Pancreatic cancer

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Abstract

Pancreatic cancer accounts for 3% of all cancers in the UK; 7000 new cases are diagnosed annually and a similar number die from the disease each year. It is usually diagnosed late and only about 10–20% of patients with pancreatic cancer are eligible for resection; after resection, the median survival is 11–20 months and the five-year survival is 7–25%. Patients with unresectable locally advanced disease have a median survival of 6–11 months, and those with metastatic disease have a median survival of 2–6 months. Accurate staging has a vital role in the management of pancreatic tumours now that non-surgical palliative options are available. CT is widely used in the preoperative staging of pancreatic neoplasms. With recent advances in MRI and endoscopic ultrasonography, it is now possible to improve the accuracy of preoperative staging, particularly with respect to local invasion and regional node involvement. Resection is the only treatment that offers the potential of cure; ideally, an R0 resection should be aimed for. Chemotherapy renders a survival advantage in the adjuvant setting, even in patients undergoing R1 resections. Palliative chemotherapy with gemcitabine can improve survival by 10–15% and other palliative therapies are aimed at relieving jaundice, controlling pain, treating malabsorption and reversing cancer cachexia.

Keywords pancreatic cancer; pancreatic ductal adenocarcinoma; palliative care; chemotherapy

Pancreatic cancer accounts for 3% of all cancers in the UK; 7000 new cases are diagnosed annually. The same number of patients die from the disease each year, and the incidence:mortality ratio is one. It is usually diagnosed late and only about 10–20% of patients with pancreatic cancer are eligible for resection. Pancreatic cancer is rare below the age of 40 years; >80% of the cases occur between the ages of 60 years and 80 years. There is a slight male preponderance, with a male:female ratio of about 1.4:1. The overall prognosis for the disease is dismal: after resection, the median survival is 11–20 months and the five-year survival is 7–25%. Patients with unresectable locally advanced disease (stage III) have a median survival of 6–11 months, and those with metastatic disease have a median survival of 2–6 months. The key to increased resection rates (and hence better outcome) is early diagnosis. The overall one-year survival has doubled from 6% to 12% over the past three decades due to improvements in palliative care.[1]

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Aetiology

The causes of pancreatic cancer are not known, but risk factors have been identified (Table 1). There is an inherited component in 10% of patients with pancreatic cancer in the absence of familial pancreatic cancer and other cancer syndromes. Familial pancreatic cancer is transmitted in an autosomal dominant manner with about 17–19% of the families having BRCA2 mutations. Pancreatic cancer may occur as part of other cancer syndromes:

- familial atypical multiple mole melanoma syndrome
- Peutz–Jeghers syndrome
- hereditary non-polyposis colorectal cancer
- familial breast-ovarian cancer syndromes
- familial adenomatous polyposis.

Pathology

The commonest exocrine tumour of the pancreas is ductal adenocarcinoma, which accounts for >80% of tumours (Table 2). About 65% of these tumours are in the head of the gland, 15% in the body and 10% in the tail; the remaining 10% are multifocal. There is an increased activation of proto-oncogenes such as K-ras, which is present in 80–90% of ductal adenocarcinomas, as well as inactivation of tumour, suppressor genes (e.g. p53) and signalling molecules such as SMAD4 and p16. Ductal adenocarcinoma is an aggressive tumour, with perineural infiltration, vascular invasion and lymph node metastases being common. Distant metastases occur early in the disease, usually to the liver, peritoneal cavity and the lungs.

Risk factors for pancreatic cancer

- Cigarette smoking is the most consistent risk factor and may be present in 25–30% of cases
- Chronic pancreatitis is associated with a 5–15-fold increased risk
- Hereditary pancreatitis (autosomal dominant–cationic trypsinogen gene) is associated with a 50–70-fold increased risk
- Diet (high intake of fat and protein; low intake of fruit and vegetables; coffee consumption; grilling or charring of food)
- Alcohol intake
- Occupations (chemists; workers in the coal, gas and metal industries)
- Adult-onset diabetes mellitus of <two years' duration
- Pernicious anaemia
- Cholelithiasis
- Previous gastric surgery

Table 1

Types of malignant tumours of the exocrine pancreas in adults

Type of tumour	Frequency (%)
Ductal adenocarcinoma	80–90
Anaplastic carcinoma	5
Others	5–10
Mucinous cystadenocarcinoma	
Mucinous non-cystic adenocarcinoma	
Acinar cell carcinoma	
Adenosquamous carcinoma	
Small cell carcinoma	
Squamous cell carcinoma	
Intraductal papillary mucinous tumours	

