Abdominal pain: is it the pancreas?

Pancreatic diseases are generally poorly understood, frequently misdiagnosed and inadequately treated. This article outlines the symptoms of pancreatic pathology and guides the practitioner through various investigations.

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Up to one-third of adult patients who present to emergency departments with abdominal pain are given a diagnosis of nonspecific abdominal pain (NSAP).[1] The incidence of NSAP as a diagnosis appears to be increasing.[2,3] One study has reported that shortly after an initial presentation of NSAP, 10.7% of patients aged 50 years and older were identified as having an intra-abdominal malignancy.[4] Approximately 30% of intra-abdominal malignancies are of the liver, biliary tract and pancreas, and 32% are colorectal cancers.[5]

Many other lesions of the pancreas (many of which are premalignant) may also present as NSAP (see the Table and Figures 1 to 4). Tumours of the ampulla (Figure 5), distal bile duct and duodenum (both benign and malignant) may also give rise to abdominal symptoms as a result of obstruction of the pancreatic duct and/or the bile duct (Figures 6a and b), leading to chronic or recurrent acute pancreatitis. Chronic pancreatitis is an important risk factor and a differential diagnosis for pancreatic cancer, as well as an often missed pancreatic pathology. The most serious of these is pancreatic cancer.

As there are approximately two million presentations of abdominal pain to GPs each year in Australia,[6] missed abdominal malignancy is a problem, with significant challenges in distinguishing NSAP from underlying serious disease. This article explores the features of pancreatic pathology that are commonly overlooked, and describes the general and specialist investigations that can be carried out in these patients so that serious and potentially malignant pathologies are not missed.

The incidence of pancreatic cancer has been increasing gradually during the past two decades and is now approximately 10 cases per 100,000 capita of population per year in Australia, with

IN SUMMARY

- **For patients over the age of 50 years with abdominal pain, one should have a high level of suspicion for the presence of underlying malignancy, particularly of the pancreas.**
- **Any demonstrated abnormality of the pancreas should be investigated further and treated as pancreatic cancer until proven otherwise.**
- **Any masses should be assessed by specialists in the field for further treatment.**
- **Patients with chronic pancreatitis are at risk for pancreatic malignancy and should be followed up by a gastroenterologist or a pancreatic surgeon.**
- **Percutaneous biopsy should not be performed prior to assessment of resectability because of the risk of the tumour seeding along the needle tract and thereby eliminating any chance of cure.**

Table. Classification of pancreatic neoplasia

- Pancreatic adenocarcinoma
- Cystic tumours (Figures 1 to 3):
  - serous cystadenoma
  - mucinous cystic neoplasm
- Intraductal papillary mucinous neoplasm (Figures 4a and b)
- Pancreatic neuroendocrine tumours
- Solid pseudopapillary tumours
- Lymphoma

an equal gender distribution. It is the fourth most common cause of cancer death in Western countries, despite being the twelfth most common malignancy.

Symptomatology of pancreatic neoplasms

Patients with abdominal pain often have vague and nonspecific symptoms and it is for this reason that the clinical manifestations of pathology may often be categorised as NSAP. The symptoms discussed below are often regarded as forming a 'typical' presentation of pancreatic pathology, but it is worth noting that these symptoms generally arise late in the course of the disease and represent an advanced pathology.

Abdominal pain

Abdominal pain is the most common presenting symptom of pancreatic pathology, occurring in about 75 to 80% of patients with pancreatic tumours, including those with small tumours (2 cm or less in diameter).

The causes of pain include obstruction of the main pancreatic duct or the bile duct, acute or chronic pancreatitis, cholangitis, neural infiltration by a tumour, and invasion by a tumour of adjacent structures. Abdominal pain usually has

