Update on pancreatic cancer

Conor J Magee, Ali Shekouh, Paula Ghaneh, John P Neoptolemos

Pancreatic cancer is one of the commonest causes of cancer death worldwide. Patients with pancreatic cancer benefit from resectional surgery (improved quality of life) and adjuvant treatment (enhanced survival). This review covers advances in the understanding of the development of pancreatic cancer, state-of-the-art clinical management and, finally, novel treatment and screening techniques.

Mr Conor J Magee is Research Fellow, **Mr Ali Shekouh** is Research Fellow, **Ms Paula Ghaneh** is Lecturer in Surgery and **Professor John P Neoptolemos** is Professor of Surgery, University of Liverpool Department of Surgery, Royal Liverpool University Hospital, Liverpool L69 3GA

Correspondence to: Professor JP Neoptolemos

The commonest form of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC). The latest figures from the Cancer Research Campaign show that PDAC was responsible for 6770 new cases in 1996 and 6560 deaths in 1998 (Coleman et al, 1999). PDAC has a median survival of 3–6 months without treatment, which increases to around 20 months with resectional surgery and adjuvant treatment (Neoptolemos et al, 2001a,b). Unfortunately, the late presentation and aggressive tumour biology of this disease mean that only a minority of patients have local disease that can be treated with 'potentially curative' surgery.

PATHOGENESIS OF PANCREATIC CANCER

Histological pathogenesis

The histological development of PDAC follows a stepwise progression with a number of distinct stages that represent increasing malignant potential referred to as pancreatic intraepithelial neoplasia types I–III (PanIN I–III) (Kern et al, 2001) (*Figure 1*). Once the basement membrane has been breached or satellites of tumour are seen then the lesion is considered to be invasive carcinoma.

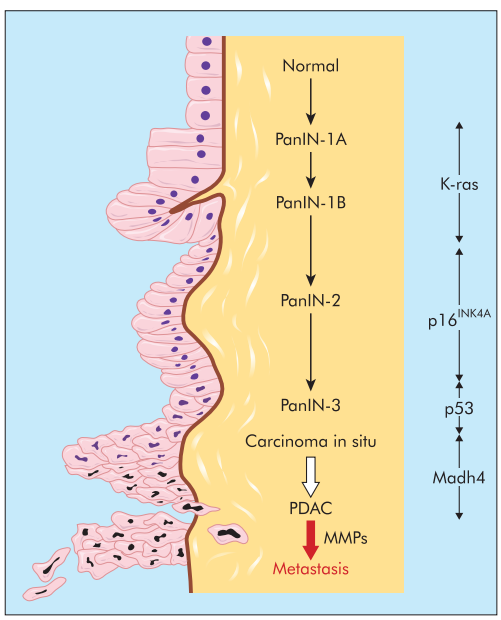


Figure 1. Histological pathogenesis of pancreatic ductal adenocarcinoma.

Molecular pathogenesis

There are four distinct genetic events that characterize the malignant phenotype (Magee et al, 2001) (*Figure 2*). Although it is tempting to consider these events as linear in nature, PDAC results from the sum total of genetic mutations that can occur at any time and in any order. The commonest genetic alteration in pancreatic cancer is a mutation of the K-ras proto-oncogene, occurring in 75–100% of series (Kawesha et al, 2000). K-ras protein normally goes through a cycle of GTP–GDP exchange and is involved in signal transduction of extra-cellular mitogenic stimuli, thus promoting cell growth and proliferation. Oncogenic K-ras is unable to hydrolyze bound GTP, resulting in constant K-ras signalling that cannot be switched off. The frequency of K-ras mutation in PDAC is the highest of any cancer, and this is a target for screening and treatment.