Table 2

Cystic tumours of the pancreas and intraductal papillary mucinous neoplasms are described in 'Pathology of exocrine neoplasms of the pancreas', page 65; neuroendocrine tumours of the pancreas are discussed in 'Miscellaneous conditions of the pancreas', page 95.[2,3]

Clinical features

The early symptoms of pancreatic cancer are non-specific (epigastric and diffuse abdominal pain, bloating, flatulence, general malaise, diarrhoea, vomiting, constipation) and easily missed. Late symptoms include localized abdominal pain, radiation to the back in cases of retroperitoneal infiltration, weight loss and jaundice. Acute and chronic pancreatitis, acute cholecystitis, upper gastrointestinal haemorrhage, neuropsychiatric disturbances, polyarthritis, painful skin nodules, pyrexia of unknown origin are also possible presentations. Important signs include an upper abdominal mass, icterus, hepatomegaly, splenomegaly, palpable gallbladder (Courvoisier's sign), periumbilical nodules (Sister Mary Joseph's node), ascites, and peripheral oedema. Migratory thrombophlebitis (Trousseau's sign) is reported in about 10% of pancreatic cancers and may be the only presenting sign. Recent-onset diabetes mellitus in older patients is present in 5% of patients and should serve as a warning sign. Physical signs usually indicate advanced disease. Tumours of the body and tail are often asymptomatic and usually present at an advanced stage, and have a worse prognosis than those in the head of the gland.

Diagnosis and investigations[4–6]

Haematological and biochemical tests

Haematological and biochemical tests are usually non-specific. Anaemia, hypoalbuminaemia, and obstructive jaundice (see page 74) on liver function tests are usually present. A disproportionate rise in the concentration transaminases in serum is usually associated with extensive liver metastases. Malabsorption of vitamin K and decreased hepatic production of vitamin K-dependant clotting factors results in a prolonged prothrombin time. Patients with pancreatic cancer may also have diabetes or impaired glucose tolerance.

Tumour markers

Tumour markers are neither tumour-specific nor pancreatic cancer-specific. CA 19-9 has high sensitivity (80%) and high specificity (60–70%) and is the most widely used tumour marker in pancreatic cancer. It is found in increased concentrations in tumours measuring ≥3 cm. It may also be elevated in benign conditions (e.g. pancreatitis, hepatitis, cirrhosis) as well as in tumours of the stomach, colon or biliary tree. Newer markers such as CA 50, CAM 17.1, ADAM9 (a disintegrin and metalloprotease) and liver–intestine cadherin are being studied.

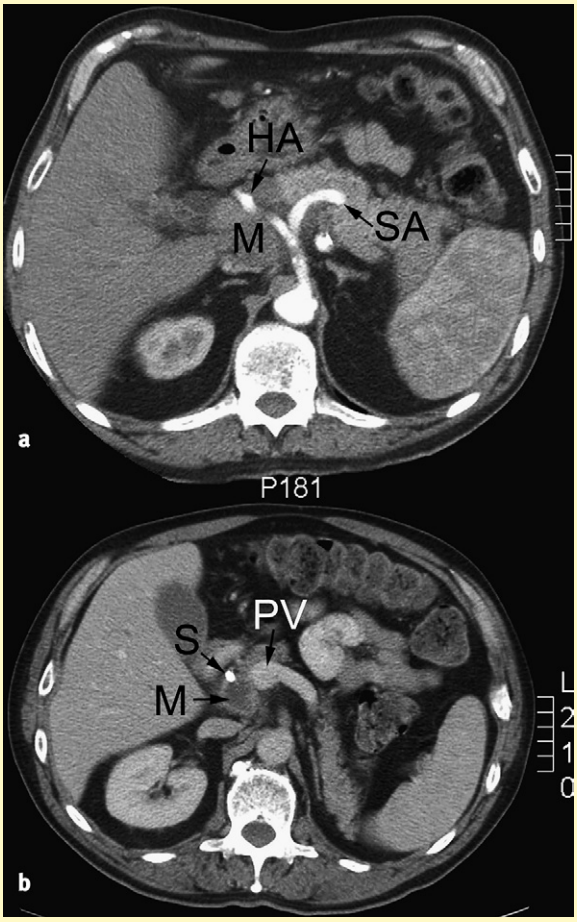
Imaging and staging

Ultrasound: transabdominal ultrasound is the initial screening investigation in patients with jaundice. It is non-invasive and can provide information about the site and size of pancreatic masses, biliary and pancreatic duct dilation, proximity of the tumour to major vessels, ascites, lymph node involvement, and hepatic metastases. Doppler ultrasound can help measure vascular invasion. Ultrasound is operator-dependent and may be inaccurate due to obesity, ascites or bowel gas. Therapeutic decisions are never based on ultrasound alone.

