Pancreatic cancer

Sanjay Dindyal
Duncan Spalding

Abstract

The most common form of pancreatic cancer is pancreatic ductal adenocarcinoma. The long-term outcome of pancreatic cancer is extremely poor: the overall median survival from diagnosis is 3–6 months without treatment, increasing to around 23 months with resectional surgery and adjuvant treatment. Pancreatic cancer is usually diagnosed late and has a biological phenotype characterized by resistance to all cancer treatment modalities and early metastasis. Jaundice is the most common presenting symptom. Endoscopic stent placement is preferable to transhepatic stenting. The average patency of metal biliary stents is about twice that of plastic stents, the latter lasting about 4 months. Curative surgery is rare. Pancreatoduodenectomy is the most appropriate resectional procedure for tumours of the head of the pancreas. The operation should be confined to specialist centres to reduce morbidity and mortality and increase resection rates. Adjuvant treatment is recommended for those who undergo resection with curative intent. Efforts should be made to obtain a tissue diagnosis in patients selected for palliation. In the event of gastric outlet obstruction, endoscopic duodenal stenting should be used in addition to palliative endoscopic biliary stenting. If chemotherapy is used for palliation, the combination chemotherapy regimen of FOLFIRINOX (leucovorin (folinic acid), 5-FU, irinotecan, oxaliplatin) is currently the treatment of choice.

Keywords Chemotherapy; MRCP; palliative care; pancreatic cancer; radiation therapy; surgery

Key points

- The most common form of pancreatic cancer is pancreatic ductal adenocarcinoma
- The long-term outcome of pancreatic cancer remains poor, with an overall median survival from diagnosis of 3–6 months without treatment and 23 months with resectional surgery and adjuvant treatment
- The most common presenting symptoms are painless progressive jaundice, weight loss and anorexia
- Appropriate investigations include CA19-9 tumour markers, dual-phase spiral CT, endoscopic ultrasound and endoscopic retrograde cholangiopancreatography
- Treatment modalities consist of resectional surgery for localized tumours and vary according to the exact site of the tumour
- Adjuvant therapy should follow pancreatic resection with curative intent
- The combination chemotherapy regimen of leucovorin (folinic acid), 5-fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) is the first-line treatment for patients with metastatic pancreatic cancer with a good performance status
- Palliative treatment remains an option for symptom control in patients with non-resectable pancreatic cancer

Introduction

The most common form of pancreatic cancer is pancreatic ductal adenocarcinoma. It has the highest ratio of diagnosis to mortality of all pancreatic tumours. The overall median survival from diagnosis is 3–6 months without treatment, increasing to around 23 months after resectional surgery and adjuvant treatment. Pancreatic cancer is usually diagnosed late and has a biological phenotype characterized by resistance to all cancer treatment modalities and early metastasis. Curative surgery is rare and requires specialized expertise, found in a limited number of centres.

Sanjay Dindyal *BSc MB BS MRCS(Eng) is a Specialist Trainee in General Surgery at Hammersmith Hospital, London, UK. Competing interests: none declared.*

Duncan Spalding *BSc(Hons) MD FRCS(Eng) FRCS(Gen Surg) is Senior Lecturer and Honorary Consultant Hepatopancreaticobiliary Surgeon at Imperial College and Hammersmith Hospital, London, UK. Competing interests: none declared.*

Epidemiology

In the UK and USA, the annual incidence of pancreatic cancer is approximately 100 per million population; it is the fourth most common cancer resulting in death in these countries. Incidence and mortality are roughly equivalent. In the UK in 2015, there were 9921 new cases of pancreatic cancer and 9263 deaths from pancreatic cancer. The incidence is higher in developed or industrialized countries in general. The disease is rare before the age of 45 years, and approximately 80% of cases occur at 60–80 years of age. Worldwide, pancreatic cancer is more common in men than women, with a male-to-female ratio of between 1.5:1 and 2:1, but recent UK figures suggest that this male preponderance has declined in the last two decades to 1.25:1.

