Pancreatic cancer

Pancreatic cancer is a highly lethal disease, for which mortality closely parallels incidence. Most patients with pancreatic cancer remain asymptomatic until the disease reaches an advanced stage. There is no standard programme for screening patients at high risk of pancreatic cancer (eg, those with a family history of pancreatic cancer and chronic pancreatitis). Most pancreatic cancers arise from microscopic non-invasive epithelial proliferations within the pancreatic ducts, referred to as pancreatic intraepithelial neoplasias. There are four major driver genes for pancreatic cancer: KRAS, CDKN2A, TP53, and SMAD4. KRAS mutation and alterations in CDKN2A are early events in pancreatic tumorigenesis. Endoscopic ultrasonography and endoscopic ultrasonography-guided fine-needle aspiration offer high diagnostic ability for pancreatic cancer. Surgical resection is regarded as the only potentially curative treatment, and adjuvant chemotherapy with gemcitabine or S-1, an oral fluoropyrimidine derivative, is given after surgery. FOLFIRINOX (fluorouracil, folinic acid [leucovorin], irinotecan, and oxaliplatin) and gemcitabine plus nanoparticle albumin-bound paclitaxel (nab-paclitaxel) are the treatments of choice for patients who are not surgical candidates but have good performance status.

Introduction
Pancreatic cancer is associated with a very poor prognosis, highlighted by the close parallel between disease incidence and mortality. 5-year survival in patients with pancreatic cancer remains as low as 6% in the USA. 2 The low survival rate is attributed to several factors, of which perhaps the most important is the late stage at which most patients are diagnosed. Most patients with pancreatic cancer are asymptomatic until the disease develops to an advanced stage. Up to 20% of patients are eligible for initial resection. 7 Even after potential curative resection, most patients will eventually have recurrence, and 5-year survival of completely resected patients is only up to 25%. 7 Tumour biology of pancreatic cancer contributes to early recurrence and metastasis, and resistance to chemotherapy and radiotherapy. Autopsy series have shown that about 90% of cases of pancreatic cancer are complicated by distant metastasis. 1

To improve prognosis, a screening programme for early diagnosis of pancreatic cancer is needed. Several risk factors for pancreatic cancer, such as a family history of pancreatic cancer, as well as personal history of cigarette smoking, chronic pancreatitis, and diabetes mellitus 18 have been identified, but there is currently no standard programme for screening patients at high risk. We review recent developments in the epidemiology, risk factors, pathology, diagnosis, and treatment of pancreatic cancer.

Epidemiology and risk factors
The American Cancer Society estimates that in 2015, about 49 000 people will be diagnosed with pancreatic cancer in the USA and 41 000 will die of the disease. Pancreatic cancer is the fourth leading cause of cancer death in the USA. Worldwide, pancreatic cancer accounts for more than 200 000 deaths every year. Total deaths from pancreatic cancer are currently increasing and are predicted to be the second leading cause of cancer death in the USA by 2030. 2 Increases in pancreatic cancer mortality have also been reported in European populations, highlighting the worldwide nature of the disease. 19

The study of geographical variation in the incidence of pancreatic cancer is complicated by substantial variation in clinical diagnostic approaches and access to care. Incidence is lowest among populations in India, Africa, and southeast Asia, but underdiagnosis in regions with poorer access to care might bias these estimates. 11 African-Americans have a higher incidence than other racial groups in the USA; however, part of the reason for this higher incidence probably results from differences in known risk factors, such as smoking and diabetes. 12,13 The incidence of pancreatic cancer also differs between the sexes: incidence is 50% higher in men than in women. 11 Pancreatic cancer is a disease of older adults, with most cases occurring in patients between 60 and 80 years of age. 11

About 10% of cases of pancreatic cancer have a familial basis, and family history of pancreatic cancer substantially increases an individual’s risk of developing the disease. 14 However, the genetic basis for most familial pancreatic cancer remains unknown. Pancreatic cancer is a feature of several genetic syndromes, but these account for a few cases of familial pancreatic cancer (table 1). 15,16 Germline mutations in BRCA2 cause increased risk of breast, ovarian, and pancreatic cancer, whereas the role of BRCA1 mutations in familial pancreatic cancer remains unclear.