Contrast-enhanced CT using thin slices (3–5 mm) is the first-line imaging method for diagnosing and staging pancreatic tumours (Figure 1). Metastatic disease to the liver, peritoneum (ascites) and lung, and involvement of the peripancreatic vessels can be detected and usually indicate inoperability. Invasion into adjacent organs (e.g. stomach, colon) and lymph node involvement may also be detected, but these features do not preclude resection. The positive predictive value of contrast-enhanced CT is low; about 25–50% of patients predicted to have resectable disease on it turn out to have inoperable tumours due to small peritoneal or liver metastases and vascular invasion not detected on contrast-enhanced CT. Multidetector dual-phase contrast-enhanced CT with three-dimensional reconstruction is improving the positive predictive value.

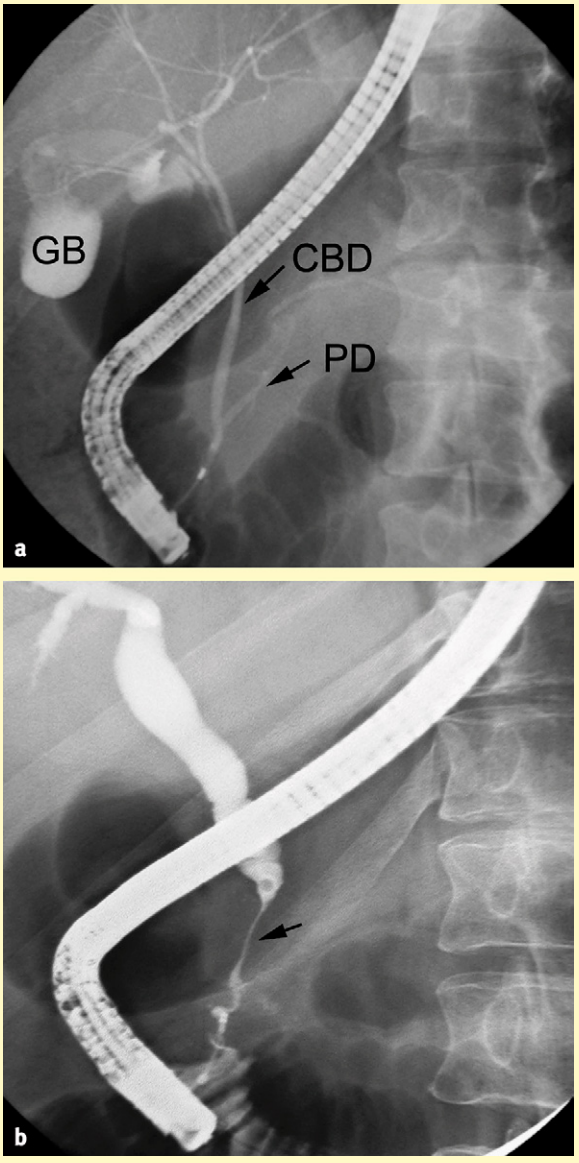
MRI offers no significant advantage over contrast-enhanced CT, more so with the advent of multidetector dual-phase contrast-enhanced CT. Magnetic resonance cholangiopancreatography (MRCP) is useful in delineating the anatomy of the biliary tree and the pancreatic duct; resolution can be improved by using gadolinium enhancement. Contrast-enhanced magnetic resonance angiography can show vascular invasion.

Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC): preoperative duct delineation is usually necessary to confirm the exact site of obstruction, exclude concurrent disease and exclude obstruction at multiple levels. PTC was often used to delineate the biliary anatomy before the widespread availability of ERCP. ERCP (Figure 2) has largely replaced PTC because it has several major advantages and, when used appropriately, can provide a definitive diagnosis. This is important because only one-third of tumours <2 cm in size are detected by CT. The advantages of ERCP over PTC are that it avoids liver puncture (with the accompanying risk of bile leakage and haemorrhage) and allows exclusion of other gastroduodenal disease, diagnosis of periampullary tumours and imaging of the pancreatic duct. Brushing and biopsy specimens can also be obtained for cytological and histological examination.



a CT of a patient with unresectable pancreatic cancer. A large mass in the head of the pancreas (M) is involving the hepatic (HA) and splenic arteries (SA). **b** CT of a patient with resectable pancreatic cancer. The mass in the head of the pancreas (M) is close to, but not involving, the portal vein (PV). A biliary stent (S) is also seen.

