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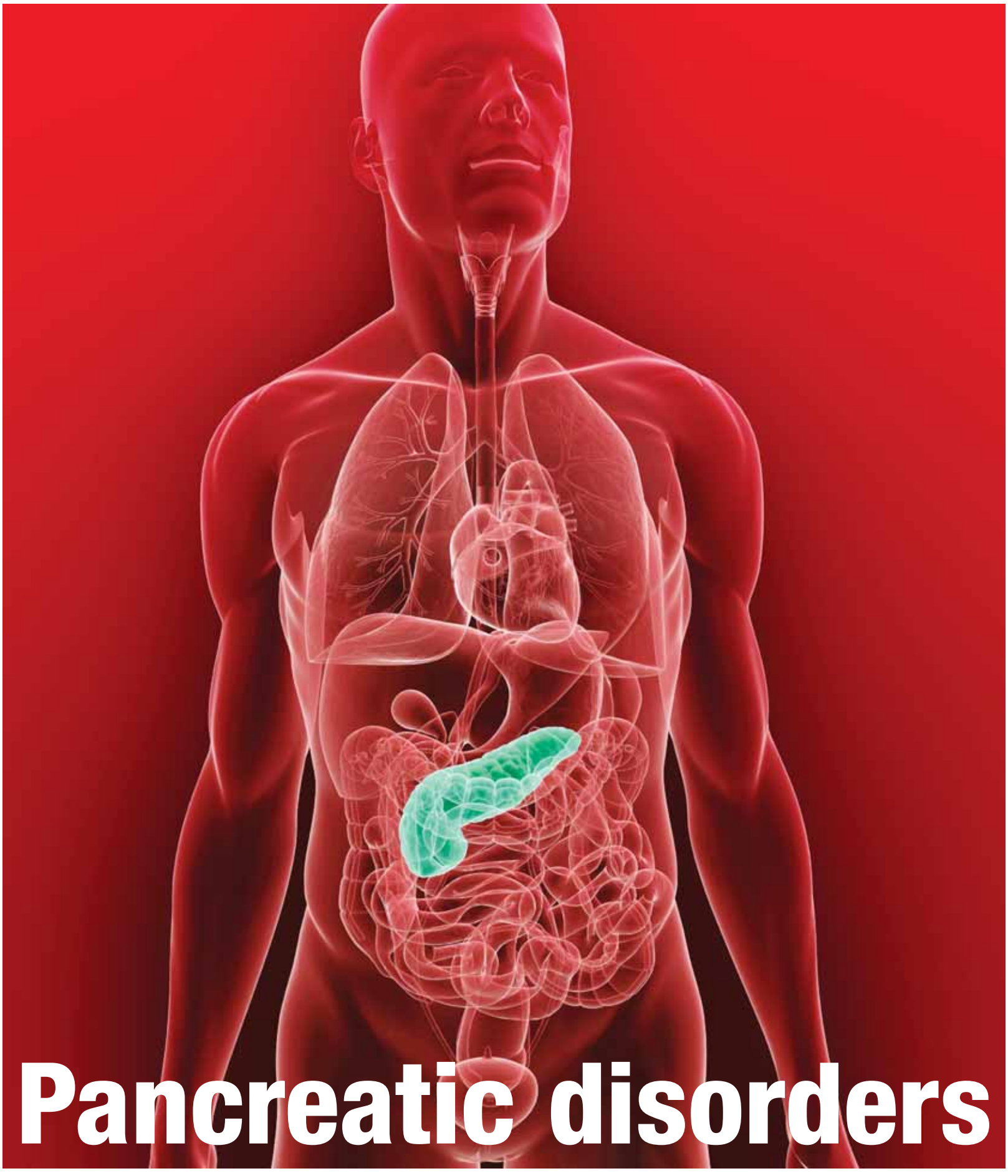

Pancreatic disorders

This article discusses the diagnosis and management of the most common and important pancreatic disorders: acute pancreatitis, chronic pancreatitis and pancreatic cancer.

Acute pancreatitis

Pathology and aetiology

ACUTE pancreatitis is the sudden onset of inflammation of the pancreas that may involve, to varying degrees, the surrounding tissues or other organ systems. In Western societies about 80% of the acute pancreatitis cases are caused by gallstones (biliary pancreatitis) or excessive alcohol consumption. The other 20% are caused by rarer causes and idiopathic pancreatitis (see box, next page).

Gallstones

Gallstones are the most common cause of acute pancreatitis in our society. The mechanism is not fully understood. It is thought that gallstones travel down the common bile duct then into the channel that drains the common bile duct and the pancreatic duct, causing transient obstruction of the pancreatic duct. This obstruction leads to the activation of pancreatic pro-enzymes within the acinar cells by intracellular lysosomal enzymes, leading to 'auto-digestion' and thus acute pancreatitis. Smaller gallstones are more likely to cause pancreatitis than larger gallstones, as they are more likely to escape the gallbladder through the narrow cystic duct.

Alcohol

Alcohol is the second most common cause of acute pancreatitis and is the most common cause of chronic pancreatitis. The patients are usually young men who consume more than 80g of alcohol a day. However, the aetiology of alcoholic pancreatitis is thought to be multifactorial (genetic, environmental, etc), as there is not a clear dose-dependent relationship as there is for alcoholic liver disease.

The mechanism of how alcohol induces acute pancreatitis is still unclear. It is thought that alcohol increases the sensitivity of acinar cells to cholecystokinin hyperstimulation,

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inside

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resulting in increased intracellular protease activation. However, several other theories have also been hypothesised.

Other causes

Other causes of acute pancreatitis are shown in the box below.

Clinical presentation

Patients usually present with an acute onset of epigastric pain that may radiate to the back and is relieved by leaning forward. The pain is usually severe, hence patients usually present themselves to hospital rather than to their GP. Some patients may volunteer a history of binge alcohol consumption that occurs before the onset of pain. Associated symptoms include nausea, vomiting, anorexia and diarrhoea. There may be fever, chill or rigors.

On examination, patients may display varying degrees of change in vital signs, and there is tenderness in the epigastric area. In severe pancreatitis, Grey–Turner's (haemorrhagic discolouration of the flanks) or Cullen's (haemorrhagic discolouration of the umbilicus) signs may be observed. Patients may sometimes present with haemodynamic instability or even in a state of profound shock in extreme cases.

Investigations

Blood tests

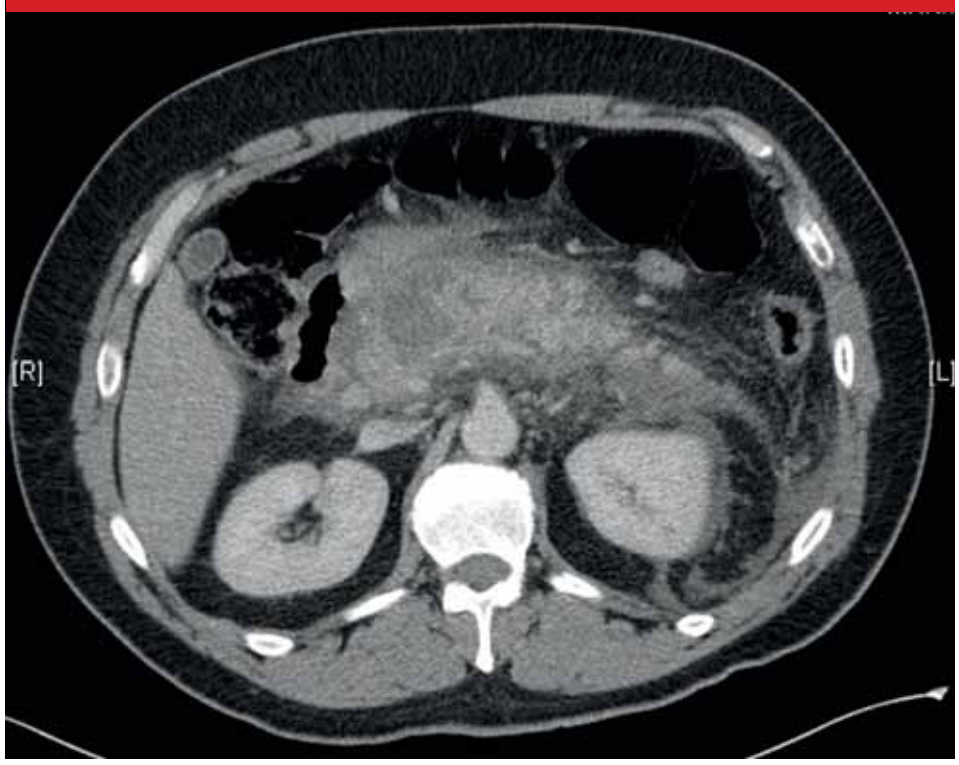
These may include FBC, EUC, LFTs, amylase, lipase, calcium, BSL, CRP, lipid profile and arterial blood gases.