Search strategy and selection criteria
We searched MEDLINE and PubMed databases for relevant randomised trials and other high-quality studies published from January, 1980, to July, 2015, with the keyword “pancreatic cancer”. We mainly selected publications from randomised trials and other high-quality studies published in known risk factors, such as smoking and diabetes. 12,13 The study of geographical variation in the incidence of pancreatic cancer is complicated by substantial variation in clinical diagnostic approaches and access to care. Incidence is lowest among populations in India, Africa, and southeast Asia, but underdiagnosis in regions with poorer access to care might bias these estimates. 11 African-Americans have a higher incidence than other racial groups in the USA; however, part of the reason for this higher incidence probably results from differences in known risk factors, such as smoking and diabetes. 12,13 The incidence of pancreatic cancer also differs between the sexes: incidence is 50% higher in men than in women. 11 Pancreatic cancer is a disease of older adults, with most cases occurring in patients between 60 and 80 years of age. 11

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Inherited disorders with increased risk of pancreatic ductal adenocarcinoma

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*Gene synonyms are shown in parentheses.

**Table 1: Inherited disorders with increased risk of pancreatic ductal adenocarcinoma**

Pancreatic ductal adenocarcinoma is by far the most common pancreatic neoplasm. It is an invasive mucin-producing gland-forming neoplasm that elicits an intense stromal desmoplastic reaction. Several histological features can help to diagnose pancreatic ductal adenocarcinoma: haphazard arrangement of glands, nuclear pleomorphism, incomplete glandular lumina, luminal necrosis, neoplastic glands immediately adjacent to muscular vessels, perineural invasion, and lymphovascular invasion (figure 1). Pancreatic ductal adenocarcinomas are divided into three grades (well, moderately, and poorly differentiated) on the basis of their degree of differentiation. In addition to the morphology of pancreatic ductal adenocarcinoma, several morphological variants have unique features.

When analysing a resection specimen from a patient with pancreatic ductal adenocarcinoma, there are several key features that must be documented in the pathology report. Like many other tumour types, pancreatic ductal adenocarcinomas are staged using the tumour, nodes, and metastasis (TNM) staging system. Tumour size and invasion into surrounding structures (such as duodenum and bile duct) must be assessed to accurately determine the T stage. Although still controversial, it has been suggested that at least 15 nodes are required for accurate N staging. The presence of invasive carcinoma and high-grade dysplasia or carcinoma in situ should be documented at all margins, including the proximal (gastric or duodenal), distal (duodenal), uncinate, bile duct, and pancreatic resection margins.

Pancreatic ductal adenocarcinoma arises from non-invasive precursor lesions. Most carcinomas arise from microscopic non-invasive epithelial proliferations within the pancreatic ducts, referred to as pancreatic intraepithelial neoplasias. These lesions are graded on the basis of architectural and cytological atypia (figure 2). Although pancreatic intraepithelial neoplasia has been previously graded using a three-tiered system, consensus recommendations published in 2015 suggest that a two-tiered system (low-grade and high-grade) is preferable. The consensus group recommends a similar system for cystic pancreatic cancer precursors (see below).

Some pancreatic ductal adenocarcinomas arise from macroscopic cystic precursors—namely, intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs). IPMNs are mucinous cysts that involve the pancreatic duct system and are by definition more than 1 cm in size. IPMNs are categorised into low-grade, intermediate-grade, and high-grade dysplasia on the basis of the degree of dysplasia in the lining epithelium. Multiple histological subtypes are also recognised, including gastric foveolar type, intestinal type, pancreatobiliary type, and oncocytic type.

Aside from family history, the most well established risk factor for pancreatic cancer is cigarette smoking, causing a 75% increased risk that persists at least 10 years after smoking cessation. Additionally, chronic pancreatitis substantially increases lifetime risk of pancreatic cancer. Patients with diabetes have a 30% excess risk of pancreatic cancer, which persists for more than 20 years after initial diagnosis of diabetes, suggesting that diabetes is not merely a marker of pancreatic dysfunction as a result of neoplasia. There is also a positive association between pancreatic cancer and obesity, specifically high body-mass index (BMI) and centralised fat distribution.
subtypes are defined as having low-grade dysplasia (gastric) or high-grade dysplasia (pancreatobiliary). Roughly a third of IPMNs have an associated invasive adenocarcinoma at the time of resection.

MCNs are far less common than IPMNs. They occur almost exclusively in women and are much more frequent in the body and tail of the pancreas. Unlike IPMNs, MCNs do not involve the pancreatic duct.