$p16^{INK4A}$ is a tumour suppressor gene and acts through the retinoblastoma (Rb) pathway to stop cellular proliferation. Loss of this pathway can occur through gene silencing (methylation), allelic loss or mutation. Around 85% of patients with PDAC have $p16^{INK4A}$ dysfunction (Kawesha et al, 2000). p53 is another tumour suppressor gene involved in cell cycle control, facilitating repair of damaged DNA and induction of apoptosis. Loss of p53 function occurs relatively late in the pathogenesis of PDAC and is found in 40–80% of cases (Kawesha et al, 2000). MADH4 is a signalling molecule involved in the transduction of stimuli from members of the transforming growth factor-β (TGF-β) family. MADH4 loss of function is associated with pancreatic cancer in around 50% of cases (Hahn et al, 1996) and also

appears to occur relatively late in the molecular pathogenesis of pancreatic cancer.

Other genetic events include disruption in the balance and activities of the matrix metalloproteinases (MMPs) and their inhibitors (TIMPs; tissue inhibitors of matrix metalloproteinases), contributing to the aggressive tissue invasion behaviour of pancreatic cancer (Jones et al, 1999a). There are many growth factor ligands and receptors that are overexpressed by a number of mechanisms, including autocrine and paracrine loops that drive cell proliferation (Ulrich, 2000). There is also marked reduction of apoptosis in pancreatic cancer associated with an imbalance of pro- and anti-apoptotic factors, such as Bax and Bcl-xL (Friess et al, 1998; Evans et al, 2001).

CLINICAL PRACTICE

Epidemiology

Pancreatic cancer is a disease of the western world and has increased in incidence dramatically over the last century. This increase is now tending to level off in men but is still slowly rising among women, probably as a result of increased tobacco smoking (Bramhall et al, 1998). In the UK, the age-standardized incidence is 10.1 per 10^5 population for men and 8.4 per 10^5 for women (Bramhall et al, 1995).

Aetiology

The two biggest risk factors for pancreatic cancer are increasing age and smoking (Bramhall et al, 1998). Although older texts mention coffee drinking as a risk factor, the evidence is so weak as to make any further consideration a non-issue, while the association between diabetes mellitus and pancreatic cancer remains unclear (Bramhall et al, 1998). Chronic pancreatitis is now recognized as a potential risk factor, with some series finding a 5–15-fold risk (Lowenfels et al, 1993). The risk is even higher in hereditary pancreatitis with estimates of a 70–100-fold increase in risk (Lowenfels et al, 1997; Howes et al, 2000). Hereditary pancreatitis is an autosomal dominant condition causing repeated attacks of pancreatitis beginning at a young age. The germline mutations affect the cationic trypsinogen gene and result in a gain of function of the digestive enzyme trypsin (Wong et al, 2001). Continuing inflammation may provide a persistent mitogenic stimulus that facilitates neoplastic transformation.

The umbrella term familial excess of pancreatic cancer (FEPC) refers to inherited conditions that result in an increased risk of pancreatic cancer among affected families. Syndromic FEPC refers to conditions with a known germline mutation that predisposes to PDAC, including Peutz–Jeghers syndrome, familial atypical mole and multiple melanoma syndrome and familial adenomatous polyposis as well as hereditary pancreatitis – among others (Wong et al, 2001).

Familial pancreatic cancer is an autosomal dominant condition with an as yet unidentified causative mutation. Diagnostic criteria are: two or more first degree relatives with PDAC, one first degree relative with early-onset PDAC (age at diagnosis less than 50 years) or two or more second degree relatives with PDAC, one of whom has early-onset PDAC (Wong et al, 2001). In families with at least two first degree relatives affected by PDAC, the relative risk may be increased 18–57-fold depending on the number of pre-existing affected relatives (Tersmette et al, 2001).

Secondary screening

Primary screening of the general population is not feasible because of the relative insensitivity of screening methods compared with the prevalence of pancreatic cancer, even when selecting those at greatest risk (older individuals who smoke tobacco). The increased risk of pancreas cancer among patients with chronic pancreatitis, hereditary pancreatitis and other FEPC syndromes, however, makes them amenable to secondary screening initiatives. The objective is pre-symptomatic diagnosis with a view to curative resection. The European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) contains over 200 families with an increased risk of pancreatic cancer. A free screening service based on K-ras and p53 mutation detection extracted from pancreatic juice at endoscopic retrograde cholangiopancreatography (ERCP) is offered to referring clinicians (*Table 1*). Mutant K-ras may be a feature of chronic pancreatitis without pancreatic cancer, but its detection permits more focused radiological investigation and targeted second tier screening of p53 status (Wong et al, 2001).

