Pancreatic cancer

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Substantial progress has been made in our understanding of the biology of pancreatic cancer, and advances in patients' management have also taken place. Evidence is beginning to show that screening first-degree relatives of individuals with several family members affected by pancreatic cancer can identify non-invasive precursors of this malignant disease. The incidence of and number of deaths caused by pancreatic tumours have been gradually rising, even as incidence and mortality of other common cancers have been declining. Despite developments in detection and management of pancreatic cancer, only about 4% of patients will live 5 years after diagnosis. Survival is better for those with malignant disease localised to the pancreas, because surgical resection at present offers the only chance of cure. Unfortunately, 80–85% of patients present with advanced unresectable disease. Furthermore, pancreatic cancer responds poorly to most chemotherapeutic agents. Hence, we need to understand the biological mechanisms that contribute to development and progression of pancreatic tumours. In this Seminar we will discuss the most common and deadly form of pancreatic cancer, pancreatic ductal adenocarcinoma.

Epidemiology

Pancreatic cancer is the fourth leading cause of cancer death in the USA and leads to an estimated 227 000 deaths per year worldwide.[1] Risk factors for this malignant disease include smoking, family history[2] of chronic pancreatitis, advancing age, male sex, diabetes mellitus, obesity, non-O blood group,[3,4] occupational exposures (eg, to chlorinated hydrocarbon solvents and nickel),[5] African-American ethnic origin, a high-fat diet, diets high in meat and low in vegetables and folate, and possibly *Helicobacter pylori* infection and periodontal disease.[1] Findings of preliminary studies suggest that metformin could protect against development of pancreatic cancer.[6] Coffee intake is not regarded as a risk factor for disease. Although the cause of pancreatic cancer is complex and multifactorial, cigarette smoking and family history are dominant. About 20% of pancreatic tumours are caused by cigarette smoking, and cancers from smokers harbour more genetic mutations than those from non-smokers.[7]

A family history of pancreatic cancer is an important risk factor for disease;[1] about 7–10% of affected individuals have a family history.[8] Familial pancreatic cancer is defined in most studies as families in which a pair of first-degree relatives have been diagnosed with pancreatic tumours. Prospective analysis of families with this malignant disease shows that first-degree relatives of individuals with familial pancreatic cancer have a ninefold increased risk of this neoplasm over the general population.[2] This risk rises to 32-fold greater in kindreds with three or more first-degree relatives with pancreatic cancer. Furthermore, evidence indicates that the risk of pancreatic cancer is modestly increased in first-degree relatives of patients with sporadic pancreatic cancer compared with the general population.[9] Of kindreds with familial pancreatic cancer, risk is highest in those with a case of young-onset pancreatic cancer (age <50 years) in the family compared with those without a young-onset case.[9] Patients with familial pancreatic cancer also have more precancerous lesions than those with sporadic pancreatic tumours[10] and have an augmented risk of developing extra-pancreatic cancers.[11]

Panel 1 describes genes known to form the inherited basis of pancreatic cancer. Once an individual's cancer predisposition gene is identified, family members can undergo genetic testing and, if appropriate, cancer screening and chemoprevention. However, germline genetic testing of patients with pancreatic cancer is probably underused, in large part because of a failure to recognise from the family history the possibility of a familial cancer syndrome. Many clinicians do not record an adequate cancer family history.[26] Usually, kindreds affected by pancreatic cancer who have mutated susceptibility genes do not manifest a high penetrance of pancreatic cancer. For this reason, and because much of the inherited sensitivity to pancreatic cancer remains unexplained, consensus guidelines have not been established to steer genetic testing for inherited susceptibility to pancreatic cancer. *BRCA2* gene testing should be considered—after appropriate genetic counselling—for patients of Jewish ethnic origin, those with a strong family history of breast cancer, or individuals with many first-degree relatives with pancreatic cancer; germline *CDKN2A* testing should be done if there is a family history of familial atypical multiple-mole melanoma (panel 1). Even without genetic testing, obtaining a detailed family history of cancer can be used for prediction of clinical risk, and mendelian risk-prediction programmes have been evaluated for their use for individuals with familial pancreatic cancer.[27]

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Search strategy and selection criteria

We searched ISI Web of Science for articles in English from the past 6 years (since the previous Seminar about pancreatic cancer was published in *The Lancet* in 2004), with the keyword "pancreatic cancer" as a topic, generated a citation report, and prioritised papers on the basis of citations and clinical or biological importance. We also included important papers published before 2004. Because of space limitations, many important references could not be included.

Pathophysiology

Pancreatic ductal adenocarcinomas evolve through non-invasive precursor lesions, most typically pancreatic intraepithelial neoplasias (figure 1, panel 2), acquiring clonally selected genetic and epigenetic alterations along the way (figure 2). Pancreatic cancers can also evolve from intraductal papillary mucinous neoplasms (figure 3) or mucinous cystic neoplasms (panel 2).

The exomes of 24 pancreatic ductal adenocarcinomas were sequenced to characterise more fully the genes mutated in pancreatic cancers.[40] The most frequent genetic abnormalities in invasive pancreatic adeno-carcinomas are mutational activation of the *KRAS* oncogene, inactivation of tumour-suppressor genes including *CDKN2A*, *TP53*, *SMAD4*, and *BRCA2*,[41] widespread chromosomal losses, gene amplifications,[40] and telomere shortening.[42] *KRAS* mutations and telomere shortening are the earliest known genetic abnormalities recorded, even in low-grade pancreatic intraepithelial neoplasias,[42,43] and telomere shortening is believed to contribute to chromosomal instability, whereas inactivation of *TP53*, *SMAD4*, and *BRCA2* happens in advanced pancreatic intraepithelial neoplasias and invasive carcinomas.[28,29] Genes mutated in a few (<20%) pancreatic cancers include oncogenes such as *BRAF*, *MYB*, *AKT2*, and *EGFR*, and tumour-suppressor genes such as *MAP2K4*, *STK11*, *TGFBR1*, *TGFBR2*, *ACVR1B*, *ACVR2A*, *FBXW7*, and *EP300*.[40] Structural analysis of mutated genes implicates *PIK3CG*, *DGKA*, *STK33*, *TTK*, and *PRKCG* as low-frequency driver mutations.[44]