An elevated serum amylase and/or lipase level (higher than three times normal) supports the diagnosis of acute pancreatitis in most cases. However, one should keep in mind that there are other conditions that can cause mildly elevated amylase and/or lipase with epigastric pain, such as peptic ulcer disease or perforation, cholecystitis, appendicitis and ischaemic bowel. If there is doubt regarding the diagnosis, an abdominal CT scan should be performed to rule out other possible causes.

Abdominal ultrasound

All patients with acute pancreatitis should have an abdominal ultrasound within the first 24 hours to assess the biliary tree, looking for any evidence of cholelithiasis, choledocholithiasis and/or dilation of the common bile duct. In the acute setting, accurate assessment may be difficult due to overlying bowel gas and abdominal tenderness. Therefore, abdominal ultrasound should be repeated once pancreatitis has resolved if the initial one is negative and no other causes are identified.

Figure 1: CT showing a lesion in the head of pancreas causing proximal dilatation in the pancreatic duct.



Causes of acute pancreatitis

Alcohol
Gallstones
Other
— medications: diuretics (thiazide and frusemide), antibiotics (metronidazole and tetracycline), steroids, azathioprine and sodium valporate
— iatrogenic causes: 3% of endoscopic retrograde cholangiopancreaticography (ERCP) when sphincterotomy has been performed
— tumour of the pancreas or ampulla of Vater, leading to pancreatic ductal obstruction
— viral infections: mumps, coxsackie B and viral hepatitis
— autoimmune pancreatitis: part of the IgG4-related autoimmune disease spectrum; can sometimes be confused with pancreatic malignancy
— blunt trauma to abdomen, such as crush injury of the pancreas against the body of the vertebral column
— hyperparathyroidism, leading to hypercalcaemia
— hyperlipoproteinaemia
— anatomical variant such as pancreatic divisum
— genetic defects such as mutations in the cystic fibrosis gene (CFTR)
— sphincter of Oddi dysfunction, leading to abnormal sphincter manometry

Patients usually present with an acute onset of epigastric pain that may radiate to the back and is relieved by leaning forward.

Computed tomography

Apart from establishing a diagnosis and excluding other causes of abdominal pain, contrast-enhanced CT may be used to detect complications of pancreatitis such as pancreatic necrosis (figure 1). Although less commonly used in Australia, a CT severity index derived using the presence of fluid collection and/or the presence or extent of necrosis can be used to predict the severity of pancreatitis. CT should be performed at least 48 hours after the onset of the symptoms, as early CT can be falsely negative. CT cholangiography can also be used to detect choledocholithiasis.

Other imaging modalities

These include:

- Magnetic resonance cholangiopancreaticography (MRCP): as endoscopic retrograde cholangiopancreaticography (ERCP) is now primarily a therapeutic tool, MRCP is increasing being used to assess choledocholithiasis and pancreatic duct anatomy.
- EUS (endoscopic ultrasound): this is an emerging imaging modality increasingly being used to diagnose microlithiasis, as well as for therapeutic purposes, such as drainage of peri-pancreatic fluid collections.

Severity

Several prognostic predictors have been developed to assess the severity of acute pancreatitis and help predicting patient outcomes.

C-reactive protein

CRP is an acute reactive protein, and patients with CRP >150mg/L are classified as having severe acute pancreatitis. However, serum CRP levels do not usually peak until about 48 hours after the onset of symptoms, and its level usually lags behind the clinical picture by that time. Its levels can also be used to monitor the clinical course of the disease.

Ranson's criteria

This uses various haematological (white cell count, haematocrit), biochemical (BSL, AST, LDH, blood urea nitrogen and base excess) and patient (age, fluid deficit, and arterial oxygen tension) parameters at admission and at 48 hours after admission to predict patient outcomes.

Management

Initial management

This includes identifying and reversing organ failure, regardless of the aetiology. Renal and respiratory systems are the most common systems involved. Patients with severe acute pancreatitis should be managed in a high-dependency or intensive care unit.

Aggressive fluid resuscitation with 6-10L of fluid in the first 24 hours is often required. Humidified oxygen should also be used for respiratory support. Vital signs, urine output, pulse oximetry and arterial blood gas for acid–base balance should be closely monitored. In some cases a central venous catheter may be inserted to measure central venous pressure.

If patients continue to deteriorate, more invasive measures such as mechanical ventilation, inotrope support and renal dialysis may be needed.

Continuing management

Prophylactic antibiotics. The role of antibiotics in preventing infection is controversial. Currently the routine use of prophylactic antibiotics in the management of acute pancreatitis is not recommended. If they are used, it should only be for a defined period of time.

Nutrition. Severe acute pancreatitis is a long and debilitating disease associated with a severe catabolic state, and nutritional support is urgently required. Substantial evidence supports the use of enteral feeding rather than total parenteral nutrition because it reduces total parenteral nutrition-related morbidity as well as costs. Enteral feeding and use of probiotics may help maintain gut barrier function and reduce the risk of endotoxaemia and systemic inflammatory syndrome.

Definitive management

ERCP. The use of ERCP in acute pancreatitis has also been much debated. Current best practice is that only patients with acute biliary pancreatitis (eg, due to gallstones) who also have acute cholangitis (fever, right upper-quadrant pain, jaundice, leucocytosis, obstructive pattern of LFTs) should undergo urgent ERCP and sphincterotomy.

Cholecystectomy. The gallbladder should be removed to prevent further attacks of biliary pancreatitis. For patients with mild acute pancreatitis, the gallbladder should ideally be removed during the same admission. However, if it is not possible, it should be performed preferably within the first four weeks after discharge.

Management of complications

Complications of acute pancreatitis include pancreatic pseudocyst, necrosis or abscess, and less commonly, haemorrhage, left-sided portal hypertension and pancreatic duct stricture.

Pancreatic pseudocysts. Peripancreatic fluid collections are detected on CT in 25% of patients with acute pancreatitis. Most of these collections require no intervention and resolve spontaneously. It is recommended to manage these fluid collections conservatively for at least 12 weeks. However, if conservative management fails, they may be drained percutaneously, endoscopically or surgically. The route of drainage depends on the contents of the pseudocyst and whether they are infected.

Pancreatic necrosis. Necrosis of the pancreas and peripancreatic tissue may occur after acute pancreatitis. If the necrosis is sterile and the patient is stable, the patient should be managed conservatively for as long as possible.

