Pancreatic cancer

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Abstract | Pancreatic cancer is a major cause of cancer-associated mortality, with a dismal overall prognosis that has remained virtually unchanged for many decades. Currently, prevention or early diagnosis at a curable stage is exceedingly difficult; patients rarely exhibit symptoms and tumours do not display sensitive and specific markers to aid detection. Pancreatic cancers also have few prevalent genetic mutations; the most commonly mutated genes are *KRAS*, *CDKN2A* (encoding p16), *TP53* and *SMAD4* — none of which are currently druggable. Indeed, therapeutic options are limited and progress in drug development is impeded because most pancreatic cancers are complex at the genomic, epigenetic and metabolic levels, with multiple activated pathways and crosstalk evident. Furthermore, the multilayered interplay between neoplastic and stromal cells in the tumour microenvironment challenges medical treatment. Fewer than 20% of patients have surgically resectable disease; however, neoadjuvant therapies might shift tumours towards resectability. Although newer drug combinations and multimodal regimens in this setting, as well as the adjuvant setting, appreciably extend survival, ~80% of patients will relapse after surgery and ultimately die of their disease. Thus, consideration of quality of life and overall survival is important. In this Primer, we summarize the current understanding of the salient pathophysiological, molecular, translational and clinical aspects of this disease. In addition, we present an outline of potential future directions for pancreatic cancer research and patient management.

The normal pancreas consists of digestive enzyme-secreting acinar cells, bicarbonate-secreting ductal cells, centro-acinar cells that are the geographical transition between acinar and ductal cells, hormone-secreting endocrine islets and relatively inactive stellate cells. The majority of malignant neoplasms of the pancreas are adenocarcinomas; rare pancreatic neoplasms include neuroendocrine tumours (which can secrete hormones such as insulin or glucagon) and acinar carcinomas (which can release digestive enzymes into the circulation). Even less common neoplasms include colloid carcinomas, pancreatoblastomas and solid-pseudopapillary neoplasms (FIG. 1). Specifically, ductal adenocarcinoma is the most common malignancy of the pancreas; this tumour (commonly and here referred to as pancreatic cancer) presents a substantial health problem, with an estimated 367,000 new cases diagnosed worldwide in 2015 and an associated 359,000 deaths in the same year[1]. Pancreatic cancer is currently the fourth highest cause of cancer death in developed countries, and if outcomes are not improved, the disease is predicted to be the second leading cause of cancer-related mortality within the next decade[2]. Risk factors such as tobacco smoking, type 2 diabetes mellitus and chronic pancreatitis account for approximately one-quarter to one-third of cases.

Pancreatic cancer is associated with an extremely poor prognosis for several reasons[3]. It is usually diagnosed at advanced stages, which is often due to non-specific and — in some cases — no symptoms, a lack of sensitive and specific tumour markers and difficulties in imaging early-stage tumours. Pancreatic cancer is aggressive, with perineural and vascular local growth and early distant metastases that preclude curative surgical resection in most patients. Pancreatic cancer is characterized by a remarkable resistance (or tolerance) to most conventional treatment options, including chemotherapy, radiotherapy and molecularly targeted therapy. Finally, pancreatic cancer harbours multiple genetic and epigenetic alterations and have complex and dense tumour microenvironments. All of these factors result in an overall 5-year survival rate of <7%, with almost all survivors at this time point being the 10–20% of patients who undergo surgical resection; for these patients, the 5-year survival rate is ~15–25%[4].

Although some areas of research and patient care have witnessed incremental progress (such as more-effective combinatorial chemotherapeutic options, new preoperative treatment strategies, better perioperative care and safer surgery), the overall effect on the prognosis of patients with pancreatic cancer has been marginal.

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Emerging strategies to treat pancreatic cancer include identifying subgroups of patients for individualized therapies, developing molecularly targeted therapies and immunotherapies, and focusing on the tumour microenvironment as a potential target. Additional areas of intense investigation are early detection, tumour marker validation and standardization of care.

In this Primer, we summarize key aspects of pancreatic cancer, from basic, translational and clinical points of view, and provide an outlook of the most important challenges to tackling this deadly disease.

Epidemiology

Analyses of population-based data must consider geographical and temporal variations in the quality of clinical diagnoses and in the proportion of histologically verified cases of pancreatic cancer, which is rarely >50%[5]. For example, differential access to health care, including advanced radiological tools, can influence the accuracy of reported pancreatic cancer rates[6].

In 2015, an estimated 367,000 new cases of pancreatic cancer were diagnosed worldwide, >50% of which occurred in high-income countries[1]. In the United States, the highest rates were registered among black individuals (12–15 cases per 100,000 men and 8–10 cases per 100,000 women); these rates are ~30–50% higher than in their white counterparts[7]. In Oceania, indigenous populations are most affected, with an >30% excess, although long-term validated statistics are unavailable. The lowest rates, which are probably influenced by under-diagnosis, were recorded in India and in Northern and Central Africa (<2 cases per 100,000 men and 1 case per 100,000 women). Mortality rates closely parallel incidence rates (FIG. 2). Increases in reported incidence and mortality have taken place since the 1970s, in particular, in high-income countries where these increases can be partially attributed to diagnostic improvements. Although some reports suggest that incidence and mortality have levelled off in Western Europe and in North America, the latest data show the incidence continuing to rise in the United Kingdom and in North America — probably as a result of an ageing population[3,8,9]. Urban populations tend to have higher rates than rural populations, reflecting the quality of diagnosis, although differences in risk factors might also be involved. Studies suggest that first-generation migrants from low-risk areas who move to high-risk areas experience rates similar to those of the country of migration after 15–20 years[10], indicating the importance of environmental factors on pancreatic cancer aetiology.

Risk factors

Age is the major determinant of pancreatic cancer. Most patients are diagnosed at >50 years of age, with peak incidence in the seventh and eighth decades of life. In terms of preventable risk factors, tobacco smoking is the most important and most studied. Smokers have a twofold to threefold higher risk of developing pancreatic cancer than non-smokers; a dose–risk relationship has been noted, as has a favourable effect of smoking cessation. The proportion of cases attributable to tobacco smoking has been estimated to be 15–30% in various populations[11–13]. Use of smokeless tobacco products can also increase the risk[14].

Obesity and low physical activity are also linked to pancreatic cancer[15,16]. Some nutritional and dietary factors, including high intake of (saturated) fats, low intake of vegetables and fruits and consumption of red and processed meats, are also associated with risk[17–19]. However, other dietary factors remain undefined and unquantified. Reports of an association between coffee consumption and pancreatic cancer risk[20] have not been confirmed by subsequent studies. Furthermore, a positive association with heavy alcohol consumption has been observed, but no such association has been shown with moderate drinking[21,22]. Heavy alcohol consumption might be related to chronic pancreatitis, which increases the risk of pancreatic cancer by more than tenfold, with little difference in attributable risk between the alcoholic and non-alcoholic forms of pancreatitis. Diabetes mellitus is both a risk factor for disease and a consequence of early-stage pancreatic cancer; long-term diabetes mellitus approximately doubles the risk of pancreatic cancer[23]. Diabetes mellitus can also be caused by pancreatic cancer (type 3c diabetes mellitus) and, accordingly, new-onset diabetes mellitus can be the first clue to the diagnosis of pancreatic cancer in elderly patients[23,24] (see Diagnosis, below). Gastrointestinal ulcer and gastrectomy are associated with a modest increased risk of pancreatic cancer, but has limited influence on overall disease burden in the modern era[25].

