive jaundice**
The most distressing feature for patients with obstructive jaundice is pruritus. Most patients are palliated with an endoscopically placed stent. Surgical bypass (hepaticojejunostomy) is now mainly performed in patients who are found to have irresectable disease during an attempt at resection.
- **Gastric Outlet Obstruction**
Gastric outlet obstruction (GOO) can be mechanical or functional. Functional obstruction probably results from tumour infiltration of the celiac nerve plexus. Surgery (gastrojejunostomy) used to be the only treatment option but endoscopic duodenal stenting is

increasingly being used in these patients who often have advanced disease and short survival.

- **Pain Management.**
Pain becomes more of a problem with advanced disease and 90% of patients eventually have moderate to severe pain. Initial medical management is multimodal with use of opiates and non-steroidal anti-inflammatory. Coeliac plexus block is effective in managing pain in patients who do not get relief from medical therapy. It involves injection of ethanol into the coeliac plexus either percutaneously or at the time of surgery.

Chemotherapy

Survival following surgical resection with curative intent is poor even for patients who have a complete (R0) resections. Five-year survival following pancreaticoduodenectomy for patients with node negative and node positive disease is 25% and 10%, respectively.

In an attempt to improve outcomes various adjuvant (following surgery) and neo- adjuvant (before surgery) therapies have been used.

Adjuvant gemcitabine based chemotherapy has become the standard of care.

Median survival following surgical resection increases from 10,4 months to 24,8 months with this therapy. Palliative chemotherapy may provide some improvement in quality of life and a minimal survival benefit. It should be considered especially in patients with good performance status.

PANCREATIC NEUROENDOCRINE TUMOURS

Pancreatic neuroendocrine tumours have an incidence of 1 to 5 cases per million individuals annually. They may present with well-described syndromes due to the hormones they secrete. Nonfunctioning neuroendocrine tumours on the other hand are large

by the time they cause symptoms and present with mass effects. The ideal treatment for neuroendocrine tumours is complete surgical resection as it offers the possibility of cure. Many patients present with irresectable disease. The aim of treatment in these patients is symptomatic control of the hormonal effects of the tumour.

INSULINOMAS

Insulinomas are the most common functioning neuroendocrine tumour of the pancreas. They occur more commonly in females (Male: Female = 2:1) and are most common in patients 40 to 50 years old.

Table 3 Insulinomas
<p>Most common functioning pancreatic neuroendocrine tumour</p> <p>90% Benign</p> <p>Small, solitary and difficult to localize</p> <p>Whipple's triad confirms diagnosis</p>
<p>Symptoms</p> <p>Neuroglycopenic symptoms eg. anxiety, confusion, seizures and loss of consciousness</p> <p>Weight gain</p> <p>Often diagnosed with neurological / psychiatric disorders</p>
<p>Treatment</p> <p>Enucleation often sufficient</p>

90% of these lesions are benign. They tend to be small, solitary lesions that can be difficult to localize. They occur at any position in the pancreas. Excessive insulin secretion results in hypoglycaemia. The differential diagnosis includes reactive hypoglycemia and factitious hypoglycemia.

The classic (Whipple) triad consists of:

- Symptoms of hypoglycaemia
- Concomitant blood glucose level of <5mmol/l
- Relief of hypoglycaemia with glucose administration

The diagnosis is confirmed with elevated C-peptide levels and insulin levels during an episode of hypoglycemia. The neuroglycopenic syndromes are often non-specific (anxiety, confusion, personality changes, seizures, loss of consciousness). Patients are often mistakenly diagnosed as having psychiatric or neurological disorders. These patients often experience weight gain, as they have to eat frequently to prevent hypoglycemia. Symptoms are often worse after fasting or early in the morning.

As insulinomas are usually small and solitary pre-operative localization can be difficult. Ultra-sound and CT combination identifies less than 40%. Octreoscan only detects 50%. The most sensitive test for localising insulinomas is endoscopic ultrasonography.

Most insulinomas can be found during exploration by an experienced surgeon. Many authorities thus argue that extensive efforts at preoperative localisation are unnecessary-except in cases of repeat surgery or MEN-1.