The rationale is that pancreatic necrotic tissue becomes organised as it 'matures' and ultimately the solid necrotic tissue liquefies and becomes a pseudocyst, which can be dealt with definitively as above. This is much simpler than necrosectomy.

However, if the patient has organ failure despite support and this is thought to be due to infected necrosis, necrosectomy may be necessary. This may be carried out via an open laparotomy or using a minimally invasive (percutaneous or endoscopic) approach.

Management of causes of acute pancreatitis

To avoid further attacks, the causes of acute pancreatitis should be treated, for example:

- Removal of the gallbladder (see above).
- Avoidance of alcohol.
- Rationalisation of medications.
- Treatment of hyperlipidaemia.

However, for patients with recurrent pancreatitis without an identifiable cause even after CT, MRCP/ERCP and EUS, a laparoscopic cholecystectomy or biliary sphincterotomy may be considered.

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Chronic pancreatitis

Background

CHRONIC pancreatitis is defined as a continuing chronic inflammatory condition of the pancreas, characterised by irreversible morphological changes of the pancreatic parenchyma, with replacement of glandular tissue by fibrosis. The incidence is about 13 per 100,000 population in Western societies. The most common symptoms on presentation are abdominal pain and/or loss of exocrine or endocrine functions secondary to parenchymal damage.

Pathology and aetiology

Alcohol abuse

Excessive alcohol consumption accounts for 60% of the cases of chronic pancreatitis in the Western world. The exact mechanism is still uncertain. However, the 'necrosis–inflammation– fibrosis' sequence is the currently accepted hypothesis. It involves repeated injury to the pancreatic parenchyma by alcohol, causing in turn recurrent cycles of inflammatory and fibrotic responses. Interestingly, only a small proportion of the general population with alcoholism develop chronic pancreatitis, leading to the hypothesis that other factors contributing to the individual's sensitivity to alcohol may be present.

Idiopathic

About 20% of patients with chronic pancreatitis are thought to have idiopathic disease. However, some of the previously thought idiopathic cases have now been found to have a hereditary cause (see below).

Hereditary

Hereditary chronic pancreatitis is a rare autosomal dominant disease that accounts for about 1% of cases. Mutations in the *PRSS1* and/or *SPINK1* genes render the enzyme cationic trypsinogen resistant to inactivation, leading to autolysis of the pancreas. Patients with hereditary chronic pancreatitis are found to have a 50-fold increase in the chance of developing pancreatic cancer.

Another hereditary cause is mutations in the *CFTR* gene that causes cystic fibrosis. A large number of the *CFTR* gene mutations have been identified and some of these genotypes result in less severe respiratory disease but are more likely to cause pancreatitis.

Autoimmune

Autoimmune pancreatitis is an uncommon but increasingly recognised form of chronic pancreatitis. It is characterised by enlargement of the pancreas and diffuse irregular narrowing of the pancreatic duct. It is associated with elevated serum IgG4 level and can also be present with other autoimmune diseases.

Figure 2: Endoscopic retrograde cholangiopancreaticography (ERCP) showing a lesion in the head of pancreas causing common bile duct obstruction and dilated bile duct proximally.

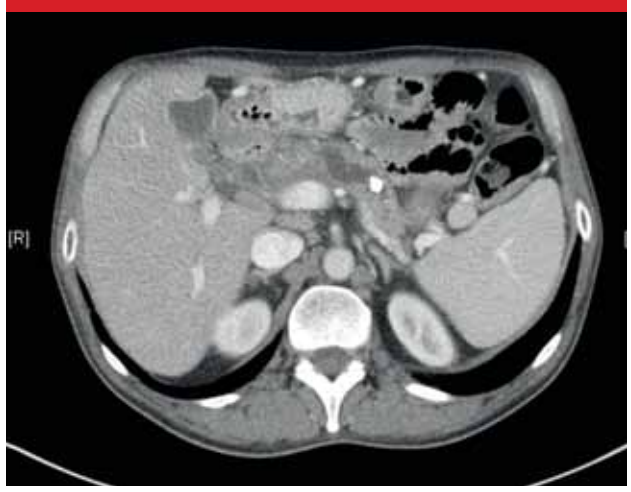
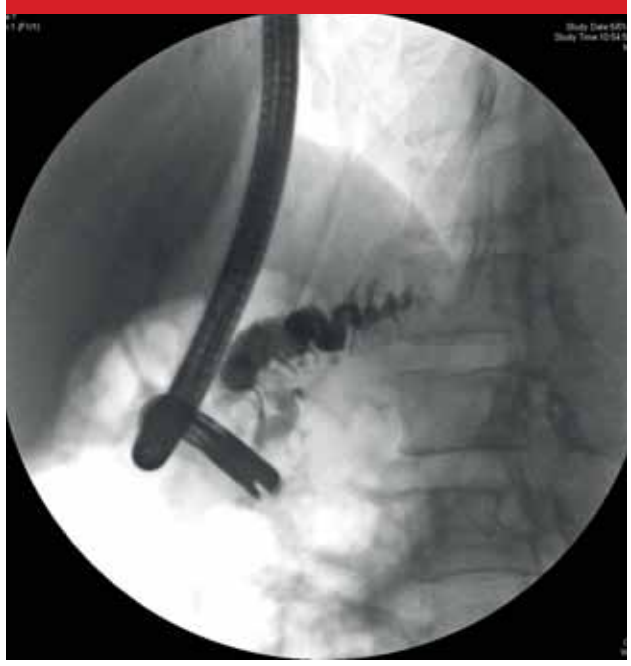


Figure 3: Chronic pancreatitis on ERCP.



Excessive alcohol consumption accounts for 60% of the cases of chronic pancreatitis in the Western world.

Others

Obstructive. Obstruction to the pancreatic duct may also cause pancreatitis. The causes may include pancreatic cancer, intraductal neoplasms, duct disruption from previous attacks, and congenital conditions such as pancreatic divisum.

Tropical. Tropical pancreatitis is rare in Australia but, as the name implies, it is prevalent in some countries near the equator. Nutritional factors such as dietary toxins and micronutrient deficiencies are thought to play a major role in the pathogenesis.

Miscellaneous. Other causes of chronic pancreatitis include hypercalcaemia associated with hyperparathyroidism, hyperlipidaemia and medications.

Clinical presentation

Pain

Pain is the most common and debilitating symptom for patients with chronic pancreatitis. The pain may range from episodic attacks that last for days to weeks with pain-free intervals, to severe and relentless pain. It is usually epigastric, radiates to the back, and may have associated nausea and vomiting. The pain may decrease over time as the pancreas 'burns out'.

Pancreatic exocrine/endocrine deficiency

The gradual replacement of the pancreatic parenchymal tissue by fibrosis leads to pancreatic insufficiency, which is usually a late complication of the disease. The deterioration in exocrine enzyme production leads to steatorrhoea, which is pale, bulky or oily stool that is offensive in smell and difficult to flush down the toilet. Diabetes may also occur and patients usually require insulin, as both the production of insulin and glucagon are reduced.

Signs

Patients may present with evidence of weight loss and signs of malnutrition. They may also present with evidence of complications of chronic pancreatitis such as abdominal mass, jaundice, gastric outlet obstruction, splenomegaly and signs of the chronic liver disease associated with chronic alcohol abuse.

Investigations

The diagnosis of chronic pancreatitis requires good history taking, imaging and some laboratory tests. While advanced chronic pancreatitis is relatively easy to identify on imaging, early chronic pancreatitis with minimal changes can be a diagnostic challenge.

Laboratory tests

There is no single specific test for the diagnosis of chronic pancreatitis. The serum amylase or lipase levels may be normal or only slightly elevated during attacks as the pancreas is replaced by fibrotic tissue.

