Pancreatic cancer

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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.

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Introduction

Pancreatic cancer is associated with a very poor prognosis, highlighted by the close parallel between disease incidence and mortality.[1] 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.[2] Even after potential curative resection, most patients will eventually have recurrence, and 5-year survival of completely resected patients is only up to 25%.[1] 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.[3]

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,[4] as well as personal history of cigarette smoking,[5] chronic pancreatitis,[6] and diabetes mellitus[7,8] 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.[9] Increases in pancreatic cancer mortality have also been reported in European populations, highlighting the worldwide nature of the disease.[10]

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.[4,14] 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).[4,15,16] Germline mutations in *BRCA2* cause increased risk of breast, ovarian, and pancreatic cancer, whereas the role of *BRCA1* mutations in familial pancreatic cancer remains

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 the past 5 years, but we did not exclude highly regarded and commonly referenced older publications. Additionally, we searched the reference lists of articles identified by this search strategy and selected those that we judged to be relevant. Review articles and book chapters are cited to provide readers with more details and references than can be accommodated in this Seminar.

For the **American Cancer Society estimates** see http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-key-statistics

	Gene*	Chromosome	Risk ratio
Familial breast and ovarian cancer	*BRCA2*	13	3·5–10
Familial atypical multiple mole melanoma syndrome	*CDKN2A* (*P16*)	9	9–47
Peutz-Jeghers syndrome	*STK11* (*LKB1*)	19	132
Hereditary pancreatitis	*PRSS1*; *SPINK1*	7; 5	50–80
Hereditary non-polyposis colorectal cancer (Lynch syndrome)	Multiple	Multiple	9
Familial pancreatic cancer	*PALB2*	16	6
Familial pancreatic cancer (monoallelic); ataxia-telangiectasia (biallelic)	*ATM*	11	Unknown

*Gene synonyms are shown in parentheses.

***Table 1*: Inherited disorders with increased risk of pancreatic ductal adenocarcinoma[4,15,16]**

controversial.[17] Germline mutations in *CDKN2A* (also known as *P16*) cause familial atypical mole melanoma syndrome, in which patients have increased risk of both melanoma and pancreatic cancer.[18] Patients with Peutz-Jeghers syndrome, caused by germline alterations in *STK11* (also known as *LKB1*), have a markedly increased risk of pancreatic cancer in addition to gastrointestinal hamartomas.[19] Patients with hereditary pancreatitis, caused by germline mutations in *PRSS1* and *SPINK1*, also have a substantially increased risk of pancreatic cancer, possibly because of repeated cycles of inflammation and repair in the pancreas.[20] Patients carrying germline mutations in the *CFTR* gene have a modestly increased risk of pancreatic cancer, possibly resulting from an increased risk of pancreatitis.[21] There is also an increased risk of pancreatic cancer in patients with Lynch syndrome, caused by germline mutations in genes encoding DNA mismatch repair proteins.[22] In addition to these well described genetic syndromes, recent studies have identified the genetic alterations underlying small subsets of familial pancreatic cancer without previously described genetic syndromes. Germline mutations in *PALB2*, whose protein product interacts with *BRCA2*, account for a small subset of patients with familial pancreatic cancer.[23] Furthermore, a separate subset of familial pancreatic cancer is caused by heterozygous germline mutations in *ATM*, which encodes a kinase involved in DNA repair and causes ataxia telangiectasia when biallelically inactivated in the germline.[24]

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.[5] Additionally, chronic pancreatitis substantially increases lifetime risk of pancreatic cancer.[6] 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.[7] There is also a positive association between pancreatic cancer and obesity, specifically high body-mass index (BMI) and centralised fat distribution.[25]

Histopathology and molecular pathology

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.[11] 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.[26]

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.[27] 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 intra-epithelial neoplasias.[28] 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[29] 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.[30] 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.[31] However, categorisation by grade of dysplasia and histological subtype are not independent, since some