Figure 1



a Endoscopic retrograde cholangiopancreatography (ERCP) showing a normal gallbladder (GB), common bile duct (CBD) and pancreatic duct (PD). **b** ERCP in a patient with pancreatic cancer. An irregular stricture (arrow) is visible in the distal common bile duct.

Figure 2

Stenting – ERCP and PTC allow the insertion of biliary stents and a combined PTC–ERCP approach may be necessary if access is difficult. Preoperative biliary stenting is controversial. A recent meta-analysis has suggested that it did not offer benefit and should not be routinely done, particularly because most of the anatomical information can be obtained using CT, MRI or MRCP.[7] Stenting provides ideal palliation for patients with jaundice who have unresectable or metastatic disease or are not fit for resection. Expandable metal stents offer excellent palliation. On the basis of current evidence, ERCP/PTC and stenting should not be used routinely in patients with resectable tumours because it may increase the rate of septic postoperative complications.[7] Pragmatically, stenting may be necessary if it is anticipated that surgery will not be undertaken for several weeks or if the concentration of bilirubin in serum is rising rapidly.

Endoscopic ultrasound is a relatively new technique. It produces high-resolution images of the pancreas using a high-frequency ultrasound probe at the end of an endoscope placed in the stomach and duodenum in close proximity to the pancreas. It may be the most accurate test for the diagnosis of pancreatic cancer; it has a higher sensitivity and specificity, particularly in evaluating tumours <3 cm in diameter, when compared to CT. Endoscopic ultrasound has a high accuracy for detecting local invasion and nodal metastases from pancreatic cancer, although results are similar when compared with dual-phase multislice multidetector CT, which also provides information about hepatic metastases. The side-viewing duodenoscope that delivers the ultrasound probe also permits the detection of ampullary and duodenal

carcinomas, and targeted fine-needle aspiration or core biopsies can be taken transduodenally under ultrasound guidance.

PET is a non-invasive imaging tool that provides metabolic (rather than morphological) information on tumours (see Chambers, CROSS REFERENCES). Malignant tissues show a higher uptake of fludrodeoxyglucose than normal surrounding tissues. PET is useful in the diagnosis of small tumours (<2 cm) and in the detection of extrapancreatic disease (e.g. peritoneal or omental metastases). Anatomical and functional imaging can be obtained simultaneously using PET–CT.

Laparoscopy

Staging laparoscopy may be undertaken before definitive surgery if imaging is inconclusive. Laparoscopy can be combined with intraoperative ultrasound to define pancreatic lesions and to exclude subtle liver metastases that may have been missed by other imaging.[8] Routine laparoscopy is not recommended because it influences the management in fewer than 14% of patients with pancreatic cancer.

Curative treatment

Pancreatic cancers are staged using the TNM classification.[6] Accurate staging has a vital role in the management of pancreatic tumours now that non-surgical palliative options are available. CT is widely used in the preoperative staging of pancreatic neoplasms. With recent advances in MRI and endoscopic ultrasonography, it is possible to improve the accuracy of preoperative staging, particularly with respect to local invasion and regional node involvement. An algorithm for the diagnosis and treatment of pancreatic cancer is shown in Figure 3.

Surgery[4,6]

Resection is the only treatment that offers the potential of cure. Ideally, an R0 resection (Table 3) should be aimed for: the long-term survival of patients having R1 and R2 resections is significantly less than that of those having R0 resections.