Management

After diagnosis resection is indicated to avoid the permanent neurological deficits that may result from prolonged periods of hypoglycaemia. Patients should consume small frequent meals (even during sleeping hours). Medical therapy consists of diazoxide and verapamil, which decrease insulin secretion. Pre-op patients should be admitted on a dextrose infusion. This should be stopped 2 hours pre op as intraoperative glucose monitoring is used as rough indication of biochemical cure. The tumour appears as brownish-red cherry like mass. In benign insulinomas enucleation is the operation of choice with the goal being to remove the tumour while preserving as much pancreatic tissue as possible. Pancreatic resection is indicated if there is evidence of malignancy

(lymph node involvement, tumour invasion, and liver mets) In cases of metastasis tumour debulking provides symptom relief. Surgical resection can affect a cure in as many as 95% of cases. In the setting of malignancy recurrence rates are in the region of 33%.

GASTRINOMAS

Gastrinomas are the second most common pancreatic endocrine cancer. 75% occur sporadically, 25% in association with MEN-1. There is a slight male predominance in the sporadic form. Gastrinomas are not limited to the pancreas with most occurring in the so-called gastrinoma triangle (see below) While 60% are malignant long-term survival is good. The diagnosis of malignancy cannot be made on histology alone but depends on identification extra pancreatic invasion or of spread to lymph nodes or distant sites Malignancy may be more common in females, MEN-1 and patients with very high gastrin levels

Table 4 Gastrinomas
2 nd most common pancreatic neuroendocrine tumour 75% sporadic, 25% associated with MEN-1 60% Malignant
Symptoms Fulminant peptic ulcer syndrome Peptic ulcers that are refractory to normal treatment Diarrhea (improves with PPI or NG tube)
Treatment High dose PPI Exclude MEN -1 Surgical excision

The gastrinoma syndrome is due to excessive an autonomous release of gastrin resulting in gastric acid hypersecretion and fulminant peptic ulcer disease (Zollinger-Ellison Syndrome). The advent of proton pump inhibitors has decreased the

fulminating nature of this disease. The main symptoms are those associated with peptic ulcer disease. 75% of patients have epigastric pain. Nearly 66% of patients have diarrhea 10% have diarrhoea as the only complaint. A unique characteristic of this diarrhoea is that it resolves with nasogastric drainage or proton pump inhibitors. Clues suggesting a gastrinoma include peptic ulcers refractory to medical therapy, peptic ulcers at unusual sites, absence of risk factors for peptic ulcers (e.g. H.pylori, NSAID use) and a secretory diarrhea that resolves with a NG tube or proton pump inhibitor.

The diagnosis is established by showing:

- Gastric Acid Hypersecretion (>15mEq/hr)
- Hypergastrinaemia (fasting level >500pg/ml)
- Patients should have stopped PPI's and H2 blockers one week prior to testing.

Management

Aims of treatment are two fold:

- Control hypersecretion of acid.
- Removal of tumour to effect cure or alter the natural history of the condition.

Although death from complications of ulcer disease was previously common, the development of potent antisecretory medicines has meant that tumour progression and metastasis are the most common cause of death. All patients should be started on antisecretory medication at the time of diagnosis (high dose PPI). It is generally accepted that surgery benefits all patients with a sporadic gastrinoma. The role of surgery in patients with MEN1 is debatable as there is less likelihood of obtaining biochemical cure and the course tends to be more benign. The use of endoscopic ultrasound and octreotide scanning means that preoperative

localisation is successful in up to 90% of cases. Most gastrinomas are located in the so-called gastrinoma triangle, which is bounded by:

- The cystic duct
- The borders of the 2nd and 3rd part of the duodenum
- The junction of the neck and body of the pancreas

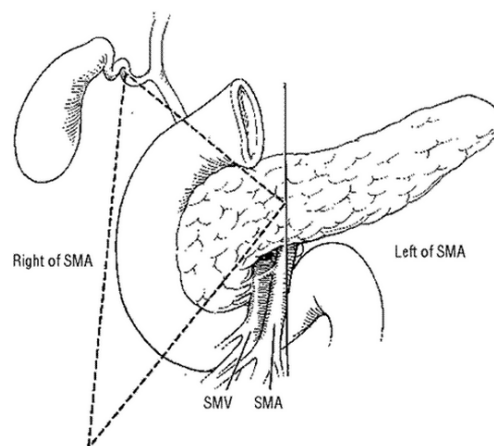


Figure 2 The Gastrinoma Triangle. Archives of surgery 1998; 138 (1):13-16

If preoperative localisation is not possible intraoperative localisation using combination of palpation, endoscopic transillumination and ultrasound should be attempted. If still not localised a longitudinal duodenotomy along the antimesenteric boarder of the 2nd part of the duodenum often facilitates localisation. Small well encapsulated pancreatic tumours are managed with enucleation. Large, poorly encapsulated lesions are managed with distal pancreatectomy or rarely pancreaticoduodenectomy — depending on location.

