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Pancreatic adenocarcinoma

Giles Bond-Smith,[1] Neal Banga,[1] Toby M Hammond,[2] Charles J Imber[1]

[1]Hepatopancreatic-biliary Surgery and Liver Transplant Unit, Royal Free Hospital, London NW3 2QG, UK
[2]Department of Surgery, St Mark's Hospital, Harrow, Middlesex
Correspondence to: G Bond-Smith
gelsmith@yahoo.co.uk

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In 2008, an estimated 217 000 new cases of pancreatic cancer were diagnosed worldwide, and in the UK 8000 new cases of pancreatic cancer are reported every year.[4-6] Worldwide, pancreatic cancer is 13th in incidence but 8th in terms of cancer death.[4] In the UK, pancreatic cancer is the 5th most common cause of cancer death in both sexes, despite being only the 11th most common cancer overall.[7] This is largely due to red flag symptoms usually appearing only once the disease has progressed to involve other structures. Consequently, only 10-20% of patients will have resectable pancreatic cancer at presentation.[7]

The term pancreatic cancer encompasses both exocrine and endocrine tumours (see box 1), of which over 80% are adenocarcinomas. The aim of this review is to update the non-specialist clinician on the cause, clinical presentation, and current management of so called curable and incurable pancreatic adenocarcinomas. The main surgical options available to the patient are discussed, including the decision making process involved in considering patients for curative surgery. The potential complications and morbidity of current treatment regimens, and their management, is covered.

Box 1 | Types of pancreatic cancer

Pancreatic exocrine cancers
Adenocarcinoma
Acinar cell carcinoma
Adenosquamous carcinoma
Giant cell tumour
Intraductal papillary mucinous neoplasm (IPMN)
Mucinous cystadenocarcinoma
Pancreatoblastoma
Serous cystadenocarcinoma
Solid and pseudopapillary tumours

Pancreatic endocrine cancers (pancreatic neuroendocrine tumours)
Gastrinoma
Glucagonoma
Insulinoma
Nonfunctional islet cell tumour
Somatostatinoma
Vasoactive intestinal peptide releasing tumour (VIPoma)

How does pancreatic cancer present?

Almost 50% of cases of pancreatic cancer are diagnosed on attending an emergency department for non-specific abdominal pain or jaundice or both. Only 13% are diagnosed via the two week wait pathway utilised by general practitioners in the UK.[8]

The peak incidence for pancreatic cancer is in the seventh and eighth decades of life. There is no difference in incidence between the sexes.[2] Courvoisier's sign, described as a palpable gallbladder in the presence of painless jaundice, occurs in less than 25% of patients. The majority of patients present with non-specific symptoms. Those presenting late frequently have symptoms secondary to metastatic spread. Approximately 80% of patients have unresectable disease at the time of diagnosis.[2]

Abdominal pain and jaundice are the most common presenting complaints. Abdominal pain predominantly features in up to two thirds of patients, and is typically located in the epigastric region, radiating through to the back, but can present as simple back pain. This can usually be attributed to direct invasion of the celiac plexus or secondary to pancreatitis. Thirteen per cent of patients will present with painless jaundice, and 46% will present with both pain and jaundice.[9] It is reported that those patients presenting with painless jaundice have a better prognosis than those patients that present with pain alone.[10] Pancreatic cancer should be considered in the differential diagnosis of any elderly patient presenting for the first time with acute pancreatitis, particularly in the absence of known precipitating factors such as gallstones or alcohol abuse.

Unexplained weight loss may occur as a result of anorexia, or malabsorption due to pancreatic exocrine insufficiency. This is usually secondary to a blocked pancreatic duct, and often manifests as steatorrhoea. Patients describe foul smelling, oily stools that are difficult to flush away. Peripancreatic oedema or a large tumour may compress the duodenum or the stomach, causing gastric outlet obstruction or delayed gastric emptying, with associated nausea and early satiety.