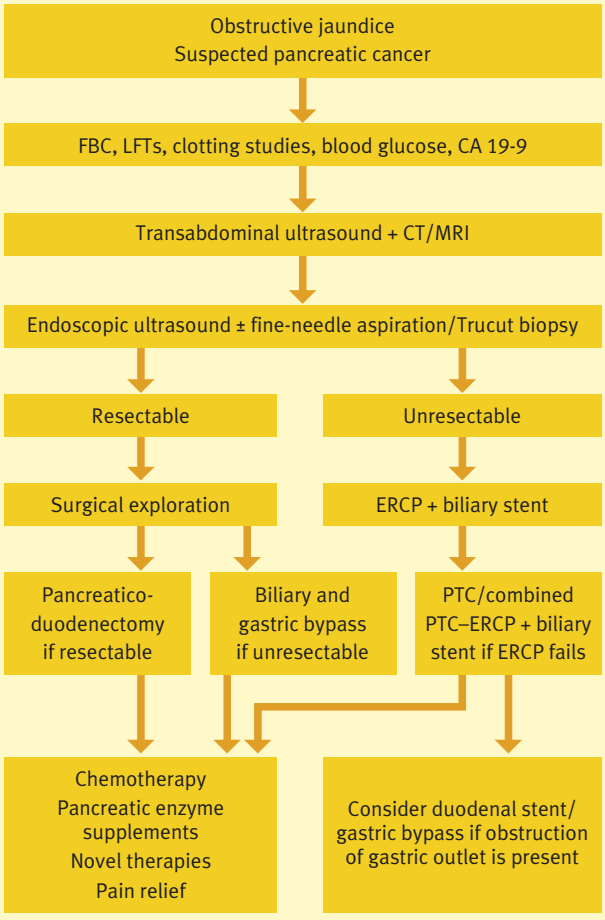
Preoperative staging should help select patients with resectable disease and patients should be assessed for medical fitness for surgery. Contraindications to resection include:

- liver, lung and peritoneal metastases
- distant lymph node metastases
- major encasement (>2 cm in length, >50% circumference) of the portal or superior mesenteric veins
- encasement of the superior mesenteric, coeliac or hepatic arteries
- cirrhosis with portal hypertension
- medical comorbidities precluding major surgery.

Tumour infiltration into the duodenum, stomach or colon, lymph node metastases within the operative field, encasement of the gastroduodenal artery and minimal invasion of the superior mesenteric or portal vein do not contraindicate resection. Resection should be undertaken in high-volume, specialized centres.

Fluid and electrolyte deficits and clotting abnormalities should be corrected before surgery. Most pancreatic cancers arise in the head of the gland and resection of these tumours can be achieved by the classical Kausch–Whipple procedure or a pylorus-preserving pancreaticoduodenectomy (Figure 4); better

Diagnosis and treatment of cancer of the pancreatic head



Discussion with the multidisciplinary team is held at all stages of the diagnostic and treatment process.

FBC: Full blood count; LFTs: Liver function tests; CA 19-9: carbohydrate antigen 19-9; ERCP: Endoscopic retrograde cholangiopancreatography; PTC: Percutaneous transhepatic cholangiography.