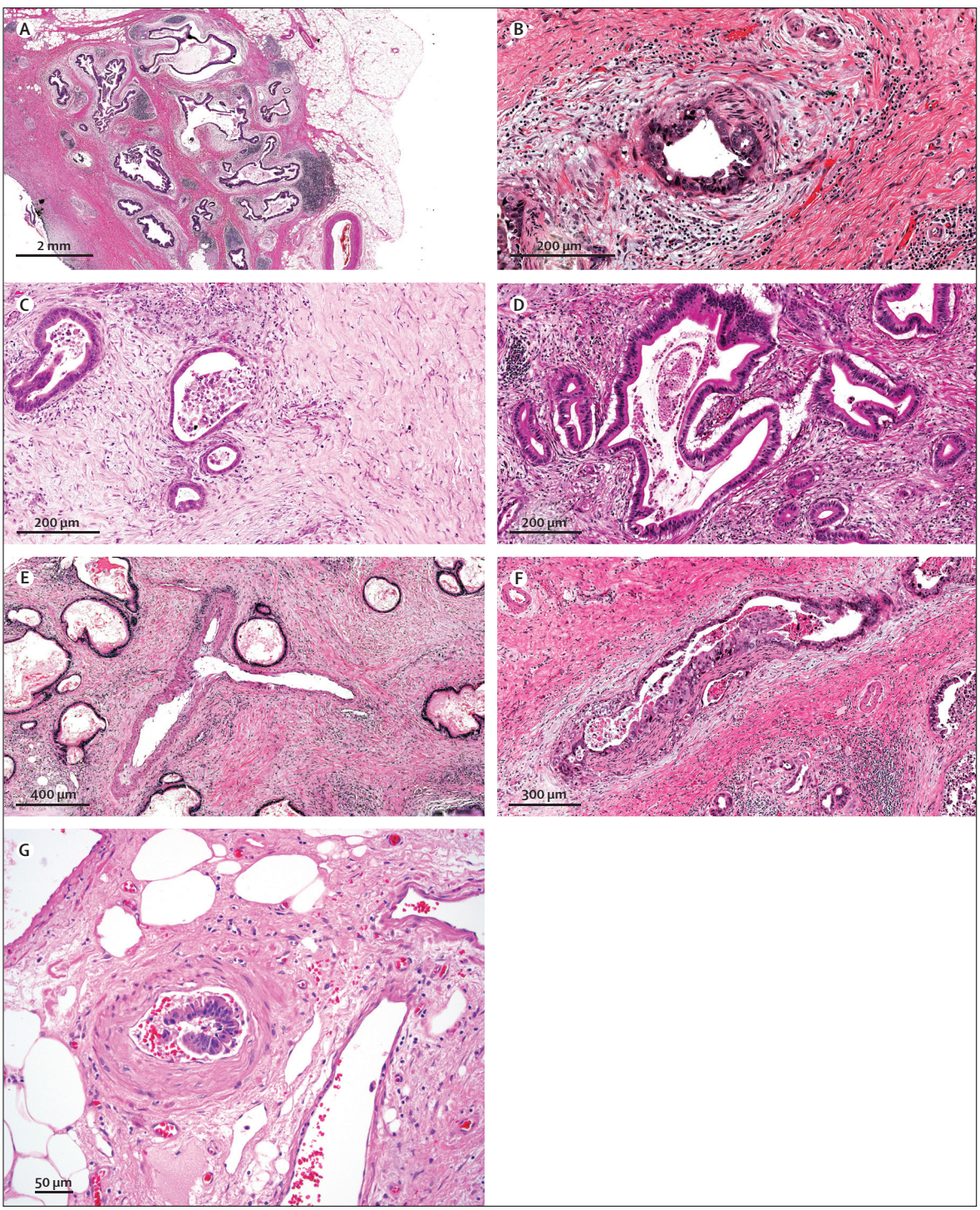

Figure 1: **Histological features of pancreatic ductal adenocarcinoma**
(A) Haphazard arrangement of glands. (B) Nuclear pleomorphism. (C) Incomplete glandular lumina. (D) Luminal necrosis. (E) Glands adjacent to muscular vessel. (F) Perineural invasion. (G) Lymphovascular invasion.

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.[32] Unlike IPMNs, MCNs do not involve the pancreatic duct

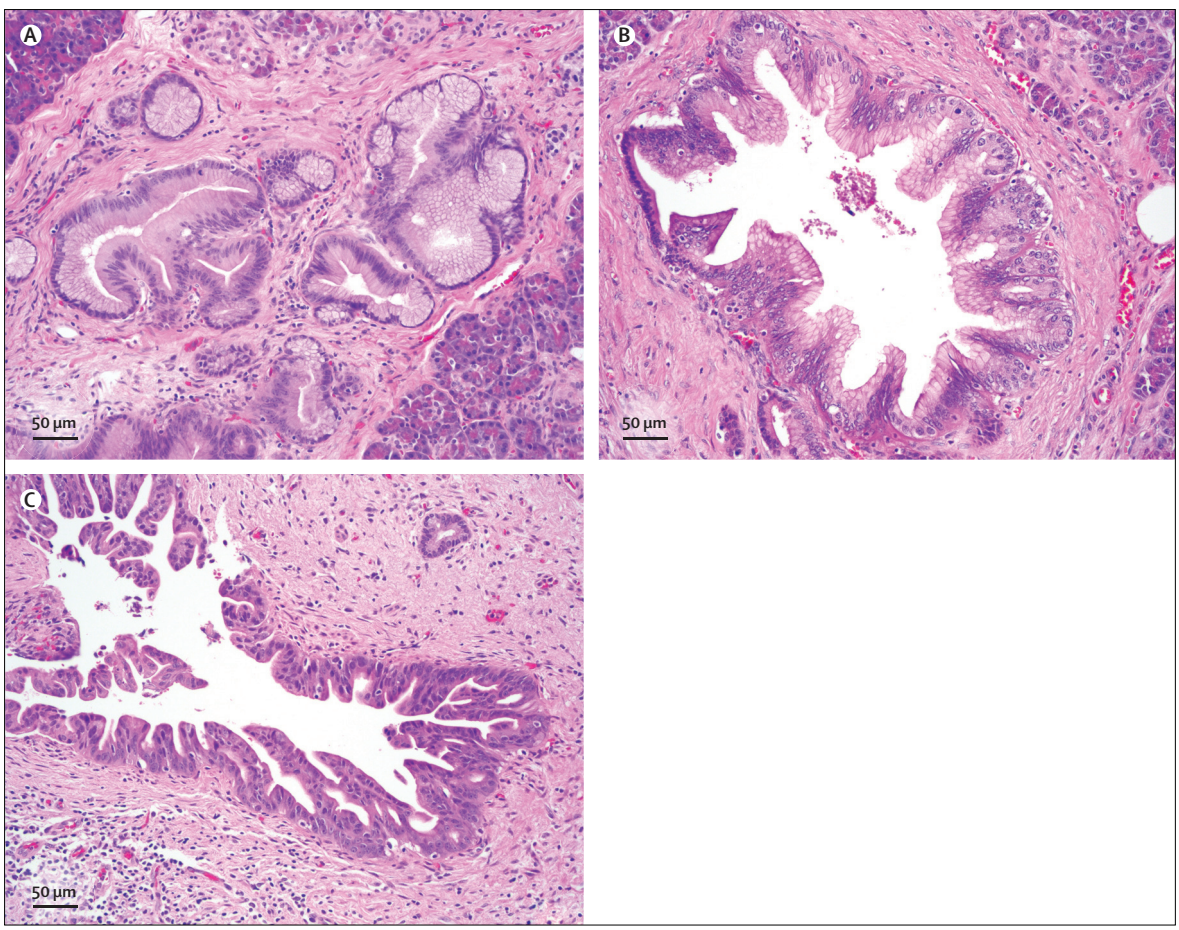

***Figure 2*: Histological grades of pancreatic intraepithelial neoplasia**
(A) Grade 1 is a flat or papillary lesion composed of uniform columnar cells with round basal nuclei and supranuclear mucin. (B) Grade 2 is a flat or papillary lesion with moderate nuclear atypia, including enlargement, hyperchromasia, and loss of polarity. (C) Grade 3 is a flat or papillary lesion with severe architectural atypia (including budding, cribriforming, luminal necrosis) as well as severe cytologic atypia (enlargement, hyperchromasia, loss of polarity, prominent nucleoli).