Development of any of the above symptoms in the presence of late onset diabetes should strongly alert the physician to the possibility of pancreatic cancer. Patients over the age of 50 years with late onset diabetes have an eightfold increased risk of developing pancreatic cancer within three years of the diagnosis compared to the general population (see box 2 for other risk factors).[11]

SOURCES AND SELECTION CRITERIA

We searched PubMed to identify peer reviewed original research articles, meta-analyses, and reviews. Search terms were pancreatic cancer, pancreatic adenocarcinoma, pancreatic neoplasia or neoplasm. Only papers written in English were considered.

SUMMARY POINTS

Pancreatic cancer can present with non-specific symptoms, such as abdominal or back pain, dyspepsia, and unexplained weight loss, as well as the classic presentation of painless jaundice
The majority of pancreatic cancer is incurable at presentation[1 2]
Whether or not pancreatic cancer is deemed curable, current surgical, endoscopic, and oncological management regimes can significantly improve quality of life
Trials are currently ongoing to improve outcomes in pancreatic cancer[3]

Previous articles in this series

The modern management of incisional hernias (*BMJ* 2012;344:e2843)
Diagnosis and management of bone stress injuries of the lower limb in athletes (*BMJ* 2012;344:e2511)
The management of overactive bladder syndrome (*BMJ* 2012;344:e2365)
Cluster headache (*BMJ* 2012;344:e2407)

The clinician should be alert to a potential diagnosis of pancreatic cancer with patients over 50 years old who present with unexplained weight loss, persistent abdominal or back pain, dyspepsia, vomiting, or change of bowel function. Currently there is no specific diagnostic algorithm for pancreatic cancer within the National Institute for Health and Clinical Excellence guidelines for cancer referral. If pancreatic cancer is suspected, patients should be referred to a high volume specialist pancreatic centre. In the UK, this can be performed via the suspected upper gastrointestinal cancer two week wait referral pathway.

What is the pathology of pancreatic cancer?

Ninety five per cent of pancreatic cancers originate from the exocrine portion of the gland. A proposed mechanism for the development of invasive pancreatic adenocarcinoma is a stepwise progression through genetically and histologically well defined non-invasive precursor lesions, called pancreatic intraepithelial neoplasias (PanINs). They are microscopic lesions in small (less than 5 mm) pancreatic ducts, and are classified into three grades (see box 3). The understanding of molecular alterations in PanINs has provided rational candidates for the development of early detection biomarkers and therapeutic targets.[12]

How do we investigate and diagnose suspected pancreatic cancer?

The most important investigative tool for the diagnosis of pancreatic cancer is computed tomography. However, certain blood tests help guide further management and can be performed while the patient is awaiting specialist review.

Box 2 | Risk factors for pancreatic cancer

Risk factors
Smoking
Alcohol
Increased BMI
Diabetes mellitus
Chronic pancreatitis
Family history of pancreatic cancer

Familial cancer syndromes
BRCA1, BRCA2
Familial adenomatous polyposis (FAP)
Peutz-Jeghers syndrome
Familial atypical multiple mole melanoma syndrome (FAMMM)
Lynch syndrome
von Hippel-Lindau syndrome
Multiple endocrine neoplasia type 1
Gardner syndrome

Other medical conditions
Inflammatory bowel disease
Periodontal disease
Peptic ulcer disease