Intraductal papillary mucinous neoplasms harbour many of the genetic alterations recorded in pancreatic intraepithelial neoplasias but with notable differences—eg, intraductal papillary mucinous neoplasms rarely inactivate *SMAD4*. Genetically engineered mouse models targeting some of the genes most commonly altered in human pancreatic cancer have been developed, and several of these recapitulate the human disease and have been used to study mechanisms and investigate therapeutic agents.[45]

In addition to the driver genes discussed above, epigenetic changes can also alter gene function in pancreatic cancers.[46] Epigenetic dysregulation includes alterations in DNA methylation and histone modifications and non-coding RNAs. Promoter methylation and gene silencing in pancreatic cancers was first reported for the tumour-suppressor gene *CDKN2A*, of which epigenetic silencing is restricted to neoplasms without genetic inactivation of *CDKN2A*.[47] Only a few classic tumour-suppressor and DNA-repair genes undergo epigenetic silencing in pancreatic cancers—eg, *MLH1* and *CDH1* are methylated in a small proportion of tumours. Many other genes are frequent targets of aberrant methylation and gene silencing in pancreatic cancers, including *CDKN1C*, *RELN*, *SPARC*, *TFPI2*, and others.[46,48-52] Some of the most commonly aberrantly hypermethylated genes in pancreatic neoplasms have been evaluated for their diagnostic or biological relevance.[33,46,53] Promoter hypomethylation of overexpressed genes has also been reported for several genes, such as *SFN*, *MSLN*, and *S100A4*,[54] and mucin genes.[55]

Alterations in microRNA expression seem to contribute to cancer development and progression. Overexpression of several microRNAs in pancreatic cancers—including miR-21, miR-34, miR-155, and miR-200—is thought to contribute to neoplastic progression.[56-59] Furthermore, since microRNAs are stable and detectable in human plasma they could be useful diagnostic markers.[57]

Genetic and epigenetic alterations of pancreatic cancers probably play a part in tumour aggressiveness and patterns of progression. Panel 3 describes major pathways affected by these alterations.

Molecular evolution of pancreatic cancers has been estimated using somatic mutations as molecular clocks. From this analysis, an initial precursor neoplastic clone will take roughly more than 10 years to evolve into a malignant clone and several additional years for metastatic subclones to emerge from within the primary

cancer.[65] Comparison of molecular alterations of a patient's primary pancreatic cancer and metastases reveals not only that almost all the major driver genes are mutated before development of invasive adenocarcinoma but also that genetic instability continues after cancer dissemination, with some genetic heterogeneity arising in different metastases.[66] Although these estimates reflect a range of tumour behaviour in different patients, they indicate that a primary cancer can reside in the pancreas for many years before metastasis, potentially providing opportunities for screening.[66,67]

Tumour microenvironment

Interactions between cancer-associated fibroblasts—the predominant stromal cell type—and neoplastic cells could contribute to tumour initiation, progression, and metastasis. Some of the best characterised pathways affected by tumour-stromal interactions are described in panel 3.

The role of the immune system in pancreatic cancer progression has focused on the potential benefit of inhibition of T regulatory lymphocytes (cells that suppress antitumour immune responses) or use of vaccines—including irradiated genetically modified pancreatic cancer cells or immunostimulatory pancreatic cancer antigens, such as overexpressed (eg, mesothelin) or mutated proteins.[68,69] Furthermore, the mechanisms of immune evasion by cancer cells and cancer-associated fibroblasts have been studied.[64,68]

The role of tumour-initiating cells (so-called cancer stem cells) in the development of pancreatic cancer is controversial. Although putative cells have been identified,[70] reconciling the notion of tumour-initiating cells with the clonal selection provided to neoplastic cells by tumorigenic mutations acquired during carcinogenesis is difficult.[71] One hypothesis is that cancer stem-cell markers identify cells most likely to survive a given cellular stress at any one time, such as the ability to grow in nude mice or survive chemotherapeutic agents.[72]

Screening to detect curable precursor lesions

The deadly nature of invasive pancreatic cancer, and recognition that most patients present with advanced stage disease,[73] has led to efforts to screen individuals with an inherited predisposition for early curable disease—such as pancreatic intraepithelial neoplasias, and non-invasive intraductal papillary mucinous neoplasms and mucinous cystic neoplasms. Family history has been used as a quantitative predictor of pancreatic cancer risk.[2,10,30–32,74] Indeed, screening has identified silent pancreatic neoplasia in many individuals with strong family histories of pancreatic cancer.[56,57] For example, in the CAPS2 trial (Cancer of the Pancreas Screening 2), about 10% of patients screened (those generally aged 50 years or older, with three blood relatives with pancreatic cancer, including at least one affected first-degree relative) had intraductal papillary mucinous neoplasms detectable by endoscopic
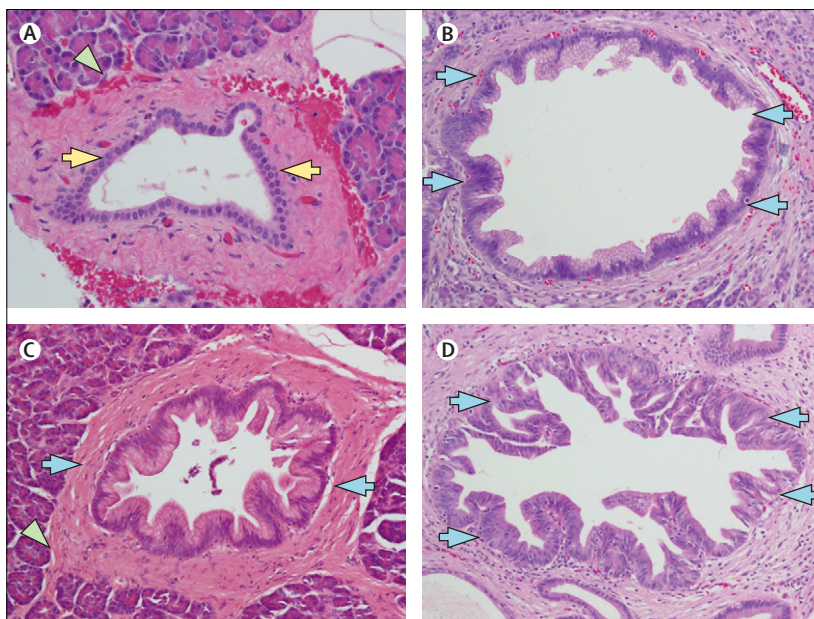

