Diseases of the pancreas

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Diseases of the pancreas often manifest late, and surgery on the gland is technically difficult. Mr Mudan summarises the presentation and treatment of the main conditions affecting the pancreas – pancreatitis and cancer.

The pancreas gland is an obscure organ in which several serious diseases can occur. Operations on the pancreas are generally regarded as the most challenging in all of surgery because surgical access is difficult and the gland sits closely related to many vital structures such as the bile duct and gallbladder. In addition, it is close to major blood vessels that carry blood to and from the intestine – the superior mesenteric artery and vein, respectively (Figure 1). Because of its location, hidden from view and difficult to image even by modern scanning techniques, diseases of the pancreas often manifest late.

ACUTE PANCREATITIS

The most common condition of the pancreas is acute pancreatitis. This is an inflammatory condition with two main causes: alcohol and gallstones.

The presentation of acute pancreatitis is with intense pain in the upper abdomen; severe dehydration, nausea and vomiting are usual. The abdomen is very tender and the pain severe enough to require strong pain medication. The diagnosis is made on clinical history and examination. Confirmation is by blood tests (raised serum amylase or lipase) and imaging either by CT or ultrasound scan, which will show a swollen pancreas and possibly fluid collections around the gland.

Causes of acute pancreatitis

In young men the cause is usually alcohol. The incidence ranges from 10 to 40 per 100,000, with a strong geographical variation towards areas of higher social deprivation and countries with high alcohol consumption. The biggest rise in incidence is in young women also engaging in binge drinking.1

The second most common cause of acute pancreatitis is gallstones. It is possible for a stone or stones to slip out from the gallbladder and into the bile duct. The bile duct and pancreas duct converge into the ampulla of Vater before they enter the intestine to discharge their fluids. Impaction of the stone in the bile duct can also cause obstruction of the pancreas duct. This in turn can lead to pancreatitis, often accompanied by jaundice. As gallstones are uncommon below the age of 40 years, it follows that pancreatitis from gallstones is mainly seen in the more elderly population. Sometimes the stones are tiny (microlithiasis), rather like grains of sand, and the gallbladder does not contain stones but sludge.

Other recognised causes of pancreatitis are sensitivity to certain drugs such as steroids and antihypertensives, severe hypothermia and metabolic conditions such as hypercalcaemia¹ and hypertriglyceridaemia.2,3 Treatment to lower the hypertriglyceridaemia by fibrates reduces the risk of pancreatitis4 and cardiovascular events. Another less common cause is dysfunction of the sphincter of Oddi, which is the valve at the end of the bile duct and pancreas duct where they converge. Failure of relaxation of the valve gives rise to high pressure in the bile duct and pancreas duct, which may cause pancreatitis.

A small group of people suffer from hereditary or familial pancreatitis caused by a mutation in the PRSS1 gene, which encodes for cationic trypsinogen and exhibits autosomal dominant transmission with a penetrance of 80 per cent.5 The presentation is with recurrent acute pancreatitis, eventually leading to chronic pancreatitis. Such individuals carry a 30–40 per cent lifetime risk of developing pancreatic cancer. They are usually looked after in regional centres where screening might be offered.

Treatment of acute pancreatitis

Although there is great variability in the severity of an attack of pancreatitis, all

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cases need to be taken seriously. There is usually profound dehydration and hospitalisation is necessary for pain control, intravenous fluids and close observation for deterioration. Thankfully most cases are mild and self-limiting. With good medical attention the patient is restored to normality within a few days.

In a few cases the pancreatitis is severe and, in spite of careful medical management, complications such as necrosis, haemorrhage and infection of the gland can occur. Such complications prolong the hospital stay and can result in fatality even in a young patient.

Rarely, operation might be required to cut away dead tissue in the pancreas or to drain infected fluid from a pancreatitis-related abscess. Such interventions are technically demanding and the timing of intervention is critical. They always require the attention of a specialist in pancreatic surgery.

The mortality from acute pancreatitis ranges from about 1 per cent in the young patient to about 30 per cent in the elderly fragile patient. Cases of alcohol-induced pancreatitis tend to carry a higher mortality risk, but this may be because of the demographic of that patient group as much as the aetiology of the pancreatitis.

**CHRONIC PANCREATITIS**

Chronic pancreatitis refers not to the severity of the condition but to the fact that the pancreas gland shows changes in its structure if examined by CT scan. Scarring and fibrosis, usually the aftermath of earlier attacks of acute pancreatitis, are present. Such structural changes are permanent and thereby referred to as being chronic. Chronic pancreatitis raises the risk of developing pancreas cancer by about 20-fold.