10% of patients have a family history of pancreatic cancer[26]. Indeed, some hereditary conditions carry an increased risk of pancreatic cancer, such as Peutz–Jeghers syndrome (TABLE 1). Mutations in *BRCA2*, *BRCA1*, *CDKN2A*, *ATM*, *STK11*, *PRSS1*, *MLH1* and *PALB2* are associated with pancreatic cancer with variable penetrance, and common variants that confer modest risk, such as those at the ABO blood group locus[27], have also been identified.

Mechanisms/pathophysiology

Carcinogenesis and molecular biology

Pancreatic cancer most frequently arises from pancreatic intraepithelial neoplasia (PanIN), the classic pre-neoplastic lesions, but can also arise from larger precursor lesions (namely, intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms)[28,29]. Pancreatic cancer exhibits aberrant autocrine and paracrine signalling cascades that promote pancreatic cancer cell proliferation, migration, invasion and metastasis. For example, many signalling molecules — such as transforming growth factor-α (TGFα), insulin-like growth factor 1 (IGF1), fibroblast growth factors (FGFs) and hepatocyte growth factor (HGF) — and their respective tyrosine kinase receptors — such as epidermal growth factor receptor (EGFR), receptor tyrosine-protein kinase erbB-2 (ERBB2; also known as HER2), HER3, IGF1 receptor (IGF1R), FGF receptors (FGFRs) and HGF receptor (HGFR; also known as MET) — activate multiple pathways that enhance pancreatic cancer cell mitogenic self-sufficiency and promote migration and invasion[30]. These signalling cascades are activated in conjunction with the activation of anti-apoptotic and pro-survival pathways, such as signal transducer and activator of transcription 3 (STAT3), nuclear factor-κB (NF-κB) and AKT[30]. Genes that are normally active during development, such as *WNT*, *SHH* and *NOTCH*, are also reactivated in some pancreatic cancers[31].

The signalling in pancreatic cancer is complex, with multiple nodes and aberrant crosstalk pathways (FIG. 3). For example, one of the aberrant signalling nodes in pancreatic cancer is characterized by enhanced activity of HGFR and EGFR, increased expression of neuropilin 1, CD44 expression and β1 integrin, and is aggravated by the ability of HGFR to form heterodimers with EGFR[32]. These alterations occur in the context of oncogenic *KRAS* and loss of *CDKN2A*, which encodes the tumour suppressor p16 (REFS 28,30). Pancreatic cancer also exhibits metabolic abnormalities and insensitivity to growth inhibitory pathways. Loss of negative growth constraints is best exemplified by aberrant TGFβ signalling, which occurs as a consequence of increased expression of TGFβ isoforms[33]. Although TGFβ is a physiological tumour suppressor, it promotes tumour progression in pancreatic cancer and many other solid tumours by exerting paracrine effects within the tumour microenvironment (see Microenvironment, below) that lead to enhanced growth and metastasis. TGFβ can also directly induce pancreatic cancer cell proliferation by activating non-canonical signalling through mitogen-activated protein kinase (MAPK) phosphorylation, proto-oncogene tyrosine-protein kinase Src (SRC) and AKT phosphorylation, and by upregulating *WNT7B* expression through canonical SMAD4-dependent mechanisms[33] (FIG. 3).

Mutational landscape and subtypes

The molecular pathology of pancreatic cancer is dominated by activating mutations in *KRAS*, which are present in >90% of tumours. Inactivating mutations of *TP53*, *CDKN2A* and *SMAD4* occur in 50–80% of pancreatic cancers, whereas other genes, including *ARID1A*, *MLL3* and *TGFBR2*, are mutated in ~10% of tumours (FIG. 4). However, few genes stand out among the myriad of infrequently mutated genes, which mostly occur at a prevalence of <2%[34–39] (reviewed in REF. 40).

Although point mutations of individual genes reveal some aspects of disease pathophysiology, other genomic events contribute to carcinogenesis and can provide insight into molecular mechanisms. For example, *CDKN2A* is commonly inactivated by methylation, and *CDKN2A* and *SMAD4* are commonly inactivated through homozygous deletion. Copy number alterations, which can be difficult to interpret due to the large number of genes that are amplified or lost in these regional events, also seem to play an important part. Four subtypes of pancreatic cancer have been proposed based on the number and location of structural variants[37] (FIG. 4c). The first three subtypes comprise tumours with stable genomes with few (<50) structural variants, those with scattered structural events (50–200) and those with unstable genomes (>200 structural variants). Those tumours with unstable genomes are suggestive of defects in DNA maintenance and are a potential biomarker for platinum and poly (ADP-ribose) polymerase (PARP) inhibitor responsiveness[37]. The fourth group, termed locally rearranged, is defined by >50 events localized to 1–3 chromosomes. These events are typically amplifications that encompass oncogenes, which can be the targets of existing therapeutics, or genomic catastrophes such as chromothripsis.

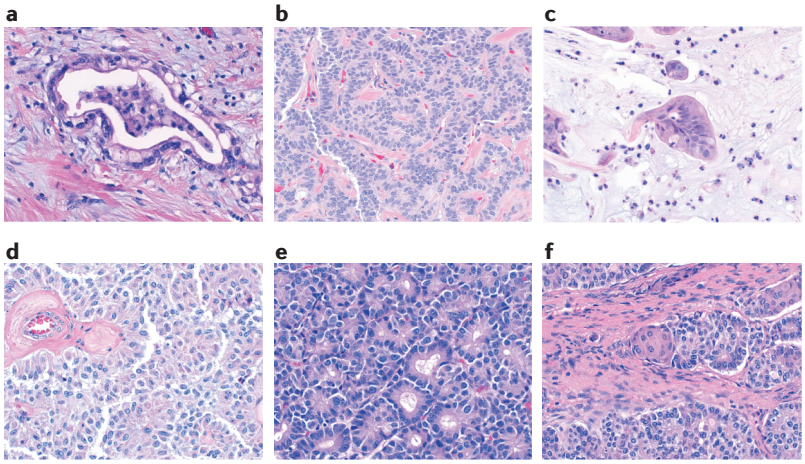

Figure 1 | **Common types of pancreatic cancer.** Adenocarcinomas comprise the majority of pancreatic neoplasms (75–80% of tumours surgically resected at the Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, over three decades). Adenocarcinomas are characterized by atypical neoplastic glands in a dense stroma (part **a**). The next most frequently occurring pancreatic neoplasms are neuroendocrine tumours (15–20%; characterized by a nested growth pattern, 'salt and pepper' nuclei and expressing the neuroendocrine markers synaptophysin and chromogranin) (part **b**); colloid carcinomas (2%; characterized by the formation of pools of mucin in the stroma) (part **c**); solid-pseudopapillary tumours (2%; characterized by poorly cohesive cells) (part **d**); acinar cell carcinomas (1%; characterized by cells with granular cytoplasm and a single prominent nucleoli) (part **e**); and pancreatoblastomas (0.5%; characterized by neoplastic cells with acinar differentiation and squamoid nests) (part **f**). The remaining tumours include variants such as adenosquamous, hepatoid, medullary, signet ring cell and undifferentiated carcinomas.