Figure 1: **Histology of PanINs and normal pancreas**
(A) Normal pancreatic duct. (B) PanIN 1. (C) PanIN 2. (D) PanIN 3. Yellow arrows=normal pancreatic duct. Green arrow head=normal acinar tissue. Blue arrows=PanINs. Magnification ×40. PanIN=pancreatic intraepithelial neoplasia.

ultrasound. However, screening brings with it the risk of overtreatment, and the randomised trials needed to ascertain if pancreatic cancer screening can save lives have not been undertaken.

Researchers are doing clinical trials to assess the best screening protocol for individuals at increased risk of pancreatic neoplasia. An ideal screening test for early pancreatic cancer would be a highly accurate blood marker that could be measured fairly non-invasively. Unfortunately, none to date have proven sufficiently specific for diagnosis.[75–78] Furthermore, the focus of screening efforts up to now has been to detect preinvasive lesions, rather than early pancreatic cancer, since resection of preinvasive lesions can prevent development of an invasive pancreatic cancer, whereas once an invasive pancreatic cancer develops, its spread beyond the pancreas is probably rapid, restricting use of markers of invasive pancreatic cancer.

Because of its ability to detect small preinvasive lesions (of about 1 cm), endoscopic ultrasound is used widely as a screening test. In the CAPS3 multicentre screening trial (ClinicalTrials.gov identifier NCT00438906), pancreatic cystic lesions were detected more frequently with endoscopic ultrasound (93%) and MRI (81%) than with CT (27%).[79] Since microscopic pancreatic intraepithelial neoplasias are usually not visible by pancreatic imaging, research is attempting to identify markers in pancreatic fluid that could reliably identify high-grade pancreatic intraepithelial neoplasias.[33,76,80] Focal preinvasive lesions evident by endoscopic ultrasound (such as intraductal papillary mucinous neoplasms) are probably most readily sampled with fine-needle aspiration.

Panel 2: Non-invasive precursors to pancreatic cancer

- The most common neoplastic precursor to invasive adenocarcinoma of the pancreas is known as PanIN (figure 1)
- PanINs are microscopic (<5 mm diameter) and are not directly visible by pancreatic imaging
- PanINs can harbour the somatic genetic alterations seen in invasive pancreatic cancers, and prevalence of these genetic alterations rises as the amount of cytological and architectural atypia in PanINs increases[28,29] (figure 2)
- Low-grade PanINs (PanIN 1) are very common with increasing age and high-grade PanINs (PanIN 3) are usually present in pancreata with invasive cancer
- Pancreata resected from individuals with a strong family history of pancreatic cancer usually have multifocal PanINs associated with lobulocentric atrophy[30–32]
- Molecular markers are being investigated to see if they can be used to estimate the burden and grade of PanIN[33]
- Molecular imaging has the potential to detect PanIN but further research is needed[34]
- Intraductal papillary mucinous neoplasms are a less frequent precursor to invasive pancreatic cancer; they are large cystic neoplasms (≥5 mm)[35] diagnosed increasingly because of improvements in pancreatic imaging[36,37] (figure 3)
- Non-invasive intraductal papillary mucinous neoplasms are classified on the basis of the amount of cytological and architectural dysplasia, as either low-grade, intermediate-grade, or high-grade dysplasia (carcinoma in situ)
- Cure rates are very high after resection of intraductal papillary mucinous neoplasms that do not have an associated invasive pancreatic cancer but, if left alone, these lesions can progress to incurable invasive cancers
- Intraductal papillary mucinous neoplasms can affect pancreatic branch ducts, main ducts, or both
- Most small asymptomatic Intraductal papillary mucinous neoplasms in branch ducts have low malignant potential, so international guidelines have been developed for their management[38]
- If the patient can tolerate surgery, resection of intraductal papillary mucinous neoplasms should be done if the neoplasm is in the main pancreatic duct, if it is associated with symptoms, if it is larger than 3 cm, and if it has a mural nodule
- By contrast, most intraductal papillary mucinous neoplasms confined to branches of the main pancreatic duct (branch-duct neoplasms) have low malignant potential but should be followed up with regular pancreatic imaging, with the imaging interval based primarily on lesion size
- Branch-duct intraductal papillary mucinous neoplasms of 1–3 cm in size should be assessed by endoscopic ultrasound and magnetic resonance cholangiopancreatography
- CT is also appropriate for intraductal papillary mucinous neoplasms, but since many patients need repeated imaging, some prefer alternate MRI and endoscopic ultrasound, thereby avoiding repeated radiation associated with CT
- Surgical resection is recommended for intraductal papillary mucinous neoplasms if high-risk stigmata are present
- Criteria for surveillance and resection could be different for patients with a strong family history of pancreatic cancer[32] because they typically have concurrent microscopic PanIN that cannot be followed up accurately by imaging
- A less frequent precursor to pancreatic cancer is the mucinous cystic neoplasm, which is composed of mucin-producing epithelial cells and an associated ovarian-type stroma[39]
- Unlike intraductal papillary mucinous neoplasms, mucinous cystic neoplasms do not communicate with pancreatic ducts
- Mucinous cystic neoplasms arise predominantly in women; about a third of these neoplastic precursors have an associated invasive carcinoma

PanIN=pancreatic intraepithelial neoplasia.