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**Figure 1: Histological features of pancreatic ductal adenocarcinoma**

(A) Haphazard arrangement of glands. (B) Nuclear pleomorphism. (C) Incomplete glandular lumina. (D) Luminal necrosis. (E) Glands adjacent to muscular vessel. (F) Perineural invasion. (G) Lymphovascular invasion.
The mucinous epithelium in MCNs is accompanied by an underlying ovarian-type stroma, a diagnostic requirement for MCNs and a key feature that distinguishes them from IPMNs. Like IPMNs, MCNs are categorised into low-grade, intermediate-grade, and high-grade dysplasia on the basis of the degree of dysplasia in their epithelial lining. About a third of MCNs harbour an associated invasive carcinoma at the time of resection.

Cancer is a genetic disease caused by the accumulation of somatic mutations in oncogenes and tumour suppressor genes. There are four major driver genes in pancreatic ductal adenocarcinoma (one oncogene and three tumour suppressor genes). \( KRAS \), which encodes a small GTPase that mediates downstream signalling from growth factor receptors, is the most frequently mutated oncogene. Somatic mutations in \( KRAS \) occur in more than 90% of tumours and cluster in specific hotspots (most commonly codon 12). \( CDKN2A \), which encodes an essential cell-cycle regulator, is the most frequently altered tumour suppressor gene, with loss of function in more than 90% of ductal adenocarcinomas. Somatic mutations in the TP53 tumour suppressor gene are also frequent—the protein encoded by TP53 has a key role in the cellular stress response and is mutated in a wide range of tumour types. The tumour suppressor gene \( SMAD4 \) mediates signalling downstream of the transforming growth factor \( \beta \) (TGF\( \beta \)) receptor and is inactivated in about 50% of tumours.

In the past few years, there has been great expansion of knowledge about the genetic alterations that underlie tumorigenesis in the pancreas. Several studies have reported whole exome and whole genome sequencing in large numbers of patients with pancreatic cancer. In addition to the four frequently altered driver genes, these studies have identified alterations in hundreds of other genes—the difficulty is distinguishing driver genes that causally contribute to tumorigenesis from passenger genes that accumulate random mutations during repeated rounds of cell division. Although functional studies in model systems are required to more conclusively define the role of a given gene in
tumorigenesis, these genetic studies have identified several other promising groups of genes as potential drivers of pancreatic tumorigenesis, including axon guidance pathway genes and chromatin remodelers. These studies have also pointed out the importance of multimodality analysis of the cancer genome to identify point mutations, copy number alterations, and structural rearrangements. Not only do these studies identify potential driver genes, but they also identify subtypes of pancreatic cancer by mutation signature that might have clinical relevance, such as response to platinum chemotherapy in tumours with an “unstable” mutation signature.

Studies of precursor lesions have outlined the timing of the genetic alterations in pancreatic tumorigenesis. Somatic KRAS mutations are present in most low-grade pancreatic intraepithelial neoplasias, suggesting that KRAS mutation is one of the earliest alterations in pancreatic tumorigenesis. Alterations in CDKN2A are also early events, with loss of p16 expression in a subset of even low-grade pancreatic intraepithelial neoplasias. By contrast, loss of Smad4 and alterations in p53 are late events, occurring in pancreatic intraepithelial neoplasia grade 3 and invasive carcinoma. Recent whole exome sequencing of pancreatic intraepithelial neoplasias and adjacent ductal adenocarcinomas showed a large proportion of shared somatic mutations in most cases, further supporting the idea that pancreatic intraepithelial neoplasias give rise to ductal adenocarcinoma. Whole exome sequencing of premalignant pancreatic cysts showed many shared driver genes with ductal adenocarcinoma, including KRAS, TP53, and SMAD4. Intriguingly, other genes seem to be drivers exclusively in cystic neoplasms—mutations in the oncogenic hotspot of GNAS occur only in IPMNs, whereas inactivating mutations in the ubiquitin ligase RNF43 occur in both IPMNs and MCNs. However, one study identified RNF43 mutations in ductal adenocarcinomas not derived from IPMNs, calling into question the specificity of mutations in this gene for cystic neoplasms.