Measurement of three-day faecal fat, levels of faecal elastase-1 and serum trypsinogen may sometimes be necessary to assess exocrine insufficiency.

If alcohol has not been identified as the cause of chronic pancreatitis, extensive investigations should be carried out before labelling patients as having idiopathic pancreatitis. These may include:

- Serum calcium.
- Lipid profile.
- CA19.9 (a marker of pancreatic carcinoma as well as other malignancies).
- IgG4.

If investigations looking for causative factors are exhausted and a hereditary/ genetic factor is suspected, patients may need to be referred to a genetic counsellor.

With the improvement in imaging techniques, pancreatic function tests are rarely performed now.

Imaging studies

Plain abdominal X-ray. Diffuse calcification detected in the pancreas on plain abdominal X-ray is considered diagnostic of chronic pancreatitis. However, when these calcifications are absent, abdominal X-ray is not a useful diagnostic test.

CT/MRI. Contrast-enhanced CT performed using a pancreatic protocol can reliably demonstrate features of chronic pancreatitis, which include pancreatic atrophy, calcification and pancreatic duct dilatation for making the diagnosis with high sensitivity and specificity (figure 2).

CT can also be used to detect complications of chronic pancreatitis such as pseudocyst, splenic or portal vein thrombosis, pancreatic mass and gastric outlet obstruction. MRI may be used instead of CT in patients with iodine contrast allergy.

ERCP/MRCP. ERCP is an accurate endoscopic test in the diagnosis of chronic pancreatitis (figure 3). However, due to its associated risk of iatrogenic acute pancreatitis, it has virtually been replaced by magnetic resonance cholangiopancreatography (MRCP) as a diagnostic tool, with ERCP now reserved for interventions only.

Endoscopic ultrasound. EUS is increasingly being used in the diagnosis of chronic pancreatitis, as it can visualise the pancreatic parenchyma and ductal system simultaneously. It can make a reliable diagnosis with high sensitivity and specificity and also has the advantage of allowing a fine-needle aspiration to be performed if necessary.

Histology

Histology is the 'gold standard' for diagnosing chronic pancreatitis. Typically, inflammatory infiltrate (mainly T cells) and connective tissue is seen between acini, which gradually disappear as they are replaced by fibrotic tissue.

Management

The three main treatment goals are the management of pain, malnutrition and complications. Chronic pancreatitis is best managed in high-volume multidisciplinary centres.

Management of pain

Pain is the most debilitating factor in patients with chronic pancreatitis and has a great impact on the quality of life. Patients with alcohol as the aetiology should be advised to abstain from alcohol to reduce the risk of further attacks. NSAIDs and opioids may be used for pain control. The use of pancreatic enzyme replacement therapy to control pain is controversial.

More invasive options may include CT or EUS-guided coeliac plexus block and thoracoscopic splanchnectomy. Surgery is sometimes necessary (see below).

Management of malnutrition

Fat malabsorption is the hallmark of exocrine insufficiency of chronic pancreatitis. Steatorrhoea is characterised by excessive fat excretion of >15g/day. For treatment, oral pancreatic enzyme replacement therapy such as Creon is required with each meal.

Acid suppression medications such as proton-pump inhibitors may be necessary for patients who continue to have pancreatic exocrine insufficiency despite high-dose enzyme replacement. This is because the low pH in the stomach may break down and inactivate the replacement enzymes prematurely. Recommendations for the management of pancreatic exocrine insufficiency were published by the Australasian Pancreatic Club recently (see Online resources, page 36).

Diabetes secondary to chronic pancreatitis can be brittle and does not usually respond to oral hypoglycaemics. Insulin is usually required.

Management of complications/surgery

Complications of chronic pancreatitis may include biliary and duodenal obstruction, pseudocysts, left-sided portal hypertension secondary to splenic vein thrombosis and pancreatic ascites.

Unresolved obstructions may have to be bypassed surgically with a hepaticojejunostomy and gastroenterostomy. Bleeding from gastric varices that form as a consequence of left-sided portal hypertension secondary to splenic vein thrombosis should be treated with a distal pancreatectomy and splenectomy.

Pancreatic pseudocysts that do not settle down with conservative management can be drained into the gastrointestinal tract either endoscopically or surgically.

Pain associated with a dilated pancreatic duct or a pancreatic mass can also be managed surgically. However, the degree of pain relief after surgical drainage procedures is variable.

Pancreatic cancer

Background

PANCREATIC cancer remains a highly lethal disease despite advances in the treatments of several other cancer types. It is the 11th most common cancer in Australia, with an incidence of 10 per 100,000 population (2181 new cases in 2005).[1]

However, as the fourth most common cause of cancer-related death, it presents a significant burden on society. The overall five-year survival is poor at about 5%, with almost 90% dying within a year of diagnosis and a consequent death-to-incident ratio (the ratio of the number of patients who have died to the number of patients diagnosed with the condition per year) approaching one. This mortality rate has changed very little in almost 50 years.

Surgical resection remains the only chance of cure, with chemotherapy and radiotherapy offering only a modest survival benefit. Unfortunately most patients (>80%) present in an advanced stage that is not amenable to surgery, due largely to the lack of early warning symptoms or any effective screening strategies. Therefore GPs play a crucial role in identifying at-risk populations and recognising subtle patient complaints that may be of pancreatic origin.

Pathogenesis and aetiology

Cancers of the pancreas can be broadly divided into those of endocrine and those of exocrine differentiation. Here we focus on cancer of exocrine origin, which constitutes most pancreatic cancer (>90%).

Pancreatic cancer, like many other cancers, is caused by complex interactions between environmental factors and genetic susceptibility.

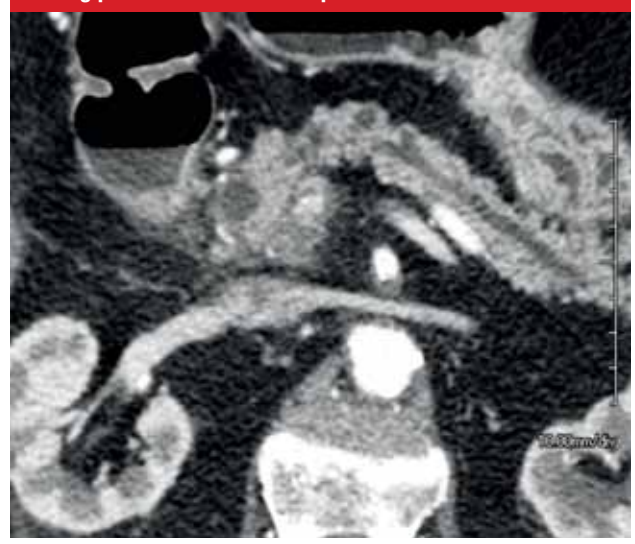
Environmental factors

Cigarette smoking is a major risk factor for pancreatic cancer. Smokers have a significantly increased risk (odds ratio 1.77) compared with never smokers.[2] However, this risk is normalised 15 years after smoking cessation.

Other risk factors include increased BMI, occupational exposure to chemicals such as beta-naphthylamine and benzidine, and chronic pancreatitis.

The relationship between diabetes mellitus and pancreatic cancer is less well defined. The association between longstanding diabetes and pancreatic cancer is modest and diminishes with time. On the other hand, there is an association between new-onset diabetes and the development of pancreatic cancer. Therefore, new onset diabetes may be a manifestation of pancreatic cancer, or it may be linked aetiologically to pancreatic cancer, making patients newly diagnosed with diabetes an at-risk group.

Figure 4: CT scan showing a lesion in the head of pancreas causing proximal dilation in the pancreatic duct.



