Biology and management of pancreatic cancer
Paula Ghaneh, Eithne Costello and John P Neoptolemos

Gut 2007;56:1134-1152
doi:10.1136/gut.2006.103333

Updated information and services can be found at:
http://gut.bmj.com/cgi/content/full/56/8/1134

These include:

References
This article cites 211 articles, 57 of which can be accessed free at:
http://gut.bmj.com/cgi/content/full/56/8/1134#BIBL

Email alerting service
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Topic collections
Articles on similar topics can be found in the following collections

Recent advances in clinical practice (7 articles)

Notes

To order reprints of this article go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to Gut go to:
http://journals.bmj.com/subscriptions/
Pancreatic cancer continues to pose an enormous challenge to clinicians and cancer scientists. With a more affluent world the global incidence of pancreatic cancer is rising. For the first time significant advances are now being made into the management of the disease. There is a more sophisticated approach to palliative care and the centralisation of pancreatic cancer services is leading to greater tumour resection rates. Newer adjuvant modalities are also greatly increasing the 5 year survival rates. The molecular basis of pancreatic cancer is now better understood than ever before, leading to the development of new diagnostic approaches and the introduction of mechanistic based treatments. Technical advances in imaging and great improvements in conventional and molecular pathology have led to a deeper understanding of the pathological variables of the disease. This is now an important time for making big inroads into what still remains the most lethal of the common cancers.

Pancreatic ductal adenocarcinoma remains one of the most difficult cancers to treat. It is the commonest cancer affecting the exocrine pancreas. In 2000, there were 217 000 new cases of pancreatic cancer and 213 000 deaths worldwide and in Europe 60 139 new patients (10.4% of all digestive tract cancers) and 64 801 deaths. In 2002 there were 7152 new cases in the UK, with similar numbers in men and women. In the USA in 2006 there were 33 730 new cases and 32 300 deaths. The late presentation and aggressive tumour biology of this disease mean that only a minority (10–15%) of patients can undergo potentially curative surgery. Major advances in the past decade have included improvements in operative mortality and morbidity through the development of specialist regional centres and improved survival using systemic chemotherapy.

Significant progress has been made in unravelling risk factors and key molecular events in pancreatic carcinogenesis, leading to potentially exciting new developments in diagnosis, screening of high-risk groups and mechanistic based treatments (MBTs).

MOLECULAR PATHOGENESIS AND THERAPEUTIC TARGETS IN PANCREATIC CANCER

Pancreatic precursor lesions
The ductal phenotype gives rise to three distinct cancer precursor lesions with distinct, although overlapping, gene alterations: mucinous cystic neoplasms, intraductal papillary mucinous neoplasms (IPMNs) and pancreatic intraepithelial neoplasia (PanINs) (box 1). PanINs are classified into early and late lesions, starting with PanIN-1A, 1B (hyperplasia) and progressing to PanIN-2 and then to PanIN-3 or carcinoma in situ (fig 1).

Alterations in oncogenic molecular pathways
K-ras
Activating mutations in K-ras, mostly codon 12 but also affecting codons 13 or 61, occur in 75–90% of pancreatic cancers. Ras is a 21 kDa membrane-bound GTP-binding protein involved in growth factor-mediated signal transduction pathways. The mutations result in a constitutively activated form of Ras in which the protein is locked in the GTP-bound state, capable of stimulating a multitude of downstream signalling cascades. K-ras mutations are often found in benign lesions of the pancreas as well as in early precursor lesions. Post-translational modification of Ras protein involves farnesylation of the C terminus, mediated by farnesyl protein transferase and is a major therapeutic target (fig 2), although farnesyl transferase inhibitors up to now have not been successful in phase III trials.

Alternative approaches that directly target K-ras are now available in the form of RNA interference and are showing promise both alone and in conjunction with radiation. Signalling pathways, downstream of Ras also offer therapeutic targets such as the Raf-MEK ERK...
pathway. Sorafenib, an inhibitor of Raf-1 kinase and vascular endothelial growth factor receptor-2 is now an FDA approved drug for the treatment of renal cell carcinoma, but despite being well tolerated, it is inactive in patients with advanced pancreatic cancer.

Growth factors and their receptors
The epidermal growth factor receptor (EGFR, also known as human EGF receptor 1 or HER 1) is a major therapeutic target for pancreatic cancer. EGFR is a transmembrane glycoprotein that consists of an extracellular ligand-binding domain with cysteine-rich regions, a hydrophobic transmembrane domain, and an intracellular tyrosine kinase domain. It is a member of the ErbB family of receptor tyrosine kinases, which includes EGFR (EGFR-1), ErbB-2 (HER-2), ErbB-3, and ErbB-4. Of these, EGFR-1, ErbB-2 and ErbB-3 have all been shown to be overexpressed in pancreatic cancer. The principal natural ligands for EGFR-1, epidermal growth factor (EGF) and transforming growth factor-α (TGF-α) are also overexpressed in this disease. By binding ligands to the extracellular domain, the EGFR causes receptor homodimerisation or heterodimerisation (with other ErbB family members). This in turn leads to phosphorylation of tyrosine residues on the intracellular domain. The phosphorylated residues then provide docking sites for intracellular mediators which activate downstream signalling pathways such as notch/hedgehog and the signal transducer and activator of transcription (STAT) family of proteins (mediates a variety of features conducive to cancer cell survival progression, including cell division, motility, invasion and adhesion).

Cetuximab is a chimeric monoclonal antibody that binds to the extracellular domain of EGFR, promoting receptor internalisation and subsequent degradation without receptor phosphorylation and activation. This diminishes the available receptor for natural ligand binding and prevents activation of EGFR-associated, downstream signalling pathways. The first clinical trial in patients with advanced pancreatic cancer tested the combination of cetuximab and gemcitabine and showed an encouraging 1-year survival rate of 32% in a phase II trial and has led to the SWOG S0502 phase III trial (target 704 patients), which has completed recruitment and is due to report.

Erlotinib (Tarceva) is an orally active small molecule that binds to the ATP binding site on the intracellular kinase domain, thus inhibiting the tyrosine kinase activity of the receptor. A recent phase III trial (569 patients) tested erlotinib in combination with gemcitabine for advanced pancreatic cancer. Overall survival was significantly better in the erlotinib arm than in the placebo controlled arm, with a median survival of 6.4 vs 5.9 months (p = 0.025) (hazard ratio = 0.81, 95% CI...
0.67 to 0.97) and 1-year survival of 24% vs 17%, respectively, the benefit mostly restricted to patients developing a distinctive rash. Erlotinib was approved by the United States FDA in 2005, but European registration is restricted to patients with metastatic disease and does not include those with locally advanced cancer.