Clinical presentation, signs, and symptoms

Most pancreatic cancers have no symptoms in the early stage. A large case-control study comparing the incidence of early pancreatic cancer symptoms suggested that pancreatic cancer is associated with 12 alarm symptoms: weight loss, abdominal pain, nausea and vomiting, bloating, dyspepsia, new-onset diabetes, changes in bowel habit, pruritus, lethargy, back pain, shoulder pain, and jaundice. Back pain (odds ratio [OR] 1·33 [95% CI 1·18–1·49]), lethargy (OR 1·42 [1·25–1·62]), and new-onset diabetes (OR 2·46 [2·16–2·80]) were identified as unique features of pancreatic cancers. Five symptoms have been shown to occur more than 6 months before diagnosis: back pain, shoulder pain, dysphagia, changes in bowel habit, and lethargy. Regarding lethargy, one systematic review described depressive symptoms as the first symptoms in about 38–45% of patients with pancreatic cancer. A recent systematic review has reported nine presenting symptoms of advanced pancreatic cancer. Of these symptoms, diabetes (97%) and abdominal pain (78–82%), which is caused by cancer-nerve interaction, are frequently reported in advanced pancreatic cancer. Although several investigators have reported that 25% of patients have upper abdominal discomfort up to 6 months before their diagnosis, early detection of pancreatic cancer still seems difficult even if symptoms raise clinicians’ suspicion.

Diagnostic investigations

Serum tumour markers

The combination of serum carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) has been reported to decrease sensitivity to 37%, but increase specificity to 84% compared with CA19-9 alone, for diagnosis of pancreatic cancer. A recent study has shown that a serum protein biomarker panel consisting of CA125, CA19-9, and laminin γC (LAMC2) can significantly improve performance in detecting pancreatic cancer compared with CA19-9 alone under several conditions (ie, all pancreatic cancer and benign conditions, p<0·005; early-stage pancreatic cancer and benign conditions, p<0·05; and early-stage pancreatic cancer and chronic pancreatitis, p<0·05). CA19-9 and CA125 have encouraging sensitivities for detecting preclinical pancreatic cancer because at a 95% specificity, CA19-9 has a sensitivity of 68% for up to 1 year and 53% for up to 2 years before diagnosis. The combination of CA19-9 and CA125 improved sensitivity because the concentration of CA125 was raised in about 20% of CA19-9-negative cases.

Transabdominal ultrasonography

Diagnostic ability of ultrasonography greatly depends on the operator’s experience and the patient’s condition in terms of obesity and bowel gas. Thus, the sensitivity and specificity of ultrasound for pancreatic cancer range from 75% to 89% and from 90% to 99%, respectively (figure 3). Studies have reported that the sensitivity of ultrasonography or contrast-enhanced ultrasonography in diagnosing pancreatic cancer is not statistically different from that of multidetector-row CT (MDCT). However, contrast-enhanced ultrasonography has a higher sensitivity than MDCT for small or medium lesions.

CT

MDCT with contrast medium is now routinely performed for the diagnosis of suspicious pancreatic lesions, assessment of resectability, assessment of vascular invasion, and diagnosis of metastatic lesions (figure 3). The following CT findings aid in the diagnosis of pancreatic cancer: hypoattenuation (sensitivity 75% and specificity 84%); ductal dilatation (50% and 78%); ductal interruption (45% and 82%); distal pancreatic atrophy (45% and 96%); pancreatic contour anomalies (15% and
92%); and common bile duct dilation (5% and 92%).

Overall accuracy of MDCT for diagnosis of pancreatic cancer is about 90%. MDCT has an accuracy of 85–95% in determining resectability.

PET

Two meta-analyses showed that \(^{18}\)F-fluorodeoxyglucose PET plus CT has no obvious advantage for diagnosing pancreatic cancer compared with current diagnostic methods (figure 3). Nonetheless, a meta-analysis concluded that the combination of PET and CT plus endoscopic ultrasonography is useful for suspected pancreatic cancer because of the high sensitivity of PET plus CT and the high specificity of endoscopic ultrasonography. There are several limitations of PET in diagnosing pancreatic cancer, including possible false-negative results in hyperglycaemia and possible false-positive results in inflammatory masses caused by pancreatitis.

Figure 3: Image findings in pancreatic cancer

(A) Transabdominal ultrasound shows hypoechoic mass lesion (arrows) in the head of pancreas (without contrast or enhancement). (B) Multidetector-row CT shows low-density mass, invading coeliac artery and stomach. (C) PET-CT shows \(^{18}\)F-fluorodeoxyglucose uptake PET in the tail of pancreas. (D) Gadolinium-enhanced MRI shows hypointensity mass (arrows) in the tail of pancreas. (E) Magnetic resonance cholangiopancreatography shows pancreatic duct stenosis of the main pancreatic duct with proximal dilation.
Several investigators have shown that the sensitivity (83–85%) and specificity (63%) of gadolinium-enhanced MRI are similar to the sensitivity (83%) and specificity (63–75%) of MDCT (figure 3).63

Diffusion-weighted imaging (DWI) is an MRI technique based on the Brownian motion of water molecules in tissue.64 Two studies have shown the usefulness of DWI in differentiating mass-forming focal pancreatitis and pancreatic cancer,65,66 whereas another study has suggested that addition of DWI to conventional MRI does not facilitate the differentiation of pancreatic cancer from chronic pancreatitis.67 MRI-DWI might be preferable to CT because it allows the precise depiction of pancreatic lesions without radiation exposure.