Aetiology

Several risk factors for pancreatic cancer have been identified, the most established being cigarette smoking, which may account for approximately 25–30% of cases. Patients with chronic pancreatitis have up to 18-fold higher risk, and there is a relative risk of 1.8 in people with type 2 diabetes mellitus compared with the general population. Data on the effects of other diseases, such as cholelithiasis, previous gastric surgery and pernicious anaemia, are considered weak overall. Other potential factors that have been examined in detail include diet (high fat and protein, low fruit and vegetable intake), coffee consumption,

alcohol and occupational exposure (to insecticides, aluminium, nickel or acylamide), although data are not robust.

Hereditary pancreatitis is associated with a 50–70-fold risk, and a 40% cumulative lifetime risk to the age of 75 years. Mutations of *PRSS1*, *SPINK1* and *CFTR* are those most commonly linked to hereditary pancreatitis. An increased risk of pancreatic cancer can occur as part of other familial cancer syndromes, including familial atypical multiple mole melanoma (mutation of the CDKN2A gene impairing the inhibitor function of proteins p16[INK4], p15[INK4b], or p18[INK4c]), Peutz–Jeghers syndrome (mutation of the tumour suppressor gene *STK11*), hereditary non-polyposis colon cancer (Lynch's syndrome; mutations of the mismatch repair genes *MLH1*, *MSH2*, *MSH6* and *PMS2*), familial breast–ovarian cancer syndromes (*BRCA1*, *BRCA2*, *PALB2*) and familial adenomatous polyposis (mutation of the tumour suppressor gene *APC*). A family history of pancreatic cancer is an important risk factor, about 7–10% of affected patients having a family history. The relative risk of patients with first-degree relatives diagnosed with pancreatic cancer compared with the general population is increased 2-, 6- and 30-fold in those with one, two and three affected family members, respectively.

Pathology

Ninety-five per cent of malignant transformations affecting the pancreas are exocrine neoplasms. Ductal adenocarcinomas of the pancreas account for >85% of these exocrine pancreatic tumours. They evolve via microscopic premalignant pancreatic lesions associated with pancreatic ducts, known as pancreatic intraepithelial neoplasias. There is a stepwise progression of pancreatic intraepithelial neoplasia from low to high grade in types 1, 2 and 3, each type accumulating clonally selected genetic and epigenetic mutations as it progresses. It has been estimated that a precursor neoplastic clone takes >10 years to evolve into a malignant clone and then several additional years for metastatic subclones to emerge.[1] Morphological variants (giant cell carcinoma, adenosquamous carcinoma, mucinous carcinoma) and acinar cell carcinoma have a similar or worse prognosis compared with ductal adenocarcinoma.

Pancreatic cancer has a propensity for perineural invasion within and beyond the gland, vascular invasion and rapid lymphatic spread. The most common sites for extralymphatic involvement are the liver, peritoneum and lung. Several other exocrine tumours arise from the pancreas, most of which – including mucinous tumours, intraductal papillary mucinous neoplasms and solid pseudopapillary tumours – carry a better prognosis than pancreatic ductal adenocarcinoma. Only 5% of malignant transformations affecting the pancreas are endocrine neoplasms, the most common being non-functioning neuro-endocrine tumours.

Clinical presentation

Trousseau's sign of migratory thrombophlebitis or venous thromboembolism has been reported in 7% of patients with pancreatic cancer, especially in the body and tail. Virchow's node (a left supraclavicular lymph node) and a Sister Mary Joseph nodule (umbilical metastatic lesion) are well-described features of advanced disease. Some 5% of patients with pancreatic cancer have developed diabetes mellitus within the previous 2 years, and many more have impaired glucose tolerance.

Carcinoma of the head of the pancreas

At least two-thirds of pancreatic cancers arise in the head of the gland.