High levels of a number of other growth factor receptors and their ligands are also expressed in pancreatic cancer and/or PanIN lesions and represent alternative targets. These include insulin-like growth factor (IGF) and its tyrosine kinase receptor, insulin growth factor receptor 1 (IGF-1R), members of the fibroblast growth factor family, the Met receptor tyrosine kinase and its ligand HGF/scatter factor and vascular endothelial growth factor (VEGF) receptors and ligands. VEGF promotes endothelial cell growth and survival, thus enhancing angiogenesis. VEGF expression occurs in 90% of pancreatic cancers, correlates with microvessel density and in moderate/high levels with reduced survival. Bevacizumab (Avastin), an anti-VEGF monoclonal antibody, showed promise in combination with gemcitabine, in a phase II trial of advanced pancreatic cancer, but the CALGB 80303 phase III trial was unsuccessful and the Avita trial, which included treatment with gemcitabine plus erlotinib with and without bevacizumab, has been closed. Multitargeted tyrosine kinase inhibitors such as, ZD6474, a dual epidermal growth factor receptor and VEGF receptor 2 small-molecule tyrosine kinase inhibitor, and sunitinib a VEGF receptor 1, 2 and 3, c-KIT, and platelet-derived growth factor receptor α and β tyrosine kinase inhibitor hold promise for pancreatic cancer treatment.

PI3K/Akt signalling pathway

The lipid kinase phosphoinositide 3-OH kinase (PI3K)/Akt pathway (fig 2) regulates cell survival, proliferation, and resistance to apoptosis. The Akt2 gene was shown to be amplified or activated in up to 60% of pancreatic carcinomas. Akt mediates the inhibition of pro-apoptotic proteins BAD and caspase 9. Downstream of Akt, the mammalian target of rapamycin (mTOR) promotes cell survival and proliferation by modulating cellular signals in response to mitogenic stimuli and various nutrients, especially amino acids. The mTOR–S6K1 signalling pathway is essential for proliferation of pancreatic cancer cells in vitro, and the mTOR inhibitor, CCI-779, which demonstrates antitumour activity, is under investigation in early-phase trials for pancreatic cancer. Akt also activates the transcription factor nuclear factor kappa B (NFκB), which promotes survival and resistance to chemotherapy. Bortezomib, a proteasome inhibitor that functions, at least in part, by stabilising the IκBα protein and inhibiting NFκB activation, is currently undergoing phase I evaluation for pancreatic cancer treatment.

Alterations in molecular pathways affecting tumour suppressor genes

p16INK4A/retinoblastoma (Rb) protein pathway

The activation of cyclin-dependent kinases (CDKs), initially in response to mitogenic signals (cyclin D-dependent kinases) and subsequently in a mitogenic-independent manner (cyclin E-dependent kinases), leads to the sequential phosphorylation of Rb, facilitating the transcription of E2F-regulated genes and consequent entry into the S-phase (fig 3). The INK4A gene product, p16INK4A, interferes with this process by binding to CDK4/CDK6, preventing the formation of active cyclin D-CDK4/CDK6 complexes. As a result, phosphorylation of Rb is suppressed, blocking entry into the S-phase. In pancreatic cancer the pRB/p16 tumour suppressor pathway appears to be
In pancreatic cancer, the INK4A gene is abrogated, most commonly through functional inactivation of the INK4A gene. Loss of p16INK4A function occurs in 80–95% of pancreatic cancers.

While p16INK4A inhibits cell proliferation by activating Rb, p19ARF (a gene overlapping with p16) accomplishes the same end through activation of p53 by inhibiting its MDM2-dependent proteolysis, although ARF may possess additional p53-independent functions. Around 40% of pancreatic cancers lose both the INK4A and ARF transcripts, mutations may occur in the p16 gene but not in the ARF gene, suggesting that INK4A loss alone may be a major event in the development of pancreatic cancer.

Transcription factor p53

More than 50% of pancreatic cancer cases have mutations in the TP53 gene. The p53 transcription factor is normally maintained at very low levels as a result of interaction with the oncoprotein HDM2 (the human homologue of MDM2), which targets p53 for proteosomal degradation. Under conditions of cellular stress, such as genotoxic damage or oncogene activation, the HDM2–p53 interaction is inhibited, and the p53 protein is stabilised. The levels of p53 thus increase and it regulates a transcription response leading to cell cycle arrest or to apoptosis (fig 3). After oncogene-mediated activation, p14ARF protein inhibits MDM2, leading to the stabilisation and thus activation of p53. A recent study found that ARF was crucial for tumour suppression, while the DNA damage-induced p53 response was dispensable.

Smad4/TGF-β pathway

Smad4, was originally isolated as a tumour suppressor gene for pancreatic cancer. Although Smad4 mutations are not particularly common in cancer, in general, pancreatic cancer is characterised by a high degree of alteration in the MADH4 locus on chromosome 18 (18q21.1) that encodes Smad4. It undergoes loss of heterozygosity in ~90% of pancreatic cancers,

### Table 1 Hereditary cancer syndromes affecting the pancreas

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene mutation</th>
<th>Pancreatic cancer lifetime risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial pancreatic cancer</td>
<td>BRCA2 in up to 20%</td>
<td>Variable dependent on pedigree—up to 50%</td>
</tr>
<tr>
<td>Family X</td>
<td>Palladin</td>
<td>Family X affected subjects carry the P239S variant</td>
</tr>
<tr>
<td>FAMMM—pancreatic cancer variant</td>
<td>BRCA1 and BRCA2</td>
<td>17% (p16 Leiden mutation)</td>
</tr>
<tr>
<td>Familial breast and ovarian cancer syndromes</td>
<td>FANCA, B, C, D1 (BRCA2), D2, E, F, G</td>
<td>Pedigree dependent</td>
</tr>
<tr>
<td>Peutz–Jeghers syndrome</td>
<td>STK11/LKB1 in up to 80%</td>
<td>? ~2% (patients &lt;50 years may carry genes)</td>
</tr>
<tr>
<td>Hereditary pancreatitis</td>
<td>VHL</td>
<td>36%</td>
</tr>
<tr>
<td>von Hippel–Lindau disease</td>
<td>ATM</td>
<td>35%</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>TP53</td>
<td>? ~5% (neuroendocrine tumours are frequent)</td>
</tr>
<tr>
<td>Li–Fraumeni syndrome</td>
<td>CFTR</td>
<td>= unusual (breast cancer is most common)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>APC</td>
<td>= ~5% (increased risk of digestive track cancers)</td>
</tr>
<tr>
<td>FAP</td>
<td>MLH1, MSH2, MSH6, PMS1, PMS2</td>
<td>? ~5%</td>
</tr>
<tr>
<td>HNPCC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FAMMM, familial atypical multiple mole melanoma; FAP, familial adenomatous polyposis; HNPCC, hereditary non-polyposis colon cancer.
and around 50% of cases have completely lost functional Smad4 protein. The loss of Smad4 has important effects on the tumour microenvironment and potentiation of invasion.

The Smad4 protein is a member of the Smad family of transcription factors and has a pivotal role in mediating signal transmission of members of the TGF-β superfamily of cytokines. TGF-β ligands and TGF-β receptors have been found to be highly expressed in pancreatic cancer. TGF-β ligands are potent regulators of cancer cell growth, differentiation and migration. Knockdown of Smad4 was shown to lead to TGF-β-induced cell cycle arrest and migration but not to TGF-β-induced epithelial–mesenchymal transition, indicating that loss of Smad4 seemed to abolish TGF-β-mediated tumour suppressive functions, while maintaining at least some TGF-β-mediated tumour promoting functions. TGF-β-based therapeutic strategies in cancer are in development.