The value of axial imaging such as CT in every patient with new-onset diabetes to screen for pancreatic cancer is still unclear, although there is some evidence to suggest that such individuals, particularly men, should be included in populations targeted for screening.

Genetic predisposition

True familial pancreatic cancer is uncommon, with 10% of pancreatic cancer thought to be familial. Susceptible individuals may be part of inherited cancer syndromes, but most patients are from families with unknown suspected germline mutations. The known inherited cancer syndromes include:

- Peutz–Jeghers syndrome (*STK11/LKB1* mutation).
- Familial breast cancer (*BRCA1* and *BRCA2* mutations).
- Familial atypical multiple mole melanoma syndrome (with p16 mutation).
- Hereditary pancreatitis (*PRSS1* mutation).

Guidelines have been proposed for pancreatic cancer surveillance in these at-risk individuals.[3]

Clinical presentation

Clinical presentation may include:

- Weight loss.
- Jaundice.
- Abdominal or back pain.
- Dyspepsia.
- Nausea.
- Depression.

It is important to have a level of clinical suspicion in patients presenting with any non-specific abdominal symptoms that persist.

As noted in the previous section, new onset of adult type 2 diabetes in younger patients may be linked to a diagnosis of pancreatic cancer. Hence the diagnosis of pancreatic cancer should be considered in patients with diabetes with unusual manifestations, such as abdominal symptoms and continuing weight loss.

Diagnosis and staging investigations

Patients should be evaluated initially by CT using a pancreatic protocol. CT is the most widely available and best-validated imaging modality for diagnosing and staging patients with pancreatic cancer. A pancreatic protocol involves triple-phase (arterial, late arterial and portal venous) imaging with thin slices (figure 4).

The late arterial phase provides the greatest difference in contrast enhancement between normal pancreatic parenchyma and pancreatic adenocarcinoma. The various phases also provide crucial information on the relationship between the tumour and surrounding arterial (coeliac axis, hepatic and superior mesenteric arteries) and venous (superior mesenteric, splenic and portal veins) structures.

Therefore, in addition to providing a diagnosis, CT also provides staging and information on the suitability for surgical resection if the tumour is localised. However, decisions concerning resectability and further management should only be made in the setting of a multidisciplinary treatment clinic.

Baseline blood tests include:

- FBC.
- Electrolytes.
- Renal function.
- LFTs.
- Amylase or lipase.
- Coagulation profile.
- CA19.9.

The tumour marker CA19.9 is the only FDA-approved pancreatic cancer biomarker. However, there are several limitations with CA19.9. First, it is detectable at basal levels in healthy patients, so its value needs to be correlated to radiological findings.

Second, it can be elevated in benign disease such as pancreatitis, obstructive jaundice caused by choledocholithiasis, and cirrhosis, and values are falsely elevated in cancer patients with obstructive jaundice. Therefore the cut-off value for diagnostic purposes needs to be modified to improve the sensitivity of the test in this setting.

Figure 5: ERCP showing a lesion in the head of pancreas causing common bile duct obstruction and dilated bile duct proximally.

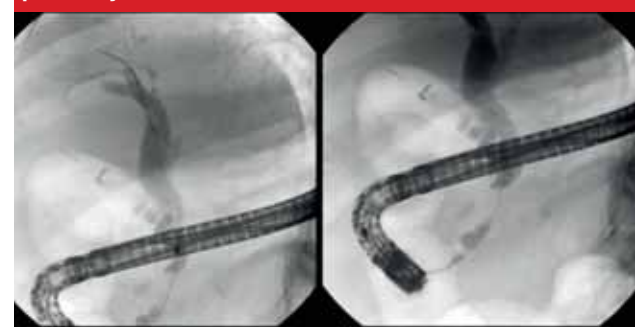
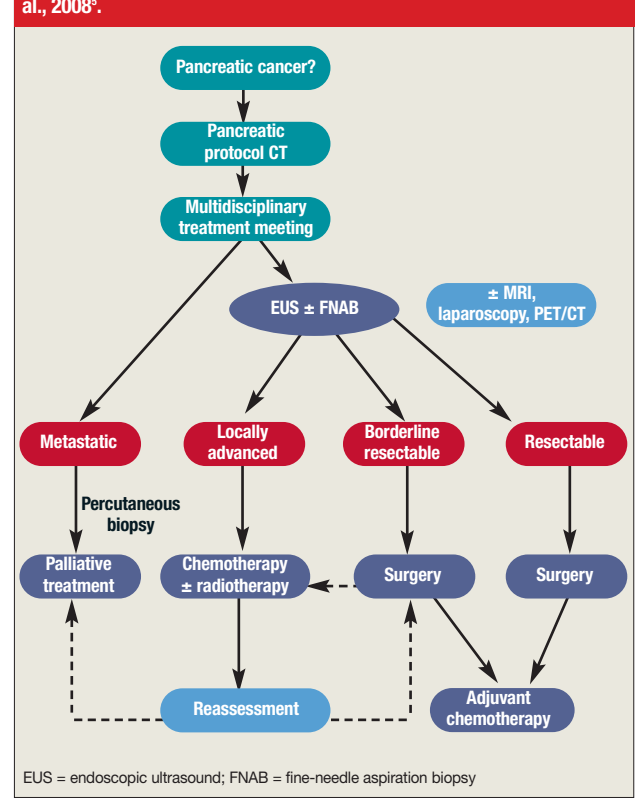


Figure 6: EUS showing a needle biopsy of a pancreatic lesion.

Figure 7: Management of patients with suspected pancreatic cancer and stage-specific treatment plan. Modified from Chang et al., 2008[5].



EUS = endoscopic ultrasound; FNAB = fine-needle aspiration biopsy

Third, 5-10% of the Caucasian population has the Lewis-antigen-negative, Le(a–b–), blood group, lacking fucosyltransferase and hence cannot synthesise CA19.9. Therefore CA 19.9 cannot be used as a biomarker in these patients. CA19.9 is not recommended as a screening test.[4]

Patients with any pancreatic mass or cyst abnormality should be referred to a pancreatic multidisciplinary treatment group or a surgeon who specialises in pancreatic disease and treats patients in a multidisciplinary environment. Advances in surgical techniques and perioperative care have seen a dramatic decrease in the morbidity and mortality rate (about 3%) in high-volume multidisciplinary centres.

Additional blood tests and/or imaging and staging procedures may then be undertaken to further evaluate the lesion. These are individualised for each patient and may include:

- MRI.
- EUS.
- PET or CT.
- Laparoscopy.
- ERCP (figure 5).

MRI should be reserved for patients with iodine contrast allergy or who cannot be exposed to radiation, or used as an adjunct to CT in patients with suspicious liver lesions that need to be better characterised.

EUS may be used as an adjunct to CT/MRI for local staging and assessment of resectability if the results of non-invasive imaging modalities are inconclusive. It should also be used in patients with a high clinical suspicion of a lesion that has not been clearly demonstrated using other modalities.

The other advantage of EUS is the ability to perform fine-needle aspiration (FNA) biopsy (figure 6). EUS-FNA should be the biopsy technique of choice in patients in whom a tissue diagnosis or tissue from regional lymph nodes may alter the course of treatment, or if neoadjuvant treatment (eg, chemoradiation before surgery) is contemplated.

The role of PET/CT in pancreatic cancer is still evolving. It is not currently rebateable under the MBS in Australia. However, PET/CT may potentially be used selectively, for example, when metastatic disease is suspected but has not been demonstrated with other imaging modalities, or if radiotherapy is being considered (to ensure there is no metastatic disease).

Diagnostic laparoscopy is a useful staging tool in identifying sub-radiological metastatic disease even after a high-quality pancreatic protocol CT scan. The yield varies, so whether it should be performed selectively or routinely is still controversial.