Whole-genome sequencing has revealed patterns in mutational mechanisms occurring during tumour development, including the effects of toxins such as tobacco exposure[41]. In addition, mechanisms of DNA damage that are operative in pancreatic carcinogenesis can be identified using this approach, and include ageing (deamination), aberrant APOBEC activity and defective DNA maintenance (namely, the *BRCA* mutational signature and defects in mismatch repair genes). Interestingly, although tobacco smoking is associated with an increased risk of pancreatic cancer, genetic signatures of tobacco exposure as seen in lung cancer are not present[42], suggesting that tobacco causes different patterns of mutation when cells are not directly exposed to smoke.

Analyses of epigenetic[43], transcriptomic[44,45] and metabolomic[46] characteristics have also provided valuable insight into pancreatic tumorigenesis. Analyses of mRNA expression have suggested molecular subtypes with potential relevance to therapeutic responsiveness, although different analyses often lead to different

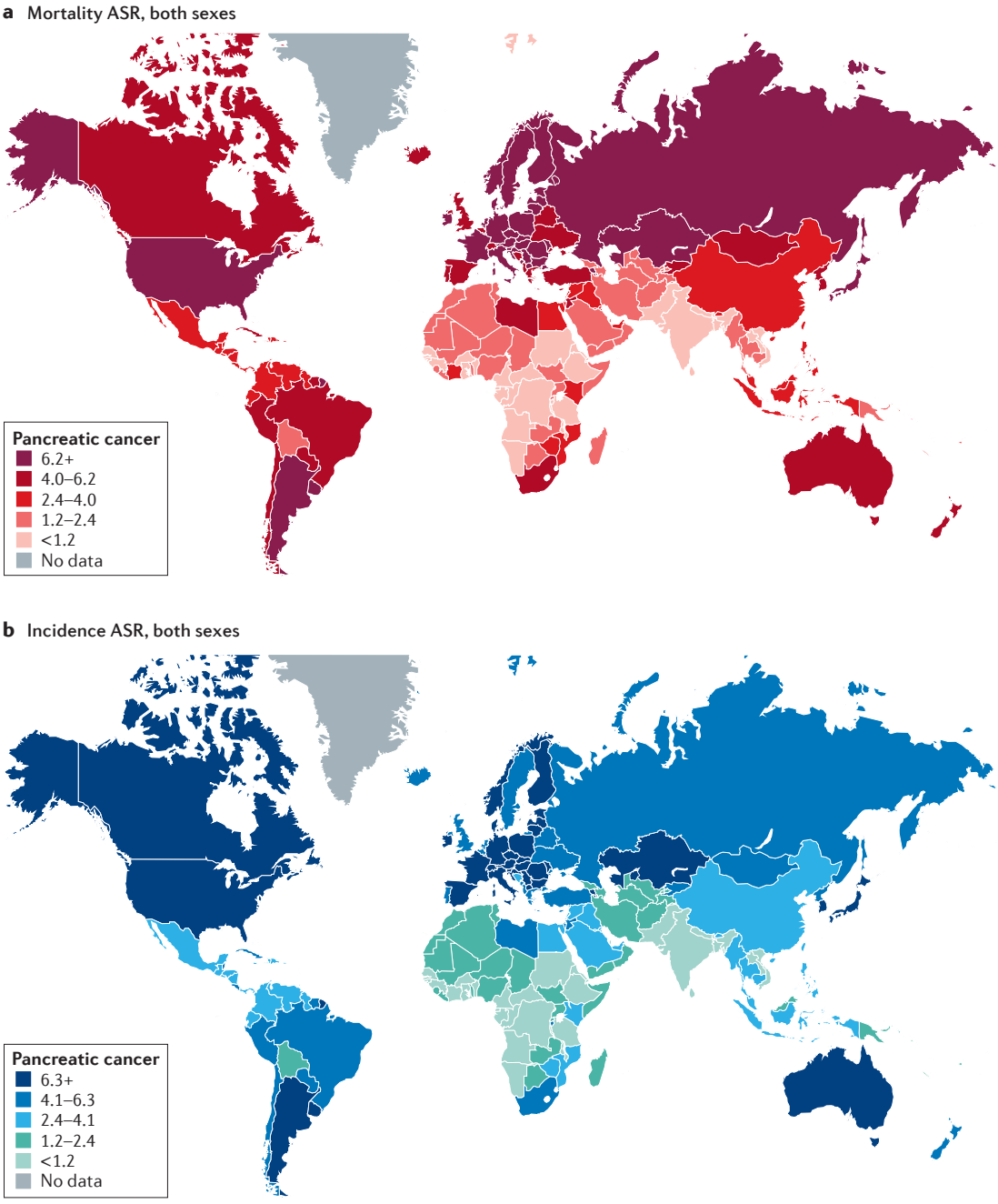

Figure 2 | **Global mortality and incidence rates of pancreatic cancer.** Estimated age-standardized rates (ASRs) of mortality (part **a**) and incidence (part **b**) for both sexes (per 100,000 persons) in 2012. Reproduced and modified with permission from Ferlay, J., Soerjomataram, I., Ervik, M., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D.M., Forman, D., Bray, F. GLOBOCAN 2012 v1.0, *Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11* [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 29 February 2016.

Table 1 | **Genetic syndromes associated with pancreatic cancer**

Syndrome	Affected genes	Relative risk*	Refs
Peutz–Jeghers syndrome	*STK11* (also known as *LKB1*)	132	275
Hereditary pancreatitis	*PRSS1*	53–67	276,277
Familial atypical multiple mole melanoma	*CDKN2A*‡	22–38	278,279
Lynch syndrome	*MSH2*, *MLH1*, *MSH6*, *PMS* and *PMS2*	9	280
Familial pancreatic cancer§	Unknown	9 (5–32 depending on the number of relatives affected)	162
Cystic fibrosis	*CFTR*	5	281
Breast and ovarian cancer syndrome	*BRCA1*, *BRCA2* and *PALB2*	2–4	282,283
Ataxia telangiectasia	*ATM*	Unknown	284
Li–Fraumeni syndrome	*TP53*	Unknown	285

Familial adenomatous polyposis (caused by mutations in the *APC* gene) is associated with ampullary and duodenal cancer but not with pancreatic cancer[286]. *Calculated against non-mutation controls. ‡The p16 gene product is affected, not the p14ARF gene product. §In which ≥2 first-degree relatives are affected.

classifications depending on the input material and the assumptions made. Microdissected epithelium from tumours classifies them into three subgroups[44], which becomes four when bulk tissue containing the tumour microenvironment is assessed and includes an additional 'immunogenic' subgroup based on stromal immune cell populations[39]. Others find two epithelial groups when transcripts from presumed normal pancreas are excluded from the analysis[45]. These epithelial subtypes seem to diverge based on their similarity to the normal or embryonic pancreas and are related to the histopathological subtype. Those that bear the least resemblance to the normal pancreas (termed squamous) are associated with poor prognoses[39]. Two stroma subtypes (normal and activated) of tumours, based on mRNA expression profiles[45], might explain the disparate findings concerning the role of the stroma[47] (see Microenvironment, below) and might provide insight into potential immunoregulatory therapeutic strategies and into predicting outcomes[48,49]. Integrated analyses of different 'omics' data sets can point towards molecular mechanisms that might play important parts in specific subtypes, paving the way for therapeutic development[39].