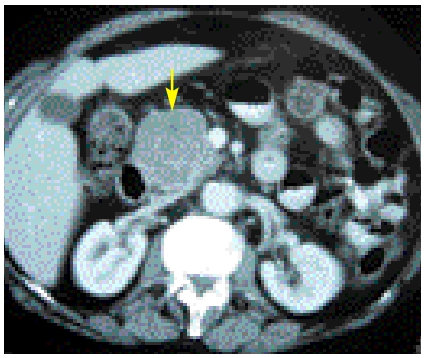
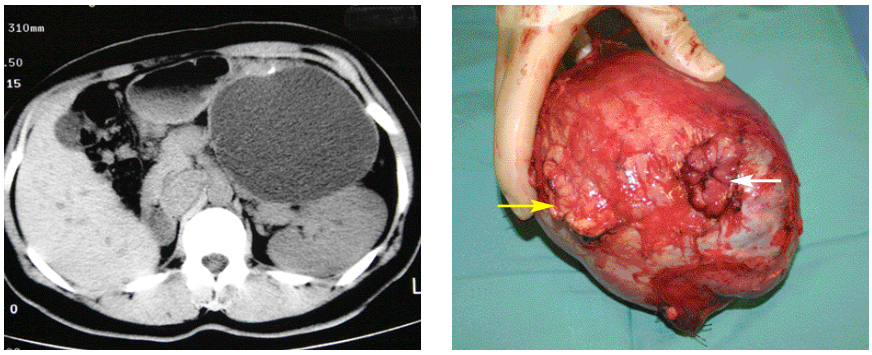


Figure 1. Axial CT scan of the upper abdomen showing a loculated microcystic lesion (arrow) in the head of the pancreas, encroaching on the portal vein. This lesion is a benign serous cystadenoma.

IMAGE COURTESY OF DR. SELVAN PATHER, SYDNEY.



Figures 2a and b. a (above left) Abdominal CT scan of the pancreatic tail in a 28-year-old woman showing mucinous cystadenocarcinoma. She was initially misdiagnosed as having a pseudocyst and treated with cystogastrostomy. b (above right) Distal pancreatectomy was carried out to resect the tumour along with a cuff of gastric tissue around the site of the previous cystogastrostomy (white arrow). The yellow arrow indicates the transaction margin through the pancreatic neck.

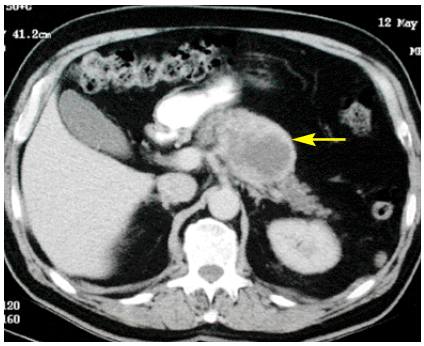
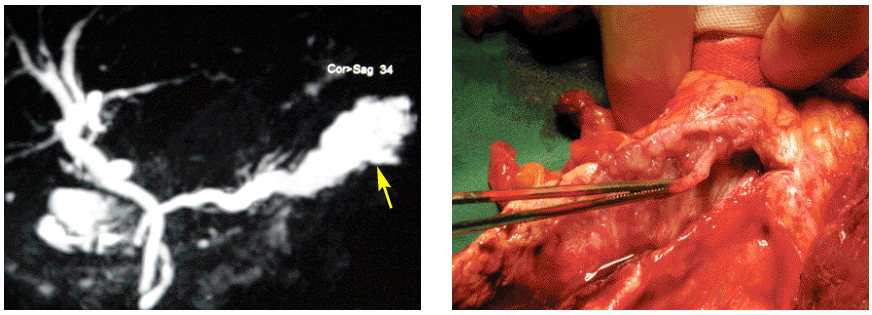


Figure 3. A large acinar cell tumour of the body of the pancreas (arrow). These tumours can be difficult to distinguish from mucinous cystic tumours.



Figures 4a and b. a (above left). Magnetic resonance cholangiopancreatography showing extensive intraductal papillary mucinous neoplasm of the pancreatic tail (arrow). b (above right). The operative specimen from a distal pancreatectomy performed on the same patient, opened along the course of the dilated pancreatic duct, showing the intraductal papillary mucinous neoplasm in the pancreatic tail.

an insidious onset over one or two months and is of a deep-seated visceral nature, originating in the epigastrium and frequently radiating through to the back or under the costal margin bilaterally. Pain is usually worse at night and in the supine position; it may interfere with the patient's sleep. It is often exacerbated by ingestion of food and may result in food avoidance, thereby contributing to weight loss in some patients.

In patients with chronic pancreatitis, there are two potential mechanisms that give rise to pain. These include persistent perineural inflammation and calculous obstruction or strictures of the pancreatic duct. Patients with persistent perineural inflammation are difficult to treat and do not generally respond to narcotic analgesia. Coeliac plexus block and/or splanchnicectomy may provide relief. These patients should be referred to a chronic pain clinic for evaluation.