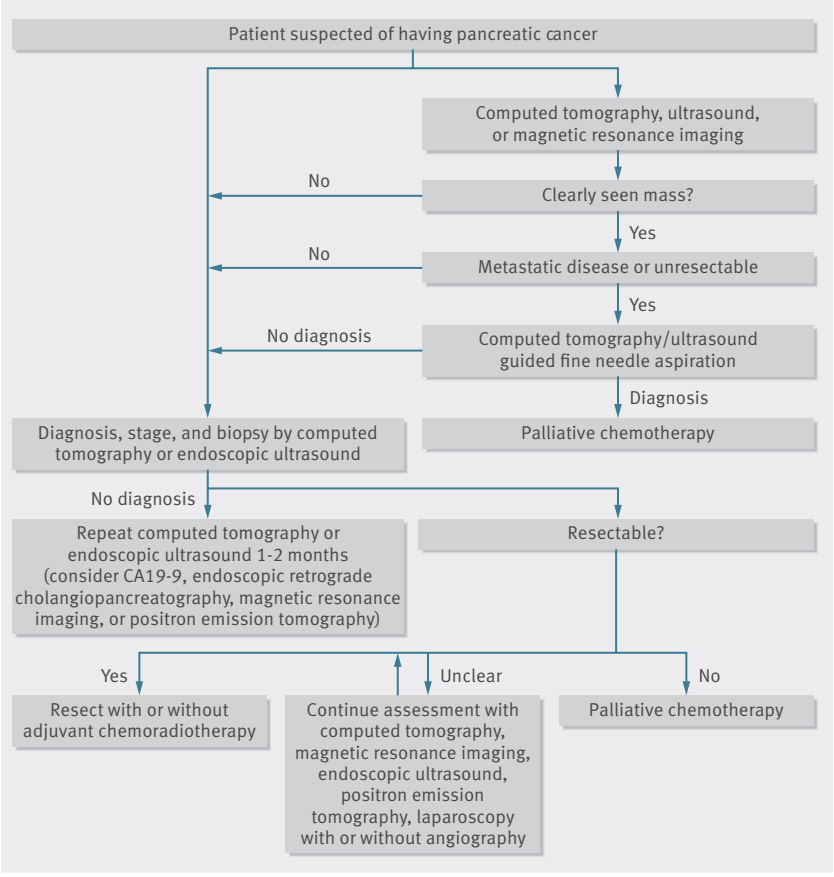

Fig 1 | Clinical management pathway

Blood tests and tumour markers

A full blood count may reveal a normochromic anaemia or thrombocytosis or both. Those presenting with obstructive jaundice will have significant elevations in serum bilirubin (conjugated and total), alkaline phosphatase, and γ-glutamyltransferase. Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) may also be raised, but usually to a lesser extent. Liver metastases alone are not frequently associated with clinically evident jaundice, but may result in relatively low grade elevations of serum alkaline phosphatase and transaminase levels.

Carbohydrate 19-9 (CA19-9), also known as sialylated Lewis (a) antigen, was first identified in pancreatic cancer patients in 1981.[13] It is now one of the most widely used serum tumour markers. CA19-9 is normally found in the cells of the biliary tract, and therefore any disease affecting these cells can cause serum elevations, including pancreatitis, cirrhosis, and cholangitis. Five per cent of the population lack the Lewis (a) antigen, and are not able to produce CA19-9, resulting in a sensitivity of 80% and specificity of 73% for pancreatic cancer.[14] As such, it is not currently recommended as a screening tool. CA19-9 does, however, have a role to play in assessing response to surgery and chemoradiotherapy, and as a surveillance tool following treatment.

With the advancement of high throughput techniques (DNA arrays and proteomics), a number of other potential molecular markers for pancreatic cancer have been identified, but to date these have not been found to be any more discriminating than CA19-9.

Imaging

Imaging is not only the most important diagnostic tool for pancreatic cancer, but will also guide the multidisciplinary team in determining whether the disease is surgically curable.

Abdominal ultrasound is safe, non-invasive, and inexpensive. Its main role is in formulating a differential diagnosis

Box 3 | Types of pancreatic intraepithelial neoplasia (PanIN)

PanIN 1 (low grade)

Minimal degree of atypia

Subclassified into PanIN 1A: absence of micropapillary infoldings of the epithelium; and 1B, presence of micropapillary infoldings of the epithelium

PanIN 2 (intermediate grade)

Moderate degree of atypia, including loss of polarity, nuclear crowding, enlarged nuclei, pseudostratification, and hyperchromatism

Mitoses are rarely seen

PanIN 3 (high grade/carcinoma in situ)

Severe atypia, with varying degrees of cribriforming, luminal necrosis, and atypical mitoses

Contained within the basement membrane

among the possible causes of obstructive jaundice. Bile duct dilation (>7 mm, or >10 mm if previous cholecystectomy) with pancreatic duct dilation (>2 mm) can be an indirect sign of pancreatic cancer (the so called double duct sign). Abdominal ultrasound is not as sensitive as computed tomography in imaging the pancreas, and small tumours (less than 3 cm) will frequently be missed.[15] Liver metastases and ascites are important findings in the work-up of a patient with suspected pancreatic cancer and can normally be visualised by ultrasound.