Clinical presentation

Early-stage pancreatic cancer is usually clinically silent, and disease only becomes apparent after the tumour invades surrounding tissues or metastasises to distant organs. Most people who present with symptoms attributable to pancreatic cancer have advanced disease.[81] Pancreatic cancer patients who have undergone abdominal CT scans for other reasons before their diagnosis are usually noted in retrospect to have had subtle abnormalities suspicious for pancreatic cancer up to 1 year before development of symptoms,[82] suggesting a missed opportunity for early detection.

Typical presenting symptoms of pancreatic cancer include abdominal or mid-back pain, obstructive jaundice, and weight loss. Weight loss can arise from anorexia, maldigestion from pancreatic ductal obstruction, and cachexia. Occasionally, pancreatic-duct obstruction could result in attacks of pancreatitis. Deep and superficial venous thrombosis is not unusual and might be a presenting sign of malignant disease. Gastric-outlet obstruction with nausea and vomiting sometimes happens with more advanced disease. Less common manifestations include panniculitis and depression. About 25% of patients with pancreatic cancer have diabetes mellitus at diagnosis and roughly another 40% have impaired glucose tolerance.[83,84] The cause of the diabetogenic state is uncertain, but diabetes is sometimes cured by resection of pancreatic cancer. Researchers are investigating whether early-stage pancreatic cancer should be looked for in older individuals with new-onset diabetes. Most people with new-onset diabetes, however, do not have pancreatic cancer.[85] Apart from weight loss, few clinical clues exist to
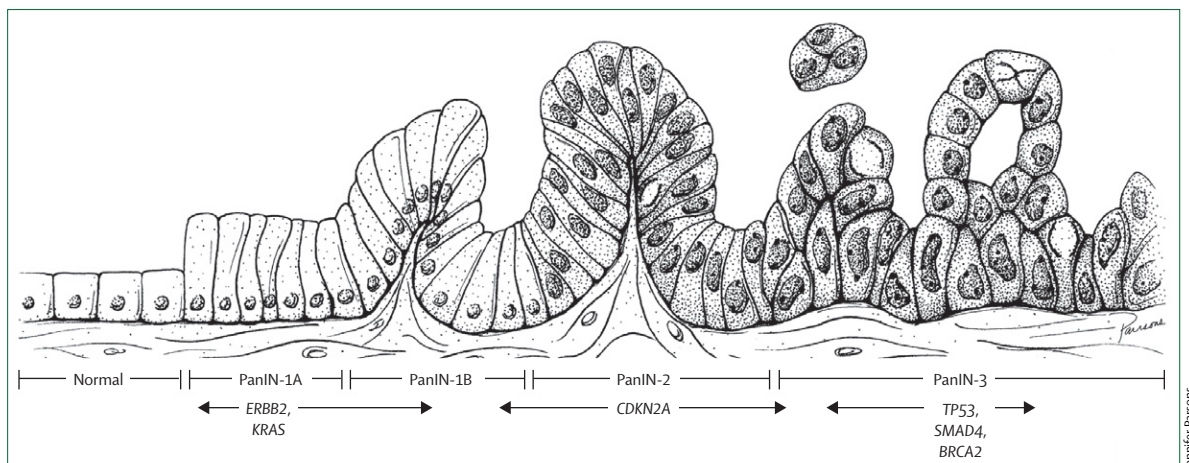
***Figure 2:* PanIN progression model, showing genetic alterations**
PanIN=pancreatic intraepithelial neoplasia. Reprinted from reference 28, with permission of the American Association for Cancer Research.

suspect pancreatic cancer in those with new-onset diabetes. Hence, screening older patients with new-onset diabetes for pancreatic cancer would need new screening tests.[86]

Diagnosis and staging

Tri-phasic pancreatic-protocol CT is the best initial diagnostic test for pancreatic cancer. It is also best for disease staging, and optimum CT scans—including 3-dimensional reconstruction—provide about 80% accuracy for prediction of resectability. The quality of CT varies, and imaging technology continues to improve. The ability of high-quality pancreatic-protocol CT scans to detect locally advanced and metastatic disease reliably has greatly reduced the number of unnecessary laparotomies and need for staging laparoscopies.[87] Endoscopic ultrasound is also highly accurate for diagnosis of pancreatic cancer, and sampling for diagnostic cytology can be undertaken at the time of endoscopic ultrasound. MRI can be used for staging in patients who cannot tolerate intravenous contrast for CT.

Clinical staging classifies patients into resectable, borderline resectable, locally advanced, and metastatic disease (panel 4).[88] It dictates the most appropriate initial treatment. Chest imaging (either chest radiography or CT) is recommended to detect pulmonary metastases. PET CT is currently not part of routine staging but can be helpful if metastases are suspected, such as for indeterminate lesions by CT, and might be better at identification of metastatic disease. Laparoscopy can spot peritoneal metastases but is not undertaken routinely before proceeding with pancreatic resection. Preoperative amounts of carbohydrate antigen 19-9 (CA19-9) of more than 100–200 U/mL predict unresectability and survival.[76,89]

Although pancreatic cancer can be strongly suspected when imaging reveals a pancreatic mass invading surrounding organs, tissue diagnosis is recommended to confirm the finding and to rule out benign disorders that
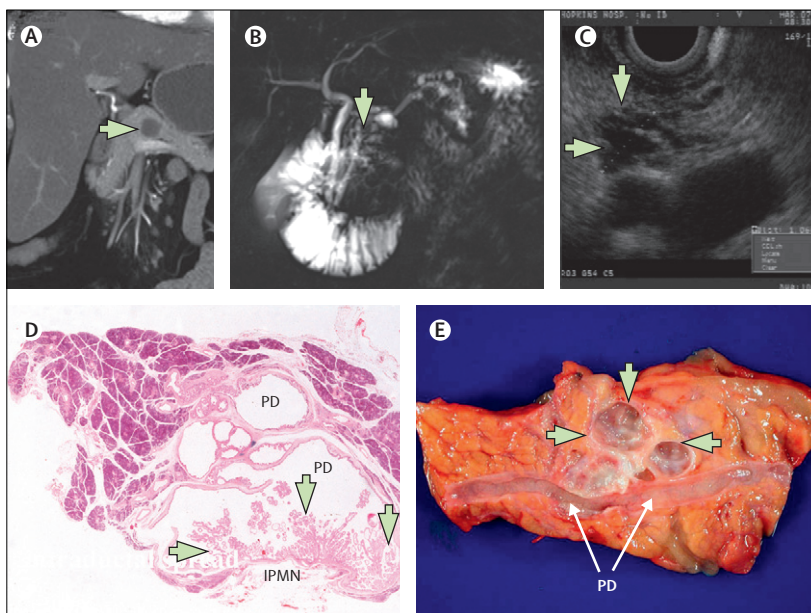