- Jaundice is present in >90% of patients as a result of either invasion or compression of the common bile duct (CBD). The jaundice is often painless but tends to be progressive and is usually accompanied by pruritus.
- Weight loss can be prominent and occurs as a result of anorexia, malabsorption (secondary to exocrine insufficiency) and diabetes mellitus.
- Pain is present in about 70% of patients at the time of diagnosis and is usually located in the epigastrium or left upper quadrant. It is often vague in nature, and radiates to the back in 25% of patients. Back pain usually indicates posterior capsule invasion and unresectability.
- Around 5% present with an atypical attack of acute pancreatitis.
- In advanced cases, duodenal obstruction results in persistent vomiting.
- Another late manifestation is gastrointestinal bleeding as a result of either duodenal invasion or varices secondary to portal or splenic vein occlusion.
- A palpable gallbladder (Courvoisier's sign) is commonly found in jaundiced patients with malignant obstruction of the lower CBD (as opposed to ductal stones).

Carcinoma of the body and tail of the pancreas

These tumours develop insidiously and are asymptomatic in their early stages. At diagnosis, they are often more advanced than lesions located in the head. There is marked weight loss with back pain in 60% of patients. Jaundice is uncommon and usually reflects advanced cancer with involvement of the porta hepatis. Vomiting sometimes occurs at a late stage from invasion of the duodenojejunal flexure. An abdominal mass is detected more often than in cancer of the head of the pancreas, and often indicates unresectability. Indeed, most cancers outside the head of the pancreas are beyond the realms of surgical cure at the time of diagnosis, because of either liver metastases or local invasion of the coeliac axis and superior mesenteric vessels.

Investigations

The investigation of patients with suspected pancreatic cancer should initially focus on establishing the diagnosis and assessing the patient's fitness to undergo potentially curative treatment.

- The most valuable tumour marker is carbohydrate antigen 19-9 (CA19-9; normal range 0–37 U/ml). A falsely elevated CA19-9 concentration can occur in non-malignant conditions such as pancreatitis, hepatic dysfunction and obstructive jaundice. Concentrations >200 U/ml confer 90% sensitivity, whereas concentrations in the thousands are associated with high specificity.
- Initially, the preferred radiological investigation is ultrasonography, which can identify pancreatic tumours,

dilated bile ducts and liver metastases, and exclude the presence of CBD stones.

- Dual-phase spiral computed tomography (CT) accurately predicts resectability in 80–90% of cases. CT features of potential unresectability include contiguous organ or vascular invasion, including the superior mesenteric and portal vein, coeliac axis and superior mesenteric artery, and distant metastases (Figure 1).
- Magnetic resonance (MR) imaging detects and predicts resectability with accuracies similar to CT. MR cholangiopancreatography (MRCP) provides detailed ductal images without risking the complications incurred by endoscopic retrograde cholangiopancreatography (ERCP).
- ERCP can confirm the typical 'double duct sign' (adjacent strictures in the bile duct and main pancreatic duct) and provides the opportunity for aspiration, brushings or biopsies of the bile duct system. It also offers a therapeutic modality, namely biliary stenting to relieve jaundice.
- Endoscopic ultrasonography (EUS) is highly sensitive for detecting small tumours that are equivocal on CT, and assessing vascular invasion, and provides a further opportunity for biopsy or fine needle aspiration.
- Positron emission tomography is mainly used for demonstrating occult metastases, although it is important to remember that hyperglycaemia can produce false-negative results because the chosen radiotracer is a glucose analogue.
- Laparoscopy, including laparoscopic ultrasound, can detect occult metastatic lesions of the liver and peritoneal cavity not identified by other imaging modalities. It is doubtful whether this invasive procedure is needed routinely.
- Preoperative biopsy is not required for a potentially resectable tumour but should be performed to confirm the diagnosis in patients who are suitable only for palliative treatment.

