Investigation of pancreatic disease

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The diagnosis of pancreatic disease is often difficult because of its retroperitoneal location and the non-specific nature of abdominal pain. There is no one test which provides all the information needed, and a series of complementary tests are generally required. This article discusses the different modalities available for investigating the patient with pancreatic disease.

The relative inaccessibility of the pancreas to direct examination and the non-specific nature of abdominal pain make the diagnosis of pancreatic disease difficult. Even when patients present with clinical signs suggestive of pancreatic disease, other biliary tract pathology causing the clinical picture must be considered as the therapeutic options vary substantially. There is no one test that provides all the information needed. Therefore the clinician caring for patients with pancreatic disease must use a series of investigations that complement each other to make an accurate diagnosis and evaluate whether conservative management or surgical intervention is required. This review is designed to outline the different modalities available for investigating patients with pancreatic disease.

LABORATORY INVESTIGATIONS

Pancreatic function tests

The pancreas has a considerable functional reserve. At least 80% of the gland must be destroyed before the patient has overt signs of glucose intolerance or exocrine insufficiency. Exocrine failure is manifest as steatorrhoea since alternate pathways can aid the digestion of amino acids and carbohydrates.

Exocrine function testing has undergone many changes; the 'traditional' invasive tests requiring duodenal intubation, which give the most accurate data (Dreiling, 1975), are now largely historical. Three-day faecal fat collection is time-consuming and unpopular in the laboratory, although faecal chymotrypsin in stool is relatively easy to measure. The most widely used tests at present are the 'tubeless' tests, of which pancreolauryl is the authors' preferred investigation. In the presence of pancreatic esterase, fluorescein dialurate taken orally is hydrolyzed to fluorescein and absorbed. Urinary fluorescence is measured and expressed as a ratio of the figure obtained on a separate day when fluorescein is given alone to test interstitial absorptive capacity. A value of less than 30% is indicative of pancreatic insufficiency (Barry et al, 1982).

Endocrine function testing is performed with a standard 75 g oral glucose tolerance test, followed by baseline and then serial serum glucose measurements. Long-term glucose control can also be measured by glycosylated haemoglobin.

In the surgical patient with pancreatic disease, predominantly chronic pancreatitis, endocrine and exocrine function should be assessed before and after operation (Jalleh and Williamson, 1992).

Tumour markers

Pancreatic carcinoma may be difficult to diagnose even when it presents clinically as obstructive jaundice. Pancreatic masses can be caused by many conditions other than neoplasm. A number of tumour markers have been identified for pancreatic carcinoma (CA19-9, CA 50, CA 195, Du-PAN 2, Span-1, TAG-72, POA), yet in clinical practice no one test has adequate sensitivity or specificity. CA19-9, a carbohydrate antigen, is the most promising known marker, but unfortunately it can also be raised in the presence of chronic pancreatitis. For this reason tumour markers have no role in the screening for early cancer in the asymptomatic patient (Klapdor, 1997), nor are they valuable in preoperative staging.

A CA19-9 level of greater than 40 μg/litre has been shown to have a sensitivity of 83% for pan-

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creatic cancer and a specificity of 68% in patients presenting with jaundice and weight loss. As the cut-off value increases so too does the sensitivity. Surgeons should base the decision concerning resectability on the results of imaging and intraoperative findings; however, in a patient with extremely elevated CA19-9 (i.e. above 10 000 u/ml), irresectability is the rule. Functioning neuroendocrine tumours can be diagnosed by the clinical syndromes they produce, and the hormones they elaborate can be isolated and quantified, although they are not true tumour markers.

PREOPERATIVE IMAGING

Conventional radiography

Plain abdominal X-rays are of limited value in pancreatic disease. In acute pancreatitis they may demonstrate a localized ileus (sentinel loop, colon cut-off) or pleural effusion. In chronic pancreatitis the presence of pancreatic calcification is a useful confirmatory sign, although computed tomography (CT) scanning is more sensitive in this regard. The value of plain radiographs lies in their ability to help exclude other pathological processes contributing to the patient's presentation (Freeney and Lawson, 1997).