***Figure 3:* Cross-sectional imaging and analysis of an IPMN**
(A) CT (coronal section). (B) Magnetic resonance cholangiopancreatography of a branch-duct IPMN.
(C) Endoscopic ultrasound. (D) Histological section of a resected main-duct IPMN (magnification ×5).
(E) Surgical pathology specimen of resected pancreas that includes a branch-duct IPMN from a patient who underwent pancreatic screening. Note, the main pancreatic duct (PD) is not involved. Green arrows indicate IPMN.
IPMN=intraductal papillary mucinous neoplasm.

present with pancreatic enlargement and obstructive jaundice, such as autoimmune pancreatitis.

Cytological diagnosis can usually be made with endoscopic ultrasound or CT-guided fine-needle aspiration. Sensitivity of endoscopic ultrasound-guided fine-needle aspiration of pancreatic masses is reported to be about 80%.[90] Identification of the cause of biliary or pancreatic-duct strictures might need endoscopic retrograde cholangiopancreatography and brushings for cytological diagnosis. The yield of cells from endoscopic brushings is low (about 20%) because of the small sample

and sometimes subtle differences between malignant and non-neoplastic reactive cells. Molecular markers could have a role as an adjunct to brush and fine-needle aspirate cytological diagnosis, but these need further evaluation.[53,91] A biopsy specimen is not needed for surgical resection when suspicion of cancer is high; generally, the resection will provide therapeutic benefit, and substantially delaying surgery to confirm a diagnosis could set back commencement of effective treatment.

Principles of management

Patients with pancreatic cancer are best managed by a multidisciplinary team that includes oncologists, surgeons, radiologists, gastroenterologists, radiation oncologists, pathologists, pain management experts, social workers, dietitians, and (when appropriate) palliative care experts.[92] Pancreatic cancer is a heterogeneous disease at the molecular, pathological, and clinical level. A patient's response to treatment and outcome depends on many factors, including the biology of their cancer, their performance status, and their pattern of disease progression.

Surgery

Operative mortality from pancreatic resection is low at most expert centres.[93] Findings of several studies show that mortality from pancreaticoduodenectomy is considerably lower in high-volume compared with low-volume centres. For this reason, consensus panels recommend that pancreaticoduodenectomy should be undertaken at institutions doing at least 15–20 of these operations a year. Furthermore, many candidates for curative resection do not undergo surgical resection.[94,95] Postoperative complications after resection include pancreatic anastomotic leaks and delayed gastric emptying. Researchers on several randomised trials have attempted to ascertain the best operative approaches to minimise postoperative complications arising from pancreaticoduodenectomy. Findings of these trials have not shown any clear advantage of one technique over another.

Portal or superior mesenteric vein resection and reconstruction is appropriate when it enables an R0 resection and can be done without increased operative morbidity.[96] Laparoscopic resection is a viable approach for selected pancreatic-tail resections.[97] Endoscopic tattooing can be used to localise small lesions before laparoscopic resection.[98]

Preoperative biliary drainage is mandatory for patients with cholangitis, those with relevant liver dysfunction, and those who are symptomatic (such as with severe pruritis). Otherwise, routine preoperative biliary drainage might not be necessary, since study findings indicate that outcomes are worse after routine preoperative drainage for individuals with obstructive jaundice from pancreatic cancer versus surgical resection alone.[99] On the other hand, in the neoadjuvant setting, obstructive jaundice needs to be corrected before initiation of chemotherapy and radiotherapy. Biliary drainage will also lower non-specific CA19-9 amounts, allowing a more reliable estimate of disease burden.

Pathological findings after surgery

Pathological assessment of the resected pancreatic tumour provides important prognostic information. The pathologist must ascertain if the surgeon has achieved a negative (R0) resection margin. An R1 margin is positive at the microscopic level but not grossly visible, and an R2 resection has grossly visible cancer at the resection margin. Standardised protocols for establishing margin status pathologically are not available, resulting in variability in assessment of margin status. One change in TNM staging (panel 4) of pancreatic cancers is that a

neoplasm extending to the portal vein or superior mesenteric vein is now deemed T3 disease if it is still resectable and the venous circulation can be reconstructed successfully.

Pathological assessment includes classification of histological variants of pancreatic ductal adenocarcinoma. Such variants consist of colloid carcinomas (associated with intestinal-type intraductal papillary mucinous neoplasms), medullary cancers (which might have microsatellite instability), and others including adeno-squamous tumours, hepatoid carcinoma, signet-ring cell cancer, undifferentiated carcinoma, and undifferentiated carcinoma with osteoclast-like giant cells.[39]

For patients with surgically resected ductal adenocarcinoma of the pancreatic head, actuarial 5-year overall survival is about 20–25%. The presence of positive resection margins, poor tumour differentiation, a large cancer, and positive lymph nodes all portend a poor prognosis.

Several markers—such as loss of SMAD4 immuno-labelling—have been associated with increased risk of development of widespread metastasis[100] and poor outcome after surgical resection.[101,102] SPARC expression in fibroblasts associated with pancreatic cancer also indicates an adverse outcome.[103]

Findings of these initial studies suggest that detailed molecular assessment of pancreatic cancers could ultimately improve clinical decision making, although even information provided by complete exome sequencing might not be sufficiently informative to guide therapeutic decision making in most patients. Furthermore, for individuals with inoperable disease, molecular profiling might be limited by what can be done on a Tru-Cut biopsy sample.