Triple phase computed tomography, preceded by non-contrast computed tomography, is currently the best technique for detecting pancreatic neoplasms and assessing resectability. It is performed in the arterial, pancreatic parenchymal, and portal venous phase (pancreas protocol computed tomography). Multidetector computed tomography is up to 90% effective at predicting the resectability of a pancreatic cancer.[16] There are reports that computed tomography can only reliably detect lesions larger than 3 cm.[14]

Endoscopic ultrasound (EUS) is becoming an increasingly important imaging modality. A recent meta-analysis showed that it had a sensitivity of 96% (range 85-100%) for diagnosing pancreatic cancer.[17] In comparison to computed tomography, diagnostic sensitivities were significantly in favour of endoscopic ultrasound, especially for small (<3cm) tumours.[12] Endoscopic ultrasound can also accurately detect the involvement of loco-regional lymph nodes.[18] It is further employed to guide fine needle aspiration (FNA) for cytological evaluation of lesions in which there is diagnostic uncertainty. The sensitivity of endoscopic ultrasound guided FNA ranges from 85% to 90% with a false negative rate of up to 15%.[19] Routine endoscopic ultrasound guided FNA of all pancreatic masses is therefore controversial. In a patient with resectable disease who is deemed physiologically fit for surgery, it is arguable whether an FNA is required, as a negative result would not rule out neoplasia, and could delay a potentially curable procedure. The benefit of FNA is mainly in those patients with unresectable disease, as the results may guide further oncological management, or in those patients with significant comorbidities in whom the risk to benefit ratio of surgical intervention is less clear.

The role of MRI (magnetic resonance imaging) remains uncertain at present. Its use in detecting small lesions and determining resectability is increasing as new, faster MRI techniques enable imaging of the pancreas with higher resolution. In a comparative study to determine the diagnostic role of endoscopic ultrasound, computed tomography, and MRI in patients suspected of having pancreatic cancer, the respective sensitivities were 94%, 69%, and 83%.[20]

Positron emission tomography (PET) scanning uses ^{18}F-fluorodeoxyglucose (FDG) to image the primary tumour and establish the presence of metastatic disease. When combined with simultaneous computed tomography scanning (PET-CT), it is more sensitive than conventional imaging for the detection of pancreatic cancer and extra-hepatic metastases. Its role in the staging of disease is, however, yet to be fully ascertained.

Similar to endoscopic ultrasound, endoscopic retrograde cholangiopancreatography with brush cytology or forceps biopsy is an effective way (90-95% sensitivity) to confirm the diagnosis of pancreatic adenocarcinoma. Endoscopic retrograde cholangiopancreatography is, however, an invasive procedure that carries a 5-10% risk of significant complications including pancreatitis, and gastrointestinal or biliary perforation, and is therefore usually reserved as a therapeutic procedure for biliary obstruction or for the diagnosis of unusual pancreatic neoplasms.

Table 1 | TNM classification of pancreatic adenocarcinoma

Tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour limited to the pancreas, 2 cm or smaller in greatest dimension
T2	Tumour limited to the pancreas, larger than 2 cm in greatest diameter
T3	Tumour extension beyond the pancreas but not involving the coeliac axis or superior mesenteric artery
T4	Tumour involves the coeliac axis or superior mesenteric artery
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Staging and treatment of pancreatic adenocarcinoma

The classification of pancreatic adenocarcinoma is shown in table 1, and how it relates to disease stage and prognosis are shown in table 2.[21 22] At present, surgical resection is the only curative treatment for pancreatic adenocarcinoma. Surgery with curative intent has a five year survival of 10-15%, and median survival of 11 to 18 months. For patients unwilling or not medically fit enough to undergo major pancreatic surgery, alternatives include systemic chemotherapy, chemoradiotherapy, image guided stereotactic radiosurgical systems (such as CyberKnife), surgical bypass, ablative therapies, and endoscopic biliary and gastrointestinal stenting. These are palliative procedures that can improve patients' quality of life by alleviating tumour related symptoms (such as pain and pruritus).

The role of the multidisciplinary team is to determine which patients are suitable to undergo curative surgery, if there is a role for preoperative (neoadjuvant) or postoperative (adjuvant) therapy, or to decide on the most appropriate mode of palliation.