Resectional surgery

Patients' fitness should be determined before they are offered resection. Those with pancreatic cancer tend to be elderly and have appreciable co-morbidity. Although chronological age is less important than physiological age, all patients being considered for pancreatic resection require a complete operative work-

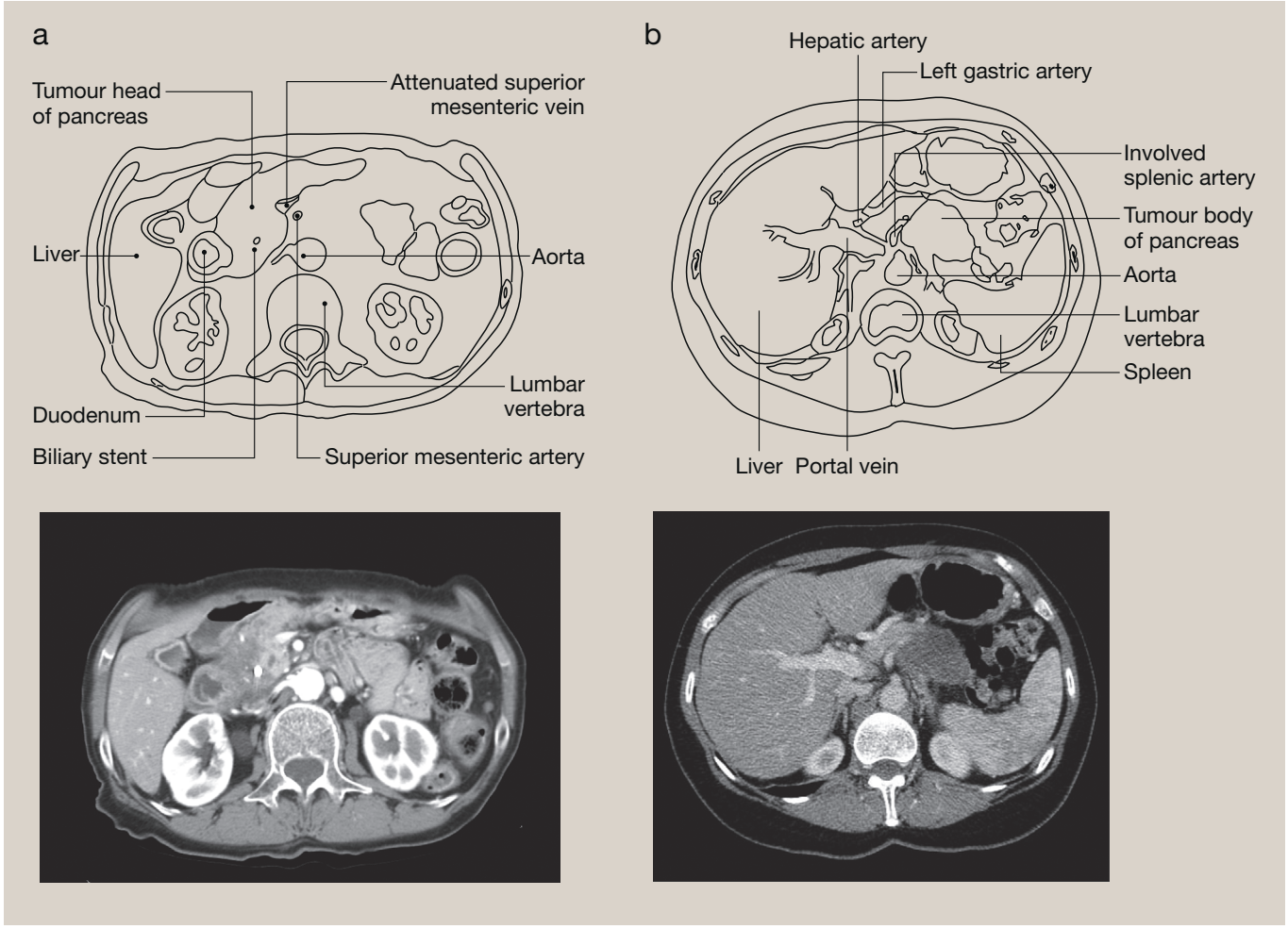

Figure 1 (**a**) CT scan showing a tumour of the head of pancreas involving the superior mesenteric vein. A plastic biliary stent previously inserted for obstructive jaundice is clearly visible. (**b**) CT scan showing a tumour of the body of the pancreas involving the splenic artery. Although the left gastric and hepatic arteries can be seen in close proximity, they are not involved and the tumour is resectable.

up. There is little evidence of benefit from routine stenting of jaundiced patients before resection. However, if operation is delayed for >10 days, it is reasonable to obtain internal biliary drainage and defer operation for up to 3 weeks to allow the jaundice to resolve. Preoperative endoscopic stenting should use plastic or covered metal stents rather than self-expanding metal ones. Biliary decompression is required on an urgent basis in jaundiced patients with acute cholangitis or renal insufficiency.

Proximal pancreatoduodenectomy

The most widely employed surgical procedure for pancreatic cancer confined to the head of the gland is the Whipple pancreatoduodenectomy, involving resection of the distal stomach, or its variant that preserves the pylorus (pylorus-preserving proximal pancreatoduodenectomy (PPPP)) (Figure 2). Operative mortality rates are <3% when undertaken in specialist centres, although the morbidity rate is still around 30%. Unfortunately, only about 20% of patients with cancer of the pancreatic head have lesions that are suitable for resection. Large series have indicated that long-term survival is comparable after PPPP and the classic Whipple operation for carcinoma of the head of the pancreas, and preservation of the entire stomach should allow improved weight gain postoperatively.

Distal pancreatectomy

This resection is indicated for a few lesions located in the body and tail of the gland and is combined with splenectomy. At the time of diagnosis, most patients have back pain and weight loss, indicating coeliac plexus involvement. The advanced nature of these lesions means that the tumours are often unresectable.