Reactivation of developmental signalling in pancreatic cancer

Notch

The Notch pathway has an important role in directing decisions about the fate of cells in the developing pancreas and in pancreatic cancer initiation and invasion. This pathway comprises cell surface-expressed notch receptors which are activated by a number of transmembrane ligands, including Delta, Serrate, and Lag-2 of the delta and jagged families expressed on neighbouring cells, thus mediating communication between adjacent cells expressing the receptors and ligands. This signalling pathway is important for the processes of apoptosis, differentiation and proliferation. Activation leads to proteolytic intramembrane cleavage of Notch receptors, releasing their active intracellular domain, which translocates to the nucleus and binds to the transcription factor CSL (RBP-Jk/CBF in mammals; Suppressor of Hairless (Su(H) in Drosophilia) inducing the transcription of a variety of target genes including the hairy enhancer of split (HES) family of transcriptional repressors. HES family members act to maintain cells in a precursor state. The pathway is active during embryogenesis, but not in the pancreas, while upregulation of a number of Notch target genes occurs in pre-neoplastic lesions and in invasive pancreatic cancer. Notch signalling promotes vascularisation in tumours and is a clear target for new drug development.

Hedgehog

Hedgehog signalling has a major role in the initiation and growth of pancreatic cancer. There are three Hedgehog family members or ligands, sonic hedgehog, Indian hedgehog and desert hedgehog, which are crucial for the development of the gastrointestinal tract. Together with the transmembrane proteins Smoothened and Patched, these signalling proteins/ligands closely coordinate organ development, as well as a variety of functions in adult tissues. Cyclopamine inhibits the Hedgehog pathway through direct interaction with Smoothened and has now entered early clinical trial development.

Sonic hedgehog may also be a feature of so called pancreatic cancer stem cells. The existence of cancer stem cells is based on the hypothesis that the ability of a tumour to grow and propagate is dependent on a small subset of cells (~5%) with special properties, which like normal stem cells, have a great potential for self-renewal and production of differentiated progeny. After a report that a clone of a distinct CD44+CD24– epithelial-specific antigen (ESA)+ could initiate human metastatic breast cancer in immunodeficient non-obese diabetic/severe combined immunodeficient mice, Li et al have recently identified a CD44+CD24+ESA+ phenotype (0.2–0.8%) isolated from primary pancreatic cancer cells with a 100-fold increased tumorigenic potential. Increased numbers of cells, however, were needed to generate tumours when injected into the pancreas compared with the subcutaneous

The pancreatic tumour microenvironment

In considering the biology of any cancer, the interplay between cancer cells and the surrounding supporting host cells, known as tumour stroma, cannot be ignored. This interplay has effects on blood vessel formation, invasion, metastasis and evasion of the host immune system. Pancreatic cancer has a particularly intense desmoplastic stroma, which can account for a large proportion of the pancreatic tumour volume. It comprises extracellular matrix, together with a number of different host cell types, including fibroblasts, small endothelial-lined vessels, residual normal epithelia and a variety of inflammatory cells, which are both locally derived and recruited from the circulation. The biology of the pancreatic tumour microenvironment is being actively researched, not least, because it is a potential therapeutic site, such as for antiangiogenic strategies, as discussed above. Targeting stromal matrix, in the form, of matrix metalloproteinase (MMP) inhibitors either with or without gemcitabine, has failed to improve patients’ outcome. This might be due to the fact that there are many closely related MMPs, and current MMP inhibitors lack sufficient specificity.

Lessons from animal models

Comprehension of transcription factor activity in the developing pancreas and elucidation of the sequence of genetic alteration in pancreatic cancer development, have been greatly advanced by the development of new genetically engineered animal models of pancreatic cancer. Targeted expression of oncogenic KRAS to pancreatic progenitor cells in mice resulted in the generation of progressive PanIN lesions, followed by low-frequency progression to invasive and metastatic adenocarcinoma. The development of pancreatic cancer was remarkably accelerated by the inclusion of mutations in INK4A/ARF or TP53. Thus it appears that activated KRAS serves to initiate PanIN formation while INK4A/ARF tumour suppressors limit the malignant conversion of these PanINs to ductal adenocarcinoma. Similarly, the concomitant expression of oncogenic
KRAS and mutant p53 in the mouse pancreas led to accelerated metastatic pancreatic cancer development compared with that seen with oncogenic KRAS alone.85 86 Mutant p53 alone did not induce a cancer phenotype.86

Immunotherapy and vaccines
The limits of conventional cytotoxic drugs in pancreatic cancer have been the main driver for the development of MBTs. In parallel with this has been an explosion of preclinical development of immunotherapies, including cancer vaccination in pancreatic cancer, but the clinical results so far have proved rather disappointing.87 Telomerase overexpression occurs early in the development of pancreatic cancer and can be targeted by telomerase vaccines such as GV1001, with promising phase II results.88 These have now led to the development of a large phase III trial (TeloVac) trial that is exploring the role of simultaneous or sequential cytotoxic and vaccine treatment in advance pancreatic cancer.

AETIOLOGY AND SECONDARY SCREENING
The biggest risk factors for pancreatic cancer are increasing age, smoking,97 new onset diabetes mellitus,98 increased body mass index,99 chronic pancreatitis,100 hereditary pancreatitis101 and an inherited predisposition for pancreatic cancer (box 2).102 103 A variety of dietary factors are also associated with an increased risk of pancreatic cancer, all of which are amenable to intervention and comprise increased red and processed meat intake of methionine and folate intervention and comprise increased red and processed meat risk of pancreatic cancer, all of which are amenable to

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Histological variants of malignant tumours of the exocrine pancreas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological type</td>
<td>Frequency (%)</td>
</tr>
<tr>
<td>Ductal adenocarcinoma</td>
<td>80</td>
</tr>
<tr>
<td>Ductal adenocarcinoma variants</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated (anaplastic) carcinoma</td>
<td>5</td>
</tr>
<tr>
<td>Mucinous non-cystic adenocarcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Mucinous non-cystic carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Signet-ring cell carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Mixed ductal-endocrine carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Osteochondroma-like giant cell tumour</td>
<td>1</td>
</tr>
<tr>
<td>Other malignancies</td>
<td></td>
</tr>
<tr>
<td>Serous cystadenocarcinoma</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Mucinous cystadenocarcinoma</td>
<td>3</td>
</tr>
<tr>
<td>Intraductal papillary-mucinous neoplasm—invasive carcinoma</td>
<td>1-3</td>
</tr>
<tr>
<td>Acinar cell carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Acinar cell cystadenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Mixed acinar-endocrine carcinoma</td>
<td></td>
</tr>
<tr>
<td>Pseudopapillary carcinoma</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pancreatoblastoma</td>
<td>Rare</td>
</tr>
</tbody>
</table>

BIOLOGY AND MANAGEMENT OF PANCREATIC CANCER
motility, and has been identified in the susceptibility locus 4q32–34 in a large family from Seattle, USA (called family X), but both the susceptibility locus and the palladin gene variant described have not been confirmed in EUROPAC families.