Table 2 | Staging and TNM (tumour, lymph node, metastasis) classification related to incidence, treatment, and prognosis

Stage	TNM classification	Clinical classification	Incidence at diagnosis (%)	5-year survival rate (%)
0	Tis, N0, M0	Resectable	7.5	15.2
IA	T1, N0, M0	—	—	—
IB	T2, N0, M0	—	—	—
IIA	T3, N0, M0	—	—	—
IIB	T1-3, N1, M0	Locally advanced	29.3	6.3
III	T4, any N, M0	—	—	—
IV	Any T, any N, M1	Metastatic	47.2	1.6

What is resectable and unresectable pancreatic cancer?

The absolute contraindications to pancreatic resection are liver, peritoneal, or distant lymph node metastases, or the patient being deemed medically unfit for major surgery. The age of the patient, size of the tumour, local lymph node metastases, and continuous invasion of the stomach or duodenum are not contraindications to resection.

Advances in surgical techniques and perioperative care mean that tumour involvement of the major vessels around the pancreas is no longer an absolute contraindication to curative resection,[23] although encasement of the hepatic artery, superior mesenteric artery, and coeliac axis means surgery is unlikely to confer any survival benefit. Pancreaticoduodenectomy with resection of the portal and/or superior mesenteric vein is safe and feasible, with a similar mortality and morbidity to pancreaticoduodenectomy without vascular resection.[24] It should, however, only be performed if a disease-free (R0) resection margin can be achieved. If an R0 resection can be obtained, median survival is vastly improved compared to resections with tumour positive margins (13 versus 6 months; p=0.0002).[25]

Neoadjuvant chemotherapy and chemoradiation

The rationale for neoadjuvant therapy is to increase the incidence of R0 resections, downstage borderline resectable disease to allow resection, and reduce loco-regional recurrence. However, there are no large multicentre randomised controlled trials of neoadjuvant therapy for pancreatic cancer. Meta-analysis of the available data shows that one third of patients with locally advanced disease without distant metastases can achieve a significant oncological response to neoadjuvant treatment increasing the chances of a achieving a R0 resection,[26] thereby reducing local recurrence and potentially improving disease-free survival.

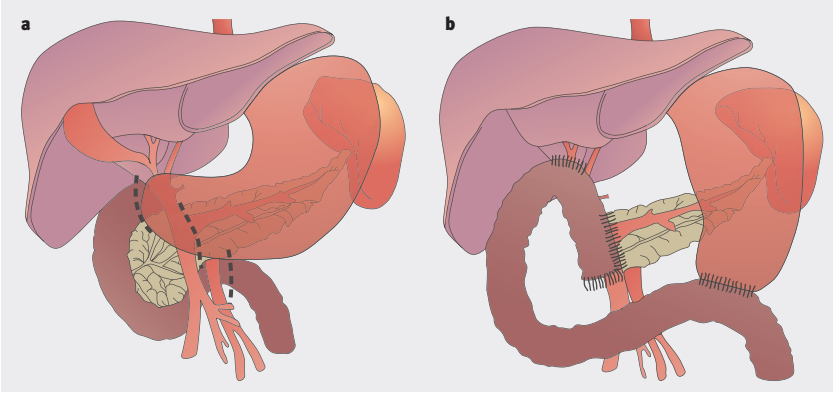

Fig 2 | A: Normal anatomy of liver, stomach, duodenum, and pancreas. Dotted lines indicate resection margins at pancreaticoduodenectomy. B: Surgical anastomoses to restore gastrointestinal continuity following a pancreaticoduodenectomy, include a gastrojejunostomy, choledochojejunostomy, and pancreaticojejunostomy (diagram not to scale)

Table 3 | Mortality following pancreatic resection in high, medium, and low volume centres[21]

Centre	No. of resections per year	30 day mortality (%)
High volume	>18	2.4
Medium volume	5-18	5.9
Low volume	<5	9.2

Curative resection

Pancreaticoduodenectomy

The majority of pancreatic adenocarcinomas (78%) are associated with the head, neck, and uncinate process of the pancreas, and require a pancreaticoduodenectomy.[27] First described in the 1930s, it involves resection of the proximal pancreas, along with the distal stomach, duodenum, distal bile duct, and gallbladder as an en bloc specimen.[28] Intestinal continuity is restored via a gastrojejunostomy, choledochojejunostomy, pancreaticojejunostomy (figs 2A and B), or pancreaticogastrostomy.