Magnetic resonance cholangiopancreatography (MRCP) allows the non-invasive delineation of the pancreatic duct and biliary tract. This technique will probably replace invasive endoscopic retrograde cholangiopancreatography (ERCP) for diagnosis of small pancreatic masses (figure 3), although its disadvantage is that it does not permit tissue sampling.68

ERCP

ERCP allows cytopathology at the transpapillary biliary stenting although its diagnostic ability seems to be limited in cases of extrinsic biliary strictures such as

![Figure 4: Endoscopic ultrasonography in pancreatic cancer](image)

(A) Endoscopic ultrasonography shows hypoechoic mass in the body of pancreas (without contrast or enhancement). (B) Contrast-enhanced endoscopic ultrasonography (CE-EUS) shows hypovascular area (right, CE-EUS) in the hypoechoic mass lesion (left, without contrast or enhancement). (C) Endoscopic ultrasonography-guided fine-needle aspiration. A 22-gauge needle is punctured into the hypoechoic mass lesion.
pancreatic cancer. Several investigators have reported that brushing cytology and aspiration cytology using an endoscopic nasopancreatic catheter placed during ERCP improve the diagnostic accuracy in pancreatic cancers.60,76 Moreover, probe-based confocal laser endomicroscopy has shown high sensitivity for the detection of malignancy in the pancreaticobiliary strictures.71

**Endoscopic ultrasonography**

The superiority of endoscopic ultrasonography over MDCT in diagnosing pancreatic cancer has been reported (figure 4, video).72–73 One retrospective study reported a sensitivity of 100% for endoscopic ultrasonography in the diagnosis of pancreatic cancer compared with 86% for MDCT,72 while another prospective study reported a sensitivity of 98% for endoscopic ultrasonography compared with 86% for MDCT.73 A meta-analysis of contrast-enhanced endoscopic ultrasonography (figure 4) reported a sensitivity of 94% and a specificity of 89% for diagnosis of pancreatic cancer.74

Endoscopic ultrasonography-guided fine-needle aspiration has a high diagnostic accuracy of more than 85–90% for pancreatic cancer (figure 4). Novel techniques, such as fanning technique,75 slow-pull technique,76 with or without liquid-based cytology,77 are attempting to further improve the accuracy of endoscopic ultrasonography-guided fine-needle aspiration. Two recent developments of this technique are “cell-block preparation”78 and “core tissue sampling”, which might be helpful in not only providing more material for histological diagnosis, but also for recently developed ancillary diagnostic techniques, such as KRAS mutation detection, microRNA profiling, and chemosensitivity testing.79–81

**Differential diagnosis from autoimmune pancreatitis**

Mass-forming pancreatitis and other pancreatic malignancies such as malignant lymphoma should be differentiated from pancreatic cancer. Most cases of mass-forming pancreatitis are autoimmune pancreatitis, which is divided into two subtypes. Type 1 autoimmune pancreatitis, the most common form, is characterised by the histological feature of lymphoplasmacytic sclerosing pancreatitis and is considered to be a pancreatic lesion of IgG4-related disease. Type 2 shows the histological feature of neutrophilic infiltration in the pancreatic duct epithelium and has no relation to IgG4.82

Autoimmune pancreatitis and pancreatic cancer have many clinical features in common, such as tendency to occur in older people (aged ≥60 years) painless jaundice, development of new-onset diabetes mellitus, and raised levels of serum tumour markers.83 Autoimmune pancreatitis is diagnosed through a combination of clinical, serological, imaging, and pathological findings.84 Serum IgG4 concentrations are frequently increased in patients with autoimmune pancreatitis, but raised serum IgG4 is also detected in 4–7% of patients with pancreatic cancer. CT findings of diffuse enlargement with delayed enhancement and capsule-like rim are quite specific to autoimmune pancreatitis. On ERCP, long irregular narrowing of the main pancreatic duct is highly suggestive of the disease. In a segmental or focal type of autoimmune pancreatitis, a histopathological approach using endoscopic ultrasonography-guided fine-needle aspiration is recommended. Rapid improvement after steroid administration excludes malignancy and confirms the diagnosis of autoimmune pancreatitis.83–84