Several studies have examined the association between genetic polymorphisms and pancreatic cancer. Although over the whole population none of the genetic polymorphisms for two carcinogen-metabolising enzymes (cytochrome P450 1A1 (CYP1A1) and glutathione S-transferase (GST)) could be directly associated with the risk of pancreatic cancer, the combination of heavy smoking and a deletion polymorphism in GSTT1 was associated with an increased risk of pancreatic cancer among Caucasians. Polymorphisms of glutathione S-transferase M1 (GSTM1) and acetyltransferases (NAT1 and NAT2) enzymes may also be associated with a modest increase in susceptibility to pancreatic cancer and chronic pancreatitis. The UDP glucuronosyltransferase (UGT1A7) gene is predominantly expressed in the human pancreas. The low detoxification activity UGT1A7*3 allele has been identified as a new risk factor of pancreatic diseases, defining an interaction of genetic predisposition and environmentally induced oxidative injury.

Several inherited cancer syndromes are associated with pancreatic cancer (table 1). The highest risk of pancreatic cancer in all of these cancer syndromes is in Peutz–Jeghers syndrome with a 120-fold lifetime risk and a 36% cumulative lifetime risk. Although responsible for this syndrome, germline mutations of the STK11/LKB1 gene are not involved in familial pancreatic cancer. Pancreatic cancer is the second most common cancer in the familial atypical multiple mole melanoma syndrome and is particularly significant in patients and families with the p16 Leiden mutation. Pancreatic cancer is also seen in some families with breast cancer and BRCA1 and BRCA2 mutations. The cumulative risk of pancreas cancer to age 75–years in BRCA2 carriers is 7%, and BRCA2 may account for as many as 5% of all cases of pancreatic cancer. It is evident that a number of these genes act as modifier genes on environmental and other genetic risk factors. RNASEL (encoding ribonuclease L) gene variants/mutations (Glu265X and Arg462Gln) implicated in sporadic and familial prostate cancer may also contribute to the tumourigenesis of sporadic and familial pancreatic cancer but do not directly cause pancreatic cancer.

Patients at high risk warrant screening, but these programmes have not been adequately assessed and at the present time secondary screening (box 3) should only be undertaken as part of an investigational study such as that organised by EUROPAC.

**Box 3 Secondary screening**
- All patients with an increased inherited risk of pancreatic cancer should be referred to a specialist centre offering clinical advice and genetic counselling and, where appropriate, genetic testing such as for BRCA2 mutations.
- Primary screening for pancreatic cancer in the general population is not feasible at present.
- Secondary screening for pancreatic cancer in high-risk cases should only be part of an investigational programme.

**PATHOLOGY, STAGING AND RESECTION MARGINS (BOX 4)**
Ductal adenocarcinoma is the most common malignant tumour of the pancreas (table 2). Characteristically, there is an intense desmoplastic reaction in the stroma surrounding these tumours. Sixty-five per cent are located within the head, 15% in the body, 10% in the tail and 10% are multifocal. Tumours of the head of the pancreas tend to present earlier with obstructive jaundice or acute pancreatitis. Tumours of the body and tail tend to present late and are associated with a worse prognosis. There are guidelines for minimum data set reporting and staging. Pancreatic ductal adenocarcinoma must be distinguished from carcinomas of the intrapancreatic bile duct, ampulla of Vater or duodenal mucosa as these tumours have a much better prognosis. In about 20% of cases it is not possible to distinguish the tissue of origin of cancers arising in the head of the pancreas, and the term “peri-ampullary cancer” is often applied. Application of chip-based DNA expression techniques will hopefully overcome this problem with the spread of molecular pathology complementing traditional histology, as even intrapancreatic bile duct cancers have genetic similarities to pancreatic ductal adenocarcinomas.

The key factors relating to prognosis are tumour grade and diameter and lymph node status. The microscopic resection margin status is also an important survival factor, although less so within the adjuvant context. A positive microscopic resection margin (R1) is operationally defined as at least one cancer cell within 1 mm of any surface of the resected specimen. A positive R1 margin is unrelated to tumour diameter but rather to histological grade and lymph node status, indicating that this has more to do with the biology of the tumour than with physical factors.

**DIAGNOSIS**
Advances in technology have meant that the sensitivity for detecting smaller lesions is improving, as is the identification of extrapancreatic spread (box 5).

**Tumour markers and proteomic signatures**
The most commonly used marker in everyday practice CA19-9 has a sensitivity of 70–90% and specificity of 90%, and is better than other markers, including CA-50 and DU-PAN-2 and CEA. False positive results are often obtained in benign obstructive jaundice, chronic pancreatitis even in the absence of bile duct obstruction and ascites. CA19-9 is particularly useful in assessing response to prognosis and treatment in advanced cases, identifying early recurrence in resected cases and as an aid in preoperative staging. New markers, including HCG, CA 72-4, osteopontin, REG4, RCAS1 and MIC-1 are under evaluation, but radically newer approaches that hold real promise are new proteomic techniques identifying unique panels of proteins associated with pancreatic cancer and protein profiles providing a distinctive pancreatic signature. Gene expression profiling may also help to categorise prognostic groups.

**Non-invasive imaging techniques**
Transabdominal ultrasound can be the initial investigation and may detect tumours >2 cm in size, dilatation of the biliary and main pancreatic ducts and possible extrapancreatic spread—notably, liver metastases, with a diagnostic accuracy of 75%.
Most pancreatic cancers are pancreatic ductal adenocarcinomas. Accurate pathological typing and staging is essential to determine the most appropriate treatment and prognostic groups. In 20% of cases it is not possible to distinguish the tissue of origin of pancreatic cancers: “peri-ampullary cancer”. Chip-based technologies will lead to a more accurate typing of tissue origin. Resection margin status needs to be clearly defined. At present, a tumour <1 mm from the margin is reported as positive.

But it is not useful in early disease, if the bile duct is not dilated and in obese patients. Therefore contrast-enhanced multidetector CT scan is the single most useful imaging procedure (using a pancreas protocol CT with 1 mm images) and can achieve diagnostic rates of 97% for pancreatic cancer. The accuracy for predicting an unresectable lesion is 90%, but the accuracy of predicting a resectable lesion is much less at 80–85%. Magnetic resonance imaging produces similar results to contrast-enhanced multislice CT and is useful for patients who cannot receive intravenous contrast. Positron emission tomography (PET) cannot differentiate inflammatory conditions from tumours accurately and the sensitivity is 71–87% with specificity of around 64–80%. The use of fusion CT-PET scanning adds little if anything to the use of CT alone. Measurement of tumour metabolism by nuclear magnetic spectroscopy holds considerable promise as a diagnostic technique but is very much in development.