system. 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.[33] 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).[34] *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.[34] 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.[34] The tumour suppressor gene *SMAD4* mediates signalling downstream of the transforming growth factor β (TGFβ) receptor and is inactivated in about 50% of tumours.[34]

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.[35–37] 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

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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 remodellers. 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.[37] 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.[37]

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.[38] Alterations in *CDKN2A* are also early events, with loss of p16 expression in a subset of even low-grade pancreatic intraepithelial neoplasias.[39] By contrast, loss of Smad4 and alterations in p53 are late events, occurring in pancreatic intraepithelial neoplasia grade 3 and invasive carcinoma.[39] 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.[40] Whole exome sequencing of premalignant pancreatic cysts showed many shared driver genes with ductal adenocarcinoma, including *KRAS*, *TP53*, and *SMAD4*.[41] 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.[41,42] 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.[37]

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.[43] 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.[43] Five symptoms have been shown to occur more than 6 months before diagnosis: back pain, shoulder pain, dysphagia, changes in bowel habit, and lethargy.[43] Regarding lethargy, one systematic review described depressive symptoms as the first symptoms in about 38–45% of patients with pancreatic cancer.[44] A recent systematic review has reported nine presenting symptoms of advanced pancreatic cancer.[45] Of these symptoms, diabetes (97%) and abdominal pain (78–82%), which is caused by cancer-nerve interaction, are frequently reported in advanced pancreatic cancer.[46] Although several investigators have reported that 25% of patients have upper abdominal discomfort up to 6 months before their diagnosis,[47] 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)[48–50] has been reported to decrease sensitivity to 37%, but increase specificity to 84% compared with CA19-9 alone, for diagnosis of pancreatic cancer.[51] 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, $p<0·05$).[52] 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.[53]

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).[54] 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).[55] However, contrast-enhanced ultrasonography has a higher sensitivity than MDCT for small or medium lesions.[55]

CT

MDCT with contrast medium is now routinely performed for the diagnosis of suspicious pancreatic lesions, assessment of resectability, assessment of vascular invasion,[56] 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

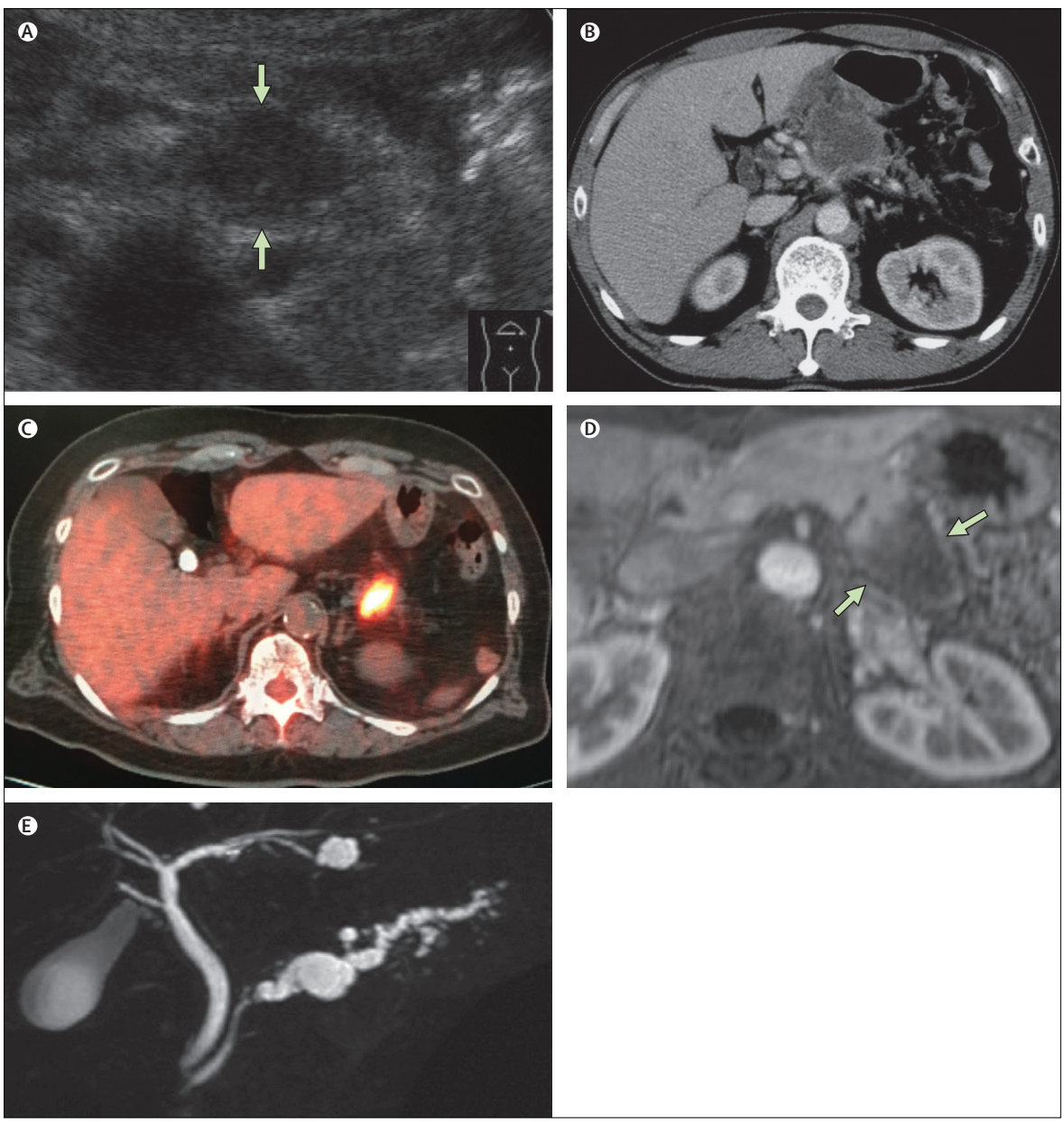

***Figure 3*: Image findings in pancreatic cancer**
(A) Transabdominal ultrasound shows hypoechoic mass lesion (arrows) in the head of pancreas (without contrast or enhancement). (B) Multidetector-row CT shows low-density mass, invading coeliac artery and stomach. (C) PET-CT shows ^{18}F-fluorodeoxyglucose 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.