**Treatment**

Treatment of pancreatic cancer includes surgery, chemotherapy, radiation therapy, and palliative care. The treatment options are selected depending on the stage of pancreatic cancer in a multidisciplinary approach (figure 5). Treatment of IPMN and MCN is reviewed elsewhere.85

**Surgery**

**Indication of surgical resection**

Surgical resection is regarded as the only treatment for cure and can result in significantly longer survival compared with other treatment options. Pancreatic cancer without distant metastasis can be divided into three categories: resectable, borderline resectable, and locally advanced, according to the extent of local extension. However, the definitions of these three categories are not uniform because the resectability depends on surgical techniques. For example, one of the most commonly used definitions of borderline resectable pancreatic cancer includes no distant metastases, venous involvement of the superior mesenteric vein or portal vein, gastro-duodenal artery encasement up to the hepatic artery, and tumour abutment of the superior mesenteric artery of less than or equal to 180°.86 In specialised centres, en bloc resection of the portal vein or superior mesenteric vein, or both, is commonly and safely practised in the setting of borderline resectable tumours involving these veins.87 However, when there is tumour abutment of the major artery such as the superior mesenteric artery, surgical resection often results in positive surgical margin.
Role of neoadjuvant therapy
To obtain better local control and, ultimately, to improve survival of patients, the role of neoadjuvant chemo(radio)therapy has been investigated in many clinical trials in the USA, Europe, and Japan. Because patients with early recurrence are not likely to benefit from surgical resections, another important rationale for neoadjuvant therapy is better selection of patients who do not have the complications of aggressive disease or latent metastasis. Also, the chance of delivering full-dose chemotherapy is better if given before surgery, and preoperative therapy may be more effective than postoperative therapy because the resected tumour bed is associated with poor drug delivery and low sensitivity to radiation because of decreased oxygenation. In patients with borderline resectable pancreatic cancer after effective neoadjuvant therapies, the possibility for an R0 resection is higher, and survival of patients who underwent surgical resection is better than that of those who did not. So far, however, there is no evidence from randomised controlled trials or meta-analyses to recommend neoadjuvant therapies in patients with borderline resectable or locally advanced pancreatic cancer. The role of neoadjuvant therapies in patients with resectable pancreatic cancer is another unanswered question—most of the clinical trials in the past have failed to recruit the necessary number of patients, probably because of fear of loss of the opportunity for surgical resection.

Surgical techniques and other considerations
Surgical techniques for pancreatic cancer include pancreaticoduodenectomy, distal pancreatectomy with splenectomy, and total pancreatectomy. There is no evidence to support the survival advantage of extended resection including wide resections of the para-aortic lymph nodes and nerve plexus. Such extended resection is associated with compromised quality of life because of intractable diarrhoea and has therefore been almost abandoned. Laparoscopic approach in surgery for pancreatic cancer is being used in some specialised centres. Retrospective cohort studies have shown that laparoscopic distal pancreatectomy for cancer is not inferior to open surgery in terms of survival and can benefit patients with an earlier return to diet and a shorter hospital stay. By contrast, laparoscopic pancreaticoduodenectomy requires highly trained surgical skills, and general applications of this technique to patients with pancreatic cancer remain unwaranted. Mortality, complications, length of hospital stay, margin status, survival, and overall cost after pancreaticoduodenectomy have been reported to be related to hospital volume. Therefore, it is recommended that pancreaticoduodenectomy should be done in specialised centres that perform a large number (>15–20) of pancreatic resections annually.