Magnetic resonance imaging produces similar results to contrast-enhanced multislice CT and is useful for patients who cannot receive intravenous contrast. Positron emission tomography (PET) cannot differentiate inflammatory conditions from tumours accurately and the sensitivity is 71–87% with specificity of around 64–80%. The use of fusion CT-PET scanning adds little if anything to the use of CT alone. Measurement of tumour metabolism by nuclear magnetic spectroscopy holds considerable promise as a diagnostic technique but is very much in development.

Invasive imaging techniques
Endoluminal ultrasonography (EUS) has similar accuracy to CT in the staging of pancreatic cancer but is undoubtedly better for the detection of early pancreatic tumours as small as 2–3 mm (fig 8). The addition of fine needle aspiration (FNA) cytology to EUS is highly accurate for identifying malignancy in lesions identified on EUS and not seen on CT scan. The drawbacks of EUS are that distant metastases and nodal involvement cannot be accurately assessed. The sensitivity and specificity of endoscopic retrograde cholangiopancreatography (ERCP) alone are 70–82% and 88–94%, respectively, in symptomatic patients or those with suspected pancreatic cancer but should no longer be used as a pure imaging tool given the developments in magnetic resonance cholangiopancreatography and EUS. ERCP is used to insert biliary stents for relief of obstructive jaundice and to gain cytological diagnosis by sampling or brushings. These can also be obtained at percutaneous transhepatic cholangiography (PTHC).

Diagnostic biopsy
Percutaneous FNA cytology has a sensitivity and specificity of 69% and 100%, respectively, for tissue diagnosis, but concerns have remained about intraperitoneal seeding, with an incidence of up to 16%. The diagnostic accuracy of EUS with FNA carries a sensitivity and specificity of >90% and ~100%, respectively, but requires an expert team with the presence of a cytologist examining the tissue specimens in the EUS suite, repeating the procedure until the diagnosis is conclusive. The incidence of carcinomatosis is much less after EUS-guided biopsy than percutaneous biopsy. A further development is the use of EUS with an endoscopic trucut biopsy needle. EUS-guided biopsy is thus the preferred procedure if histological confirmation is needed in cases of advanced pancreatic cancer before chemotherapy or to diagnose small uncharacterised lesions.

Laparoscopy and laparoscopic ultrasound
Laparoscopy with laparoscopic ultrasound enables intraoperative scanning of the liver and pancreas to be performed and is highly predictive of resectability, altering the management of 15% of patients already assessed as resectable by dual-phase helical CT. Selective laparoscopy based on the serum level of CA19-9 is a more efficient strategy, reducing the proportion of patients undergoing laparoscopic ultrasound from 100% to around 45% while increasing the yield from 15% to 25%.
Pancreatic cystic neoplasms are being increasingly identified with the wider employment of high-quality abdominal imaging and comprise at least 15% of all pancreatic cystic masses (box 6). The three most common primary pancreatic cystic neoplasms are serous cystic neoplasm, mucinous cystic neoplasm and intraductal papillary mucinous neoplasm (IPMN). Serous cystic neoplasms predominantly affect women, are found mostly in the head of pancreas and represent 30% of primary cystic neoplasms. Mucinous cystic neoplasms also are found more often in women, but mostly in the body and tail of the pancreas, and represent 40% of primary cystic neoplasms. Unlike IPMNs the cyst does not communicate with the main pancreatic duct. IPMNs tend to affect more men than women, can involve a part or the whole of the pancreatic ductal system, affect older patients and represent 30% of primary pancreatic cysts.

Pathology
Serous cystic neoplasms consist of a well-demarcated spongy, honeycomb mass with small cysts lined by a simple cuboidal epithelium with glycogen-rich cytoplasm (fig 9) and rarely progress to serous cystadenocarcinoma. Mucinous cystic neoplasms consist of a larger often solitary cyst to begin with and may have a septum or septae contained within the cyst lined by simple mucinous columnar epithelium and there is a characteristic ovarian-type stroma (fig 10). IPMNs are classified as arising either from the main duct (fig 11) or branch duct (fig 12) and can be mixed. They are characterised by intraductal proliferation of neoplastic mucinous cells forming papillae and excessive mucous secretion. These changes lead to dilatation of the main pancreatic duct or branch duct. IPMNs arising in the branch ducts are less aggressive than those arising in the main duct, which have a high incidence of malignant lesions. There is a greatly increased risk of colorectal cancer and other extrapancreatic cancers in patients with IPMN. There is also an increased risk of developing other cancers of the pancreas.

Diagnosis
Serous cystic neoplasms may be polycystic or honeycomb as on cross-sectional imaging with a central scar (fig 9), and are sometimes calcified but may also appear to be solid. Mucinous cystic neoplasms may have thick irregular walls with papillary invaginations (fig 12) and sometimes peripheral calcification. The characteristic radiological feature of IPMN is side-branch cystic dilatation in communicating with the main pancreatic duct or dilation of the main pancreatic duct (figs 11 and 13) full of mucus readily seen at endoscopy or dilatation; malignant potential may be related to size (≥3 cm) and mural nodules. Early lesions may be evaluated by intraductal pancreatoscopy and intraductal ultrasonography. Fluid by FNA from serous cystic neoplasms lacks mucin. The cyst fluid from mucinous cystic neoplasms is viscous and will stain positive for mucin with high levels of CEA or CA19-9.

Management options
If a lesion can be positively identified as a serous cystic neoplasm then a conservative approach with regular follow-up imaging is justified, particularly if the patient is frail or elderly. Mucinous cystic neoplasms should be resected if the patient is fit for major surgery owing to the high malignant potential. All main duct IPMNs should be resected if the patient is fit, combined with frozen section assessment of the main pancreatic duct resection margin; the patient should be prepared to undergo a total pancreatectomy. Patients with relatively benign features of branch duct IPMN (diameter <3.5 cm, absence of nodules and thick walls, CA 19-9 <25 kU/l, absence of recent-onset or worsened diabetes, absence of jaundice or of any other symptom) may be managed with cystic neoplasms may have thick irregular walls with papillary invaginations (fig 12) and sometimes peripheral calcification. The characteristic radiological feature of IPMN is side-branch cystic dilatation in communicating with the main pancreatic duct or dilation of the main pancreatic duct (figs 11 and 13) full of mucus readily seen at endoscopy or dilatation; malignant potential may be related to size (≥3 cm) and mural nodules. Early lesions may be evaluated by intraductal pancreatoscopy and intraductal ultrasonography. Fluid by FNA from serous cystic neoplasms lacks mucin. The cyst fluid from mucinous cystic neoplasms is viscous and will stain positive for mucin with high levels of CEA or CA19-9.
regular follow-up imaging instead of resection in certain patients.\(^{176}\)

### TREATMENT OF PANCREATIC CANCERS

#### Inoperable disease

The treatment of patients who have localised advanced disease, metastases or performance status is directed at symptom control (box 7).