Microenvironment

Pancreatic cancers characteristically have an abundant and dense collagenous stroma (desmoplasia)[50], resulting in a considerable hypoxic environment for cancer cells (see Pathology, below). This stroma is composed of extracellular matrix (ECM) proteins — collagens, fibronectin and laminin — as well as non-collagenous proteins such as glycoproteins, proteoglycans and glycosaminoglycans. Other factors in the stroma that possibly mediate the interaction of cancer cells with the ECM include growth factors, osteopontin, periostin and serine protein acidic and rich in cysteine. Cellular elements of the stroma include pancreatic stellate cells, which produce the collagenous matrix (activated stellate cells have also been referred to as cancer-associated fibroblasts in the literature), infiltrating immune cells, endothelial cells and neuronal cells (FIG. 5). The immune cell complement in pancreatic cancer includes T cells (a majority being $CD4^+$ regulatory T cells), myeloid-derived suppressor cells, macrophages and mast cells[51]. Overall, the immune cell infiltration suggests an immunosuppressive phenotype, even at the earliest stages of pancreatic cancer (PanINs and IPMNs[52,53]). A growing body of evidence suggests that $CD4^+$ regulatory T cells in the stroma play a crucial part in warding off the host immune system. This feature is clinically important because factors that mediate the suppression of active antitumour immunity — such as the ligand for programmed cell death protein 1 (PD-1), PD-L1, expressed on cancer cells — form the basis of novel immunotherapeutic approaches currently under study in pancreatic cancer[54] (see Management, below).

However, whether the extent of stroma expansion influences clinical outcomes remains debatable. The largest study to date, with 233 patients, reported an association between the numbers of activated pancreatic stellate cells and poor clinical outcome[55], but this finding was not corroborated by two subsequent, smaller studies[56,57]. The differences in the findings are likely to be a result of differences in the assessment or calculation of stromal activity as well as in the patient cohorts selected for study. Most recently, a study of 145 patients reported that in early-stage (T1–T2) pancreatic tumours, moderate-to-strong α-smooth muscle actin expression (a marker of activated pancreatic stellate cells) was associated with poorer clinical outcomes than tumours with low levels of α-smooth muscle actin expression, as assessed by overall and progression-free survival[58].

Notably, an active bidirectional interaction between stromal stellate cells and cancer cells has been demonstrated by both *in vitro* and *in vivo* approaches[59], with each cell type stimulating proliferation and migration functions of the other (FIG. 5). Moreover, stellate cells can inhibit cancer cell apoptosis, thereby increasing their survival, and also facilitate the formation of a cancer stem cell niche that has been suggested to have a role in chemoresistance as well as recurrence of the disease[60]. Furthermore, pancreatic stellate cells can travel from the primary tumour to distant metastatic sites, where they might aid the seeding and growth of metastatic cancer cells[61].