Chemotherapy
Adjuvant chemotherapy for resected pancreatic cancer
The ESPAC-01 trial showed that adjuvant chemotherapy with folinic acid (leucovorin) and fluorouracil significantly improved survival in patients with resected pancreatic cancer, compared with chemotherapy alone. Another randomised trial, CONKO-001, showed increased disease-free survival and overall survival with the use of adjuvant gemcitabine for six cycles compared with no adjuvant treatment after surgery. In general practice, adjuvant chemotherapy with gemcitabine is given after surgery for resectable pancreatic cancer when the patient can tolerate chemotherapy. A randomised phase 3 trial of adjuvant chemotherapy to test the non-inferiority of oral S-1, a fluoropyrimidine derivative, to gemcitabine, was done in Japan (JASPAC-01). 2-year overall survival was 70% in the S-1 group compared with 53% in the gemcitabine group, and it has been reported that S-1 is not inferior to, but superior to, gemcitabine (hazard ratio 0.56 [95% CI 0.42–0.78]; p<0.001). On the basis of these results, the regimen of adjuvant therapy has already changed in Japan. The results have to be validated in other countries for worldwide use. Several randomised studies comparing various neoadjuvant chemo(radio)therapies against upfront surgery are in progress around the world. A phase 3 trial (Prep-02/JSAP-05) comparing neoadjuvant chemotherapy with gemcitabine plus S-1 followed by surgery versus upfront surgery in patients with resectable pancreatic cancer is expected to provide definitive results in terms of survival.

First-line chemotherapy for metastatic pancreatic cancer
Chemotherapy is the mainstay of treatment for metastatic pancreatic cancer. In a landmark clinical trial to compare gemcitabine and fluorouracil published in 1997, median survival was only 4–41 months in the fluorouracil control group compared with 5–65 months in the gemcitabine chemotherapy group. Since then, gemcitabine has been a standard of chemotherapy, and several clinical trials have compared novel regimens against gemcitabine monotherapy. In a phase 3 trial, the addition of erlotinib to gemcitabine improved progression-free survival and overall survival compared with gemcitabine alone, although this improvement was small (table 2). A subgroup analysis showed that patients who developed a skin rash of grade 2 or higher after use of erlotinib might have a more significant survival benefit. Therefore, continuous chemotherapy with gemcitabine plus erlotinib is recommended only in those patients who develop skin rash after administration.

In the phase 3 ACCORD-11 trial, the FOLFIRINOX regimen (oxaliplatin 85 mg/m², folinic acid [leucovorin] 400 mg/m², irinotecan 180 mg/m², bolus fluorouracil 400 mg/m², infusional fluorouracil 2400 mg/m² over 46 h, every 14 days) was shown to be better than gemcitabine in terms of response, progression-free survival, and overall survival in patients with metastatic...
pancreatic cancer (table 2).\textsuperscript{101} The patient selection criteria in this study were more rigorous than those in other studies, because only patients aged 75 years or younger with good performance status were enrolled. The exclusion criteria included high bilirubin concentration (>1.5 times the upper limit of normal range) to reduce the irinotecan-induced toxicity caused by cholestasis. Although the survival benefit is attractive, it must be noted that FOLFIRINOX was associated with an increased risk of febrile neutropenia, sensory neuropathy, and gastrointestinal toxicities. Therefore, this regimen is recommended only for patients aged 75 years or younger with good performance status and without significant risk of cholestasis or cholangitis.

Another phase 3 trial, the MPACT trial, showed that gemcitabine plus nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is superior to gemcitabine alone in terms of response, progression-free survival, and overall survival in patients with metastatic pancreatic cancer (table 2).\textsuperscript{104} In this trial, 10% of patients were older than 75 years and 8% of patients had Eastern Cooperative Oncology Group (ECOG) performance status 2; these patients would not be eligible for the ACCORD-11 trial of FOLFIRINOX. The adverse effects of gemcitabine plus nab-paclitaxel seem to be more manageable and this regimen can be used in a wider range of patients compared with FOLFIRINOX.

In summary, on the basis of current evidence, both FOLFIRINOX and gemcitabine plus nab-paclitaxel are the treatments of choice for patients who can tolerate these regimens. Gemcitabine plus erlotinib may be another option for patients who develop skin rash. Gemcitabine monotherapy may be indicated in patients with compromised performance status.

### Second-line chemotherapy for metastatic pancreatic cancer

Following progression during first-line chemotherapy, second-line chemotherapy might benefit patients with good performance status and should be considered,\textsuperscript{105} although there is no established evidence regarding the regimen of second-line chemotherapy.

### Radiation therapy

**Definitive chemoradiation therapy for locally advanced pancreatic cancer**

The potential merits of chemoradiation therapy have been intensively studied in patients with locally advanced pancreatic cancer. However, there have been long-lasting debates about the survival benefits of chemoradiation therapy.\textsuperscript{106} The ECOG 4201 trial compared chemoradiotherapy with chemotherapy in patients with locally advanced pancreatic cancer and median survival was 9.2 months for chemotherapy with gemcitabine and 11.1 months for chemoradiotherapy. However, the number of recruited patients was too small to draw any definitive conclusions.\textsuperscript{107,108} Findings from a randomised study comparing chemoradiation therapy and chemotherapy after 4 months of gemcitabine with or without erlotinib (LAP 07) showed that administering chemoradiation therapy was not superior to continuing chemotherapy in patients with locally advanced pancreatic cancer.\textsuperscript{109} Further investigations are needed to validate the potential survival advantages of chemoradiation therapy.