92%); and common bile duct dilation (5% and 92%).[57] Overall accuracy of MDCT for diagnosis of pancreatic cancer is about 90%.[57] MDCT has an accuracy of 85–95% in determining resectability.[58,59]

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).[60,61] 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.[62] 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.

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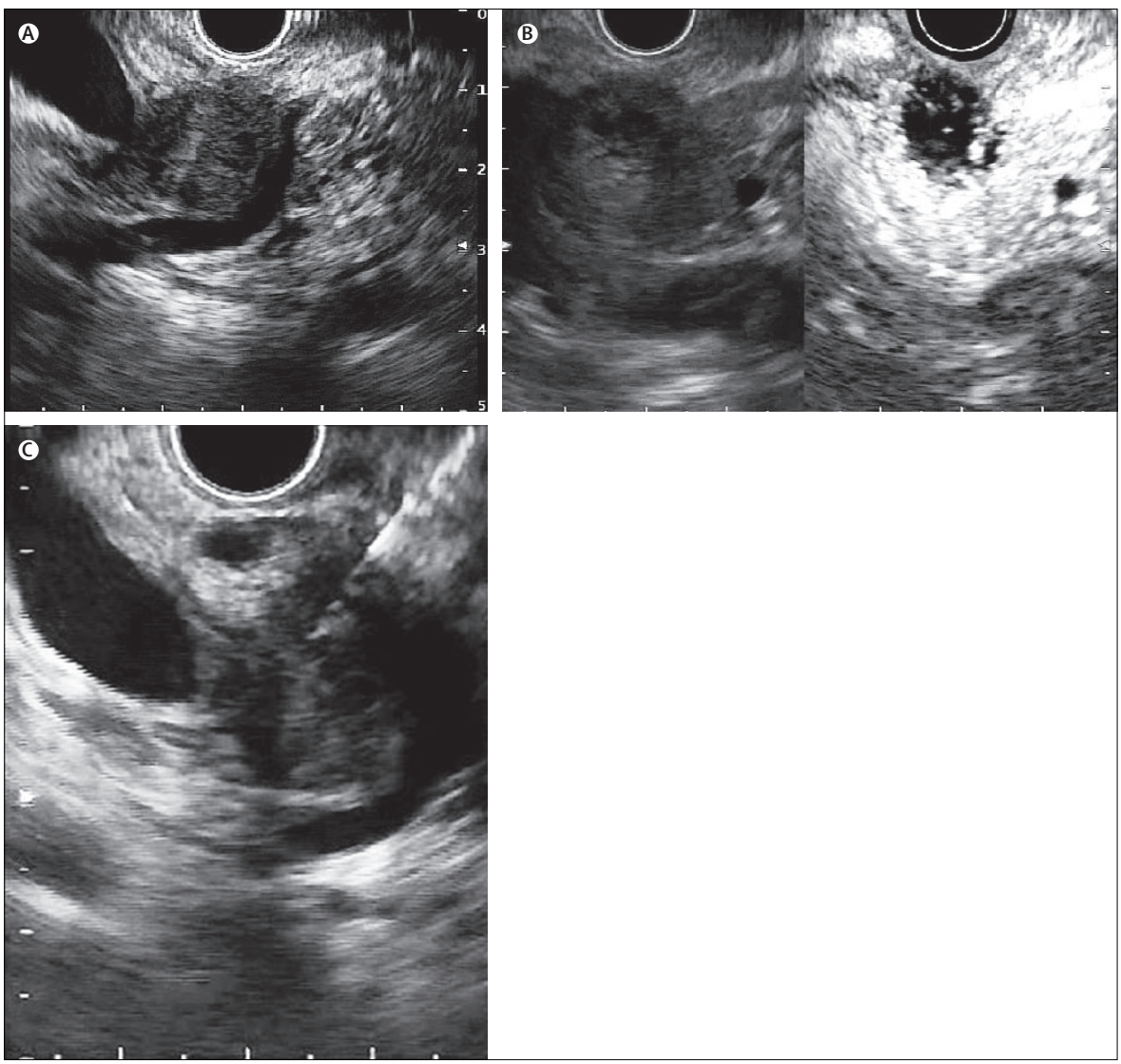

Figure 4: **Endoscopic ultrasonography in pancreatic cancer**
(A) Endoscopic ultrasonography shows hypoechoic mass in the body of pancreas (without contrast or enhancement). (B) Contrast-enhanced endoscopic ultrasonography (CE-EUS) shows hypovascular area (right, CE-EUS) in the hypoechoic mass lesion (left, without contrast or enhancement). (C) Endoscopic ultrasonography-guided fine-needle aspiration. A 22-guage needle is punctured into the hypoechoic mass lesion.

MRI

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

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.[69,70] Moreover, probe-based confocal laser endomicroscopy has shown high sensitivity for the detection of malignancy in the pancreaticobiliary strictures.[71]

Endoscopic ultrasonography

See Online for a video on endoscopic ultrasonography in pancreatic cancer

The superiority of endoscopic ultrasonography over MDCT in diagnosing pancreatic cancer has been reported (figure 4, video).[72,73] One retrospective study recorded 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, gastroduodenal 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.

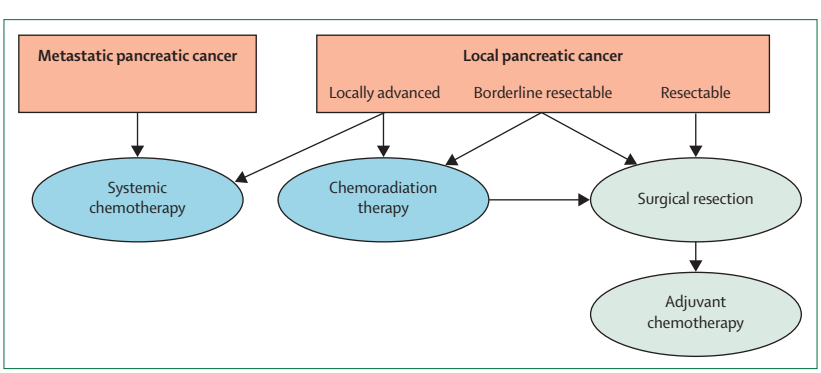

Figure 5: **Schematic algorithm of treatment for pancreatic cancer**

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.[88] 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.[89]