ERCP and biliary stent placement is indicated for the management of obstructive jaundice and pruritus in patients who are not surgical candidates. Preoperative biliary drainage in jaundiced patients using ERCP remains controversial. However, preoperative ERCP and biliary stent placement should be considered in patients who are symptomatic or septic, or in those whom surgical resection is significantly delayed.

Management

Once staged, individuals are directed towards a stage-specific treatment plan (figure 7).

Resectable disease

For patients with resectable disease, surgical resection with adjuvant therapy is the only possibility of cure. For tumours of the head of pancreas (60-70% of resectable tumours), a pancreaticoduodenectomy, or Whipple's procedure, is performed. For tumours of the body or tail of the pancreas, a left-sided or distal pancreatectomy is performed.

A Whipple's resection (figure 8, page 36) involves en bloc resection of the head of the pancreas, duodenum, gall bladder and common bile

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duct with or without the gastric antrum. The common hepatic duct, pancreatic duct and the gastric–duodenal remnant are anastomosed to a loop of jejunum to restore GI continuity. Synchronous vascular resection may also be performed for tumours invading the superior mesenteric/splenic/portal vein and/or common hepatic artery.

Historically, the Whipple's procedure carried a 'bad' name, as it was associated with a perioperative mortality of 30% in the 1940s and 25% in the 1960s, significantly higher than the five-year survival rate. Patients undergoing palliative bypasses appeared to have equivalent, if not better overall outcomes than patients who underwent pancreaticoduodenectomy, raising doubts regarding the value this intervention. However, with advances in surgical techniques and improvements in anaesthetic and perioperative care, the current 30-day in-hospital mortality is less than 4% in high-volume centres.

After surgical resection, all patients should be considered for adjuvant chemotherapy. Adjuvant 5-flurouracil (5-FU)–leucovorin or adjuvant gemcitabine are superior to observation only. Adjuvant gemcitabine and adjuvant 5-FU–leucovorin have equivalent efficacy.[6,7] However, gemcitabine is preferred over 5-FU as therapy for most patients owing to its more favourable toxicity profile.

The role of routine adjuvant chemoradiation is still controversial. A recent meta-analysis suggests adjuvant radiotherapy is only effective in patients with involved surgical margins.[8]

Locally advanced/unresectable or metastatic disease

The treatment of locally advanced, surgically unresectable disease is less uniform across centres. If the patient is considered suitable for surgery, a course of chemoradiation may be given to potentially 'downstage' the tumour. The patient will be reassessed for resectability after chemoradiation. Unfortunately, downstaging happens infrequently (<5%).

The treatment for patients with metastatic disease is either chemotherapy or best supportive care, depending on fitness and performance status. Gemcitabine is the current first-line chemotherapy and provides some clinical benefit but only a modest survival advantage. However, these patients need to be monitored very closely, as their clinical status may change very rapidly and comfort-directed measures should be paramount.

Although gemcitabine has only a modest effect overall, there are responsive subgroups who receive significant benefit. Predicting who will benefit before treatment is a current major research focus internationally. The combination of gemcitabine and a new formulation of paclitaxel for metastatic pancreatic cancer is currently in early-stage clinical trials.

Figure 8: Schematic drawing before and after Whipple's pancreatico-duodenectomy procedure (Reproduced with permission from The NSW Pancreatic Cancer Network).

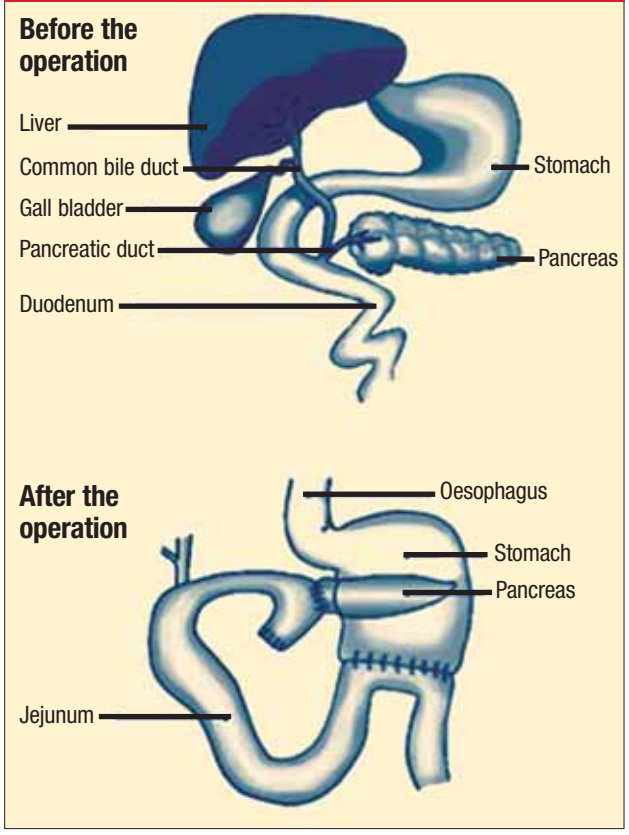


Figure 9: MRCP of a large, branch-duct, intraductal, papillary mucinous neoplasm of the tail of the pancreas.

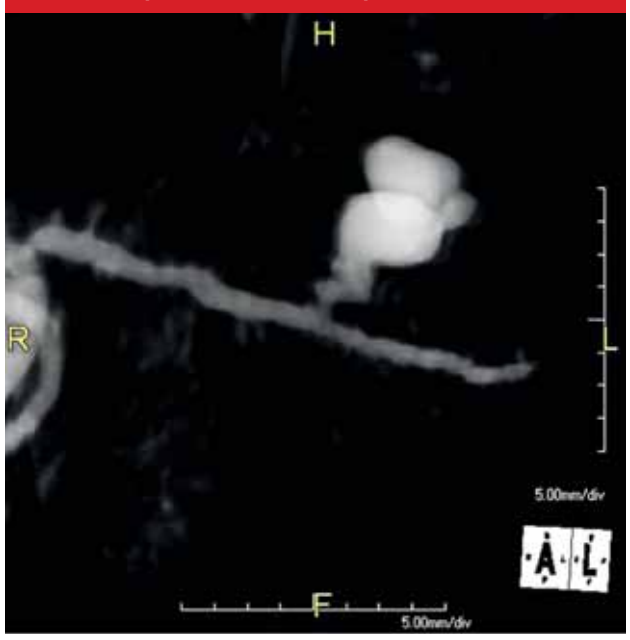
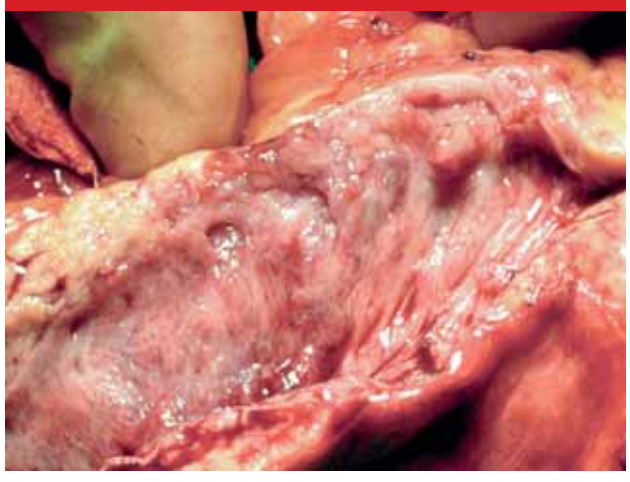


Figure 10: Resection specimen of main-duct, intraductal, papillary mucinous neoplasm of the pancreas (duct opened).