### Palliative care

Palliative care is as important as other therapies, because patients with pancreatic cancer require palliation at some point. Obstructive jaundice and obstruction of the duodenum in patients with pancreatic cancer require surgical, endoscopic, or radiological interventions. With technical advances in endoscopic intervention during the past decade, percutaneous biliary drainage has been replaced by endoscopic stenting in most cases. The use of a large diameter metal stent is preferred to that of a small caliber plastic stent because of the longer patency time and lower incidence of cholangitis.\textsuperscript{110} For gastric outlet obstruction, both surgical gastrojejunostomy and endoscopic duodenal stents are used. Endoscopic duodenal stents are preferred in patients with a short life expectancy, poor performance status, or both.

### Future perspectives

Screening programmes in high-risk individuals including familial pancreatic cancer kindreds are expected to yield more patients with pancreatic cancer at an early stage.\textsuperscript{111} There are several directions for future studies on pancreatic cancer. First, the correlation of genetic alterations with clinically important features, such as pattern of recurrence and response to chemotherapy, will facilitate the translation of these findings into
clinically useful assays. The Individualized Molecular Pancreatic Cancer Therapy (IMPaCT) trial has shown that a subset of patients with aberrations in their tumour genomes can be targeted with specific therapies. Better understanding of the mutational landscape will further expand the use of targeted chemotherapy and other therapeutic options. Second, investigation of other types of alterations, including epigenetic, transcriptional, and proteomic alterations, might identify additional targets for novel approaches to diagnosis and therapy. Finally, therapies targeting specific altered genes or pathways will bring personalised medicine for each individual. In patients with BRCA1 or BRCA2 mutations, molecularly targeted therapies inhibiting the enzyme poly(ADP-ribose) polymerase (PARP) may be more effective, and a worldwide clinical trial of olaparib, a small-molecule PARP inhibitor, is underway.

Immunotherapy is one of the emerging therapeutic options. Although no benefit in overall survival has been shown in previous clinical trials, new approaches to immunotherapy might have important roles in the treatment of pancreatic cancer in the future. Other promising novel approaches to pancreatic cancer treatment include therapies targeting the desmoplastic stroma as well as those targeting hypoxia and other aspects of pancreatic cancer metabolism.

Contributors
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Declaration of interests
We declare no competing interests.

References
1. Peutz-Jeghers syndrome is associated with an increased risk of pancreatic carcinoma. The mutation associated with this risk in PJ syndrome is:
   a. BRAC1
   b. CDKN2A
   c. STK11
   d. SPINK1

2. Characteristics of mucinous cell neoplasms of the pancreas include
   a. More common in males
   b. More common than IPMN’s
   c. More common in the pancreatic body and tail than in the head
   d. Do not involve the pancreatic duct system
   e. Typically have an ovarian-type stroma

True or False

3. New onset diabetes mellitus, a known occurrence in pancreatic cancer, is rarely seen in autoimmune pancreatitis mimicking pancreatic cancer

4. Depression may be the first symptom of pancreatic cancer in about 40%-45% of cases.

5. A PET-CT can reliably differentiate between pancreatic carcinoma and inflammatory mass of the pancreas.

6. For patients older than 75 years and/or with a low performance status, the combination of gemcitabine + folfirinox is recommended

7. Neoadjuvant therapy improves prognosis in patients with borderline resectable or locally advanced pancreatic cancers.

8. Late events in the genetic alterations leading to pancreatic carcinoma include loss of Smad5 and alterations in P53

9. The increased risk for pancreatic cancer in smokers decreases to baseline risk 1 year after smoking cessation

10. The benefits of radiation therapy for pancreatic cancer remain unproven.

11. For patients younger than age 75 and with good performance status, the combination therapy Folfirinox (oxaliplatin, folinic acid, irinotecan and fluorouracil) is the preferred first line chemotherapeutic agent.

12. Pancreatic cancer most commonly arises from the acinar cells.

13. Elevated IgG4 in serum can be found in up to 7% of patients with pancreatic cancer