Patients with pain resulting from calculous obstruction or strictures of the pancreatic duct respond well to endoscopic or surgical decompression procedures and should be referred for assessment by a surgeon. Occasionally, resection is warranted for symptomatic relief and/or exclusion of surreptitious malignancy.

Jaundice

Jaundice occurs in over half of all patients with pancreatic neoplasms and may be associated with abdominal pain or be an isolated symptom. It is progressive in nature and characteristically of a cholestatic picture. It may arise in patients with tumours of the body and tail of the pancreas, but in this situation it is regarded as a late sign indicating metastasis to the liver or hilar lymph nodes.

Jaundice may be present in up to three-quarters of patients with tumours of the pancreatic head. Courvoisier's law states that a distended or palpable gall bladder in the presence of jaundice is unlikely to be secondary to calculous biliary disease.

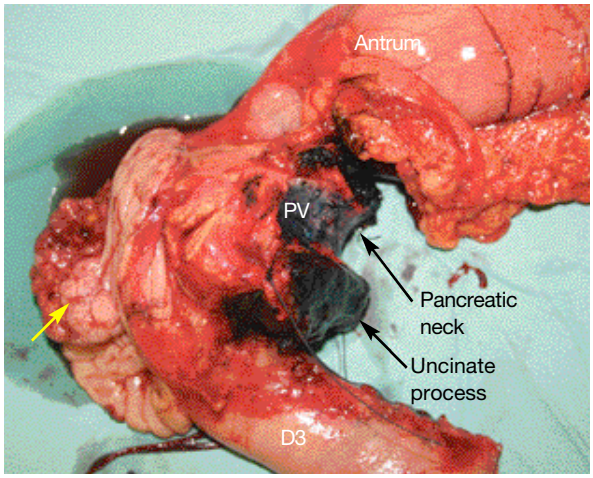


Figure 5. Operative specimen from a Whipple partial pancreatico-duodenectomy showing a large ampullary tumour invading into the duodenum (yellow arrow).

ABBREVIATIONS: D3 = third part of duodenum; PV = portal vein groove.

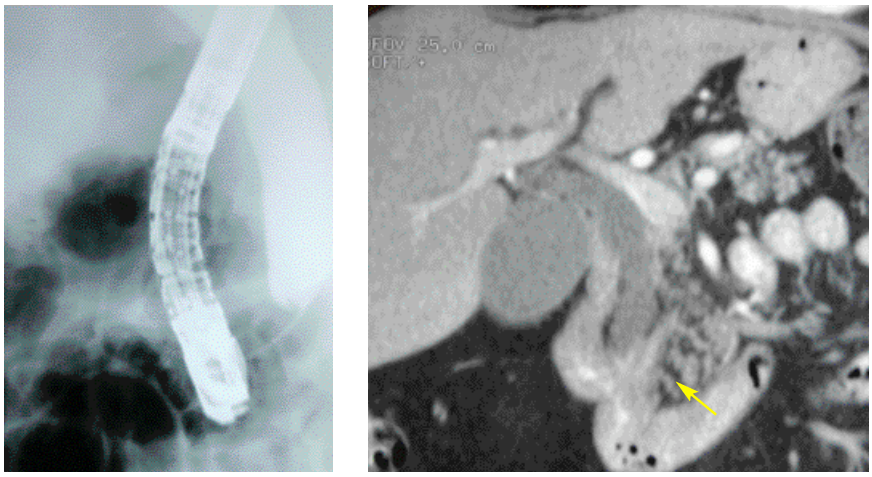
Weight loss

Weight loss is reported in about one-third of patients with pancreatic cancer and may be due to a combination of food avoidance, anorexia, early satiety, vomiting, malabsorption and the catabolic metabolism associated with malignancy.

Diabetes mellitus

In approximately 60% of patients with pancreatic ductal adenocarcinoma, diabetes mellitus is diagnosed within the 12 months preceding the diagnosis of pancreatic malignancy. Conversely, about 1% of patients aged 50 years or older who are diagnosed with diabetes mellitus will be diagnosed with a pancreatic malignancy within three years.[7]

In individuals who have had diabetes for a long period of time, development of pancreatic malignancy may cause sudden deterioration in diabetic control and progression to insulin dependence. The relative risk of developing pancreatic cancer in individuals with diabetes is 2.0, but it is unclear whether it is a risk factor for, or an early consequence of, malignancy.