GLUCAGONOMA

These are rare tumours. Patients with the glucagonoma syndrome suffer from cachexia, malnutrition and protein depletion (protein catabolism necessary to sustain gluconeogenesis). Other features include a characteristic rash (necrolytic migratory erythema—

vesiculopustular rash on the groins) glucose intolerance and deep venous thrombosis. Many patients present late in the course of the disease, with tumour size averaging 5cm at the time of diagnosis and commonly with metastasis. Localisation is usually possible with a contrast CT scan. Complete surgical resection is the only possibility of a cure — this is possible in less than 30% of cases. Even if complete resection is not possible palliative debulking is indicated for symptomatic relief.

NON-FUNCTIONING NEUROENDOCRINE TUMOURS

These are the most common pancreatic neuroendocrine tumour. They are equally common in males and females with a peak incidence in the 40's and 50's. These patients do not present with an identifiable syndrome like the functional tumours. They are often diagnosed as large palpable masses or due to compressive symptoms. Metastatic disease is present in 60% of patients at the time of diagnosis. Complete surgical resection offers the only possibility of a cure.

CYSTIC NEOPLASMS OF THE PANCREAS

Pancreatic cysts are being diagnosed with increased frequency due to improved imaging techniques. More than 90% of pancreatic cysts are pseudocysts associated with acute or chronic pancreatitis. Before making the diagnosis of a pseudocyst it is important to consider if the cyst is in fact neoplastic (especially if there is no preceding history of pancreatitis).

There are four main types of pancreatic cystic neoplasms:

- Serous cystic neoplasms
- Mucinous cystic neoplasms
- Intraductal papillary mucinous neoplasms

- Solid pseudopapillary neoplasms

Serous cystic neoplasms

These tumours are most common in the seventh decade and are more common in females. They are solitary and microcystic. The epithelial cells are cuboidal, with glycogen rich cytoplasm. The cyst fluid is clear and contains no mucous. These tumours are benign and do not undergo malignant transformation. Surgical intervention would only be considered for large or symptomatic tumours.

Mucinous cystic neoplasms

These tumours are most common in perimenopausal females (>95% female, mean age 50y). They are macrocystic and lined by columnar mucin producing cells with an "ovarian-type" stroma. The cyst fluid is viscous, filled with mucin-related glycoproteins and has high CEA levels. Mucinous cystic neoplasms have malignant potential and may give rise to an invasive carcinoma that resembles ductal adenocarcinoma. For this reason it is recommended that these lesions be resected.

Intraductal papillary mucinous neoplasms [IPMN]

These tumours are more common in men with a peak incidence in the sixties. They are characterised by ductal dilatation and mucin production. Mucin exudes from the ampulla, which is patulous with a fish eye appearance. This finding at ERCP is almost diagnostic. These lesions undergo malignant transformation. Cure requires complete surgical resection; this may require a total pancreatectomy.

Solid Pseudopapillary Tumour

80% of these tumours occur in females with a mean age of 25. Despite being malignant they tend to follow an indolent course with only

15% of patients developing metastasis. These tumours tend to be large at the time of diagnosis and patients may present with a palpable mass or compressive symptoms. Surgical resection is curative.

Acinar Cell Tumours

Acinar cell tumours are rare. They may produce various pancreatic enzymes such as lipase, trypsin and chymotrypsin. About 10% of patients develop a lipase hypersecretion syndrome characterised by subcutaneous fat necrosis, polyarthralgias and eosinophilia. These tumours are clinically aggressive with a prognosis only slightly better than pancreatic ductal adenocarcinoma.



This work is licensed under a [Creative Commons Attribution 3.0 Unported License](https://creativecommons.org/licenses/by/3.0/).