Sixty to ninety per cent of cases of chronic pancreatitis in men have a history of prolonged high alcohol intake, whereas in women this figure is unknown. Chronic pancreatitis is said to be related to the duration and amount of alcohol consumption; an intake of greater than 80g/day over six to twelve years is said to increase the risk. Only about 10 per cent of patients with acute alcoholic pancreatitis progress on to chronic pancreatitis, hence the relationship is far from complete and other factors must be important in the aetiology of chronic pancreatitis.

Women exposed to high alcohol intake develop changes in the pancreas and other organs in a shorter time than do men. The symptoms may vary from nothing to continuous and unremitting upper abdominal pain, sometimes with radiation into the back. Unfortunately nothing can be done to reverse the damage.

**Management of chronic pancreatitis**

The management centres on limiting any aggravating factors such as alcohol and easing the activity of the pancreas by administration of pancreatic enzyme supplements. Pain is managed by painkillers according to its severity. Special pain-control techniques such as coeliac axis neurolysis (destruction of the nerves that carry pain sensation from the pancreas to the brain) are difficult to perform, cannot be repeated and the effect is short lived, usually only a few months.

There are several operations for the treatment of chronic pancreatitis and none is uniformly effective or satisfactory. Even complete removal of the pancreas, which is guaranteed to lead immediately to insulin-dependent diabetes, is not guaranteed to relieve the pain. This probably occurs through a permanent irritation of the nerves despite removal of the gland. Entering into this area of treatment is without doubt the role of the pancreatic specialist.

Another means of treating chronic pancreatitis that is still regarded as investigational rather than mainstream is total pancreatectomy with islet cell autotransplantation. In this technique the pancreas is removed surgically and the substance of the explanted pancreas disaggregated to allow extraction of the islet cells. These are then injected back into the patient’s liver with the idea that they will function and prevent diabetes. The technology has developed over the past 40 years or so but as yet its application in the treatment of chronic pancreatitis is not widely accepted. The damaged pancreas may not yield enough islets to be useful in transplantation and the longevity of the transplanted islets tends to be about two years before they fail and diabetes develops; long-term pain control is variable.

**PANCREAS CANCER**

Cancer of the pancreas, sometimes referred to as the silent killer because the diagnosis is not usually apparent until late in the disease, is an uncommon cancer with an incidence of about 1/100,000 (6000 cases per year in the UK). When we speak of pancreas cancer we are usually referring to adenocarcinoma of the pancreas, which arises from the pancreas ducts. Other types of cancer can occur but are very rare.

Pancreas ductal adenocarcinoma is about as common in men as women and the average age of diagnosis is in the late 60s. Family history is a known risk factor, although the causative genes have not yet been identified. Peutz-Jeghers syndrome, hereditary breast and ovarian cancer and familial pancreatitis are other hereditary syndromes for which there are recognised identifiers and that are associated with a higher risk of pancreas cancer. Environmental factors such as obesity, smoking (active or passive) and diabetes are recognised risk factors. The sudden onset of diabetes in midlife should alert the astute doctor to the possibility of pancreas cancer.

**Signs and symptoms of pancreas cancer**

The most common presentation is with jaundice (80 per cent). Jaundice is best seen in the whites of the eyes, which turn yellow, followed by the skin. The urine is
usually a rust colour and the stool is said to be like soft clay. These changes occur because the bile duct is crushed by the pancreas cancer and bile cannot leave the liver. It leaks into the blood, giving rise to the clinical picture described.

Careful inquiry nearly always reveals that the patient had been experiencing some vague and often ignored symptoms for several months. These include weight loss, discomfort in the epigastrium, nausea, indigestion, especially of fatty foods, and pale fatty stool. Back pain, like a screwdriver being driven between the shoulder blades, is not uncommon and usually a sign that the cancer will be large and probably irresectable. A cancer presenting with jaundice is usually located in the head of the pancreas.

Other common causes of sudden onset of jaundice include gallstones. A gallstone can migrate out of the gallbladder and into the bile duct, causing impaction and obstruction of the duct. In this case there is usually, but not always, intense colicky pain in the upper abdomen.

Tumours located in the body or tail of the pancreas tend not to cause jaundice and come to attention much later with symptoms of back pain, weight loss and persistent upper abdominal pain. It is uncommon for a pancreatic cancer involving the body or tail of the pancreas to be resectable; often spread of the cancer to other organs (metastases) is already evident.