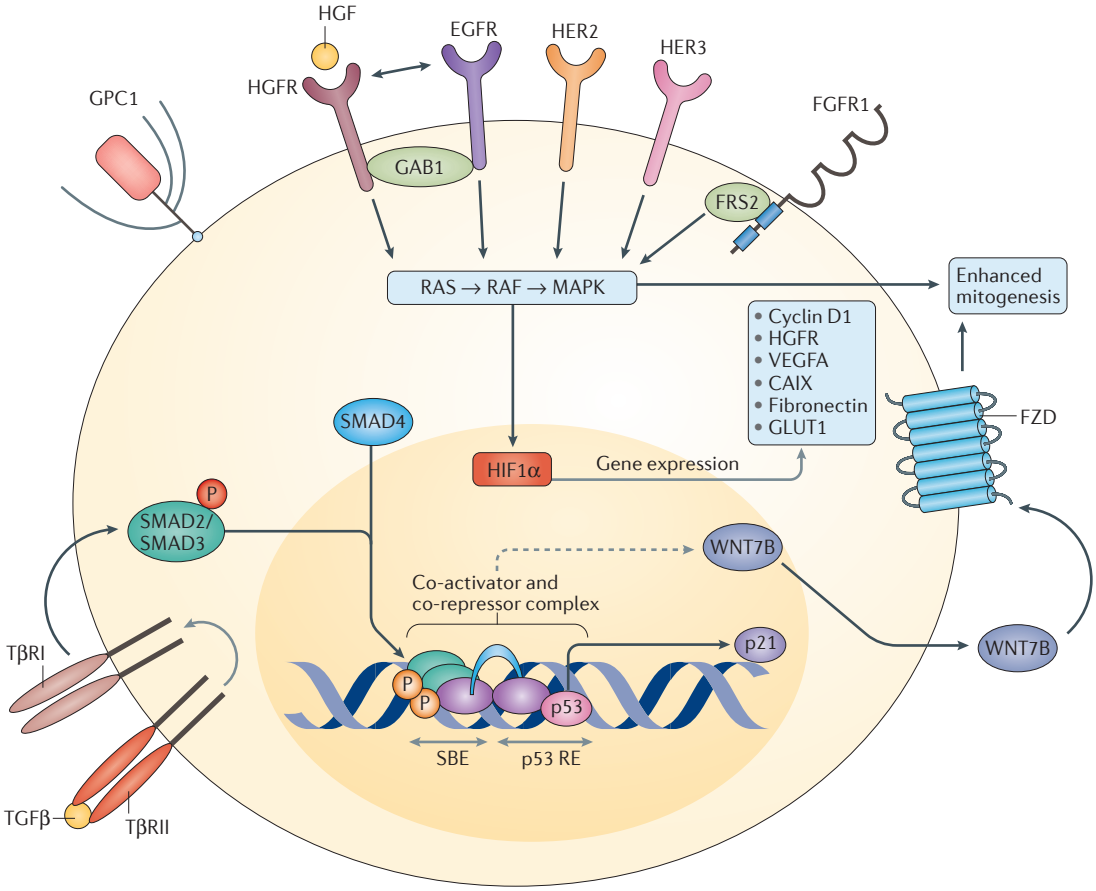

Figure 3 | **Aberrant signalling pathways in pancreatic cancer.** Epidermal growth factor receptor (EGFR) forms homodimers upon ligand binding, but can also form heterodimers with receptor tyrosine-protein kinase erbB-2 (ERRB2; also known as HER2) and HER3; in the context of oncogenic *KRAS* and overexpression of multiple ligands that bind to EGFR and HER3, downstream signalling is excessively activated[265]. Similarly, hepatocyte growth factor (HGF) receptor (HGFR) signalling is enhanced owing to increased expression of neuropilin 1, integrins and CD44 variants (notably, CD44v6), all of which interact with the receptor to enhance the ability of HGF to stimulate migration and invasion[266]. Moreover, increased levels of β1 integrin in pancreatic cancer can enhance EGFR signalling[267]. Both HGFR and EGFR are more efficiently activated by their ligands in the presence of the docking protein growth factor receptor-bound protein 2 (GRB2)-associated binding protein 1 (GAB1). Importantly, the crosstalk between EGFR family members and between EGFR and HGFR occurs in the context of mutated *KRAS* and relatively high levels of HGF and ligands that bind to the EGFR family[28,30]. Some of these ligands are heparin-binding, and their signalling becomes more sustained in the presence of the heparan sulfate proteoglycan glypican 1 (GPC1), which is overexpressed in pancreatic cancer[33,268]. These binding events lead to the activation of canonical RAS, RAF and mitogen-activated protein kinase (MAPK) signalling, as well as other pathways such as signal transducer and activator of transcription 3 (STAT3), phosphatidylinositol 3-kinase (PI3K) and AKT pro-survival signalling (not shown), and enhanced mitogenesis, invasion and metastasis. In the case of fibroblast growth factor receptor 1 (FGFR1), downstream signalling is dependent on the presence of the FGFR substrate 2 (FRS2) adaptor protein that leads to RAS activation through GRB2 and the SOS exchange factor. MAPK translocates to the nucleus, exerting transcriptional regulatory actions that lead, among others, to the expression of hypoxia-inducible transcription factor 1α (HIF1α), which is also induced by the hypoxic environment in pancreatic cancer. HIF1α in turn enhances the expression of multiple genes, including cyclin D1 (*CCND1*), *HGFR*, vascular endothelial growth factor A (*VEGFA*), carbonic anhydrase IX (*CAIX*), fibronectin and glucose transporter 1 (*GLUT1*; also known as *SLC2A1*). By contrast, transforming growth factor-β (TGFβ) signalling is mediated by serine/threonine kinase receptors; TGFβ binds to the type II TGFβ receptor (TβRII) homodimer, which activates the type I TGFβ receptor (TβRI) homodimer. The serine/threonine kinase activity of TβRI leads to the activation of canonical signalling through the phosphorylation (P) of SMAD2 and SMAD3, subsequent association with SMAD4, translocation to the nucleus, and interactions with SMAD-binding elements (SBEs) and co-activators or co-repressors to modulate gene transcription. Importantly, as a consequence of enhanced mitogenic signalling, increased cyclin D1 activity and increased CDK4 and CDK6 activity in the context of the frequent loss of *CDKN2A* (encoding p16), pancreatic cancer is associated with retinoblastoma-associated protein (encoded by *RB1*) dysfunction. In the absence of the inhibitory actions of RB1 on the cell cycle, TGFβ-mediated growth inhibition is lost because p21 is not upregulated, even in the presence of wild-type *TP53*, which induces p21 through a p53 response element (RE). Loss of RB1 function can also be associated with the conversion of TGFβ to a direct pancreatic cancer cell mitogen through the activation of non-canonical signalling pathways that includes MAPK and PI3K, and through TGFβ-mediated induction of WNT7B via a SMAD4-dependent mechanism (dashed arrow). The increased release of WNT7B activates frizzled receptors (FZDs) to induce mitogenesis.

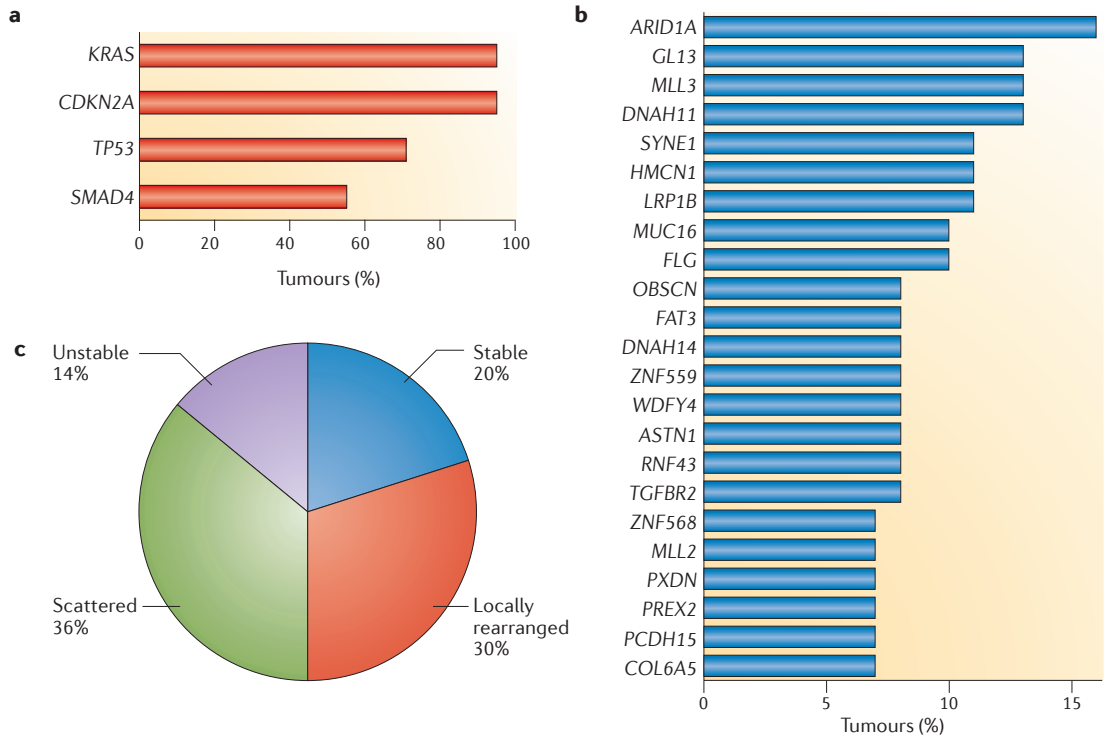

Figure 4 | **Gene alterations in pancreatic cancer. a** | Commonly altered genes in pancreatic cancer include *KRAS*, *CDKN2A*, *TP53* and *SMAD4*. Activating (*KRAS*) and inactivating (*CDKN2A*, *TP53* and *SMAD4*) mutations as well as homozygous deletions and other mechanisms of gene inactivation, such as promoter hypermethylation, are taken into account[37,269]. **b** | Less commonly mutated genes in pancreatic cancer determined using MutSig analysis[37]. **c** | Pancreatic cancer subtypes have been proposed based on the number and location of structural rearrangements[37]. Stable genome tumours have few (<50) structural variants, tumours designated as scattered have more structural events (50–200) and those designated as unstable have >200 structural genome variants. Locally rearranged tumours are defined by a large number of events localized to 1–3 chromosomes.