Morbidity following pancreaticoduodenectomy can be as high as 40%; the most common complications being delayed gastric emptying, pancreatic fistula formation, and pancreatic insufficiency.[29] The operation has wide ranging, 30 day mortality, partly dependent on the surgical volume of the centre where the procedure is performed (see table 3).[30]

Distal pancreatectomy

This procedure is performed for tumours of the body and tail of the pancreas, and carries a morbidity and mortality of 28.1% and 1.2% respectively.[31] The most common major complication is pancreatic fistula formation, due to leakage of pancreatic fluid from the pancreatic duct at the resection margin.[32] Laparoscopic distal pancreatectomy can be safely performed in high volume centres with experience in laparoscopic and pancreatic surgery, and results in less intra-operative blood loss, a shorter time to oral intake, and a shorter postoperative hospital stay than open surgery.[33] Centres that have developed expertise in laparoscopic distal pancreatectomy are now also performing laparoscopic pancreaticoduodenectomy, although this remains rare.

Adjuvant chemotherapy and chemoradiation after curative resection

Treatment regimes have previously employed 5-fluorouracil and radiotherapy.[34] The ESPAC-1 trial in 2004 showed a clear advantage for adjuvant chemotherapy in patients with resected pancreatic cancer over chemoradiotherapy, which had a deleterious impact on survival.[35] ESPAC-3 showed

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

Hruban RH, Adsay NV, Albores-Saavedra J, Compton C, Garrett ES, Goodman SN, et al. Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. *Am J Surg Pathol* 2001;25:579-86—describes a new classification system for pancreatic cancer

Safi F, Roscher R, Beger HG. Tumour markers in pancreatic cancer. Sensitivity and specificity of CA 19-9. *Hepatogastroenterology* 1989;36:419-23—summarises the role of CA19-9 in pancreatic cancer

Yeo CJ, Cameron JL, Lillemoe KD, Sohn TA, Campbell KA, Sauter PK, et al. Panctreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity and mortality. *Ann Surg* 2002;236:355-66—report of a trial showing no benefit for extended lymphadenectomy at the time of pancreaticoduodenectomy for pancreatic cancer

Zavoral M, Minarikova P, Zavada F, Salek C, Minarik M. Molecular biology of pancreatic cancer. *World J Gastroenterol* 2011;17:2897-908—review of molecular biology of pancreatic cancer

Hruban RH, Canto MI, Goggins M, Schulick R, Klein AP. Update on familial pancreatic cancer. *Adv Surg* 2010;44:293-311—introduction to familial pancreatic cancer

Dieterich S, Gibbs IC. The CyberKnife in clinical use: current roles, future expectations. *Front Radiat Ther Oncol* 2011;43:181-94.

Resources for patients

Pancreatic Cancer UK (www.pancreaticcancer.org.uk)

Cancer Research UK (www.cancerresearchuk.org)

Pancreatic Cancer Action (www.pancreaticcanceraction.org)

Macmillan Cancer Support (www.macmillan.org.uk)

Patient.co.uk (www.patient.co.uk)

HPB London (www.hpblondon.com)

TIPS FOR NON-SPECIALISTS

- Patients in the UK with suspected pancreatic cancer should be referred to a specialist pancreatic centre via the two week wait pathway
- Pancreatic cancer should always be considered in the differential diagnosis of an elderly patient with unexplained weight loss, even in the absence of abdominal pain or jaundice
- Multidetector computed tomography is the initial investigation of choice
- All patients with pancreatic cancer should be assessed and managed in a high volume specialist pancreatic centre

ONGOING RESEARCH

ESPAC 4 trial: Phase III trial to investigate whether combination adjuvant chemotherapy (gemcitabine and capecitabine) in patients who have undergone resection of pancreatic cancer improves survival when compared to adjuvant chemotherapy (gemcitabine) alone