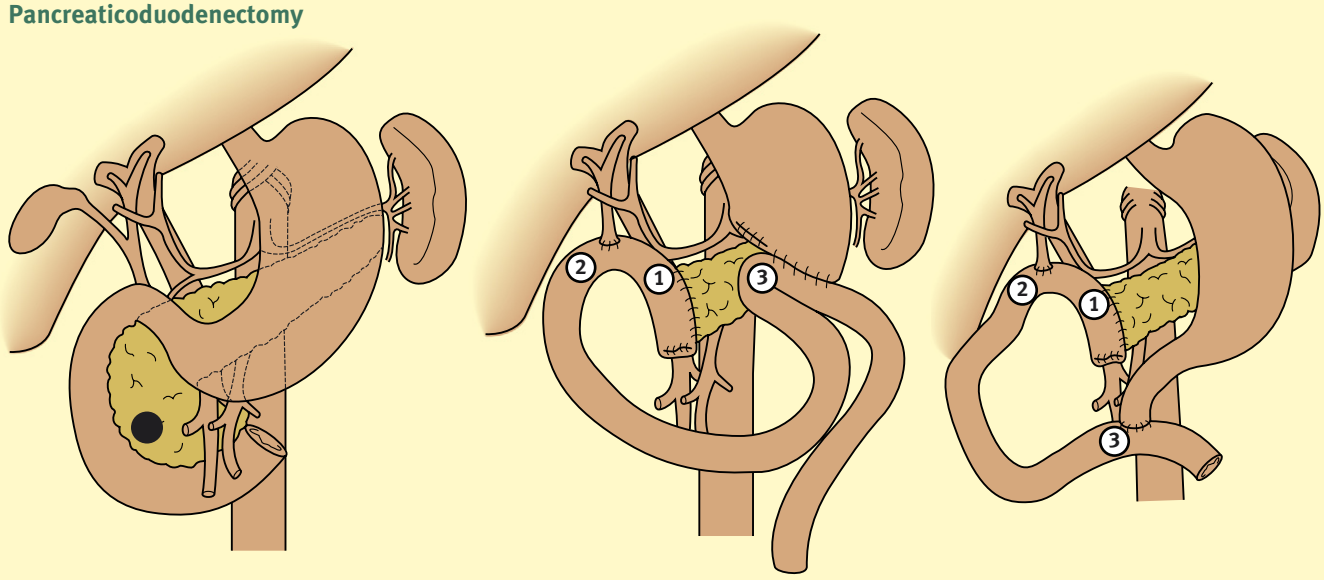
Figure 3

Completeness of resection

Resection	Description
R0	Complete clearance of macroscopic tumour with clear histological resection margins, even if lymph node metastases are present
R1	Complete clearance of macroscopic tumour with positive histological resection margins
R2	Incomplete resection of macroscopic tumour

Table 3

Pancreaticoduodenectomy



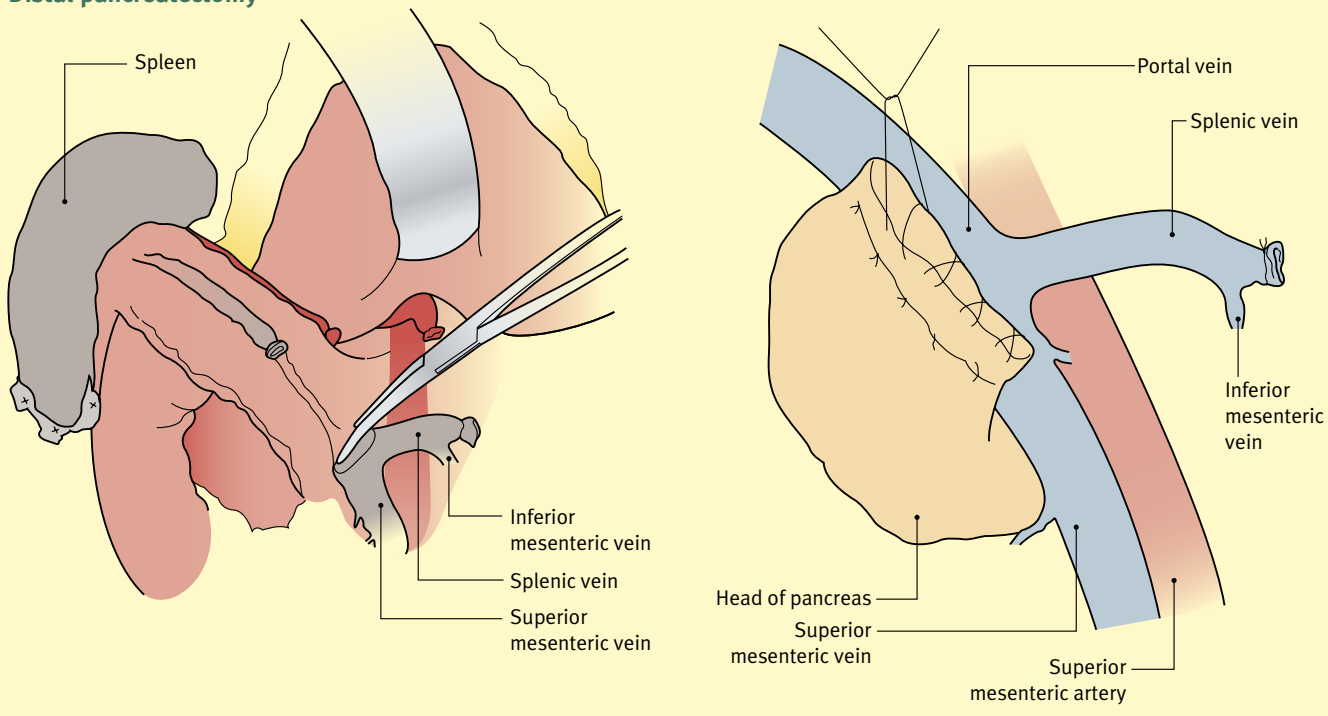
a Undissected anatomy of a patient with a cancer of the pancreatic head

b Classical Kausch–Whipple reconstruction (1: Pancreaticojejunostomy; 2: Hepaticojejunostomy; 3: Gastrojejunostomy)

c Reconstruction after a pylorus-preserving pancreaticoduodenectomy (1: Pancreaticojejunostomy; 2: Hepaticojejunostomy; 3: Duodenojejunostomy)