Interactions of pancreatic stellate cells with other stromal cells have also been reported. For example, stellate cells increase the proliferation of endothelial cells and endothelial tube formation (a measure of angiogenesis), effects mediated by vascular endothelial growth factor (VEGF) and/or HGF (both secreted by stellate cells)[61,62]. Pancreatic stellate cells might also contribute to immune evasion in pancreatic cancer by sequestering tumour-suppressive $CD8^+$ T cells in the stroma[63], inducing apoptosis of T cells via the secretion of galectin 1 (a β-galactoside-binding protein)[64] and stimulating the migration of myeloid-derived suppressor cells into the stroma[65]. This cascade then induces degranulation of mast cells, leading to the release of tryptase and IL-13, which stimulates the proliferation of pancreatic stellate cells and tumour cells[66]. Degranulation of mast cells also induces cytokine production by macrophages — leading to further activation of pancreatic stellate cells[67]. In the presence of stellate cells, neurite growth towards cancer cells and invasion of neurons by cancer cells is increased, an effect possibly mediated by the Sonic Hedgehog signalling pathway[68]. Interestingly, stellate cells have been suggested to have a role in the new-onset diabetes mellitus (type 3c) of pancreatic cancer via their inhibition of β-cell function in pancreatic islets[69] (FIG. 5).

Although the weight of evidence to date indicates a facilitatory role for stromal pancreatic stellate cells in tumour growth and metastasis, recent studies (using genetic techniques[57,70] or signalling pathway inhibition[70,71] to deplete myofibroblast numbers and function) have controversially suggested that the stroma has a protective role in pancreatic cancer. These discrepant findings serve as a reminder that the influence of the stroma might be highly dependent on context and timing. For example, during early carcinogenesis, upregulation of stellate cell-produced stroma could reflect the host's attempt to isolate tumour cells, but in later stages of tumour development the cancer cells may be able to subvert stromal stellate cells into cancer-permissive cells.

Metabolic reprogramming

Changes in cell metabolism are a hallmark of carcinogenesis. Adaptation to the microenvironment and oncogenes are key drivers in this process. As outlined above, pancreatic cancer is characterized by a severely hypoxic and nutrient-deprived microenvironment[72,73] and by oncogenic *KRAS* mutations in the vast majority of cases. Pancreatic cancer cells have adapted to survive in these conditions through various mechanisms, mainly driven by hypoxia-inducible transcription factor 1α (HIF1α)[74,75] and oncogenic *KRAS* (FIG. 6).

Furthermore, pancreatic cancer cells exhibit high levels of autophagy, a self-degradative process for cellular organelles and macromolecules, as well as dependence

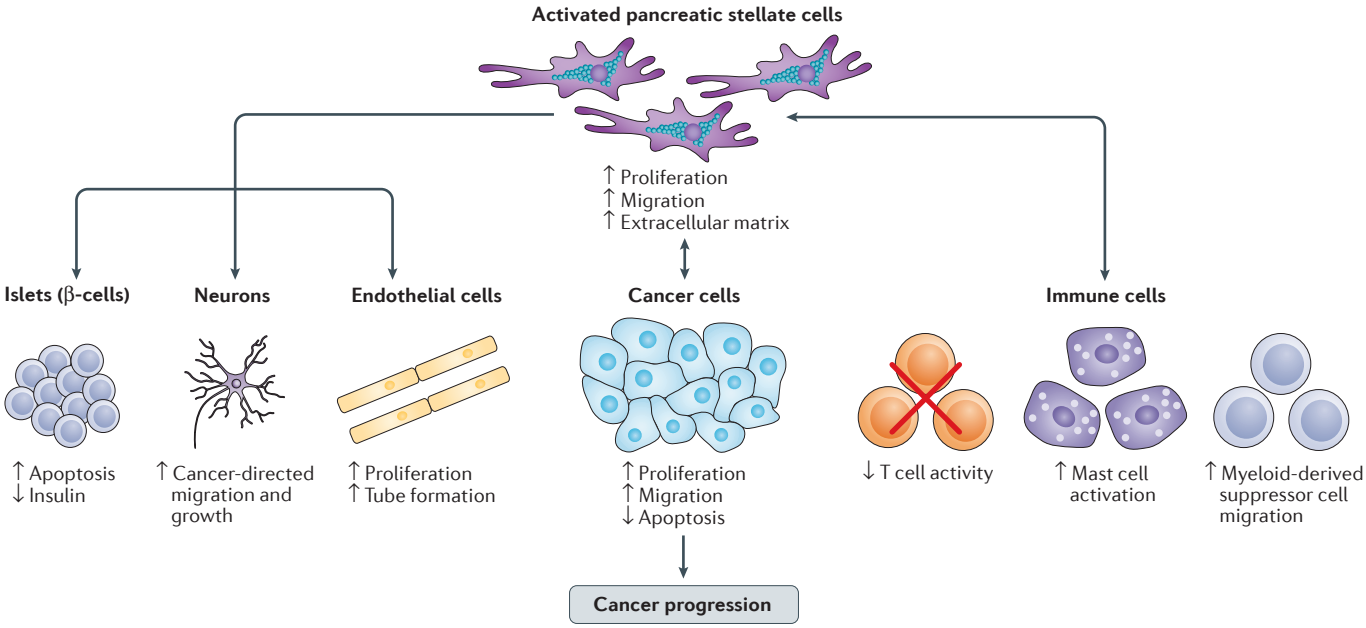

Figure 5 | **Pancreatic stellate cells in pancreatic cancer.** Pancreatic stellate cells are stromal cells that can interact with cancer cells, with other cells in the desmoplastic reaction (including immune cells, endothelial cells and neurons) and with β-cells in islets. All of these interactions are thought to facilitate the progression of pancreatic cancer.

on MITF/TFE transcription factors to activate the autophagy–lysosome system to maintain intracellular amino acid levels[76,77]. Genetic or pharmacological inhibition of autophagy substantially delays tumour development in genetically engineered mutant mice (GEMM) and in xenograft models of pancreatic cancer[76], and *KRAS*-driven pancreatic cancers respond to autophagy inhibition probably independently of *TP53* status[78,79]. Macropinocytosis (a distinct pathway of endocytosis) is an important way in which extracellular proteins are transported into *KRAS*-transformed pancreatic cancer cells[80]. Indeed, macropinocytic protein uptake and lysosomal degradation are necessary to meet the requirements for glutamine as well as other amino acids of pancreatic cancer cells[81], thereby reducing the dependence on free extracellular glutamine[80]. Blockade of macropinocytosis reduces pancreatic cancer cell growth in a *KRAS*-transformed xenograft model[80].

Targeting specific metabolic adaptions is an emerging strategy for pancreatic cancer (reviewed in REF. 82). These strategies include blocking key regulators of tumour metabolism such as pyruvate kinase isoform M2 (PKM2), lactate transport and autophagy.

Disease models

Model systems of pancreatic cancer are widely available and have substantially improved our knowledge of this disease. Contemporary pancreatic cancer models complement the traditional cell line and xenograft models[83], and include GEMM[84–86] and organoid cultures[87–89].