Adjuvant and neoadjuvant treatment
Adjuvant therapy

Adjuvant treatment is recommended for individuals who undergo pancreatic resection with curative intent.[104] It is generally given once patients have recovered from surgery (1–2 months). Baseline CT scans and CA19-9 concentrations should be obtained before initiation of adjuvant treatment. The benefit of this therapy has been established from findings of randomised controlled trials (GITSG,[105] CONKO-001,[106] and RTOG-9704[107]) and retro-spective studies.[108–111] In the GITSG trial, fluorouracil-based chemoradiation was superior to observation alone.[105] Addition of radiation to adjuvant chemotherapy is unproven and controversial. Researchers on the ESPAC-1 trial compared chemotherapy with chemo-radiation and noted that chemoradiation failed to increase survival and was perhaps harmful, although the trial had limitations with respect to its design and variability in radiation delivery.[112,113] The RTOG-9704 trial compared gemcitabine with fluorouracil before and after fluorouracil-based chemoradiation. In an updated analysis of this trial, the treatment arms did not differ by

much.[107] Workers on the ESPAC-3 trial compared adjuvant gemcitabine with fluorouracil and noted no dif-ference in survival.[114] The conclusion of the CONKO-001 trial was that gemcitabine was superior to observation alone, with median overall survival of 22·8 versus 20·2 months.[106] Since RTOG-9704 and CONKO-001 differed by design (CONKO-001 excluded patients with concentrations of CA19-9 >90 U/mL) and study population (CONKO-001 had fewer participants with node-positive

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Panel 4: Staging of pancreatic cancer

Clinical staging[88]

Local or resectable (about 10%, median survival 17–23 months)
- Stage 0 (Tis, N0, M0)
- Stage IA (T1, N0, M0)
- Stage IB (T2, N0, M0)
- Stage IIA (T3, N0, M0)
- Stage IIB (T1, N1, M0; T2, N1, M0; T3, N1, M0)

Borderline resectable (10%, median survival up to 20 months)
Stage 3 disease with tumour abutment or <180° circumference of the superior mesenteric artery or coeliac arteries, or a short segment of hepatic artery or the superior mesenteric vein, pulmonary vein, or confluence of these veins

Locally advanced or unresectable (about 30%, median survival 8–14 months)
- Stage III (T4, any N, M0)

Tumour encasement >180° circumference of the superior mesenteric artery or coeliac arteries, any unreconstructable venous involvement

Metastatic (about 60%, median survival 4–6 months)
- Stage IV (any T, any N, M1)

TNM classification

T=primary tumour
TX: primary tumour cannot be assessed
T0: no evidence of primary tumour
Tis: carcinoma in situ (includes the PanIN 3 classification)
T1: tumour restricted to the pancreas, ≤2 cm greatest dimension
T2: tumour restricted to the pancreas, >2 cm greatest dimension
T3: tumour extends beyond the pancreas, no involvement of coeliac axis or superior mesenteric artery (or extension to the portal vein or superior mesenteric artery, but still resectable)
T4: tumour affects the coeliac axis or superior mesenteric artery (unresectable primary tumour)

N=regional lymph node
NX: regional lymph nodes cannot be assessed
N0: no regional lymph-node metastasis
N1: regional lymph-node metastasis

M=distant metastasis
M0: no distant metastasis
M1: distant metastasis

or margin-positive disease) they are not comparable directly, but their results suggest that benefit is similar whether patients receive adjuvant chemotherapy or chemoradiotherapy. These findings, together with results of the ESPAC-1 trial, lead many oncologists to conclude that adjuvant chemotherapy is beneficial and that evidence is scant for a role of conventional adjuvant radiotherapy. Therefore, in many centres (particularly in Europe), patients receive adjuvant chemotherapy without radiotherapy. Some centres, particularly in the USA, still use adjuvant chemoradiotherapy, suspecting that radiotherapy can be helpful in some patients, and clinical trials to date have not ruled out such a benefit.

Individuals most likely to benefit from adjuvant treatment are those who have undergone an R0 resection. Many people with an R1 resection have inferior median survival compared with those with R0 resections (range 8–18 *vs* 20–25 months). After surgical resection, patients are likely to develop systemic (>70%) and local recurrence (>20%). Worldwide, clinicians are beginning to delay radiotherapy until after an adequate course of chemotherapy, to prevent metastatic disease, so only patients who are free of disease 4–6 months after systemic treatment will receive adjuvant radiotherapy. This approach is being assessed in the international phase III adjuvant trial (EORTC, US Intergroup, RTOG-0848). Although delaying radiotherapy might be adequate for individuals with R0 resections, it is not suitable for patients with R1 resections if a delay will increase the risk of local recurrence. The role of adjuvant treatment after distal pancreatectomy is controversial and based mainly on studies from individual institutions.[115]

Other adjuvant regimens are under investigation. The combination of adjuvant interferon alfa-2b, cisplatin, and continuous-infusion fluorouracil concurrently with external-beam radiation had unacceptably high toxic effects.[116] Adjuvant trials underway include those testing the role of erlotinib, the combination of gemcitabine, docetaxel, and capecitabine (NCT00882310), and the granulocyte-macrophage colony-stimulating factor-secreting vaccine for pancreatic cancer, with or without cyclophosphamide as a T regulatory-depleting agent (NCT00727441). A summary of important, completed, phase III adjuvant trials is outlined in table 1, and other ongoing and completed trials are described in the webappendix (pp 1–3).

Neoadjuvant therapy

Is neoadjuvant therapy as effective or superior to adjuvant treatment for pancreatic cancer? Although no data are available from randomised controlled trials to support neoadjuvant over adjuvant therapy, findings of a meta-analysis suggest the proportion of patients who can have resection is similar, whether or not neoadjuvant treatment is given.[117] Neoadjuvant therapy does yield partial responses and has the potential to downstage patients with borderline resectable disease,[117] and it is

usually recommended in this setting.[118] Neoadjuvant treatment can detect patients whose disease progresses rapidly and, therefore, it could help to select those who might not benefit from surgical resection. Another potential advantage of neoadjuvant therapy is that postoperative complications do not delay or preclude administration of adjuvant treatment. Conversely, tumour response rates to current neoadjuvant therapies are not high, and delaying surgical resection could also allow disease progression. For this reason, patients undergoing neoadjuvant therapy should be restaged before surgical resection.