Radical pancreatectomy

More radical approaches for pancreatic ductal adenocarcinoma include total pancreatectomy; this conveys no survival advantage and has profound adverse metabolic and nutritional effects. The procedure can be justified when there is diffuse involvement of the whole pancreas without evidence of spread, and in patients already requiring insulin. However, total pancreatectomy does have a role in patients with hereditary pancreatitis, in whom the operation is performed prophylactically to prevent pancreatic cancer, and in patients with main duct intraductal papillary mucinous neoplasms, in whom disease is often multifocal and confined to the duct.

Radical and extended resections, to include the portal vein and a block of lymphatic tissue around the origins of the coeliac and superior mesenteric arteries, have been proposed. Although some centres have reported mortality rates of 3–7%, there are no data to indicate that this more radical approach is associated with increased survival. Resection of the portal or superior mesenteric vein to ensure free margins is appropriate if isolated vein involvement is discovered at operation. This extension of the procedure does not increase the operative mortality or morbidity rate, nor is long-term outcome affected. Focus has now shifted to the superior mesenteric artery, and resectability is now dictated by whether or not this is involved. Resection of the superior mesenteric artery increases postoperative morbidity and mortality rates without an improvement in survival, so this radical approach has now largely been abandoned.

Laparoscopic pancreatic resection

Advances in operative techniques and technology have led to an increase in the number of laparoscopic distal pancreatectomies (LDPs) and laparoscopic pancreaticoduodenectomies being performed. A laparoscopic approach has the potential benefits of identifying occult metastases and not delaying chemotherapy. Although retrospective, there are now enough data to confirm that LDP is a safe treatment for benign and non-invasive lesions of the pancreas. However, owing to the lack of conclusive data, it remains difficult to make clear recommendations about whether this should be the operation of choice for malignancy.