Genetically engineered mutant mice. Mouse models of pancreatic cancer somatically target mutant alleles to the mouse pancreas. Such autochthonous models accurately mimic the human disease and have confirmed causative roles for many mutant genes previously identified in the human pancreatic cancer genome. Indeed, GEMM have revealed that oncogenic *KRAS* is uniquely sufficient to initiate PanIN[84,85] and that such mice spontaneously progress to locally invasive and metastatic pancreatic cancer. When combined with oncogenic *KRAS*, additional orthologous mutations in the canonical tumour suppressor genes *CDKN2A* (encoding p16), *TP53* or *SMAD4* have been shown to accelerate pancreatic tumour progression of varying histology[86,90–94], and this strategy is the standard method to query the function of a potentially pathogenetic allele. Furthermore, novel pancreatic cancer genes and pathways can also be discovered using transposon insertional mutagenesis strategies in sensitized mice[95–97].

Genetic requirements for pancreatic cancer progression can be established by incorporating concomitant germline or conditional alleles into traditional GEMM models. Indeed, this strategy has revealed the importance of various signalling pathways, including EGFR[98] and NRF2 (REF. 99), in tumour initiation. Similarly, to assess the role of genes in tumour maintenance, flexible GEMM using regulatable alleles have been used to confirm the dependency of pancreatic cancer on continuous expression of oncogenic *KRAS*[100,101] and loss of *TP53* (REF. 102). For example, silencing of oncogenic *KRAS* identified new metabolic alterations in pancreatic cancer that offer therapeutic opportunities[100,103].

Cellular biological processes involving neoplastic and microenvironmental interactions can also be carefully probed using GEMM. Studies of GEMM have surprisingly revealed that acinar and endocrine cells are more capable of initiating PanIN than ductal cells[85,104–107], although this finding seems context dependent inasmuch as ductal cells can be effective in initiating pancreatic cancer in the setting of gain-of-function mutations

in *TP53* (REF. 108). In addition, studies of GEMM have suggested that histologically early-stage PanIN cells are capable of local invasion and intravascular dissemination[71] and have identified a potent stimulatory role for pancreatic inflammation[85] and myeloid cells[109,110] in pancreatic cancer pathogenesis. GEMM have also demonstrated that pancreatic cancer differentiation is influenced by the juxtaposition of activated pancreatic stellate cells[57,71]. Finally, pathophysiological sequelae of pancreatic cancer, such as cachexia[111] and pain[112], and the role of obesity[113] and the intestinal microbial flora[114] can also be evaluated in GEMM.

Therapeutic studies using GEMM led to the realization that human pancreatic cancer contains a markedly deficient vasculature[115], which spurred the development of methods to increase intratumoural perfusion and drug delivery. Although the clinical development of Hedgehog pathway inhibitors has thus far been disappointing and has not clarified whether intratumoural perfusion is limiting[116,117], several analogous approaches using pegylated hyaluronidase[118,119] and synthetic vitamin D analogues[120] are under active investigation. Several factors that suppress the immune response in pancreatic cancer have also been identified, stimulating multiple clinical efforts[121–124]. Finally, therapies that target the RAS pathway effectors[125] and parallel pathways (such as Notch[126]) have demonstrated some activity in GEMM, again motivating clinical development.

Mice harbouring pre-invasive neoplasms and advanced pancreatic cancer represent ideal systems to develop diagnostic methods. Accordingly, early detection strategies for pancreatic cancer have been pioneered in GEMM, including the discovery of the potential imaging biomarkers plectin 1 (REF. 127) and claudin 4 (REF. 128), blood biomarker panels[129] and circulating exosomes containing glypican 1 (REF. 130). Many of these biomarkers have been corroborated in human samples, and clinical assessment is ongoing (see Biomarkers, below).

To decrease mouse breeding times and costs, several strategies have been developed, including the mutagenesis of pancreatic cancer-sensitized embryonic stem cells followed by blastocyst injection and chimaera analysis[102], and the direct intrapancreatic delivery of recombinant viruses harbouring gene-editing constructs to rapidly generate pancreatic cancer models[131]. The near future should also herald the development of multi-recombinase model systems to control the temporal expression of several alleles at different stages of tumour progression. These approaches require sophisticated transgenic and surgical capabilities and might be ideal for certain applications.

Organoid cultures. Recently, 3D organoid cultures representing human and mouse pancreatic cancer have been described[88]. Organoids can be cultured indefinitely, molecularly characterized and subjected to drug screens. Furthermore, the orthotopic transplantation of human organoids recapitulates some of the stages of tumour progression, thereby providing a model of early human pancreatic cancer. As organoids can be readily established from small biopsy specimens, obtained from pancreatic tumours, they can in principle be used to characterize the unique molecular characteristics of and identify effective therapeutic approaches for individual patients. Such a precision medical approach using organoids is undergoing evaluation for patients with pancreatic cancer. A related current goal is the establishment of a sufficient collection of human organoids to determine whether they reflect the diversity of pancreatic cancer that was previously reported through sequencing studies[34,36,44]. In this regard, organoids might recapitulate the heterogeneity of human pancreatic cancer better than GEMM (FIG. 7).