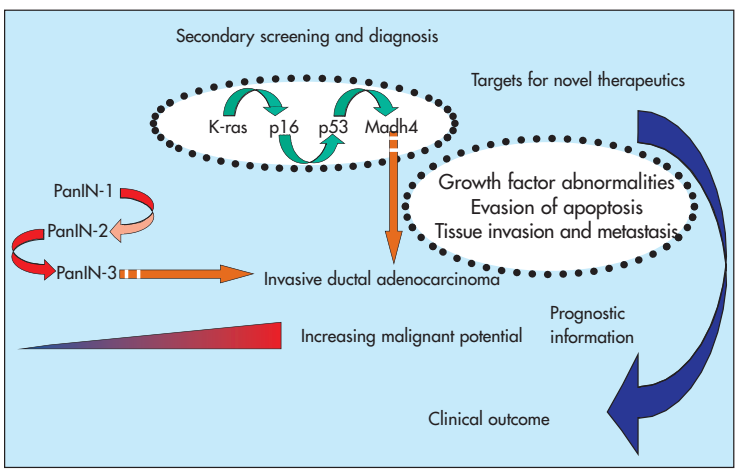


Figure 2. Schematic pathogenesis of pancreatic ductal adenocarcinoma with clinical implications.

Presentation

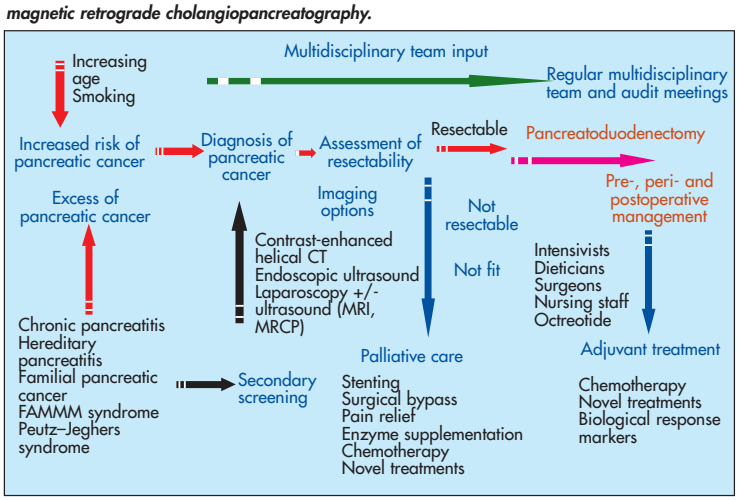
The classical presentation is of jaundice, weight loss and abdominal discomfort or pain; any one of these warrants investigation in the older patient. Weight loss is almost invariably the result of the interruption of the gastrointestinal flow of both bile and pancreatic juice. The jaundice is obstructive in nature because of a tumour arising in the head of the pancreas (~80%) and invading the intra-pancreatic bile duct. Unfortunately, most patients present with non-specific symptoms that delay the diagnosis. Patients may also present with acute pancreatitis, acute cholangitis, diabetes mellitus or deep vein thrombosis. Clinical signs include jaundice, hepatomegaly, palpable gallbladder (Courvoisier's sign – seen in ~40%), cachexia, Troisier's sign – involved Virchow's node, and ascites. Persistent back pain and/or partial relief of pain by sitting upright (especially at night-time) almost invariably indicates non-resectable disease as a result of an invasion of the coeliac plexus.