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.[90–92] 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.[93] By contrast, laparoscopic pancreaticoduodenectomy requires highly trained surgical skills, and general applications of this technique to patients with pancreatic cancer remain unwarranted.[94]

Mortality, complications, length of hospital stay, margin status, survival, and overall cost after pancreaticoduodenectomy have been reported to be related to hospital volume.[95,96] Therefore, it is recommended that pancreaticoduodenectomy should be done in specialised centres that perform a large number (>15–20) of pancreatic resections annually.[96]

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.[97] 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.[98] 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).[99] 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<0·0001).[100] 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.[101] 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).[102] 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

	Number of patients	Disease-free survival, months (95% CI)	HR (95% CI)	Median overall survival, months (95% CI)	HR (95% CI)
Moore et al[102]					
Gemcitabine	284	3·55 (NR)	..	5·91 (NR)	..
Gemcitabine plus erlotinib	285	3·75 (NR)	0·77 (0·64–0·92)	6·24 (NR)	0·82 (0·69–0·99)
Conroy et al (ACCORD11)[103]					
Gemcitabine	171	3·3 (2·2–3·6)	..	6·8 (5·5–7·6)	..
FOLFIRINOX	171	6·4 (5·5–7·2)	0·47 (0·37–0·59)	11·1 (9·0–13·1)	0·57 (0·45– 0·73)
Von Hoff et al (MPACT)[104]					
Gemcitabine	430	3·7 (3·6–4·0)	..	6·7 (6·0–7·2)	..
Gemcitabine plus nab-paclitaxel	431	5·5 (4·5–5·9)	0·69 (0·581–0·821)	8·5 (7·9–9·5)	0·72 (0·617–0·835)

HR=hazard ratio. NR=not reported. FOLFIRINOX=fluorouracil, folinic acid (leucovorin), irinotecan, and oxaliplatin. nab-paclitaxel=nanoparticle albumin-bound paclitaxel.

Table 2: **Findings of representative randomised phase 3 studies of chemotherapy for metastatic pancreatic cancer**

pancreatic cancer (table 2).[103] 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).[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,[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.[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.[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.[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.[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.[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.[112] Better understanding of the mutational landscape will further expand the use of targeted chemotherapy and other therapeutic options.[37] 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.[113]

Immunotherapy is one of the emerging therapeutic options. Although no benefit in overall survival has been shown in previous clinical trials,[114] new approaches to immunotherapy might have important roles in the treatment of pancreatic cancer in the future.[115] 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.[116]

Contributors

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Declaration of interests

We declare no competing interests.

References

1 Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA Cancer J Clin* 2014; **64:** 9–29.

2 Gillen S, Schuster T, Meyer Zum Büschenfelde C, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010; **7:** e1000267.

3 Kamisawa T, Isawa T, Koike M, et al. Hematogenous metastases of pancreatic ductal carcinoma. *Pancreas* 1995; **11:** 345–49.

4 Hruban RH, Canto MI, Goggins M, et al. Update on familial pancreatic cancer. *Adv Surg* 2010; **44:** 293–311.

5 Iodice S, Gandini S, Maisonneuve P, et al. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. *Langenbecks Arch Surg* 2008; **393:** 535–45.

6 Raimondi S, Lowenfels AB, Morselli-Labate AM, et al. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. *Best Pract Res Clin Gastroenterol* 2010; **24:** 349–58.

7 Bosetti C, Rosato V, Li D, et al. Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium. *Ann Oncol* 2014; **25:** 2065–72.

8 Sah RP, Nagpal SJS, Mukhopadhyay D, et al. New insights into pancreatic cancer-induced paraneoplastic diabetes. *Nat Rev Gastroenterol Hepatol* 2013; **10:** 423–33.

9 Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014; **74:** 2913–21.

10 Malvezzi M, Bertuccio P, Levi F, et al. European cancer mortality predictions for the year 2014. *Ann Oncol* 2014; **25:** 1650–56.

11 Hruban RH, Boffetta P, Hiraoka N, et al. Ductal adenocarcinoma of the pancreas. In: Hruban RH, Hiraoka N, Iacobuzio-Donahue C, et al. WHO classification of tumours of the digestive system. In: Bosman FTJ, Lakhani SR, Ohgaki H, eds. WHO classification of tumours, 4th edn. Lyon: International Agency for Research on Cancer, 2010: 281–91.

12 Chang KJ, Parasher G, Christie C, et al. Risk of pancreatic adenocarcinoma: disparity between African Americans and other race/ethnic groups. *Cancer* 2005; **103:** 349–57.

13 Silverman DT, Hoover RN, Brown LM, et al. Why do black Americans have a higher risk of pancreatic cancer than white Americans? *Epidemiology* 2003; **14:** 45–54.

14 Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Res* 2004; **64:** 2634–38.

15 Solomon S, Das S, Brand R, et al. Inherited pancreatic cancer syndromes. *Cancer J* 2012; **18:** 485–91.

16 Rustgi AK. Familial pancreatic cancer: genetic advances. *Genes Dev* 2014; **28:** 1–7.

17 Couch FJ, Johnson MR, Rabe KG, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2007; **16:** 342–46.

18 Goldstein AM, Fraser MC, Struewing JP, et al. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. *N Engl J Med* 1995; **333:** 970–74.

19 Giardiello FM, Welsh SB, Hamilton SR, et al. Increased risk of cancer in the Peutz-Jeghers syndrome. *N Engl J Med* 1987; **316:** 1511–14.

20 Lowenfels AB, Maisonneuve P, DiMagno EP, et al, and the International Hereditary Pancreatitis Study Group. Hereditary pancreatitis and the risk of pancreatic cancer. *J Natl Cancer Inst* 1997; **89:** 442–46.

21 McWilliams RR, Petersen GM, Rabe KG, et al. Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations and risk for pancreatic adenocarcinoma. *Cancer* 2010; **116:** 203–09.

22 Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. *JAMA* 2009; **302:** 1790–95.

23 Jones S, Hruban RH, Kamiyama M, et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. *Science* 2009; **324:** 217.