PanGen-EU study: A large European case control study involving the collection of epidemiological, clinical, and biological information on pancreatic cancer, which aims to validate previous findings as well as explore developmental and progression mechanisms for pancreatic cancer

TeloVac trial: Phase III trial comparing combination chemotherapy (gemcitabine and capecitabine) with concurrent and sequential immunotherapy using the telomerase vaccine (GV1001) in locally advanced and metastatic pancreatic cancer. It is closed to recruitment and the results are expected soon

there was no difference between 5-flurouracil/folinic acid and gemcitabine, which is now the most commonly used chemotherapy agent.[36] The ESPAC-4 trial is currently in phase 3, and compares gemcitabine alone against combination therapy of gemcitabine plus capecitabine in patients within one year of a potentially curative resection.

Palliative treatment

Biliary tract or duodenal obstruction can be relieved by surgical, endoscopic, or radiological techniques. Palliative chemotherapy usually involves gemcitabine based regimes. Monoclonal antibodies and the telomerase vaccine GV1001 (the TeloVac trial) are currently under investigation to prolong survival in patients with unresectable or metastatic pancreatic cancer.[3]

How are common postoperative and palliative problems managed?

Locally advanced disease and pancreatic surgery can lead to exocrine insufficiency causing fat malabsorption, which tends to present as excess flatulence, diarrhoea, fatty and offensive smelling stools, or progressive weight loss. These symptoms can be significantly improved by prescribing supplemental pancreatic enzymes (pancreatin). Pancreatin is inactivated by gastric acid and therefore works best when taken with food. There is no linear relationship between the dose of pancreatic enzymes and the symptoms of exocrine insufficiency, so there is no definitive starting dose. Normally the pancreatin preparation is started at a dose of 25 000 to 40 000 units per meal and titrated according to effect on the individual patient.[15]

Delayed gastric emptying is common, causes considerable discomfort, and can prolong the patient's hospital stay. General treatment measures include long term nasogastric drainage, correction of fluid and electrolyte abnormalities, commencement of a proton pump inhibitor or an H_2 antagonist, and nutritional supplementation. Prokinetic medications (such as metoclopramide) to improve gastric emptying can also be considered.[15] The onset of delayed gastric emptying shortly after surgery (or an episode of pancreatitis), can indicate an intra-abdominal fluid collection and should be investigated by either ultrasound or computed tomography.

Pancreatic fistulas can result following an anastomotic leak. This is a difficult problem to resolve, with a reported incidence of 0-25%.[37] Early recognition is crucial as a pancreatic fistula may be associated with intra-abdominal sepsis, pseudoaneurysm formation, and possible haemorrhage. If haemorrhage occurs, often preceded by a so called herald bleed, then urgent angiographic imaging is needed to identify and control the source of bleeding, via coil embolisation. The management of simple pancreatic fistulation is still debated. Some advocate conservative management, which includes treatment of sepsis, drainage of intra-abdominal collections, nasogastric suction, total parenteral nutrition, and reducing pancreatic secretions, whereas others favour reoperation.

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ANSWERS TO ENDGAMES, p 56 For long answers go to the Education channel on bmj.com

PICTURE QUIZ

Multiple annular lesions on the legs

1 Given the history of travel in an area endemic for Lyme disease and the history of asymptomatic expanding annular lesions, the most likely diagnosis is multiple lesions of erythema migrans associated with Lyme disease.

2 Left untreated, Lyme disease can affect the nervous, cardiovascular, and musculoskeletal systems.

3 No consensus guidelines are available on the treatment of Lyme disease. NHS guidance suggests doxycycline 100 mg twice daily or amoxicillin 500 mg three times daily for 14 days for erythema migrans. If these drugs are contraindicated, prescribe oral cefuroxime axetil 500 mg twice daily for 14 days.

CASE REPORT

A woman with generalised weakness, hypokalaemia, and metabolic acidosis

1 Distal renal tubular acidosis.

2 Primary Sjögren's syndrome.

3 Oral potassium and bicarbonate replacement.

STATISTICAL QUESTION

Non-parametric statistical tests for independent groups: numerical data

The Kruskal-Wallis test (answer *c*) would most likely have been used to compare length of hospital stay in the three groups.