Investigations
The patient with jaundice will need urgent hospital attention and prolonged jaundice can lead to problems with kidney function unless carefully managed. Investigation of jaundice or symptoms suspicious of pancreas cancer begins with the history of the problem and examination of the patient, followed by blood tests to look at the severity of the jaundice and to check the kidney function and clotting ability of the blood, which can be reduced by the presence of jaundice.

While awaiting investigation and treatment, it is usual for the patient to receive intravenous fluid to protect the kidneys and vitamin K injection to correct the clotting.

Imaging by ultrasound scan at least, but more probably CT scan, is essential. In well over 90 per cent of cases this is enough to yield a diagnosis either of gallstones or of pancreas cancer. Both CT and ultrasound scan are quick tests and the patient is required to starve for at least four hours before being scanned. Sometimes an MRI scan may be required.

Treatment of gallstones
If the jaundice is caused by gallstones, the solution is relatively simple and the patient will need an endoscopic retrograde cholangiopancreatography (ERCP). This involves passing a long flexible telescope through the mouth and into the duodenum, through which the stone in the bile duct can be extracted. This is relatively straightforward and is performed under sedation. The patient will usually be discharged home the next day.

In the UK all cases of suspected pancreas cancer are discussed by the multidisciplinary team, comprising surgeons, gastroenterologists, radiologists, oncologists and clinical specialist nurses. Each pancreatic multidisciplinary team has its own local procedures and protocols, but treatment pathways are broadly similar across the country. For example, all patients undergo staging, where the size and extent of disease is established; a treatment plan is then established for each individual patient at the multidisciplinary meeting.

If the advice is for operation, the patient can be informed and prepared by the surgical team. Some surgeons prefer to operate on the patient immediately, even if jaundiced. In our multidisciplinary team we prefer the jaundiced patient to have an ERCP and stent insertion to stretch and unblock the bile duct and relieve the jaundice. The urgency is then out of the situation and one can focus more clearly on assessing the patient for operation.

There is no blood test that is diagnostic for pancreas cancer. Once the jaundice clears, the tumour marker CA19.9, which is normally elevated in a jaundiced patient, becomes relevant and if it remains elevated is strongly indicative of pancreas cancer.16 Above a value of 200 in the non-jaundiced patient can be considered diagnostic of pancreas cancer to a certainty of >95 per cent. However, a normal CA19.9 does not exclude pancreas cancer as some tumours (at least 10 per cent) do not secrete this marker.
While the jaundice is clearing, other tests to assess operability and degree of spread can be carried out. In the pancreas the sensitivity and specificity for a diagnosis of cancer is as yet not sufficient to use a PET scan as a diagnostic tool, although the trend for improvement in this modality may yet make it the diagnostic test of choice. Rather, in the presence of a pancreatic mass thought to be cancer, a whole-body PET scan is a way of looking for spread of cancer to sites in the body other than the site of the primary cancer.

At present we are looking to identify the presence of secondaries not detected by the earlier conventional imaging methods. Common sites of secondary spread from a pancreas cancer are to the liver and lungs. The probability of secondaries from cancer less than 2cm in diameter is low, whereas above this size the risk of distant secondaries at presentation is about 25 per cent and local nodal metastases are common. The presence of a secondary will usually mean that the patient will not benefit from operation, and treatment by other means can be initiated quickly.

Another type of spread of pancreas cancer is by peritoneal disease. The larger cancers can spread by tiny deposits sometimes no bigger than sugar crystals onto the peritoneal surface. These are too small to be seen by scans and the surgeon might carry out a laparoscopy to rule out such peritoneal disease before committing to the main operation. Sometimes this staging laparoscopy can be carried out on the day of the proposed operation or as a separate procedure a week or so before the main operation. Enhanced staging in this way identifies about 20 per cent of patients who would otherwise have had operation but without realising the benefit, and thus allows these patients to be treated by other means as quickly as possible. These extra tests can usually be acquired quickly and the additional time to operation of the operable patient does not have any detrimental effect on long-term outcome.

After careful diagnosis and staging tests, about 10–15 per cent of patients presenting with pancreas cancer are considered suitable for operation. Some patients fall into a borderline group where operation is probably not possible, usually because the cancer is stuck to important blood vessels nearby. The trend in managing these patients is to consider them for neoadjuvant therapy in order to improve the operability. This means using chemotherapy and radiation to control or shrink back the cancer before operation and is a proven strategy in other cancers such as advanced gastric and oesophageal cancer.

Patients who progress and go on to develop metastatic disease while on treatment can be spared the trauma of operation as it would not have helped them, and those who respond well can be encouraged to undergo operation as it is likely that they are going to do well. Neoadjuvant therapy is an increasingly popular strategy in the treatment of several cancers, including pancreas cancer.