24 Roberts NJ, Jiao Y, Yu J, et al. ATM mutations in patients with hereditary pancreatic cancer. *Cancer Discov* 2012; **2:** 41–46.

25 Arslan AA, Helzlsouer KJ, Kooperberg C, et al, and the Pancreatic Cancer Cohort Consortium (PanScan). Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). *Arch Intern Med* 2010; **170:** 791–802.

26 Fukushima N, Hruban RH, Kato Y, et al. Ductal adenocarcinoma variants and mixed neoplasms of the pancreas. In: Fukushima N, Klimstra DS, Kloppel G, et al. WHO classification of tumours of the digestive system. In: Bosman FTJ, Lakhani SR, Ohgaki H, eds. WHO classification of tumours. 4th edn. Lyon: International Agency for Research on Cancer, 2010: 292–95.

27 Tomlinson JS, Jain S, Bentrem DJ, et al. Accuracy of staging node-negative pancreas cancer: a potential quality measure. *Arch Surg* 2007; **142:** 767–723, discussion 773–74.

28 Hruban RH, Adsay NV, Albores-Saavedra J, et al. Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. *Am J Surg Pathol* 2001; **25:** 579–86.

29 Basturk O, Hong SM, Wood LD, et al. A Revised classification system and recommendations from the Baltimore consensus meeting for neoplastic precursor lesions in the pancreas. *Am J Surg Pathol* 2015; **39:** 1730–41.

30 Adsay NV, Fukushima N, Furukawa T, et al. Intraductal neoplasms of the pancreas. In: Adsay NV, Furukawa T, Hruban RH, et al. WHO classification of tumours of the digestive system. In: Bosman FTJ, Lakhani SR, Ohgaki H, eds. WHO classification of tumours, 4th edn. Lyon: International Agency for Research on Cancer, 2010: 304–13.

31 Furukawa T, Klöppel G, Volkan Adsay N, et al. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. *Virchows Arch* 2005; **447:** 794–99.

32 Zamboni G, Fukushima N, Hruban RH, et al. Mucinous cystic neoplasms of the pancreas. In: Zamboni G, Hruban RH, Kloppel G. WHO classification of tumours of the digestive system. In: Bosman FTJ, Lakhani SR, Ohgaki H, eds. WHO classification of tumours, 4th edn. Lyon: International Agency for Research on Cancer, 2010: 300–03.

33 Vogelstein B, Papadopoulos N, Velculescu VE, et al. Cancer genome landscapes. *Science* 2013; **339:** 1546–58.

34 Wood LD, Hruban RH. Pathology and molecular genetics of pancreatic neoplasms. *Cancer J* 2012; **18:** 492–501.

35 Jones S, Zhang X, Parsons DW, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science* 2008; **321:** 1801–06.

36 Biankin AV, Waddell N, Kassahn KS, et al, and the Australian Pancreatic Cancer Genome Initiative. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature* 2012; **491:** 399–405.

37 Waddell N, Pajic M, Patch AM, et al, and the Australian Pancreatic Cancer Genome Initiative. Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature* 2015; **518:** 495–501.

38 Kanda M, Matthaei H, Wu J, et al. Presence of somatic mutations in most early-stage pancreatic intraepithelial neoplasia. *Gastroenterology* 2012; **142:** 730–33.

39 Maitra A, Adsay NV, Argani P, et al. Multicomponent analysis of the pancreatic adenocarcinoma progression model using a pancreatic intraepithelial neoplasia tissue microarray. *Mod Pathol* 2003; **16:** 902–12.

40 Murphy SJ, Hart SN, Lima JF, et al. Genetic alterations associated with progression from pancreatic intraepithelial neoplasia to invasive pancreatic tumor. *Gastroenterology* 2013; **145:** 1098–109.

41 Wu J, Jiao Y, Dal Molin M, et al. Whole-exome sequencing of neoplastic cysts of the pancreas reveals recurrent mutations in components of ubiquitin-dependent pathways. *Proc Natl Acad Sci USA* 2011; **108:** 21188–93.

42 Wu J, Matthaei H, Maitra A, et al. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. *Sci Transl Med* 2011; **3:** 92ra66.

43 Keane MG, Horsfall L, Rait G, et al. A case-control study comparing the incidence of early symptoms in pancreatic and biliary tract cancer. *BMJ Open* 2014; **4:** e005720.

44 Cosci F, Fava GA, Sonino N. Mood and anxiety disorders as early manifestations of medical illness: a systematic review. *Psychother Psychosom* 2015; **84:** 22–29.

45 Sharma C, Eltawil KM, Renfrew PD, et al. Advances in diagnosis, treatment and palliation of pancreatic carcinoma: 1990-2010. *World J Gastroenterol* 2011; **17:** 867–97.

46 Li J, Li Y, Cao G, et al. Early manifestations of pancreatic cancer: the effect of cancer-nerve interaction. *Med Hypotheses* 2013; **81:** 180–82.

47 Grahm AL, Andrén-Sandberg A. Prospective evaluation of pain in exocrine pancreatic cancer. *Digestion* 1997; **58:** 542–49.

48 Ni XG, Bai XF, Mao YL, et al. The clinical value of serum CEA, CA19-9, and CA242 in the diagnosis and prognosis of pancreatic cancer. *Eur J Surg Oncol* 2005; **31:** 164–69.

49 Safi F, Schlosser W, Kolb G, et al. Diagnostic value of CA 19-9 in patients with pancreatic cancer and nonspecific gastrointestinal symptoms. *J Gastrointest Surg* 1997; **1:** 106–12.

50 Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. *Eur J Surg Oncol* 2007; **33:** 266–70.

51 Gattani AM, Mandeli J, Bruckner HW. Tumor markers in patients with pancreatic carcinoma. *Cancer* 1996; **78:** 57–62.

52 Chan A, Prassas I, Dimitromanolakis A, et al. Validation of biomarkers that complement CA19.9 in detecting early pancreatic cancer. *Clin Cancer Res* 2014; **20:** 5787–95.

53 O'Brien DP, Sandanayake NS, Jenkinson C, et al. Serum CA19-9 is significantly upregulated up to 2 years before diagnosis with pancreatic cancer: implications for early disease detection. *Clin Cancer Res* 2015; **21:** 622–31.