Figure 4

Distal pancreatectomy



a Splenectomy and distal pancreatectomy: posterior dissection

b Pancreatic remnant after a distal pancreatectomy

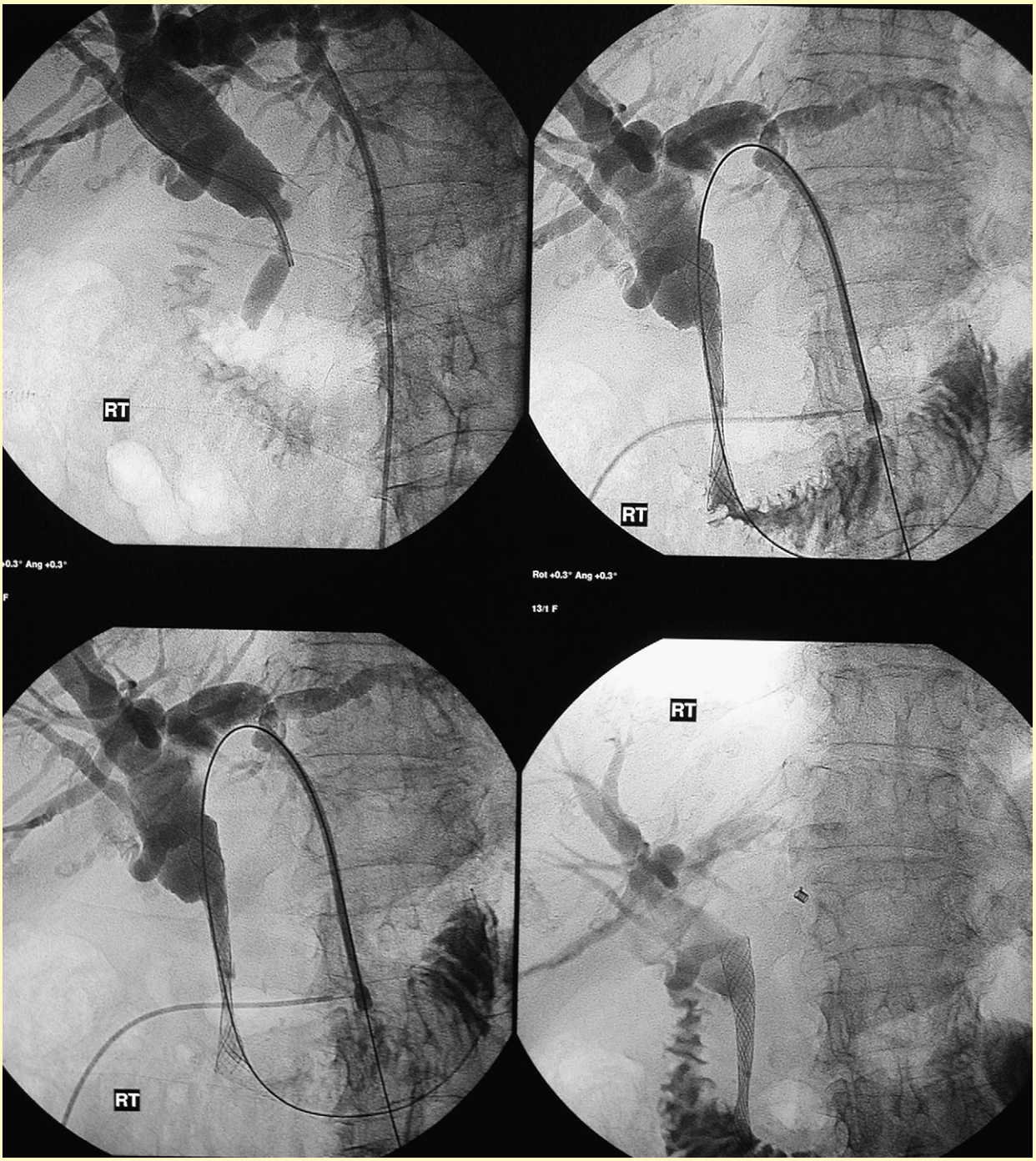
Figure 5

postoperative gastric function is achieved by the latter. The operation consists of three stages:

- assessment of resectability
- resection
- reconstruction.