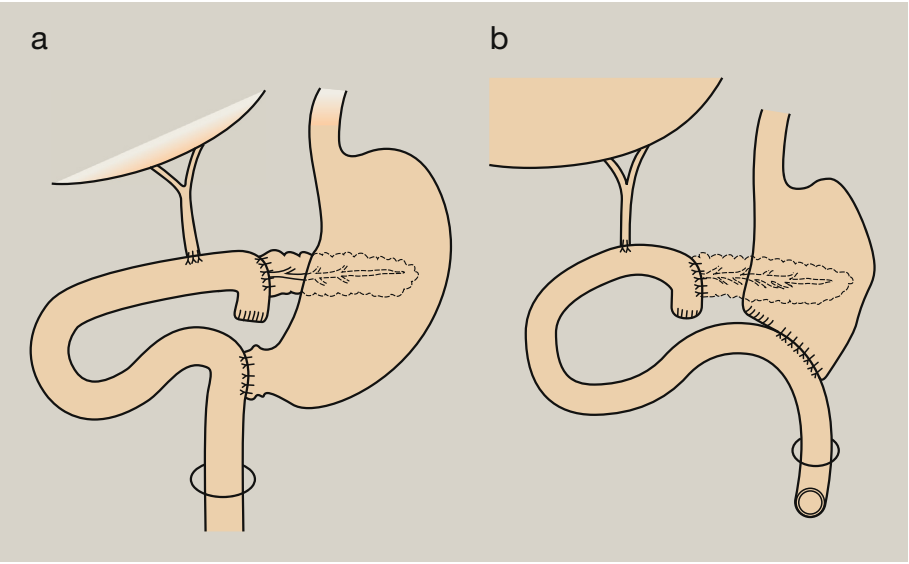

Figure 2 Reconstruction after (**a**) pylorus-preserving proximal pancreatoduodenectomy, and (**b**) Whipple's procedure.

Outcome

Long-term survival: overall, pancreatic cancer has an appalling prognosis. In most units, a true 5-year survivor after resection of pancreatic cancer is exceptional, although rates of up to 15% have been reported. Gudjonsson highlighted the poor prognosis of the disease in a review of 340 papers on pancreatic cancer in 1995.[2] An overall survival rate of <0.4% was found, the best overall survival rate among surgical studies being only 3.6%. Nevertheless, because of the lack of other options, surgical resection remains the only potential cure for pancreatic cancer, especially when it can be performed with acceptable complication rates. Even among those patients destined to develop recurrence, resection of the cancer is likely to extend worthwhile survival.

Physiology: quality of life after PPPP is generally good. Diet can be normal, although pancreatic malabsorption often requires enzyme supplementation. Diabetes mellitus is a rare complication.

Adjuvant therapy after 'curative surgery'

Adjuvant treatment is recommended for patients who undergo pancreatic resection with curative intent; this includes systemic therapy to reduce the risk of metastases, and radiation therapy to reduce the risk of loco-regional failure. A series of randomized controlled trials initially established that 6 months of chemotherapy with either fluorouracil (5-FU) or gemcitabine, when compared with observation, improved overall survival. Adjuvant gemcitabine subsequently became the standard of care based on the European Study group for Pancreatic Cancer-3 (ESPAC-3) trial, which showed similar survival and less toxicity than with adjuvant 5-FU/folinic acid (median survival 23.6 and 23 months, respectively).

More recently the ESPAC-4 trial, comparing gemcitabine and capecitabine with gemcitabine alone, has shown median overall survivals of 28 and 25·5 months.[3] In addition, and encouragingly, the Phase III Unicancer GI PRODIGE 24/CCTG PA.6 trial, comparing the adjuvant modified combination chemotherapy regimen of FOLFIRINOX (leucovorin [folinic acid], 5-FU, irinotecan, oxaliplatin) with gemcitabine has revealed median overall survivals of 54.4 versus 35 months, respectively.[4] A clear consensus regarding adjuvant chemotherapy after pancreatic resection with curative intent is now emerging, so the role of this treatment is no longer controversial.