#### Pain

Intractable pain is a major problem and often necessitates the use of high-dose opiate analgesia. Complementary approaches include intraoperative, percutaneous CT-guided or EUS neurolytic coeliac plexus block\(^{140}\) 177–179 and bilateral or unilateral thoracoscopic splanchnicectomy.\(^{180}\) In general, the results are disappointing and are particularly poor for patients with tumours in the body and tail of the pancreas. Pain control with coeliac plexus block was improved in a randomised study compared with systemic analgesia, but this was not reflected in the quality of life or survival.\(^{178}\)

#### Weight loss

Weight loss initially is due to pancreatic exocrine insufficiency owing to obstruction of the main pancreatic duct as well as exclusion of bile acids from obstruction of the main bile duct. Fat malabsorption may also contribute to abdominal pain and bloating. Relief of biliary obstruction and pancreatic enzyme supplementation will alleviate these symptoms.\(^{181}\) Cachexia can be a marked feature of the later stages of pancreatic cancer, with no good treatment.

#### Biliary and duodenal obstruction

Biliary stenting using ERCP is the preferred option with the combined PTHC-endoscopy approach employed only if the former is technically not possible.\(^{182}\) The life of a plastic stent is about 3 months, causing recurrent jaundice. Self-expanding metal (and covered) stents have greatly reduced the risk of obstruction and acute cholangitis. Metal stents should be used for patients with a good performance status and favourable prognosis (locally advanced primary tumour <3 cm) and plastic ones for those patients with metastases and tumours ≥3 cm in diameter.\(^{182}\) Expandable metal stents are being increasingly deployed endoscopically for duodenal obstruction (occurs in ~15%), with a technical success rate of around 85%, but may be associated with serious complications, including perforation, fistula and bleeding and recurrent obstruction due to stent migration or fracture.\(^{183}\) Surgical bypass (open and laparoscopic) can be used to relieve jaundice using a Roux-en-Y loop hepatojejunostomy, and duodenal obstruction by gastrojejunostomy, especially in younger patients and both can be achieved laparoscopically.\(^{184}\) 185

#### Chemotherapy

Pancreatic ductal adenocarcinoma is highly resistant to conventional methods of cytotoxic treatment and radiotherapy (box 8).\(^{186–189}\) Few chemotherapeutic agents have been shown to
have reproducible response rates of more than 10%. 5-Fluorouracil (5FU) is an inhibitor of thymidylate synthetase (essential for synthesis of DNA nucleotides) and has been the most widely used in advanced pancreatic cancer, with a median survival of around 5–6 months and is better than the best supportive care. A pivotal trial in 1997 meant that the nucleoside analogue, gemcitabine, replaced 5FU as the preferred drug. Although the median survival improvement in favour of gemcitabine compared with 5FU was slight (5.7 vs 4.4 months), the 1-year survival rate was more encouraging (18% vs 2%), and most importantly, the toxicity was relatively mild and achieved a better clinical response (24% vs 5%, respectively).

Capecitabine (Xeloda) is a new oral, fluoropyrimidine carbamate that is sequentially converted to 5FU by three enzymes located in the liver and in tumours, including pancreatic cancer. The Cancer Research UK GemCap trial comparing gemcitabine alone or in combination with capecitabine demonstrated significantly improved survival with this combination than with gemcitabine alone and is supported by other studies. A recent meta-analysis has demonstrated that combination gemcitabine chemotherapy is better than gemcitabine alone; the best combinations may be with capecitabine or platinum-based agents, allowing for acceptable levels of toxicity of the combinations.

**Chemoradiotherapy and follow-on chemotherapy**

Radiotherapy has been widely used for the treatment of pancreatic cancer. The main drawback is the limit on the dosage owing to the close proximity of adjacent radiosensitive organs. External beam radiotherapy is routinely used with 5FU as a radiosensitising agent (chemoradiotherapy), although gemcitabine is now being evaluated as an alternative radiosensitiser. Newer techniques such as conformal radiotherapy are now being used, but these studies almost invariably employ follow-on chemotherapy once the chemoradiotherapy has been completed. A recent meta-analysis demonstrated that chemoradiotherapy is better than radiotherapy alone and that there is no survival difference between chemoradiotherapy plus follow-on chemotherapy and chemotherapy alone. A recent phase III study compared chemoradiotherapy and follow-on gemcitabine with gemcitabine alone in patients with locally advanced disease. The trial was closed prematurely because of significant toxicity in the combination arm and significantly reduced median survival in the combination arm (8.4 vs 14.3 months; p = 0.014).

**Newer agents**

A number of new agents and MBTs have been developed from the molecular understanding of pancreatic cancer, which are now being assessed in large phase III trials in advanced pancreatic cancer (table 3).

**Resectable disease**

**Selection and staging**

Once the pancreatic cancer has been identified, the patient needs to be assessed for fitness for major surgery and the
Chemotherapy will improve survival and quality of life in patients with advanced pancreatic cancer. Chemoradiotherapy and follow-on chemotherapy are no better than chemotherapy alone. The best chemotherapy combination available at the present time is gemcitabine combined with either capcitabine or a platinum agent with acceptable toxicity. Where possible, patients with advanced pancreatic cancer should be offered treatment with new therapeutic drugs as part of an early drug development programme or as part of a phase III randomised controlled clinical trial. New agents will be expensive but will become increasingly targeted based on molecular profiling.

Box 8 Palliative therapy in advanced pancreatic cancer

- Chemotherapy will improve survival and quality of life in patients with advanced pancreatic cancer.
- Chemoradiotherapy and follow-on chemotherapy are no better than chemotherapy alone.
- The best chemotherapy combination available at the present time is gemcitabine combined with either capcitabine or a platinum agent with acceptable toxicity.
- Where possible, patients with advanced pancreatic cancer should be offered treatment with new therapeutic drugs as part of an early drug development programme or as part of a phase III randomised controlled clinical trial.
- New agents will be expensive but will become increasingly targeted based on molecular profiling.

Box 9 Surgery in pancreatic cancer

- Surgical resection should be confined to specialist centres; increased resection rates and survival and decreased hospital costs, morbidity and mortality.
- Endoscopic biliary drainage before surgery does not influence surgical outcome but may assist with logistical planning.
- Pancreateoduodenectomy with or without pylorus preservation is the most appropriate procedure.
- Portal vein resections are needed in about 10% of resections but should not be performed routinely.
- Arterial reconstruction cannot be supported except in exceptional circumstances.
- Extended radical resections should not be undertaken because of increased mortality and morbidity and reduced quality of life.
- Use of prophylactic somatostatin analogues reduces postoperative morbidity.

Surgical techniques

Preoperative endoscopic stenting does not influence surgical outcome, but it may facilitate logistical planning of staging and treatment. Metal stents should be avoided in patients who have tumours that may be resectable because of the tissue reaction they invoke, although resection is still technically possible. The aim of surgery is to achieve an R0 resection: complete clearance of macroscopic tumour with clear microscopic resection margins, even if there are lymph node metastases. In practical terms a large proportion of patients (at least 35%) are histologically staged as R1: complete clearance of macroscopic tumour with positive resection margins: R2 resections result in incomplete resection of macroscopic tumour and should be treated in the same category as patients with locally advanced pancreatic cancer as they have an equally poor prognosis. Resecting these patients may lead to longer survival than chemoradiotherapy.