The optimum neoadjuvant regimen is not yet known, although combination chemotherapy schedules are usually given.[117] Since no advantage has been recorded of neoadjuvant treatment over adjuvant therapy for patients with clearly resectable disease, and strong evidence exists that adjuvant therapy increases survival, most centres use adjuvant treatment, reserving neoadjuvant therapy for patients with borderline resectable disease.

Management of borderline resectable disease

Resections are attempted in many patients with borderline resectable cancer (ascertained by clinical staging) if the clinician suspects that an R0 resection can be achieved. Optimum preoperative staging can target individuals who should undergo initial chemoradiotherapy rather than surgery.[92,119] The regimens used for adjuvant and neoadjuvant chemoradiotherapy are those typically administered to patients with borderline resectable disease. In an uncontrolled study of individuals with borderline resectable pancreatic cancer, those receiving neoadjuvant therapy and deemed eligible for pancreatic resection had significantly better survival than those who did not have pancreatectomy.[120] Patients with borderline resectable disease who require vein resections seem to benefit also from adjuvant treatment.[121]

Management of advanced disease

Survival is significantly better for patients with locally advanced disease (median survival 9–15 months) than for those with metastatic disease (3–6 months). Chemotherapy is the mainstay of treatment for individuals with advanced disease—provided they have adequate performance status—but is not helpful for those with poor performance status. Gemcitabine is standard for patients with advanced pancreatic cancer: it induces a partial response in a few people and can alleviate symptoms in some with advanced tumours.[122–124]

Fixed-dose gemcitabine might enable maximum intracellular accumulation of the active triphosphate form of the drug. In one study, fixed dosing resulted in better responses than standard gemcitabine infusion but produced more haematological toxic effects.[125] Such a benefit has not been recorded in other studies. Markers have been identified that predict response to gemcitabine (and fluorouracil) but are not sufficiently

predictive to affect the decision to use gemcitabine.[76,126,127] Unfortunately, most pancreatic cancers do not respond to gemcitabine alone.

Treatment of locally advanced disease

Chemoradiotherapy downstages about 30% of patients with locally advanced disease to resectable pancreatic cancer, and these individuals go on to achieve median survival similar to that for those who are initially resectable without any preoperative treatment.[117] Chemotherapy alone is sometimes used for patients too frail to tolerate radiation. Findings of trials in which attempts have been made to ascertain whether chemotherapy alone is preferable to chemoradiation in patients with locally advanced disease have been inconclusive. The National Comprehensive Cancer Network recommends use of chemoradiation (fluorouracil and 50–60 Gy radiotherapy) followed by systemic chemotherapy (usually 4 months of gemcitabine).[128] Fluorouracil or gemcitabine can be used as a radio-sensitiser: in the locally advanced setting, chemoradiation regimens containing gemcitabine yield similar results to those with fluorouracil.[129,130]

Although chemoradiotherapy is usually given before systemic chemotherapy, some evidence suggests that scheduling chemotherapy before chemoradiotherapy might be preferable.[131] In patients destined to have rapidly progressive disease, metastases will probably show up during initial chemotherapy and therefore unnecessary local radiotherapy will be avoided.

Radiation therapy

Fractionated radiation therapy is typically delivered as 45–60 Gy over about 6 weeks (1·8–2·0 Gy/day), with fluorouracil or capecitabine—an oral fluoropyrimidine—as a radiosensitiser. In the adjuvant setting, 45 Gy is delivered initially to the tumour bed, surgical anastomosis, and regional lymph nodes. Subsequently, additional radiation (about 5–15 Gy) is directed at the tumour bed to target microscopic extension. Preoperative CT scans (with oral and intravenous contrast) and surgical clips are used to calculate the optimum volume and localisation of radiation. Adjuvant chemoradiotherapy is generally not given to patients who have received neoadjuvant chemoradiotherapy. In the neoadjuvant, borderline, and locally advanced settings, the radiotherapy field targets the tumour bed and adjoining margin with or without adjacent lymph nodes. The radiation volume encompasses the gross tumour volume—ie, a surrounding volume (0·5–2·0 mL) to target microscopic extension (the clinical treatment volume) and an additional 0·5–2·0 mL to account for errors in estimation of tumour size. Smaller margins of radiation are possible when optimum tumour imaging techniques are used and have the advantage of minimising radiation to adjacent normal structures. Advances in radiation techniques such as intensity-modulated radiation therapy and stereotactic body radiation therapy enable dose escalation and sparing of healthy tissues that could improve tumour control with tolerable side-effects, but these modalities need further assessment in prospective clinical trials. The current role of chemoradiotherapy in pancreatic cancer was detailed in a consensus statement.[132]

Treatment of metastatic disease

Gemcitabine-based combination treatments have been assessed for advanced pancreatic cancer. Since fluorouracil and gemcitabine are both approved for use in patients with pancreatic cancer, the combination of gemcitabine and capecitabine has been evaluated for individuals with advanced pancreatic tumours in phase 2 and phase 3 clinical trials. For example, findings of a phase 3 trial showed that, compared with gemcitabine alone, the combination of gemcitabine and capecitabine yielded a better response and longer progression-free survival, with a trend towards increased overall survival.[133] In another study,[134] significant overall survival benefits of this combination were reported in the subgroup of patients with good performance status, and data from a meta-analysis indicated a significant overall survival benefit for this combination.[133] Conroy and colleagues[135] noted, in a phase 3 trial, that for patients with good performance status, the combination of fluorouracil, folinic acid, irinotecan, and oxaliplatin led to median survival of 11 months (vs 6·8 months for gemcitabine alone).