Ultrasound

Real-time scanners with high resolution provide excellent anatomical definition of the pancreas, biliary tree and adjacent blood vessels. The ability to visualize the pancreas in the setting of acute pancreatitis is difficult because of the overlying bowel gas associated with an ileus. In the non-acute setting, ultrasound (US) can demonstrate swelling of the gland, associated fluid collections and dilatation of both the biliary and pancreatic ductal system. The addition of Doppler scanning demonstrates vascular compression and subsequent turbulent flow or occlusion of the portal vein and its tributaries (Benson and Gandhi, 2000).

US scanning should be the first investigation in a patient with obstructive jaundice to confirm the presence of extrahepatic biliary dilatation and the likely cause, whether gallstone or tumour. Endoscopic US has become an important modality in assessing pancreatic masses, especially when they are small (<3 cm) (Muller et al, 1994) or of neuroendocrine origin; it provides additional information regarding vascular and possible lymph node involvement. It must be remembered that enlarged lymph nodes may only be reactive and not necessarily malignant. A newer experimental technique of intraductal ultrasonography has been reported (Furukawa et al, 1994).

Computed tomography

This is the single most useful investigation for the pancreatic surgeon. The information obtained is similar to that obtained with ultrasonography, but the images are easier to interpret and are less operator-dependant. There are many different protocols for image acquisition, but in the authors' opinion a special pancreatic protocol using 5 mm slices, a spiral technique and intravenous contrast enhancement is optimal (Coley et al, 1997).

In acute pancreatitis, CT provides valuable prognostic information and helps to determine whether operative intervention is necessary (i.e. infective pancreatic necrosis). In chronic pancreatitis, CT provides data regarding the presence of an inflammatory mass, calcifications, duct ectasia, pseudocyst and involvement of adjacent viscera (*Figure 1*). In neoplastic disease it provides accurate information with regard to vascular anatomy, resectability and tumour stage.

Magnetic resonance imaging

This technique is increasingly used in the preoperative assessment of pancreatic disease. At present it is not considered to be superior to CT scanning, although it does have the added advantage of non-invasive imaging of the biliary tree. Magnetic resonance cholangiopancreatography relies on the differential images cast by fluid and solid structures in a strong magnetic field (*Figure 2*). It requires no ductal cannulation and therefore does not have the complications associated with endoscopic retrograde cholangiopancreatography (ERCP). At present the delineation

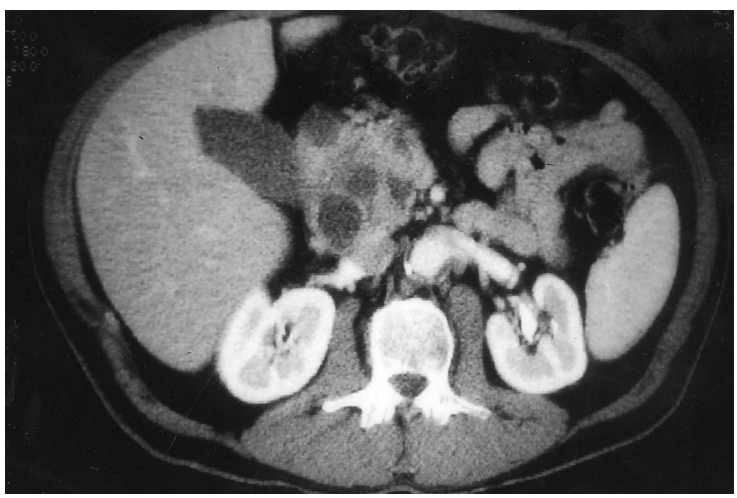

Figure 1. Computed tomography scan showing multiple pseudocysts in pancreatic head.

Figure 2. Magnetic resonance cholangiopancreatography showing bile duct stone in distal common bile duct.

of the anatomy is not as good, nor can interventional techniques be employed (Sica et al, 1999). Similarly magnetic resonance angiography (MRA) is increasingly used.

Positron emission tomography

This experimental technique has been shown to aid in the diagnosis of pancreatic cancer and to help differentiate it from chronic pancreatitis. A sensitivity of 94% and a specificity of 88% for the diagnosis of malignancy have been reported (Friess et al, 1995). The principle of positron emission tomography (PET) is based on functional changes that occur in pancreatic cancer cells caused by enhanced glucose metabolism. A glucose analogue 2(18F)-fluoro-2-deoxy-D-glucose (FDG) — a radiopharmaceutical that closely resembles the endogenous compound but remains in the abnormal tissue longer — makes an ideal tracer to be used with PET (Berberat et al, 1999).