The standard operation for tumours of the head of the pancreas is the Kausch–Whipple partial pancreateoduodenectomy (KW–PPD). There are various methods of reconstruction involving the pancreatic anastomosis. The benefit from a pancreatectogastrostomy rather than a pancreatojejunostomy is still unclear, and there may be no advantage for the routine use of pancreatic stents. The pylorus-preserving partial pancreateoduodenectomy (PP–PPD) is the most commonly used resection approach, which despite being a smaller procedure is as effective as a KW–PPD (table 5). Patients with tumours of the pancreatic body or tail undergo left pancreatectomy usually with en bloc resection of the spleen and hilar lymph nodes. There is no role for total pancreatectomy unless this is the only means by which an R0 resection can be achieved. Extended radical lymphadenectomy is associated with significantly increased morbidity without any survival benefit and is now rejected for routine practice. Involvement of paraaortic lymph nodes (Japanese Pancreas Society Lymph Node Station 16b1) is not a contraindication to resection and should probably be included as part of the routine resection procedure. Postoperative morbidity remains high at around 40% even in supraregional units. Independent risk factors are age >70 years, extended resections and main pancreatic duct diameter <3 mm. Postoperative complications may be reduced by the prophylactic use of octreotide.

Adjuvant treatment

Radical resection alone will result in a 5-year survival of only 10% owing to recurrence after surgery. Nearly all patients develop metastatic disease, most commonly of the liver and peritoneum but also the lungs, and this may occur with or without local recurrence. Although chemoradiation to the area of the resection may reduce the local failure rate, survival length is the same as with systemic chemotherapy. After pancreatic resection, the most important independent prognostic markers are lymph node status, tumour size and tumour grade. The results from two large randomised trials show that adjuvant systemic chemotherapy will increase the 5-year survival from 9% to 12% with resection alone to 21–29%.
and 23% with either 5FU and folinic acid or gemcitabine, respectively (box 10).\textsuperscript{223–225} Table 6 summarises all the randomised trials of adjuvant systemic chemotherapy.\textsuperscript{168–173} The ESPAC-3(v2) trial comparing adjuvant gemcitabine and 5FU has closed to recruitment with 1030 patients, with 2-year survival as the end point. The survival benefit of adjuvant chemotherapy is maintained irrespective of the type of operation used and whether or not patients develop postoperative complications.\textsuperscript{229}

Adjuvant chemoradiotherapy has been used in the USA on the basis of a small randomised trial\textsuperscript{230 231} as well as apparently improving survival as reported in a non-randomised series of patients,\textsuperscript{232 233} but these results have not been confirmed in large randomised trials,\textsuperscript{223 224 234 235} so the focus has moved to whether chemoradiotherapy and follow-on chemotherapy represents a better alternative than chemotherapy alone (table 7).\textsuperscript{223 224 230 231 234 236} The results of meta-analysis using individual patient data reject the use of chemoradiation and provide powerful evidence for systemic chemotherapy.\textsuperscript{235}

The RTOG 9704 trial\textsuperscript{236} has recently reported median and 3-year survival rates. This study used background 5FU-based chemoradiotherapy together with pre- and post-chemoradiation systemic chemotherapy comprising either 5FU or gemcitabine. The original sample size was 330 patients, but this was increased to 518 patients to enable assessment of survival in patients with pancreatic head tumours. The results showed no difference in median survival or 3-year survival in all patients. There was, however, a significant improvement in survival with the gemcitabine-based treatment in patients who had tumours...
of the pancreatic head. These findings are in keeping with survival noted in the equivalent groups in the ESPAC-1 trial and do not show any advantage over chemotherapy alone.

The EORTC trial 40013 plans to recruit 538 patients with resectable pancreatic cancer and compare gemcitabine chemotherapy with gemcitabine followed by chemoradiotherapy. There is an initial phase II part to assess feasibility and toxicity.

Neoadjuvant therapy has also been advocated to increase resection rates, reduce positive resection margins and for the early treatment of micrometastatic disease, but at present there is little evidence to support this approach and randomised trials are lacking.187 204

**CONCLUSIONS**

Pancreatic cancer is a formidable disease to diagnose and treat. Surgical approaches have become more standardised and are

### Table 4

<table>
<thead>
<tr>
<th>Factors contraindicating resection</th>
<th>Factors not contraindicating resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver, peritoneal or other metastasis</td>
<td>Continuous invasion of duodenum, stomach or colon</td>
</tr>
<tr>
<td>Uncertain whether distant lymph node metastasis influence prognosis</td>
<td>Lymph node metastasis within the operative field</td>
</tr>
<tr>
<td>Major venous encasement: &gt; 2 cm in length, &gt; 50% circumferential involvement</td>
<td>Para-aortic lymph node involvement</td>
</tr>
<tr>
<td>Superior mesenteric, coeliac or hepatic artery encasement</td>
<td>Venous impingement or minimal invasion of superior mesenteric and hepatic portal veins</td>
</tr>
<tr>
<td>Severe comorbid illness</td>
<td>Gastro-duodeno-alimentary encasement</td>
</tr>
<tr>
<td>Cirrhosis with portal hypertension</td>
<td>Age of patient</td>
</tr>
</tbody>
</table>

### Table 5

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of resection</th>
<th>Patients (n)</th>
<th>Median survival (months)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin and Lin 2005213</td>
<td>Pylorus-preserving pancreatoduodenectomy</td>
<td>14</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standard pancreatoduodenectomy</td>
<td>19</td>
<td></td>
<td>Delayed gastric emptying (p&lt;0.05)</td>
</tr>
<tr>
<td>Tran et al 2004214</td>
<td>Pylorus-preserving pancreatoduodenectomy</td>
<td>47</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standard pancreatoduodenectomy</td>
<td>43</td>
<td>11 (NS)</td>
<td>NS</td>
</tr>
<tr>
<td>Seiler et al 2005215</td>
<td>Pylorus-preserving pancreatoduodenectomy</td>
<td>37</td>
<td>19.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standard pancreatoduodenectomy</td>
<td>43</td>
<td>18.2 (NS)</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 6