Surgery for pancreas cancer

The operation for a mass located in the head of the pancreas is called a pancreatoduodenectomy and involves removing the head of the pancreas, the bile duct, gallbladder and duodenum. The operation was first described by Alessandro Codivilla in 1898 and first performed by a German surgeon, Walther Kausch, in 1909, but is commonly referred to by the eponym Whipple’s operation after Alan Whipple, an American surgeon working in the 1930s at the Memorial Hospital in New York (now known as Memorial Sloan-Kettering Cancer Center), who refined the technique and went on to describe many modifications.

This is a major undertaking requiring a great deal of technical skill and is regarded as one of the most difficult operations in the whole of surgical practice. The operation is carried out under general anaesthetic and performed through a cut in the upper abdomen. The typical hospital stay for Whipple’s operation is about seven to ten days. More recently there is a trend to performing the operation by laparoscopic means, although this has not yet become popular.

As with all major operations, complications can occur and delay discharge. A severe complication can even be fatal and the accepted mortality risk for such an operation in good centres is below 5 per cent. A patient undergoing Whipple’s operation might expect to take three to six months to recover. Weight loss of about 10–15 per cent is usual and may take the best part of a year to make up. Because about 50 per cent of the pancreas by weight has been removed in the operation, there may be pancreatic endocrine insufficiency resulting in diabetes and need for insulin therapy, and exocrine insufficiency requiring enzyme supplement tablets or powder to be taken with meals.

Tumours arising in the body or tail of the pancreas give rise to symptoms only very late and are usually not operable at the time of presentation. Operable tumours are staged similarly by PET scan to rule out secondaries and then considered for distal pancreatectomy. This operation when performed for pancreas cancer involves concomitant removal of the spleen, which sits on the tip of the pancreas. Distal pancreatectomy and splenectomy is more suitable for laparoscopic operation, especially if the tumour is small.

The spleen aids in defence against bacterial infections and a patient who is going to have splenectomy should have vaccination with pneumococcus, haemophilus and meningococcal vaccine at least two weeks before operation. Some surgeons like the patient who has had splenectomy to take a small dose of penicillin every day for life, but this is not universally agreed. However, annual influenza vaccination is recommended.
The majority of patients operated for pancreas cancer will be offered adjuvant chemotherapy after recovery from operation. The drug usually used is gemcitabine and is given intravenously.

**Prognosis after surgery**

The prognosis from pancreas cancer that has been removed by operation relates to the size and spread of the cancer and in particular whether there is spread to the lymph glands. Small tumours, less than 2cm, may not have spread to the lymph glands, but above this size spread is usual. Pancreas cancer spreads to other organs early and although not detected by the preoperative scans, it is common that secondaries will start to show up at about one year from operation.

The usual site of recurrence is in the liver and lungs. Local recurrence may also occur; this is in the location where the tumour used to be and is as a result of some cancer cells being left behind at operation, which continue to grow over time. A patient with recurrence can be treated like a patient who was inoperable at the time of diagnosis and receive palliative chemotherapy. The overall five-year survival or cure rate from pancreas cancer after operation remains dismally low at less than 5 per cent. As yet no good chemotherapy exists and early diagnosis remains an elusive goal.

**Other pancreatic tumours**

Cancers of the pancreas other than those described above are rare. Pancreatic neuroendocrine tumours, which are cancers arising from the hormone-secreting cells within the pancreas, have an incidence of about 1 in 500,000 and are slightly more common in men. The majority (>90 per cent) do not secrete hormones. In general they are thought to grow very slowly. The presentation is usually with symptoms of pain in the upper abdomen and not uncommonly the tumour is large and already shows spread to the liver. Even if this type of cancer has spread to the liver, it is usually the case that several effective lines of treatment can be deployed and the cancer kept under control for many years.

An insulinoma is a type of neuroendocrine cancer of the pancreas that does secrete hormone. Uncontrolled insulin secretion from the insulinoma results in very low blood sugars, which can manifest as fainting, sweating, rapid pulse and anxiety. Clearly this is very dangerous and insulinomas require urgent removal. They are usually small and can be very difficult to locate within the pancreas; often lengthy investigations are required.

Other tumours of the pancreas are yet rarer and include acinar cancer, lymphoma and sarcoma. The prognosis of these is variable, but the presentation is often similar to pancreatic cancer, and the initial investigations are the same.

**Declaration of interests:** none declared.

**REFERENCES**