Cholangiopancreatography

Over the last 30 years ERCP has assumed a dominant role in pancreatic imaging. The procedure is carried out under intravenous sedation with a side-viewing duodenoscope to visualize the ampulla and cannulate the biliary and pancreatic ducts. In acute pancreatitis, ERCP may demonstrate the causative gallstone in the bile duct and allow extraction by means of endoscopic sphincterotomy. In chronic pancreatitis, ERCP plays a crucial role in delineating pancreatic duct size and allowing a rational choice between duct drainage and resection.

Assessment of disease severity can be based upon ERCP criteria and will show communication with pseudocysts and associated pancreatic strictures besides bile duct stenosis or calculi. It also permits endoscopic therapies either as an adjunct to subsequent surgical intervention, or as definitive or palliative therapy for benign and malignant conditions.

ERCP is an invasive investigation with a complication rate of 1–3%. The most prevalent complications are acute cholangitis, acute pancreatitis, duodenal perforation and haemorrhage. Sometimes ERCP is technically impossible, for example with previous Billroth II gastrectomy or gastric outlet obstruction. In this instance percutaneous transhepatic cholangiography is a useful alternative to visualize and decompress an obstructed biliary tree.

Angiography

The use of visceral angiography has diminished recently as a result of the ability of Doppler US, MRA and contrast-enhanced CT scans to demonstrate major vascular involvement in pancreatic carcinoma and chronic pancreatitis. However, coeliac and superior mesenteric arteriography remains a useful way of demonstrating the frequent vascular anomalies seen in the porta hepatis, while the venous phase films are the most sensitive way of detecting compression of the superior mesenteric, splenic or portal veins (Appleton et al, 1989). Retrograde flow or collateral circulation confirm that occlusion is present.

In the case of neuroendocrine tumours or some cystic tumours, a classical tumour blush can be demonstrated, including metastatic hepatic lesions not seen on CT (*Figure 3*). Selective venous sampling can be employed to localize small tumours. Angiography also plays an important therapeutic role in the treatment of haemobilia and haemosuccus pancreaticus.

INTRAOPERATIVE IMAGING

Laparoscopy

Staging laparoscopy is unrivaled in its ability to demonstrate previously unsuspected, small-volume intra-abdominal metastasis typically affecting the liver and peritoneum in patients with pancreatic and periampullary carcinoma who are being considered for definitive surgical

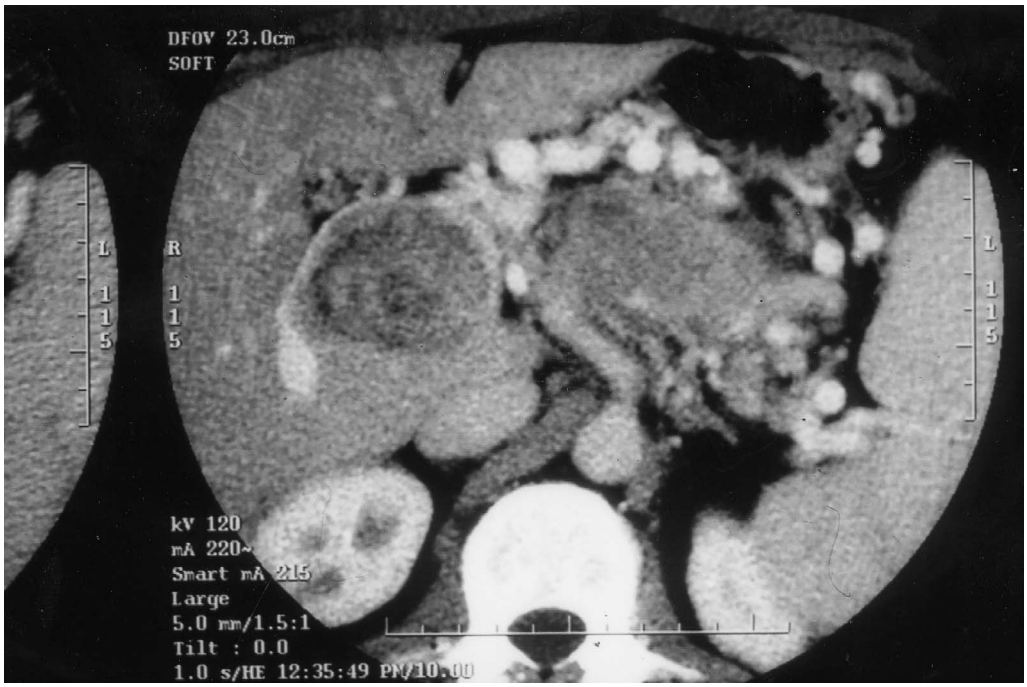

Figure 3. Computed tomography scan demonstrating large portal vein thrombosis with tumour.