<table>
<thead>
<tr>
<th>Series</th>
<th>Period</th>
<th>Patients (n)</th>
<th>Regimen</th>
<th>Median survival (months)</th>
<th>Actuarial survival (% 1 Year 2 Years 3 Years 5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakkevold et al216</td>
<td>1984–7</td>
<td>61</td>
<td>SFU/DOX/MMC</td>
<td>23</td>
<td>70 27 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31</td>
<td>Observation</td>
<td>11 (p = 0.02)</td>
<td>45 30 8</td>
</tr>
<tr>
<td>Takada et al217 (pancreas only)</td>
<td>1986–92</td>
<td>81</td>
<td>MMC/SFU</td>
<td></td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td>1986–92</td>
<td>77</td>
<td>Observation</td>
<td></td>
<td>18 (NS)</td>
</tr>
<tr>
<td>Kosuge et al218</td>
<td>1992–2000</td>
<td>45</td>
<td>SFU/cisplatin</td>
<td>12.5</td>
<td>26.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44</td>
<td>Observation</td>
<td>15.8</td>
<td>14.9 (NS)</td>
</tr>
<tr>
<td>ESPAC-1223</td>
<td>1994–2000</td>
<td>238</td>
<td>SFU/FA</td>
<td>19.7</td>
<td>Hazard ratio = 0.66 (95% CI 0.52 to 0.83) (p = 0.005)</td>
</tr>
<tr>
<td>Interim—all patients</td>
<td></td>
<td>253</td>
<td>–</td>
<td>14.0 (p = 0.005)</td>
<td></td>
</tr>
<tr>
<td>ESPAC-1219</td>
<td>1994–2000</td>
<td>75</td>
<td>SFU/FA</td>
<td>21.6</td>
<td>44.0 29.0</td>
</tr>
<tr>
<td>Final—individual treatment groups</td>
<td></td>
<td>69</td>
<td>Observation</td>
<td>16.9</td>
<td>38.7 10.7 (p = 0.009)</td>
</tr>
<tr>
<td>Oettle et al225</td>
<td>1998–2004</td>
<td>179</td>
<td>Gemcitabine</td>
<td>22.1</td>
<td>34 22.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>177</td>
<td>Observation</td>
<td>20.2</td>
<td>20.5 11.5 (p = 0.06)</td>
</tr>
</tbody>
</table>

DOX, doxorubicin; FA, folinic acid; SFU, 5-fluorouracil; MMC, mitomycin.
safer, with much improvement in both morbidity and mortality in specialised centres. Diagnosis has improved using conventional imaging methods, and appropriate treatment decisions can be made because of these improvements. Palliative treatment is improving, including the use of endoscopic stent placement with better but less than effective pain relief, and pancreatic enzyme supplementation. Chemotherapy regimens can prolong survival in patients with advanced disease without reducing their quality of life. At present only pancreatic resection can improve survival significantly. A further improvement in survival is achievable with adjuvant chemotherapy but not chemoradiotherapy. The molecular mechanisms responsible for pancreatic cancer point to earlier diagnosis and targeted treatments, using new genetic and biological approaches. Pancreatic cancer surgery can only be performed within a regional pancreas cancer. This is now a very encouraging phase for pancreatic cancer surgery. Using new genetic and biological approaches.

ACKNOWLEDGEMENTS
We gratefully acknowledge the provision of figures from staff at the Royal Liverpool University Hospital Trust: pathology figures are kindly supplied by Dr Fiona Campbell, consultant histopathologist, Department of Pathology and also Dr Jutta Luettges, Klinikum Saarbrücken, Germany; radiology figures are kindly supplied by Dr Jonathan Evans, consultant radiologist, Department of Radiology; and EUS figures are kindly supplied by Dr Martin Lombard, consultant gastroenterologist, Department of Gastroenterology.

Table 7 Adjuvant chemoradiotherapy: randomised controlled trials

<table>
<thead>
<tr>
<th>Series</th>
<th>Period</th>
<th>Patients (n)</th>
<th>Regimen</th>
<th>Median survival (months)</th>
<th>Actuarial survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 Year</td>
</tr>
<tr>
<td>GISTG 9173 (1033)</td>
<td>1987–95</td>
<td>21</td>
<td>40 Gy/SFU, with SFU maintenance</td>
<td>21</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>–</td>
<td>10.9</td>
<td>18</td>
</tr>
<tr>
<td>Klinkenbijl et al (24)</td>
<td>1987–95</td>
<td>110</td>
<td>40 Gy/FU</td>
<td>24.5</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>108</td>
<td>–</td>
<td>19</td>
<td>51</td>
</tr>
<tr>
<td>ESPAC-1 (223)</td>
<td>1994–2000</td>
<td>175</td>
<td>40 Gy/SFU</td>
<td>15.5</td>
<td>(hazard ratio was 1.18 (95% CI 1.09 to 1.55))</td>
</tr>
<tr>
<td>Interim results—all patients</td>
<td>1994–2000</td>
<td>178</td>
<td>± SFU/FA maintenance</td>
<td>16.1</td>
<td>10</td>
</tr>
<tr>
<td>ESPAC-1 (223)</td>
<td>Final—2 × 2 factorial</td>
<td>1994–2000</td>
<td>145</td>
<td>40 Gy/SFU</td>
<td>15.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>144</td>
<td>± SFU/FA maintenance</td>
<td>14.8</td>
<td>41</td>
</tr>
<tr>
<td>ESPAC-1 (224)</td>
<td>Final—individual treatment groups</td>
<td>1994–2000</td>
<td>69</td>
<td>Observation 40 Gy/SFU</td>
<td>16.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>73</td>
<td>40 Gy/SFU</td>
<td>13.9</td>
<td>21.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75</td>
<td>SFU/FA</td>
<td>21.6</td>
<td>44.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>72</td>
<td>40 Gy/SFU</td>
<td>19.9</td>
<td>35.5</td>
</tr>
<tr>
<td>RTOG 9704 (34)</td>
<td>1998–2002</td>
<td>221</td>
<td>Gem before CRT, 50.4 Gy/ SFU, gem after CRT</td>
<td>16.9</td>
<td>20.6</td>
</tr>
<tr>
<td>All patients = 538</td>
<td>221</td>
<td>SFU before CRT, 50.4 Gy/ SFU, SFU after CRT</td>
<td>(p = 0.15)</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Eligible = 442</td>
<td>187</td>
<td>Gem before CRT, 50.4 Gy/ SFU, gem after CRT</td>
<td>20.6</td>
<td>(p = 0.009)</td>
<td></td>
</tr>
<tr>
<td>Head of pancreas only— eligible = 381</td>
<td>194</td>
<td>SFU before CRT, 50.4 Gy/ SFU, SFU after CRT</td>
<td>16.9</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

CRT, chemoradiation; FA, folinic acid; SFU, 5-fluorouracil; Gem, gemcitabine.

Authors’ affiliations
Paula Ghaneti, Eithne Costello, John P Neoptolemos, Division of Surgery and Oncology, University of Liverpool, UK
Funding: Cancer Research UK, CORE and EU Biomed Programmes 5 and 6.
Conflict of Interest: None.

REFERENCES


Larsson SC, Howes N, Chari ST, Coughlin SS, Laheru D, Hingorani SR, Jones LE, Bramhall SR, 81


86 Neoptolemos JP, Stoeckli DD, Dunn JA, et al. For the members of the European Study Group for Pancreatic Cancer (ESPAC), et al. Influence of resection margins on survival for patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy within the ESPAC-1 randomized controlled trial. Ann Surg 2001;234:758–68.


89 DeWitt J, Devereaux BM, Lehman GA, et al. Comparison of endoscopic ultrasound and computed tomography for the preoperative evaluation of


178 Chauvet F, Mornex F, Bonnettela F, et al. Phase III trial comparing initial chemoradiotherapy (intermittent cisplatin and infusional 5-FU) followed by gemcitabine vs. gemcitabine alone in patients with locally advanced non


www.gutjnl.com Downloaded from gut.bmj.com on 6 July 2008

BIOLOGY AND MANAGEMENT OF PancreATIC CANCER