Neoadjuvant therapy

Neoadjuvant therapy has the potential advantages of being able to down-stage borderline resectable disease, detect individuals whose disease progresses rapidly and would therefore not benefit from surgery and avoid delay in the administration of adjuvant therapy. The ideal neoadjuvant regimen is not known yet, although there has recently been growing interest in using the multiagent chemotherapy regimens that have shown activity in patients with metastatic disease (see below). Most centres currently reserve neoadjuvant therapy for patients with disease that is of uncertain suitability for resection. The ESPAC-5 trial has just finished recruiting; this Phase II study will compare immediate surgery versus chemotherapy (gemcitabine and capecitabine or FOLFIRINOX) before surgery versus chemo-radiotherapy (capecitabine) before surgery.

Palliative treatment

Because barely 20% of patients with pancreatic cancer are suitable for curative resection, good palliative therapy is extremely important.

Relief of jaundice

Older studies have shown that endoscopic stent insertion at the time of ERCP is associated with lower morbidity and procedure-related mortality rates than the percutaneous transhepatic approach. Results are better with metal than plastic stents, so this technique is appropriate for patients with better life expectancy or in whom a plastic stent has become occluded. Where stents cannot be placed endoscopically, the percutaneous transhepatic route must be used.

The results of controlled trials of palliation of obstructive jaundice by stenting or surgical bypass do not favour one method for use in all cases. The advantages of operation include unequivocal assessment of resectability, better long-term bile duct patency, a lower risk of cholangitis and the ability to perform a gastric bypass to provide prophylaxis against future duodenal obstruction. Stenting, on the other hand, has fewer immediate complications and a shorter initial treatment time. Mortality rates and median survival times are similar with the two techniques. Currently, a surgical biliary and gastric bypass is usually reserved for patients whose tumour is found to be unresectable at the time of a planned resection.

Relief of duodenal obstruction

After biliary bypass or biliary stenting alone, approximately 17% of patients develop duodenal obstruction and require subsequent intervention. For this reason, prophylactic duodenal bypass is recommended at the time of biliary bypass in those found to have unresectable disease at operation. In the palliative setting, gastric outlet obstruction is now usually relieved by an endoscopically placed self-expanding metal stent.

Relief of pancreatic pain

In addition to oral analgesics, other approaches to relieving pain include pancreatic ductal decompression by endoscopic or surgical means. Percutaneous or laparoscopic ablation of the coeliac ganglia, using 5% phenol or 50% alcohol, can provide effective palliation of pain, as can thoracoscopic division of the splanchnic nerves. Finally, external-beam radiotherapy can also provide pain relief.

Treatment of advanced pancreatic cancer

Patients with locally advanced pancreatic cancer have a median survival of 6–10 months; those with metastatic pancreatic cancer usually survive only 3–6 months. The use of radiation therapy as part of the management of locally advanced disease is

controversial as findings of randomized studies attempting to ascertain whether chemotherapy alone is preferable to chemo-radiotherapy have been inconclusive. Chemotherapy is the mainstay of treatment in advanced metastatic disease. Until recently, gemcitabine was the standard agent of choice, but in 2011 a Phase III trial comparing FOLFIRINOX with gemcitabine alone showed a significant improvement in median overall survival (11.1 versus 6.8 months) and 1-year survival (48.4 versus 20.6%), along with improved global health status and quality of life.[5] Based on these results, it is now recommended that FOLFIRINOX is used as the first-line treatment for patients with metastatic cancer with a good performance status.