intervention (Bemelman et al, 1995; Conlon et al, 1996). In addition peritoneal fluid can be sent for cytological analysis and suspicious lesions can be biopsied. There is, however, the small but definite risk of tumour dissemination and port site implantation (Fernandez-del Castillo and Warshaw, 1995).

The addition of laparoscopic US can further enhance the detection of metastatic disease within the liver as well as downgrading a CT diagnosis of metastasis by the demonstration of benign lesions such as cysts. Several studies have shown that laparoscopic US does not overstage tumour status, while detection of vascular invasion has also proved reliable with this modality (John et al, 1999).

Intraoperative US at laparotomy

Direct application of the US probe to the surface of the pancreas at open operation provides high-resolution images. This technique, intraoperative US at laparotomy (IOUS), is of particular value in identifying small endocrine tumours, but it can also be used to demonstrate the pancreatic duct and vascular structures. IOUS is always used in conjunction with bimanual palpation. In a further attempt to increase the detection of portal vein involvement in pancreatic cancer, intravascular US has recently been employed (Nakao and Keneko, 1999). At present this procedure can only be viewed as experimental.

Operative pancreatography

Despite improvements in preoperative imaging of the pancreatic ductal tree, there is still a role for operative pancreatography (Desa and Williamson, 1990). On-table pancreatography is particularly valuable in chronic pancreatitis when ERCP has failed to demonstrate the entire pancreatic ductal tree (*Figure 4*). Ductography or cystography can be used to demonstrate a duct-pseudocyst communication or to pursue an unexpected finding.

PANCREATIC BIOPSY

There is a definite but limited role for percutaneous biopsy (fine needle aspiration or core

Figure 4. On table pancreatogram demonstrating dilated duct of chronic pancreatitis.

biopsy) of the pancreas, notably in the confirmation of diagnosis in a tumour that is clearly irresectable or in a patient who is not a candidate for laparotomy. The reported sensitivity of percutaneous fine needle aspiration in diagnosing malignant disease of the pancreas varies between 55% and 97%, with a specificity of 100% in most studies (Ihse et al, 1999). One limitation is the occurrence of false-negative results, and these should not influence the decision-making process when on clinical grounds the mass appears to be a resectable malignancy. Intraoperative pancreatic biopsy can also prove difficult because of the presence of chronic pancreatitis that so often surrounds pancreatic carcinoma.

Direct pancreatic biopsy is thought to be followed by complications such as haemorrhage, fistula, pancreatitis or abscess formation, although reported rates vary between 0 and 10% (Ihse et al, 1999). One way to lower the potential risk of complications is to use the transduodenal route when the lesion is located in the pancreatic head, so that any leakage will occur into the bowel lumen; however, the sampling may be less precise by that means. If preoperative, postoperative or palliative chemoradiotherapy is to be performed then histological confirmation of malignancy must be obtained.

CONCLUSION

The clinician caring for patients with pancreatic disease has a wide array of investigations in his/her armamentarium. When used in conjunction these techniques substantially improve the diagnostic accuracy, but a complete set in every patient would be wasteful and inappropriate. Prospective randomized trials are required to determine the value of some of the newer modalities. HM

Conflict of interest: none.

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KEY POINTS

- Ultrasound scanning should be the first investigation in a patient with obstructive jaundice.
- A computed tomography scan is the single most useful investigation for the pancreatic surgeon.
- There is no role for preoperative percutaneous pancreatic biopsy of patients who are considered operative candidates.
- Tumour markers have no role in the screening for early cancers in the asymptomatic patient.
- Staging laparoscopy with laparoscopic ultrasound is unrivalled at demonstrating previously unsuspected small intra-abdominal metastasis.
- Newer investigational techniques are being developed to help determine the resectability of malignant neoplasms.