Figures 6a and b. a (left). Endoscopic retrograde cholangiopancreatography showing the typical abrupt cut-off of a malignant stricture of the distal common bile duct, with obstructive dilatation of the duct proximal to the stricture in a jaundiced patient. b (right). Coronal CT scan of the abdomen showing malignant obstruction of the distal bile duct (arrow), with proximal dilatation.

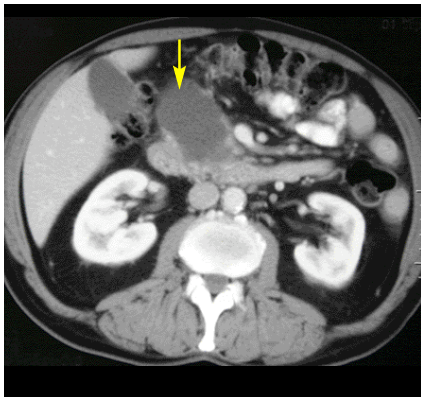


Figure 7. Axial CT scan of the abdomen showing a pancreatic pseudocyst (arrow). Aspiration of the fluid under endoscopic ultrasonography guidance showed a high amylase level and absence of tumour markers.

Miscellaneous presentations

Miscellaneous presentations include paraneoplastic syndromes associated with neuroendocrine or carcinoid tumours, migratory superficial thrombophlebitis, acanthosis nigricans, Troisier's sign, Sister Mary Joseph nodule, gastrointestinal haemorrhage, gastric outlet obstruction, portal venous thrombosis and abdominal masses.

Investigations

Most investigations for pancreatic symptoms are directed towards therapeutic planning by the specialist. However, the role of GPs in directing the initial investigation towards establishing a diagnosis of pancreatic pathology should not be underestimated.

Abdominal CT scans will detect the most potentially significant pancreatic lesions and should be performed in all patients with pancreatic symptoms before other more invasive investigations (such as endoscopy) are carried out. Early specialist referral is essential for patients who need further investigation, have pancreatic pathology detected on first line investigations, or have ongoing symptoms despite a negative CT scan.

General investigations

Abdominal CT scans and sonography

Abdominal CT scans and sonography often complement each other and are first line investigations in patients suspected of pancreatic and biliary disorders. They are useful in diagnosis, staging and monitoring of disease. Abnormalities detected by these methods should be further characterised using a pancreatic protocol CT scan, performed with intravenous contrast, but without oral contrast, taking 3 mm cuts through the pancreas, combined with a triple-phase CT scan of the liver. This improves visualisation of the pancreas and aids detection of hepatic metastases.

Small tumours in the head of the pancreas may occasionally be missed on general abdominal protocol CT scanning, but a bulky head with atrophic changes of the body and tail of the pancreas and/or a 'double duct sign' (dilatation of both the pancreatic duct and the common bile duct) are suggestive and should trigger further investigation.

Full blood count and biochemical analysis

Full blood count and biochemical analysis, including serum electrolytes, renal and liver function tests, fasting blood glucose, serum amylase, lipase, calcium, magnesium and phosphate, should be performed as baseline measures.

Tumour markers

Tumour markers, particularly cancer antigen 19-9 (CA 19-9), are useful as diagnostic adjuncts and for monitoring disease progression and response to therapy. However, they lack the specificity required for use in the diagnosis of pancreatic cancer. The CA 19-9 level should be interpreted with caution in cases of biliary obstruction, as it may be spuriously elevated in this situation, although a value greater than 1000 units is unlikely to be associated with benign obstruction.

Specialist investigations

Endoscopic ultrasonography

A histological diagnosis is essential for therapeutic decision making and prognostication and this can be achieved by endoscopic ultrasonography and fine needle aspiration biopsy. This technique involves the use of an endoscope fitted with an ultrasound transducer near the tip.

Endoscopic ultrasonography is more sensitive than a CT scan for patients with pancreatic pathology. Fluid aspirates from cystic tumours may be analysed for amylase level and the presence of carcinoembryonic antigen (CEA), CA 19-9 and mucus. These analyses will help distinguish cystic tumours from pancreatic pseudocysts (Figure 7), and will determine the type of cystic tumour and likelihood of malignancy.