54 Conrad C, Fernández-Del Castillo C. Preoperative evaluation and management of the pancreatic head mass. *J Surg Oncol* 2013; **107:** 23–32.

55 Fan Z, Li Y, Yan K, et al. Application of contrast-enhanced ultrasound in the diagnosis of solid pancreatic lesions--a comparison of conventional ultrasound and contrast-enhanced CT. *Eur J Radiol* 2013; **82:** 1385–90.

56 Zhang Y, Huang J, Chen M, et al. Preoperative vascular evaluation with computed tomography and magnetic resonance imaging for pancreatic cancer: a meta-analysis. *Pancreatology* 2012; **12:** 227–33.

57 Ahn SS, Kim MJ, Choi JY, et al. Indicative findings of pancreatic cancer in prediagnostic CT. *Eur Radiol* 2009; **19:** 2448–55.

58 Diehl SJ, Lehmann KJ, Sadick M, et al. Pancreatic cancer: value of dual-phase helical CT in assessing resectability. *Radiology* 1998; **206:** 373–78.

59 Lu DS, Reber HA, Krasny RM, et al. Local staging of pancreatic cancer: criteria for unresectability of major vessels as revealed by pancreatic-phase, thin-section helical CT. *AJR Am J Roentgenol* 1997; **168:** 1439–43.

60 Wang Z, Chen JQ, Liu JL, et al. FDG-PET in diagnosis, staging and prognosis of pancreatic carcinoma: a meta-analysis. *World J Gastroenterol* 2013; **19:** 4808–17.

61 Rijkers AP, Valkema R, Duivenvoorden HJ, et al. Usefulness of F-18-fluorodeoxyglucose positron emission tomography to confirm suspected pancreatic cancer: a meta-analysis. *Eur J Surg Oncol* 2014; **40:** 794–804.

62 Tang S, Huang G, Liu J, et al. Usefulness of 18F-FDG PET, combined FDG-PET/CT and EUS in diagnosing primary pancreatic carcinoma: a meta-analysis. *Eur J Radiol* 2011; **78:** 142–50.

63 Park HS, Lee JM, Choi HK, et al. Preoperative evaluation of pancreatic cancer: comparison of gadolinium-enhanced dynamic MRI with MR cholangiopancreatography versus MDCT. *J Magn Reson Imaging* 2009; **30:** 586–95.

64 Balci NC, Perman WH, Saglam S, et al. Diffusion-weighted magnetic resonance imaging of the pancreas. *Top Magn Reson Imaging* 2009; **20:** 43–47.

65 Fattahi R, Balci NC, Perman WH, et al. Pancreatic diffusion-weighted imaging (DWI): comparison between mass-forming focal pancreatitis (FP), pancreatic cancer (PC), and normal pancreas. *J Magn Reson Imaging* 2009; **29:** 350–56.

66 Takeuchi M, Matsuzaki K, Kubo H, et al. High-b-value diffusion-weighted magnetic resonance imaging of pancreatic cancer and mass-forming chronic pancreatitis: preliminary results. *Acta Radiol* 2008; **49:** 383–86.

67 Sandrasegaran K, Nutakki K, Tahir B, et al. Use of diffusion-weighted MRI to differentiate chronic pancreatitis from pancreatic cancer. *AJR Am J Roentgenol* 2013; **201:** 1002–08.

68 Maccioni F, Martinelli M, Al Ansari N, et al. Magnetic resonance cholangiography: past, present and future: a review. *Eur Rev Med Pharmacol Sci* 2010; **14:** 721–25.

69 Yamaguchi T, Shirai Y, Nakamura N, et al. Usefulness of brush cytology combined with pancreatic juice cytology in the diagnosis of pancreatic cancer: significance of pancreatic juice cytology after brushing. *Pancreas* 2012; **41:** 1225–29.

70 Mikata R, Ishihara T, Tada M, et al. Clinical usefulness of repeated pancreatic juice cytology via endoscopic naso-pancreatic drainage tube in patients with pancreatic cancer. *J Gastroenterol* 2013; **48:** 866–73.

71 Meining A, Shah RJ, Slivka A, et al. Classification of probe-based confocal laser endomicroscopy findings in pancreaticobiliary strictures. *Endoscopy* 2012; **44:** 251–57.

72 Agarwal B, Abu-Hamda E, Molke KL, et al. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. *Am J Gastroenterol* 2004; **99:** 844–50.

73 DeWitt J, Devereaux B, Chriswell M, et al. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. *Ann Intern Med* 2004; **141:** 753–63.

74 Gong TT, Hu DM, Zhu Q. Contrast-enhanced EUS for differential diagnosis of pancreatic mass lesions: a meta-analysis. *Gastrointest Endosc* 2012; **76:** 301–09.

75 Bang JY, Magee SH, Ramesh J, et al. Randomized trial comparing fanning with standard technique for endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic mass lesions. *Endoscopy* 2013; **45:** 445–50.

76 Nakai Y, Isayama H, Chang KJ, et al. Slow pull versus suction in endoscopic ultrasound-guided fine-needle aspiration of pancreatic solid masses. *Dig Dis Sci* 2014; **59:** 1578–85.

77 Attam R, Arain MA, Bloechl SJ, et al. "Wet suction technique (WEST)": a novel way to enhance the quality of EUS-FNA aspirate. Results of a prospective, single-blind, randomized, controlled trial using a 22-gauge needle for EUS-FNA of solid lesions. *Gastrointest Endosc* 2015; **81:** 1401–07.

78 Qin SY, Zhou Y, Li P, Jiang HX. Diagnostic efficacy of cell block immunohistochemistry, smear cytology, and liquid-based cytology in endoscopic ultrasound-guided fine-needle aspiration of pancreatic lesions: a single-institution experience. *PLoS One* 2014; **9:** e108762.

79 Brand RE, Adai AT, Centeno BA, et al. A microRNA-based test improves endoscopic ultrasound-guided cytologic diagnosis of pancreatic cancer. *Clin Gastroenterol Hepatol* 2014; **12:** 1717–23.

80 Jabbar KS, Verbeke C, Hyltander AG, et al. Proteomic mucin profiling for the identification of cystic precursors of pancreatic cancer. *J Natl Cancer Inst* 2014; **106:** djt439.