TABLE 1.
European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) secondary screening protocol for pancreatic cancer in high risk groups

Initial criteria	Full ethical approval
	Identification of familial pancreatic cancer and hereditary pancreatitis cases
	Full genetic counselling before any screening test
	Enrolment of patients and family members >40 years of age
Clinical procedures	ERCP with aspiration of pancreatic juice
	Imaging of pancreas (spiral CT and endoscopic ultrasound)
Laboratory analysis and follow-up	Analysis of pancreatic juice for K-ras mutation
	If mutant K-ras is detected, then further analysis of p53 and DNA methylation status, followed by yearly reinvestigation
	If wild-type K-ras is detected, then follow up is 3-yearly

CT= computed tomography; ERCP=endoscopic retrograde cholangiopancreatography. From Wong et al (2001)

Figure 3. Management of pancreatic cancer. CT = computed tomography; FAMMM = familial atypical mole and multiple melanoma syndrome; MRI = magnetic resonance imaging; MRCP = magnetic retrograde cholangiopancreatography.



Diagnosis

There have been major advances in the diagnosis of pancreatic cancer, although we are some way from an ideal 'single-stop' diagnostic investigation. Once the diagnosis is suspected, it is mandatory that all further management is undertaken by a specific pancreas tumour multidisciplinary team (NHS Executive, 2001a) (*Figure 3*). Experienced units tend to use a combination of clinical history and examination alongside contrast-enhanced helical computed tomography and ERCP. In addition, there is selective use of other imaging modalities, such as endoluminal ultrasound, magnetic resonance imaging, magnetic cholangiopancreatography and laparoscopy with laparoscopic ultrasound. This approach allows the correct diagnosis to be made in the great majority of cases, e.g. the accuracy at the Regional Pancreas Tumour Centre in Liverpool is around 95%.

Once pancreatic cancer has been identified, the next step is to assess whether the tumour is resectable. A tissue diagnosis is essential before diagnosing unresectable disease, but for patients undergoing resection, it is not a prerequisite because of the relatively poor sensitivity of biopsy techniques. Nevertheless, wider use of brush cytology at ERCP should be encouraged in part to help improve the diagnostic rate in non-regional centres. With advanced imaging technology, the accuracy of resectability is very high, although the final arbiter of resectability in radiologically marginal cases is surgical exploration in a regional centre.

The presentation and radiological findings of chronic pancreatitis and pancreatic cancer overlap in a significant proportion of cases. Thus, around 5–10% of patients with presumed pancreatic cancer will turn out to have chronic pancreatitis on the resection specimen histology. Conversely, around 5% of patients with presumed chronic pancreatitis that undergo resection will have pancreatic cancer diagnosed on final histology. This diagnostic dilemma places a significant degree of stress on surgical decision making given the context of a procedure with a 5% mortality rate and a morbidity rate of around 40%. The development of novel diagnostic and prognostic investigations based on the molecular pathogenesis of pancreatic cancer will play a major role in the future diagnosis of pancreatic cancer.

Treatment

Unresectable disease: The presence of peritoneal, liver and/or distant metastases or the invasion of local major blood vessels preclude resection. These features are present in around three quarters of patients with PDAC on initial presentation. Further management in these patients is directed towards symptom palliation and improving quality of life (*Figure 3*). The gain in survival in the absence of resection is still rather small in absolute terms.

Obstructive jaundice can be managed effectively by endoluminal stent insertion. In technically difficult cases, the combined (or rendezvous) procedure involving the percutaneous insertion of a guide wire under radiological control followed be endoscopic stent insertion is to be preferred to percutaneous transhepatic stent insertion. The initial good outcome from stent insertion compared with surgical decompression is counterbalanced by the frequency of stent blockage, especially with plastic stents (Smith et al, 1994). Self-expandable metal stents (e.g. Wallstents®, Boston Scientific, USA) are less likely to clog but are very expensive. On a cost–benefit basis, metal stents may be reserved for patients with smaller tumours (<3 cm) since survival is appreciably longer than in those with larger tumours (or metastases) in whom plastic stents are more suitable (Prat et al, 1998). Surgical decompression of the biliary tree is best used in younger patients with a reasonable life expectancy or in those patients in whom resection is not possible at exploration.

Duodenal obstruction can follow treatment for biliary obstruction in around 20% of patients (Smith et al, 1994). Accordingly, many units (including the authors') fashion a prophylactic gastrojejunostomy as part of the primary palliative procedure. The use of expandable metal duodenal stents is a further option but still fraught with many technical problems.