In phase 3 clinical trials, the combination of gemcitabine and the epidermal growth factor receptor (EGFR) inhibitor, erlotinib, was modestly superior to gemcitabine alone.[136] Erlotinib—a tyrosine kinase inhibitor of the catalytic domain of EGFR—is approved by the US Food and Drug Administration for use in pancreatic cancer. As suspected with colorectal cancer, the benefit of erlotinib might be for patients with pancreatic cancers containing wild-type *KRAS*, but evidence for this notion was absent in a subgroup analysis.[136] The combination of gemcitabine, erlotinib, and bevacizumab versus gemcitabine and erlotinib has been compared in the phase 3 AVITA trial.[137] No difference in the primary endpoint of overall survival was recorded, but progression-free survival was superior in the triple-drug arm. A summary of phase 3 clinical trials for advanced pancreatic cancer is provided in table 2 and in the webappendix (pp 1–3).

Many combination chemotherapy regimens that show initial promise in phase 2 trials fail to confirm increased survival in phase 3 studies. Meta-analyses have been used to overcome the disadvantage of small clinical trials. For example, in a meta-analysis of about 3600 patients in phase 3 trials, overall survival was better when gemcitabine was combined with either a platinum-based drug or a fluoropyrimidine, compared with gemcitabine alone,[138,139] especially for individuals with very good performance status.

Another treatment undergoing investigation is nanoparticle-formulated paclitaxel. The combination of

gemcitabine (1000 mg/m²) with this formulation of paclitaxel (125 mg/m²) has been reported in abstract form to have good response rates and is now being tested in phase 3 trials (NCT00844649).

No standard second-line treatment exists for pancreatic cancer: many patients with advanced disease progress too rapidly to tolerate such regimens. Second-line fluoropyrimidine-based therapy is sometimes used if gemcitabine has been given as first-line treatment. In the CONKO-003 trial,[140] patients who failed gemcitabine first-line therapy had better overall survival if they received oxaliplatin with fluorouracil and folinic acid than fluorouracil and folinic acid alone.

Measurement of tumour response

CT is the standard method for measurement of tumour burden, and clinical trials usually use RECIST (response evaluation criteria in solid tumours) criteria to gauge tumour response. However, CT-based measurements of tumour size do not always quantify treatment response accurately and are usually only established after two cycles of treatment, which is a long time for patients with low survival. Although not sufficiently accurate for diagnosis, serial CA19-9 concentrations predict treatment response or disease relapse.[76] Amounts of mutant DNA in plasma have been shown to represent tumour burden and response to treatment accurately, in patients with colorectal cancer, and it is likely to be useful for individuals with pancreatic and other neoplasms.[141] Furthermore, changes in mutant DNA in plasma can be recorded within days of treatment. Moreover, once novel tumour DNA rearrangements are identified in a cancer, their detection in the circulation is feasible.[142]

Investigational treatments for advanced pancreatic cancer

The success of targeted treatments in other cancers supports the need for further research to identify new targets and better predictors of response to therapy. Several targeted agents are undergoing clinical trials for pancreatic cancer.[143,144] Ongoing studies are shown in the webappendix (p 3).

Pancreatic cancer cells with defects in the BRCA2-PALB2-Fanconi DNA repair pathway are sensitive to poly (ADP-ribose) polymerase (PARP) inhibitors.[53,54] PARP enzymes add large branched chains of poly (ADP-ribose) on nicked DNA, which cause separation of histones from DNA, to enable DNA repair. In phase 1/2 clinical trials of patients with a germline *BRCA2* gene mutation, response rates of about 40% were recorded with olaparib for recurrent breast and ovarian cancer.[145] Clinical trials of PARP inhibitors for patients with pancreatic cancer are currently underway.

The hedgehog pathway inhibitor GDC-0449 (Genentech, San Francisco, CA, USA) is under investigation in a phase 2 clinical trial, in combination with gemcitabine and the nanoparticle formulation of paclitaxel, in patients with metastatic pancreatic adenocarcinoma (NCT01088815). Other therapeutic agents being studied include the multikinase inhibitor, sorafenib, and agents targeting SRC (dasatinib), γ secretase, MTOR, TNFSF10 (also known as TRAIL), and IGF1. Endoscopic treatments are under investigation for pancreatic cancer, including endoscopic delivery of chemotherapy, cryotherapy, photodynamic therapy, and radiofrequency ablation, but no evidence exists that these agents are as effective as standard treatment.

Clinical trial design is always important when investigating new agents but especially so in pancreatic cancer, for which mortality is high and therapeutic benefits are typically modest. Many clinical trials in pancreatic cancer have to overcome obstacles such as enrolment factors (patients with heterogeneous outcomes arising from poor performance status or different patterns of advanced disease), trial design difficulties (underpowered trials), and the scarcity of predictive markers (and adequate tumour tissue) to identify subgroups who will respond to treatment.[146]

Supportive care

Findings show that palliative care can help patients even as they are undergoing treatment for advanced disease.[147] Supportive care begins with provision of support and information from the time of diagnosis and the appropriate amount of hope for the patient's stage of disease.[148]

Pain management is an important component of treatment. Identification of the cause of pain can guide effective therapy. Pain from coeliac plexus infiltration can be treated effectively with endoscopic ultrasound or CT-guided ablation of the plexus. Radiation can relieve pain from locally advanced disease. Most patients with pancreatic-head cancers will develop obstructive jaundice and benefit from biliary stenting. Metal stents remain patent for longer than do plastic ones.[149] About 20% of individuals develop gastric-outlet obstruction and benefit from duodenal wall stents or PEG (percutaneous endoscopic gastrostomy) placement for decompression. Owing to the effectiveness of endoscopic wall stents, surgical management of obstructive jaundice and gastric-outlet obstruction is usually not necessary, although it could provide better palliation for individuals with long life expectancy.

Since patients with pancreatic cancer frequently develop venous thromboembolism, prophylaxis is recommended. Because of the nature of the hypercoagulable state, findings of several randomised trials indicate that low-molecular-weight heparin provides better prophylaxis than warfarin.[150]

Pancreatic enzyme therapy is sometimes needed because of pancreatic-duct blockage or sparse pancreatic-gland tissue. The Johns Hopkins Pancreatic Cancer website and support groups such as the Pancreatic Cancer Action Network and Pancreatic Cancer UK provide invaluable information and support for patients and their families.

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