81 Fuccio L, Hassan C, Laterza L, et al. The role of K-ras gene mutation analysis in EUS-guided FNA cytology specimens for the differential diagnosis of pancreatic solid masses: a meta-analysis of prospective studies. *Gastrointest Endosc* 2013; **78:** 596–608.

82 Kamisawa T, Zen Y, Pillai S, et al. IgG4-related disease. *Lancet* 2015; **385:** 1460–71.

83 Kamisawa T, Imai M, Yui Chen P, et al. Strategy for differentiating autoimmune pancreatitis from pancreatic cancer. *Pancreas* 2008; **37:** e62–67.

84 Shimosegawa T, Chari ST, Frulloni L, et al, and the International Association of Pancreatology. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 2011; **40:** 352–58.

85 Tanaka M, Fernández-del Castillo C, Adsay V, et al, and the International Association of Pancreatology. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 2012; **12:** 183–97.

86 Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol* 2009; **16:** 1727–33.

87 Bockhorn M, Uzunoglu FG, Adham M, et al, and the International Study Group of Pancreatic Surgery. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2014; **155:** 977–88.

88 He J, Page AJ, Weiss M, et al. Management of borderline and locally advanced pancreatic cancer: where do we stand? *World J Gastroenterol* 2014; **20:** 2255–66.

89 Van Laethem JL, Verslype C, Iovanna JL, et al, and the European Society for Medical Oncology. New strategies and designs in pancreatic cancer research: consensus guidelines report from a European expert panel. *Ann Oncol* 2012; **23:** 570–76.

90 Evans DB, Farnell MB, Lillemoe KD, et al. Surgical treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. *Ann Surg Oncol* 2009; **16:** 1736–44.

91 Nimura Y, Nagino M, Takao S, et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. *J Hepatobiliary Pancreat Sci* 2012; **19:** 230–41.

92 Jang JY, Kang MJ, Heo JS, et al. A prospective randomized controlled study comparing outcomes of standard resection and extended resection, including dissection of the nerve plexus and various lymph nodes, in patients with pancreatic head cancer. *Ann Surg* 2014; **259:** 656–64.

93 Shin SH, Kim SC, Song KB, et al. A comparative study of laparoscopic vs. open distal pancreatectomy for left-sided ductal adenocarcinoma: a propensity score-matched analysis. *J Am Coll Surg* 2015; **220:** 177–85.

94 Mesleh MG, Stauffer JA, Asbun HJ. Minimally invasive surgical techniques for pancreatic cancer: ready for prime time? *J Hepatobiliary Pancreat Sci* 2013; **20:** 578–82.

95 Begg CB, Cramer LD, Hoskins WJ, et al. Impact of hospital volume on operative mortality for major cancer surgery. *JAMA* 1998; **280:** 1747–51.

96 Vincent A, Herman J, Schulick R, et al. Pancreatic cancer. *Lancet* 2011; **378:** 607–20.

97 Neoptolemos JP, Stocken DD, Friess H, et al, and the European Study Group for Pancreatic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; **350:** 1200–10.

98 Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA* 2013; **310:** 1473–81.

99 Maeda A, Boku N, Fukutomi A, et al. Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 in patients with resected pancreatic cancer: Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC-01). *Jpn J Clin Oncol* 2008; **38:** 227–29.

100 Sudo K, Nakamura K, Yamaguchi T. S-1 in the treatment of pancreatic cancer. *World J Gastroenterol* 2014; **20:** 15110–18.

101 Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; **15:** 2403–13.

102 Moore MJ, Goldstein D, Hamm J, et al, and the National Cancer Institute of Canada Clinical Trials Group. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; **25:** 1960–66.

103 Conroy T, Desseigne F, Ychou M, et al, and the Groupe Tumeurs Digestives of Unicancer, and the PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364:** 1817–25.

104 Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369:** 1691–703.

105 Pelzer U, Schwaner I, Stieler J, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. *Eur J Cancer* 2011; **47:** 1676–81.

106 Huguet F, Girard N, Guerche CS, et al. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: a qualitative systematic review. *J Clin Oncol* 2009; **27:** 2269–77.

107 Loehrer PJ Sr, Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 2011; **29:** 4105–12.

108 Philip PA. Locally advanced pancreatic cancer: where should we go from here? *J Clin Oncol* 2011; **29:** 4066–68.

109 Takaori K, Bassi C, Biankin A, et al. International Association of Pancreatology (IAP)/European Pancreatic Club (EPC) consensus review of guidelines for the treatment of pancreatic cancer. *Pancreatology* 2015; published online Nov 12. doi: 10.1016/j.pan.2015.10.013.

110 Soderlund C, Linder S. Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial. *Gastrointest Endosc* 2006; **63:** 986–95.

111 Canto MI, Harinck F, Hruban RH, et al, and the International Cancer of Pancreas Screening (CAPS) Consortium. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut* 2013; **62:** 339–47.

112 Chantrill LA, Nagrial AM, Watson C, et al, and the Australian Pancreatic Cancer Genome Initiative (APGI), and the Individualized Molecular Pancreatic Cancer Therapy (IMPaCT) Trial Management Committee of the Australasian Gastrointestinal Trials Group (AGITG). Precision medicine for advanced pancreas cancer: the Individualized Molecular Pancreatic Cancer Therapy (IMPaCT) Trial. *Clin Cancer Res* 2015; **21:** 2029–37.

113 Deeks ED. Olaparib: first global approval. *Drugs* 2015; **75:** 231–40.

114 Yamaue H, Tsunoda T, Tani M, et al. Randomized phase II/III clinical trial of elpamotide for patients with advanced pancreatic cancer: PEGASUS-PC Study. *Cancer Sci* 2015; **106:** 883–90.

115 Lutz ER, Wu AA, Bigelow E, et al. Immunotherapy converts nonimmunogenic pancreatic tumors into immunogenic foci of immune regulation. *Cancer Immunol Res* 2014; **2:** 616–31.

116 Stromnes IM, DelGiorno KE, Greenberg PD, et al. Stromal reengineering to treat pancreas cancer. *Carcinogenesis* 2014; **35:** 1451–60.