Intractable pain is a depressing feature of end-stage pancreatic cancer which is best managed by a palliative care team as part of the multidisciplinary team. The mainstay of pain relief is oral opiates. Supplementary techniques include neurolytic coeliac plexus blockade, performed at surgery or by percutaneous guided computed tomography (Rykowski and Hilgier, 2000), and thoracoscopic splanchnicectomy (Leksowski, 2001), unfortunately all with less than satisfactory results.

Much of the weight loss is the result of the combined effects of biliary obstruction and pancreatic exocrine failure following obstruction of the main pancreatic duct in the head of the pancreas. Thus, it is essential that all patients are treated with high-dose enteric-coated pancreatic enzyme supplements (such as Creon®, Solvay Pharmaceuticals, USA) (Bruno et al, 1998).

Chemotherapy has been shown to prolong the length of life in unresectable pancreatic cancer compared with no treatment in several randomized controlled trials (reviewed in Magee et al, 2002). Radiotherapy is sometimes used for the palliation of pain, but there have been no randomized controlled trials to show better survival over no active treatment or convincingly against chemotherapy. Radiotherapy followed by chemotherapy is used in the USA, but there are no trial data to show that there is any extra survival benefit to using chemotherapy alone. Most chemotherapeutic regimens are based on the agent 5-fluorouracil (5FU), a thymidylate synthase inhibitor that interferes with DNA synthesis. There is wider use of the nucleoside analogue gemcitabine, which has been shown to extend life marginally (5 weeks) compared with 5FU alone, but this is based on only one randomized trial (Burris et al, 1997). Advanced pancreatic cancer has been used as a testing ground for novel therapeutic regimens (*Table 2*). It is hoped that at least some of these promising new agents will be shown to significantly prolong life and become available for routine clinical use (Ghaneh et al, 2001; Halloran et al, 2001; Magee et al, 2002).

Resectable disease: All surgically fit patients with potentially resectable disease should proceed to surgical exploration in a regional centre (NHS

TABLE 2.
Novel therapeutic approaches to pancreatic cancer presently undergoing clinical trials

Therapeutic approach	Mode of action
Farnesyl transferase inhibitors	Block farnesylation of newly synthesized ras Ras cannot reach cell membrane and becomes functionally inactive
Herceptin	Antibody to the Erb-B2 oncogene, blocking mitogenic signalling
Gastrin receptor antibody	Blocks extracellular mitogenic signalling
Irinotecan	Topoisomerase inhibitor, prevents religation of DNA, induces double-stranded DNA breaks which stimulates apoptosis
TNP-470	Antiangiogenic agent
Marimastat	Matrix metalloproteinase inhibitor
Docetaxel	Microtubule inhibitor and member of the taxane family
Ras peptide immunotherapy	Uses mutant ras peptide to stimulate host immune response that may destroy tumour cells
Heat-shock protein–peptide vaccination	Tumour-derived peptide provides autologous vaccine to stimulate immune response
Gene therapy	Delivery of cytolytic viruses targeting mutant p53 cells; p16 and p53 replacement; gene-directed enzyme prodrug therapy

From Ghaneh et al (2001), Halloran et al (2001), Magee et al (2002)

Executive, 2001b). In the UK, only between 2.6% and 4.0% of patients with pancreatic cancer undergo resection in district general hospitals (Bramhall et al, 1995; Northern and Yorkshire Cancer Registry Information Service (NYCRIS), 2000). In comparison, the resection rates are much higher in regional units – around 40% at the Royal Liverpool University Hospital Regional Pancreas Tumour Centre. The fitness of the patient needs to be determined before offering resection. Patients with pancreatic cancer tend to be elderly (80% are over 60 years of age) and have a significant incidence of co-morbidity. Chronological age is less important than physiological age, but all patients being considered for surgery require a complete preoperative work-up. In the authors' unit, patients are assessed by consultant anaesthetists with an interest in pancreatic surgery and in addition undergo cardiac (electrocardiogram, multiple uptake gated assay scan) and pulmonary investigations (spirometry).