There are several ways, in addition to what has been depicted in the figures, to restore gastrointestinal continuity after resection. There is no role for total pancreatectomy unless this is the only way to achieve an R0 resection. There is no evidence that an extended lymphadenectomy ± portal vein resection is superior to a standard lymphadenectomy. A distal (left) pancreatectomy with splenectomy and *en bloc* lymph node dissection (Figure 5) is indicated for cancers in the body and tail of the gland.

A surgical mortality of <5% has been achieved in most specialized centres, but resection for pancreatic cancer has a



Percutaneous transhepatic cholangiogram showing a distal common bile duct stricture and deployment of an expandable metal stent.

Figure 6

morbidity rate of >30%. In addition to the medical complications that accompany complex surgery, major surgical complications include pancreatic fistulae, delayed gastric emptying, haemorrhage, wound infection, intra-abdominal sepsis, acute pancreatitis, portal vein thrombosis, chylous ascites and bile leaks. Postoperative therapy using the somatostatin analogue octreotide (50 μg s.c. t.d.s. for 5–7 days) may help reduce the incidence of pancreatic fistulae. The reoperation rate is about 10% and the mortality rate for reoperations can be up to 60%.

Prognosis and adjuvant therapy: the most important prognostic markers for survival after pancreatic resection are lymph node status, tumour size, tumour grade and resection margin status.[9,10] Median survival after pancreatic resection is 11–20 months and five-year survival is 7–25%. Most patients develop recurrent disease within two years of surgery, usually at the resection site, peritoneum and liver. Neoadjuvant therapy has been advocated to increase resection rates and decrease the occurrence of positive resection margins, but evidence for benefits is limited.

The recently published ESPAC-1 trial compared 5-fluorouracil-based chemotherapy, chemoradiotherapy, a combination of the two, and no treatment in the adjuvant setting.[9] It showed that there was a survival benefit with chemotherapy, but chemoradiotherapy did not render a survival benefit. These effects were also observed in patients who had R1 resections, and adjuvant chemotherapy is now recommended for patients with pancreatic cancer. Adjuvant chemotherapy with 5-fluorouracil, doxorubicin and mitomycin-C has also been shown to have a survival benefit (see WEBSITE).

Palliation[11,12]

Chemotherapy: >80% of patients with pancreatic cancer have unresectable tumours because of locally advanced disease or metastatic disease. Pancreatic ductal adenocarcinoma cells are resistant to conventional cytotoxic agents. 5-fluorouracil and gemcitabine (the agent of choice) have been used as chemotherapeutic agents in patients with advanced disease but the survival benefit has been 10–15% at best. There is no evidence that radiotherapy is better than chemotherapy alone and the results of chemoradiotherapy have also been disappointing.

Stents and surgery: palliation of jaundice can be achieved by biliary stents (ERCP or PTC) or surgery. Patients with advanced tumours, should have biliary stent insertion because they are unlikely to survive for long; patients with a good performance status and small but unresectable tumours should have a surgical biliary bypass (Roux-en-Y hepaticojejunostomy). The median life of a plastic biliary stent is 6–10 weeks and expandable metal stents provide more prolonged palliation of obstructive jaundice (Figure 6). Palliation of gastric outlet obstruction is achieved by a gastric bypass or by endoscopic placement of expandable metal stents in the duodenum.

Pain management: analgesics are recommended according to the WHO analgesic ladder. Pain may be intolerable in advanced disease and endoscopic pancreatic duct decompression, ablation (percutaneous, endoscopic ultrasound-guided, laparoscopic, or open) of the coeliac ganglia using 5% phenol or 50% ethanol and thoracoscopic division of the splanchnic nerves relieves pain. Local radiation ± chemotherapy may palliate pain.

Other measures: pancreatic enzyme supplements are useful if patients have features of malabsorption. ω-3 fatty acids (fish oil) and thalidomide may help reverse the cachexia associated with advanced pancreatic cancer and improve quality of life.

New therapies are in the development stage and include gene therapy (replacement of tumour suppressor genes, suicide-gene therapy, oncolytic-virus therapy, targeting apoptotic pathways and immunomodulatory gene therapy), anti-angiogenic therapy and immunotherapy. These should be used only in randomized clinical trials.

Macmillan Nurses liaise between health professionals in the hospital and the community; they provide emotional and psychological support for the patient and carer throughout the illness (see Wilcock, CROSS REFERENCES). ◆

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WEBSITE

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