The future

Surgical resection remains the mainstay of treatment for pancreatic cancer. Although it improves the otherwise poor prognosis, it is essentially palliative in most cases. Earlier diagnosis remains the focus of much investigation. Although it is acknowledged that screening for the minority of individuals with an inherited predisposition for pancreatic cancer is of value, there is no agreement on the most effective method of screening or on the optimal interval between screenings. Functional studies have shown that *KRAS* mutations are crucial for sustained growth of pancreatic adenocarcinoma, and loss of expression leads to rapid tumour regression. Targeting of *KRAS* is therefore the subject of both pre-clinical and clinical investigations. ◆

KEY REFERENCES

1 Yachida S, Jones S, Bozic I, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature* 2010; **467:** 1114–7.

2 Gudjonsson B. Carcinoma of the pancreas: critical analysis of costs, results of resections, and the need for standardized reporting. *J Am Coll Surg* 1995; **181:** 483–503.

3 Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017; **389:** 1011.

4 Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med* 2018; **379:** 2395–406.

5 Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364:** 1817–25.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 70-year-old man presented with a 3-week history of progressive jaundice associated with pruritus, and weight loss. He had no associated pain, and was otherwise fit and well with no significant past medical history.

On clinical examination, a palpable soft mass was identified in the right upper quadrant.

Investigations

- Bilirubin 112 micromol/litre (0–20)
- Alkaline phosphatase 376 U/litre (30–130)
- CA 19–9 300 U/ml (0–37)
- CT of the abdomen suggested a mass in the head of his pancreas but showed a typical 'double duct sign' (dilatation of both the common bile duct and main pancreatic duct). There was no evidence of vascular invasion, and no liver or lung lesions

What is the most appropriate next step in his management?

A. Request an MRI scan of the abdomen to confirm a mass in the head of the pancreas
B. Perform endoscopic ultrasonography and biopsy of the pancreas
C. Perform endoscopic retrograde cholangiopancreatography and insertion of a biliary metal stent
D. Counsel him for a Whipple's pancreatoduodenectomy.
E. Refer the patient to an oncologist

Question 2

A 45-year-old woman presented with a severe chest infection. She had a history of HIV infection and thalassaemia trait.

Investigations

- Haemoglobin 152 g/litre (115–165)
- White cell count 5.6 $\times$ 10^9/litre (4.0–11.0)
- C-reactive protein 20 mg/litre (<10)
- Bilirubin 15 micromol/litre (1–22)
- Alanine aminotransferase 23 U/litre (5–35)
- Alkaline phosphatase 64 U/litre (45–105)
- Amylase 70 U/litre (60–180)
- CT of the thorax incidentally noted a 17 mm, well-defined, hypervascular lesion in the head of the pancreas. This was abutting, but not obstructing, her common bile duct and main pancreatic duct

What is the most appropriate next step in her management?

A. Request an MRI scan of the abdomen
B. Perform an endoscopic ultrasound scan and biopsy of the lesion
C. Perform endoscopic retrograde cholangiopancreatography and prophylactic insertion of a plastic biliary stent
D. Counsel her for a Whipple's pancreatoduodenectomy
E. Reassure the patient and arrange reimaging in 3–6 months.

Question 3

A 67-year-old man presented with a 4-week history of progressive jaundice, intermittent vomiting and weight loss. He also had abdominal and back pain.

On clinical examination, he was jaundiced, cachectic and dehydrated, with a palpable mass in the epigastrium.

Investigation

- CT scan of the abdomen showed a 5 cm tumour in the head of the pancreas, with involvement of the superior mesenteric vein and artery, and evidence of gastric outlet obstruction. There were no liver or lung lesions

The man was treated with intravenous fluids and insertion of a nasogastric tube.

What is the most appropriate next step in his management?

A. Refer for palliative chemotherapy
B. Offer a surgical biliary and gastric bypass
C. Perform positron emission tomography to exclude occult metastases
D. Perform a percutaneous biopsy
E. Perform endoscopic ultrasonography, biopsy and insert biliary and duodenal metal stents.