Over three quarters of pancreatic cancers are found in the head of the pancreas, and hence the Kausch–Whipple pancreatoduodenectomy is the keystone of most pancreatic resections. This involves the removal of the pancreatic head, uncinate process, common bile duct, duodenum, proximal jejunum, gallbladder and distal stomach. More recently, a pylorus-preserving variant has become widely used with the advantage of maintaining gastrointestinal physiology without sacrificing oncological effectiveness. There has been a consensus statement on standard operative technique and pathological reporting which will allow accurate interpretation of series from different centres (Pedrazzoli et al, 1999; Jones et al, 1999b).

Pancreatic surgery is technically demanding because of the complex and variable vascular anatomy that comprises the pancreatic bed and the need for three (or four) anastomoses following resection, of which the pancreatojejunostomy is technically the most demanding. The most important variable is surgical experience; the best results are achieved by meticulous surgery practised by experienced surgeons using a technique with which they are familiar and comfortable. Many units, including the authors' own, prefer the duct to mucosa anastomosis covered by an internal–external stent. The mortality rate in specialist units is <6%, although morbidity is still around 40% (Halloran et al, 2002) (*Table 3*). The authors' unit presently has a mortality rate of <5% despite the patient population having a median American Anesthesiology Association risk score of III (significant co-morbidity) and a ~40% resectability rate. The use of the somatostatin analogue octreotide has reduced the incidence of postoperative complications following pancreatic resection (Büchler et al, 1992; Halloran et al, 2002), and there is increasing evidence that fistulation of the pancreatic anastomosis is also reduced by the use of pancreatic stents (Roder et al, 1999). It is clear that low mortality rates are associated with the experience of units that comes with having a high throughput of patients (NYCRIS, 2000; NHS Executive, 2001b; Halloran et al, 2002).

TABLE 3.
Morbidity associated with pancreatic resection reported by major units over the past decade

Complication	Incidence
Pancreatic fistula	10.4%
Delayed gastric emptying	9.9%
Bleeding	4.8%
Wound infection	4.8%
Intra-abdominal abscess	3.8%
Median hospital stay	13–18 days
Reoperation rate	4–9%
Reoperative mortality rate	23–67%

From Halloran et al (2002)

Following pancreatic resection, the 5-year survival rate is reported as 17–24%, with median survivals of 10–18 months (Ghaneh et al, 1999b; Magee et al, 2002). Important prognostic factors are lymph node status, tumour size and, most important of all, tumour grade (Neoptolemos et al, 2001a). The R classification that defines the extent of resection also needs consideration: a R2 resection is one where macroscopic tumour has been left behind, a R1 resection has at least one tumour cell within 1 mm of any one of the resection margins and a R0 resection is free of tumour cells for at least 1 mm from all of the resection margins (even if there are lymph node metastases). Thus, a R2 resection is considered to be a palliative resection. Patients with a R1 resection survive much less than those with a R0 resection, but this is related to the biological nature of R1 tumours (tending to be poorly differentiated with lymph node metastases) rather than being related to tumour size (Neoptolemos et al, 2001b). Although the R0/R1 status predicts survival, it is not an independent predictor once other prognostic variables have been taken into account (Neoptolemos et al, 2001b). There is considerable interest in molecular prognostic markers, but none as yet have a clearly defined role in clinical practice (Ghaneh et al, 1999a; Kawesha et al, 2000) (*Table 4*).

Attempts to improve surgical outcomes by radical resections with extended lymphadenectomy have not been effective (Pedrazzoli et al, 1998). An alternative approach has been the use of adju-

vant systemic treatments, e.g. chemotherapy or radiotherapy (Ghaneh et al, 1999b). The evidence for any individual modality has been weak because of the lack of randomized controlled trials of adequate power (Kalser and Ellenberg, 1985; Bakkevold et al, 1993; Klinkenbijl et al, 1999). There is no definitive answer to the question of which treatment for pancreatic cancer, if any, is the most effective. An enormous step forward was made recently with the publication of the European Study Group for Pancreatic Cancer trial 1 (ESPAC-1) results (Neoptolemos et al, 2001a). This pivotal study recruited 541 patients from 11 countries and compared 5FU-based chemotherapy, chemoradiotherapy, a combination of the two and no treatment. The key findings were:

1. Chemoradiotherapy had no survival benefit
2. Chemotherapy probably had a survival benefit
3. There was great improvement in quality of life after surgery irrespective of the type and use of adjuvant therapy.