Endoscopic ultrasonography is also useful for assessment of lymph node invasion, both by morphological features and by aspiration cytology. The risk of tumour seeding following this technique is not clinically relevant as the needle tract is completely excised during resection of any tumour.

Endoscopic retrograde cholangiopancreatography

For tumours of the ampulla, duodenum, distal bile duct and distal pancreatic duct, endoscopic retrograde cholangiopancreatography (ERCP) may be a useful means to obtain tissue for histological diagnosis and for biliary stent placement for either temporisation or palliation of jaundice. Biliary stent placement is best avoided before evaluation by endoscopic ultrasonography, because the presence of foreign material distorts tissue planes, making interpretation difficult.

CT cholangiography or MRI/magnetic resonance cholangiopancreatography

CT cholangiography or MRI/magnetic resonance cholangiopancreatography (Figure 8) may provide additional

information about the local extent of disease. CT cholangiography is not useful in patients with jaundice because the contrast medium cannot be adequately concentrated in the bile. CT angioportography and three-dimensional reconstruction of the portal vein (Figure 9) may help determine whether there is invasion of the portal vein or coeliac axis.

Positron emission tomography

Positron emission tomography (PET) scanning may occasionally be useful for evaluating the presence of distant metastases.

Other nuclear medicine scans

Other nuclear medicine scans, including radiolabelled octreotide scans and PET-CT scans, are frequently useful in the diagnosis and staging of pancreatic neuroendocrine tumours.

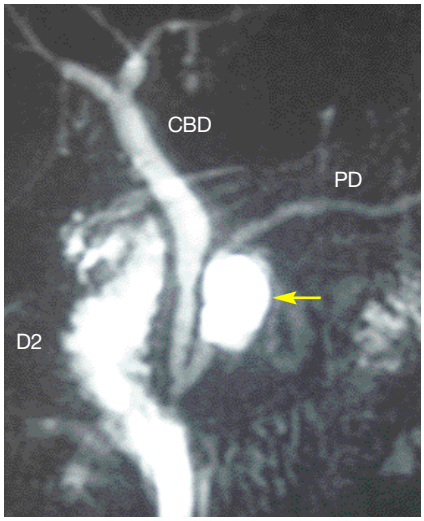


Figure 8. Magnetic resonance cholangiopancreatography showing a branch duct intraductal papillary mucinous neoplasm (arrow).

ABBREVIATIONS: CBD = common bile duct; D2 = second part of duodenum; PD = pancreatic duct.

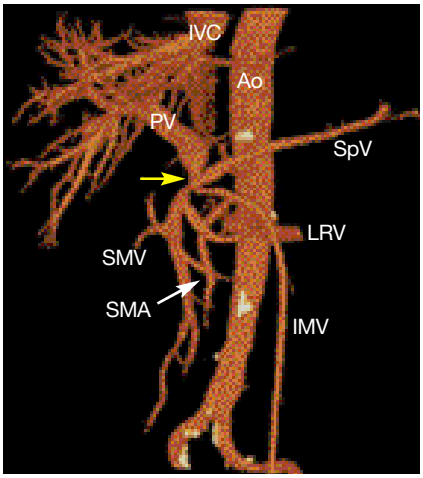


Figure 9. CT angioportography with three dimensional reconstruction of the portal vein showing tumour invasion at its origin (yellow arrow).

ABBREVIATIONS: Ao = aorta; IMV = inferior mesenteric vein; IVC = inferior vena cava; LRV = left renal vein; PV = portal vein; SMA = superior mesenteric artery; SMV = superior mesenteric artery; SpV = splenic vein.

continued

Staging laparoscopy/laparotomy

Staging laparoscopy is often used to assess for peritoneal spread, lymphadenopathy and liver metastases, and its utility may be extended by the addition of laparoscopic ultrasonography. Rarely, laparotomy may be required to obtain tissue for diagnosis, but it is usually reserved for patients who require operative intervention for bypassing obstruction of the biliary tree or gastric outlet.

Percutaneous biopsy

To avoid the risk of the tumour seeding along the needle tract and thereby precluding any potential for cure, percutaneous biopsy should not be performed before assessing resectability, other means of obtaining tissue have been exhausted and the tumour is deemed unresectable.

Chronic pancreatitis

Chronic pancreatitis may be difficult to diagnose. A past history of recurrent attacks of acute pancreatitis is not reliable in diagnosing chronic pancreatitis because 50% of attacks are not recognised (particularly if clinicians rely exclusively on clinical and biochemical criteria) and recurrent attacks may be subclinical.