Prognosis and follow-up

There is no consensus on how patients should be followed up postoperatively. However, patients should be followed up regularly by their surgeon and GP and the nutritional status and any evidence of recurrence should be monitored.

We follow patients up with three-monthly clinic visits for the first two years, then six-monthly clinic visits up to five years, then yearly after that. Physical examination and CA19.9 assay is performed at each clinic visit and CT scan every 3-6 months in the first two years, then on each visit after that.

The overall median survival in the recent ESPAC-3 adjuvant therapy trial was about 23 months.[7] However, the median survival from a community cohort is shorter, as not every patient is suitable for adjuvant chemotherapy, for various reasons, and patients from randomised controlled trials are a highly selected group.

Key strategies to improve overall outcomes of pancreatic cancer

A recent review of the National Cancer Database in the US revealed some concerning figures regarding clinician attitudes and outcomes for pancreatic cancer. About half (52%) of patients fit for surgery with clearly resectable and potentially curable stage I pancreatic cancer without any identifiable contraindications failed to undergo surgery.[9] This suggested there is a nihilistic attitude towards pancreatic cancer among clinicians, leading to significant under-utilisation of surgery and therefore poorer outcomes.

We have recently published a review suggesting four key issues need to be addressed if we are to improve the overall outcomes for patients with pancreatic cancer:[5]

- Specialist treatment team referral: volume–outcome relationships have been recognised for decades in cardiovascular procedures and more recently in cancer treatment. It is now well accepted that cancer patients should be treated in specialised centres to achieve the best possible outcomes. Patients and their families should be given the opportunity to access such services.
- Improving the quality of multidisciplinary care in hospitals: outcomes for patients with pancreatic cancer can also be improved through a holistic, multidisciplinary approach. Critical aspects of such care include accurate, timely and consistent staging, stage-specific treatment plans, and multidisciplinary treatment from specialised surgeons, gastroenterologists, medical oncologists, radiation oncologists, radiologists, histopathologists, palliative care specialists, dietitians and nurse specialists.
- Ensuring complete surgical resections of tumours: the long-term survival of patients depends on the complete macroscopic resection of tumour, as patients with gross incomplete resection survive less than one year, equivalent to that for patients with locally advanced disease.
- Detection and appropriate management of premalignant lesions: in other organs, such as the colon, breast, and cervix, treatment of premalignant conditions has resulted in improved outcomes. There is now compelling evidence that pancreatic ductal adenocarcinomas arise from non-invasive precursor lesions. There are three predominant types: pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasm (figures 9 and 10) and mucinous cystic neoplasm.

With increasing usage of high-resolution imaging techniques, these cystic precursor lesions are being increasingly identified both in symptomatic and asymptomatic individuals. Therefore, early detection and the standardisation of evidence-based treatment of these precursor lesions provide the best opportunity to prevent invasive adenocarcinoma of the pancreas.

The future: personalised cancer care

There is now compelling evidence that the genomic heterogeneity of cancer leads to different molecular phenotypes with disparate sensitivities to therapy in histologically indistinguishable cancers. Therefore, knowledge of the molecular phenotype of an individual's cancer before treatment allows for the selection and early delivery of the optimal therapeutic regimen, to improve overall outcomes and minimise morbidity and cost.

Such genotype guided therapeutic approaches are already being used in the clinic, such as treating patients with HER-2-positive breast cancer with trastuzumab and patients with *c-kit*-positive GI stromal tumours with imatinib, but not in pancreatic cancer. The Individualised Molecular Pancreatic Cancer Therapy (IMPACT) trial is now underway. The proposed study is an exploratory, open-label, randomised phase II study in advanced pancreatic cancer using genetic sequence data and gene expression to direct first-line treatment. The participating patients will be randomised to current standard of care (gemcitabine) or the experimental arm, which is gemcitabine plus a targeted treatment based on the genetic makeup of the tumour.

Conclusion

Pancreatic cancer remains one of the deadliest diseases in our community, with an overall five-year survival of <5%. This has not changed for almost 50 years. This is in part due to the late presentation and diagnosis of patients and a poor response to chemotherapy and radiotherapy.

Medical practitioners should consider pancreatic cancer as a potential diagnosis when older patients present with persisting subtle abdominal symptoms, especially if other risk factors are present. Although only 15-20% of patients are suitable for surgery, these individuals have a 25% chance of cure and should be given that option.

Summary — Pancreatic cancer

- Pancreatic cancer is the fourth most common cause of cancer-related death in Western societies including Australia.
- Patients usually present at an advanced stage when surgery is not suitable, leading to a poor prognosis (overall five-year survival of <5%).
- Clinical presentation may include, but is not restricted to, weight loss, jaundice, abdominal or back pain, dyspepsia, nausea and depression.
- A CT scan using pancreatic protocol should be performed if pancreatic disease is suspected.
- All patients with a pancreatic lesion should be referred to a specialist pancreatologist promptly and to be treated in a multidisciplinary setting in a high-volume centre.
- Surgery remains the only chance of cure, with chemotherapy offering modest effect with an overall five-year survival of 20-25% and median survival of 20-25 months in patients who undergo surgery and adjuvant chemotherapy.
- Palliative therapy may include chemotherapy and endoscopic stenting aiming to improve quality of life.
- Pancreatic cancer is a current focus of research internationally and the Australian Pancreatic Cancer Genome Initiative (APGI) is contributing to the International Cancer Genome Consortium (ICGC) in pancreatic cancer.

References and Further reading

Available on request from julian.mcallan@reedbusiness.com.au

Online resources

- Australasian Pancreatic Club. Recommendations for the management of pancreatic exocrine insufficiency: www.mja.com.au/public/issues/193_08_181010/too10364_fm.html
- Australian Pancreatic Cancer Network: www.pancreaticcancer.net.au
- International Cancer Genome Consortium (ICGC): www.icgc.org

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GP's contribution

DR ASHLEY BERRY
Oatley, NSW

Case study

MRS M, 55, an obese woman with type 2 diabetes, presented to her local hospital one year ago with increasing left iliac fossa pain, which had been present for one week. Her appetite was slightly reduced but there was no nausea, vomiting, constipation, diarrhoea, weight loss or melaena. She had had a laparoscopic cholecystectomy five years earlier.

She had an extraordinarily detailed workup that included haematology, biochemistry, amylase, colonoscopy, upper and lower abdominal ultrasound, kidney–ureters–bladder X-ray and chest, abdominal and pelvic CT scans. She was found to have a 3cm mass in her pancreas, most likely an incidental finding. She did not have a CA 19.9 test.

She was followed up over three months and the size of the asymptomatic mass increased to 4cm. After much deliberation, the surgeon decided it was best to remove the mass and Mrs M underwent removal of the distal third of her pancreas.

Despite her obesity and diabetes, she recovered well. Histology showed that the mass was a pseudocyst, cause unknown; she had had no previous attacks of pancreatitis, trauma or other risk factors for a pseudocyst.

Questions for the author

The surgeon was reluctant to do an ultrasound-guided FNA of the mass in case Mrs M developed pancreatitis, yet others would recommend this before surgery. What is your view on this?

The overall complication (pancreatitis and others) rate associated with biopsy of the pancreas is small (0.5-3%). However, this risk in most case scenarios is acceptable to establish a diagnosis for the pancreatic mass. There are, however, two issues to be aware of:

- The preferred technique for FNA of a pancreatic mass is endoscopic ultrasound, as there is a small risk of needle-track seeding (of malignant cells) if a pancreatic cancer is biopsied percutaneously. If needle-track seeding occurs, the patient's cancer has been converted from a potentially curable to an incurable stage 4 disease.
- Biopsy of the body and tail of the pancreatic lesions should be selective, as the needle track is not resected as if the lesion was in the head of the pancreas when the duodenum is removed as part of the Whipple's procedure.