Similar but less dramatic effects were observed in patients with R1 resection margins (Neoptolemos et al, 2001b). The rejection of chemoradiotherapy by ESPAC-1 is highly significant and directs future studies to the use of chemotherapeutic agents alone. To address this, ESPAC-3 has begun recruiting patients (contact j.almond@liv.ac.uk) and will randomize postoperative patients to a control arm, 5FU or gemcitabine.

CONCLUSIONS

In the UK, pancreatic cancer services are undergoing radical changes. The inverse correlation between hospital volume and pancreatic surgery mortality (NHS Executive, 2001b) has driven the need for pancreatic surgery to be performed by appropriately experienced surgeons in centres with the requisite supportive facilities (NHS Executive, 2001b). Such high volume hospitals have shown improved morbidity rates, reduced hospital costs, reduced hospital stay and better patient outcomes (Neoptolemos et al, 1997; NYCRIS, 2000). Identical results are reported from the USA (Birkmeyer et al, 1999), Holland (Gouma et al, 2000) and Finland (Sand and Nordback, 1996). This requires centralization of pancreatic surgery, and the NHS (the largest single health provider in the western world) has instructed regional health authorities to concentrate pancreatic surgery in designated cancer centres that will serve an adult population of 2–4 million (NHS Executive, 2001a). There are undoubtedly 'islands of excellence' where single surgeons practise a high standard of pancreatic surgery in smaller units, but the numbers of resections that can be carried out by a single surgeon are not enough to permit meaningful statistical analysis. This lack of auditability prevents service development and bolsters the case for regionalization of services. The development of such regional centres for pancreatic cancer will have dramatically improve clinical outcome and improve the clinical base for the expected advances in basic and clinical research. HM

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TABLE 4.
Molecular prognostic factors in pancreatic ductal adenocarcinoma

Prognostic factor	Clinical significance
K-ras mutation subtype (GaT, cGT and GcT)	Decreased survival
Increased erb-B3	Tumour progression
Enhanced TGF-β isoform expression	Decreased survival
TGF-β receptor I and II expression	Advanced tumour stage
Bcl-xL expression	Decreased survival
Bax expression	Increased survival
Overexpression of acid and basic FGF	Advanced tumour stage
HER2/neu expression	Early oncogenesis, well-differentiated tumour
MMP-2, -3 and TIMP-1	Invasive phenotype
MMP-9:E-cadherin ratio >3.0	Poor prognosis
Increased PD-ECGF	Decreased survival
Increased angiopoetin	Decreased survival
Increased vascular endothelial growth factor	Liver metastasis, reduced survival
CA19-9	Predicts treatment response

From Ghaneh et al (1999a), Kawesha et al (2000). FGF = fibroblast growth factor; MMP = matrix metalloproteinase; PD-ECGF = platelet-derived endothelial cell growth factor; TGF = transforming growth factor; TIMP = tissue inhibitors of matrix metalloproteinases.

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KEY POINTS

- Pancreatic cancer needs to be managed in regional specialist units involving multidisciplinary teams.
- There are a number of inherited conditions with an increased risk of pancreatic cancer.
- Endoscopic stenting, pain relief and pancreatic enzyme supplementation must be available in advanced pancreatic cancer.
- 5-fluorouracil-based chemotherapy prolongs survival in advanced pancreatic cancer, and patients should be encouraged to enter trials of novel drugs.
- If possible, pancreatic resection should be offered, as this provides the best quality of life.
- Adjuvant chemoradiotherapy is of no benefit, but adjuvant chemotherapy may improve survival. Patients are encouraged to enter trials of novel forms of adjuvant treatment.