'Seeding of the tumour along the needle tract during percutaneous biopsy can preclude any potential for cure.'

Patients with symptomatic chronic pancreatitis should be treated based on their symptoms and risk of concurrent malignancy. Since chronic pancreatitis is a recognised risk factor for pancreatic cancer, malignancy should be considered and excluded. These patients should be referred to a specialist pancreatic unit because treatment is often complex and difficult to carry out, but it has the potential for total alleviation of pain and improvement in endocrine and exocrine function at a potentially curable stage of the disease (Figure 10).

Management of suspected pancreatic malignancy

Any pancreatic abnormality shown on CT scan should trigger referral of the patient because the outcome for invasive pancreatic cancer is poor. These patients should be assessed by a pancreatic surgeon and presented to a multidisciplinary tumour committee, regardless of radiological appearance or clinical

features. Multicentre analyses have repeatedly shown that upper gastrointestinal tract malignancies treated in centres with a high patient volume have better outcomes than similar cases in centres with a low patient volume.[8,9]

In 1 to 2% of patients with a pancreatic mass, the histological diagnosis will be lymphoma or a neuroendocrine tumour, both of which have a more favourable prognosis than pancreatic ductal adenocarcinoma despite an aggressive appearance on imaging studies.

Fewer than 10% of patients with pancreatic ductal adenocarcinoma survive beyond three years from the time of diagnosis. To a large extent this is due to the advanced stage of disease at presentation, with up to 80% of cases being unsuitable for curative resection because of advanced locoregional or metastatic disease. The greatest hope of cure for patients with pancreatic cancer relies on the appropriate treatment of precursor lesions. Many of these lesions are cystic and detectable with routine imaging, such as CT.

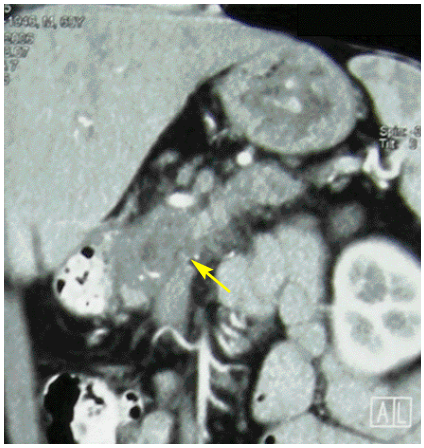


Figure 10. Coronal CT scan of the upper abdomen showing a poorly defined mass in the head of the pancreas (arrow) in a patient with recurrent bouts of pancreatitis. Malignancy was suspected, but could not be excluded on endoscopic ultrasonography guided fine needle aspiration biopsy, and the patient proceeded to resection. Histological examination showed chronic pancreatitis without evidence of malignancy, and the patient remains symptom free.

Recent advances in our understanding of the molecular biology of pancreatic tumours are expected to give clinicians the ability to tailor treatment to individual patients by predicting response to particular therapeutic modalities.[10,11] These advances, coupled with a higher index of suspicion and earlier detection of pancreatic cancer, will help improve outcomes for these patients.

continued

Conclusion

A higher index of suspicion and earlier investigation of unexplained abdominal symptoms may lead to an earlier diagnosis of patients with pancreatic cancer and a greater potential for cure. Patients with any demonstrated pancreatic pathology (including cystic lesions of the pancreas) or who have normal initial investigations and ongoing symptoms potentially attributable to the pancreas should be referred at the earliest opportunity to a specialist pancreatic unit for further evaluation.

A recent study published in *Annals of Surgery* has shown that because of a defeatist attitude of clinicians towards pancreatic cancer, over half of patients diagnosed with early and resectable disease were not offered an operation. This denied this group of patients a 20% chance of cure, and highlights that significant improvements in outcomes for these patients can be made through the application of existing knowledge.[12]

Percutaneous biopsy should not be performed before assessment of resectability because of the risk of the tumour seeding along the needle tract and thereby eliminating any chance of a cure.

Appropriate treatment of patients with pancreatic cancer (particularly treatment of precursor lesions) carried out with low complication rates in specialist units will improve outcomes for these patients.

A useful resource is the NSW Pancreatic Cancer Network (www.pancreaticcancer.net.au or phone 02-9295 8332). MT

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Further reading

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