The management of any pancreatic lesion should be discussed in a multidisciplinary treatment meeting.

In such a patient with an asymptomatic mass, what is the chance of it being pancreatic cancer? Would a serum CA19.9 have been useful?

All symptomatic and asymptomatic pancreatic masses should be considered as potentially malignant until proven otherwise. The possibility of such a mass being a malignant lesion depends on age, risk factors and family history, but most pancreatic cancers are sporadic.

CA19.9 can be a very helpful tumour marker and it is the only FDA-approved tumour marker for pancreatic cancer. However, there are a few caveats:

- It should not be used as a screening test because of the low incidence of pancreatic cancer in the general population and because mass screening using CA19.9 would lead to a large number of false-positive results.
- About 10% of the population have Lewis-antigen-negative blood type and do not produce CA19.9. Therefore the CA19.9 level in these patients with pancreatic cancer will still be in the normal range or very close to 0.
- CA19.9 can be detected in normal healthy individuals and can also be elevated in benign conditions such as pancreatitis, cholecystitis or obstructive jaundice secondary to choledocholithiasis.

General questions for the author

When I was an RMO in casualty we used to see acute pancreatitis often. Yet despite increasing alcohol consumption and obesity, it is rare in GP land. How common are acute and chronic pancreatitis now, and what percentage are malignant?

Patients with acute pancreatitis are seen quite commonly in the hospital setting. Where I work we would see about 5-8 admissions with acute pancreatitis each week, most of which are due to gallstones, then excessive alcohol consumption. Acute pancreatitis secondary to malignancy is rare and accounts for <5%. However, malignancy is always a differential diagnosis to be considered, especially in patients who have an atypical history or CT appearance.

Patients with chronic pancreatitis are seen less often, as symptoms are less well defined and perhaps there is a general lack of awareness of the disease. However, efforts are being made to improve the recognition and management of the disease, especially from the point of pancreatic enzyme deficiency replacement.

Smoking, obesity, exposure to chemicals such as beta-naphthylamine and benzidine, and perhaps diabetes, are said to be risk factors for pancreatic cancer. Which occupations involve such chemicals? Should people with diabetes, especially those newly diagnosed, be having regular ultrasound or MRI to monitor the pancreas?

The value of performing CT on every patient with newly diagnosed diabetes is still debatable. However, CT should be considered in patients with abdominal symptoms or any other alarming or atypical symptoms.

Both beta-naphthylamine and benzidine are aromatic amines used to make dyes. Both are known human carcinogens, causing pancreatic and bladder cancers and have been replaced or significantly withdrawn from use in most industries. Workers with prolong exposure to dye or dye manufacturing may be at an increased risk.

How to Treat Quiz

Pancreatic disorders — 10 June 2011

INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points. We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

ONLINE ONLY

www.australiandoctor.com.au/cpd/ for immediate feedback

1. Which TWO statements regarding acute pancreatitis are correct?
a) Obstruction of the pancreatic duct by gallstones may activate pancreatic enzymes, resulting in auto-digestion of the pancreas
b) Larger gallstones are more likely to cause pancreatitis than smaller gallstones
c) Acute pancreatitis typically occurs in young men who consume >80g alcohol a day
d) There is a clear dose-dependent relationship between alcohol and acute pancreatitis

2. Which TWO drugs are associated with acute pancreatitis?
a) Thiazide diuretics
b) Cephalosporin antibiotics
c) Steroids
d) Calcium-channel blockers

3. Which TWO statements regarding acute pancreatitis are correct?
a) Patients may sometimes present with haemodynamic instability or even in a state of profound shock
b) An elevated serum amylase and/or lipase level is always diagnostic of acute pancreatitis
c) If there is doubt regarding the diagnosis, an abdominal CT scan should be performed to rule out other possible causes
d) Abdominal ultrasound is not useful in the first 24 hours after presentation

4. Which TWO statements regarding acute pancreatitis are correct?
a) CT scan should be performed within 24 hours of the onset of the symptoms to detect complications such as pancreatic necrosis and fluid collections
b) Serum CRP can be used to monitor the clinical course of acute pancreatitis
c) Initial management includes the identification and reversal of organ failure, in particular renal and respiratory failure
d) Pancreatic necrosis and peri-pancreatic fluid collections are usually managed surgically

5. Which TWO statements regarding chronic pancreatitis are correct?
a) The morphological changes of the pancreatic parenchyma are usually reversible
b) The most common presentation is abdominal pain and/or loss of exocrine or endocrine functions
c) Patients with hereditary forms of chronic pancreatitis are at greatly increased risk of pancreatic cancer
d) Pancreatic exocrine or endocrine insufficiency is an early complication

6. Which TWO statements regarding chronic pancreatitis are correct?
a) The abdominal pain may decrease over time as the pancreas 'burns out'
b) The production of both insulin and glucagon may be reduced
c) A normal amylase or lipase level excludes the diagnosis
d) Faecal fat measurements are unhelpful for the diagnosis of exocrine insufficiency

7. Which TWO statements are correct?
a) Pancreatic calcifications on abdominal X-ray are invariably present in a patient with chronic pancreatitis
b) Contrast-enhanced CT scan is a highly sensitive and specific test for chronic pancreatitis
c) Endoscopic retrograde cholangiopancreaticography (ERCP) is the recommended imaging modality for the diagnosis of chronic pancreatitis
d) Endoscopic ultrasound can visualise the pancreatic parenchyma and ductal system and allows a fine-needle aspiration biopsy if necessary

8. Which TWO statements regarding the management of chronic pancreatitis are correct?
a) A coeliac plexus block and thoracoscopic splanchnectomy may be considered if oral analgesics fail to control pain
b) Oral pancreatic enzyme replacement therapy is required with each meal for treatment of exocrine insufficiency
c) Proton-pump inhibitors are contraindicated in patients receiving pancreatic enzyme replacement
d) Diabetes secondary to chronic pancreatitis usually responds to oral hypoglycaemics

9. Which TWO statements regarding pancreatic cancer are correct?
a) Cigarette smoking is a major risk factor for pancreatic cancer
b) Persons with longstanding diabetes are regarded as being at risk of pancreatic cancer
c) Clinical presentation may include weight loss, jaundice, abdominal or back pain, dyspepsia, nausea and depression
d) The tumour marker CA19.9 is not present in healthy individuals

10. Which TWO statements regarding the treatment of pancreatic cancer are correct?
a) CA 19.9 is recommended as a screening test
b) ERCP to insert a biliary stent is indicated for the management of obstructive jaundice and pruritus in patients who cannot undergo surgery
c) Perioperative mortality for curative surgery is about 30%
d) All patients should be considered for postoperative (adjuvant) chemotherapy

CPD QUIZ UPDATE

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2011-13 triennium. You can complete this online along with the quiz at **www.australiandoctor.com.au.** Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

Australian Doctor Education

HOW TO TREAT Editor: **Dr Giovanna Zingarelli**
Co-ordinator: **Julian McAllan**
Quiz: **Dr Giovanna Zingarelli**

NEXT WEEK The next How to Treat explores the most common malignancy in young men aged 20-40 — testicular cancer, which has had a threefold increase in incidence over the past 50 years, for reasons not completely understood. The authors are **Dr Anthony Linton**, medical oncology fellow, Concord Repatriation General Hospital, NSW; and **Dr Peter Grimison**, staff specialist in medical oncology, Royal Prince Alfred Hospital, and clinical senior lecturer, University of Sydney, NSW.