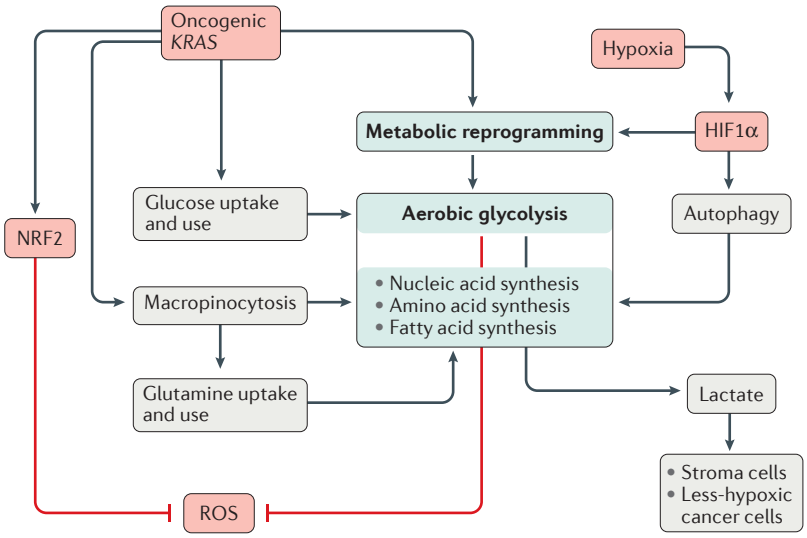

Figure 6 | **Metabolic reprogramming in pancreatic cancer.** Pancreatic cancer cells switch to aerobic glycolysis with increased lactate formation, which might in turn be an important nutrient for components of the microenvironment and less-hypoxic cancer cells[270]. Glucose uptake and use is increased, partially as a result of oncogenic *KRAS*-induced expression of glucose transporter 1, hexokinase 1 and hexokinase 2, as well as other mechanisms[82,100]. The use of glucose for aerobic glycolysis reduces the oxidation of pyruvate in the tricarboxylic acid cycle and subsequent oxidative phosphorylation, thereby limiting the production of reactive oxygen species (ROS). Furthermore, oncogenic *KRAS* induces nuclear factor erythroid 2-related factor 2 (NRF2), which activates numerous antioxidant pathways to maintain low levels of ROS. Glutamine uptake is also increased in pancreatic cancer as *KRAS*-driven cells depend on glutamine metabolism[103]. In pancreatic cancer, glutamine is necessary for synthesizing proteins and nucleic acid and for maintaining the redox state[82]. In addition, the hexosamine biosynthetic pathway in which glutamine and glucose are channelled is activated, thereby increasing *O*-GlcNAcylation (a conjugation of *N*-acetylglucosamine) of several proteins that are important for survival under hypoxic conditions[271]. Increased fatty acid synthesis from glutamine-derived α-ketoglutarate instead of glucose-derived pyruvate is supported by hypoxia-induced enzymes involved in fatty acid synthesis[272,273]. Pancreatic cancer cells frequently overexpress these enzymes[274]. To maintain their biomass needs, pancreatic cancer cells depend on autophagy[76] and rely on *KRAS*-dependent macropinocytosis (nonselective endocytosis)[80] to transport extracellular proteins into cancer cells for energy supplies. HIF1α, hypoxia-inducible transcription factor 1α.

Diagnosis, screening and prevention

Biomarkers

A neoplastic cell in the pancreas can take >10 years to generate distant metastases[132], providing a large window of opportunity for early detection[133]. Indeed, biomarkers are needed not only for detection but also for response evaluation in palliative and neoadjuvant settings, as well as for post-resection follow-up.

Several types of diagnostic biomarkers could be useful in pancreatic cancer. The most widely used biomarker is serum cancer antigen 19–9 (CA19-9), which is a sialylated lacto-*N*-fucopentaose II related to the Lewis-a antigen that is also adsorbed onto the surface of erythrocytes. Unfortunately, CA19-9 lacks sufficient sensitivity or specificity to be useful for early pancreatic cancer diagnosis, but is routinely used to monitor disease progression, recurrence and/or therapy response[134]. Similarly, the presence of circulating tumour cells derived from pancreatic cancer could be diagnostic, but are present in only some patients with metastatic disease. By contrast, circulating tumour DNA encoding mutant KRAS has been detected at the time of diagnosis in 43% of patients with localized disease[135], suggesting that circulating tumour DNA consisting of a panel of mutated genes such as mutated *KRAS* or mutated *TP53* could serve as a non-invasive early diagnostic test[136]. Similarly, systemic metabolic alterations might be a harbinger of pancreatic cancer, as has been demonstrated by the presence of increased circulating branched chain amino acids, which might be indicative of tissue protein breakdown, in early-stage disease in GEMM with pancreatic cancer and in some patients 2–5 years before a diagnosis of pancreatic cancer[137].

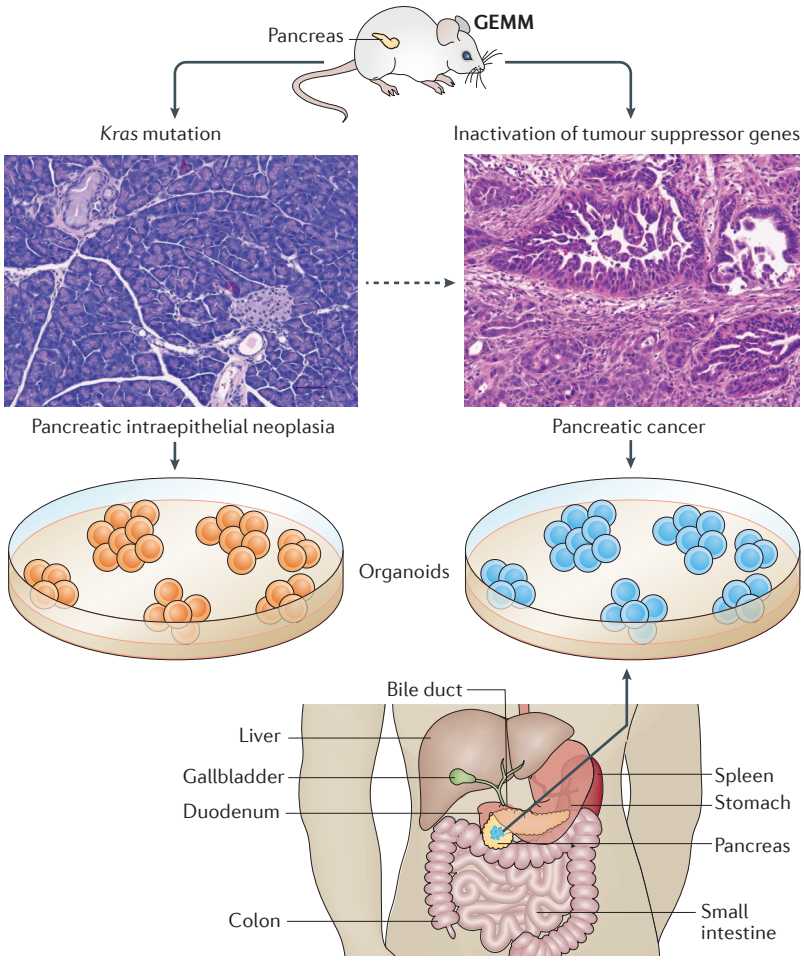

Figure 7 | **Models of pancreatic cancer.** Genetically engineered mutant mice (GEMM) models and organoid models prepared from GEMM as well as from patients with pancreatic cancer are available experimental systems for pancreatic cancer research laboratories. For example, to generate GEMM, activating *Kras* mutations can be introduced, and tumour suppressor genes (such as *Cdkn2a*, *Trp53* and *Smad4*) can be inactivated or deleted, leading to pancreatic intraepithelial neoplasia and eventually pancreatic cancer (as shown in the histological images). For further study, organoids can be prepared from these lesions or directly from patient-derived tissue specimens.

Several studies have identified potential novel biomarkers for early pancreatic cancer diagnosis. First, antibody microarrays using sequential plasma samples from GEMM with pancreatic cancer and from pre-diagnosis patients in the observational Women's Health Initiative generated a highly specific protein signature consisting of oestrogen receptor 1, HER2 and tenascin C[138]. Second, the presence of the heparan sulfate proteoglycan glypican 1 on the outer layer of circulating exosomes has been observed in both GEMM and patients with early-stage disease, suggesting that exosome analysis could be useful for early diagnosis[130]. Exosomes also carry an internal cargo of proteins, nucleic acids and microRNAs that could yield additional diagnostic benefit. For example, the presence of adrenomedullin in exosomes from patients with pancreatic cancer has been associated with type 3c diabetes mellitus, which may precede diagnosis by several months to 2 years[139]. Thus, assaying exosome-bound adrenomedullin could help to diagnose pancreatic cancer earlier. Plasma microRNA signatures[140] might also be diagnostic for pancreatic cancer, and such assays could be refined to facilitate early diagnosis. Last, circulating mesothelin has also been proposed as a protein biomarker; furthermore, mesothelin-specific T cells can potentially be used to devise immune interventions targeting this biomarker[141,142].

Diagnosis

The clinical manifestations of pancreatic cancer are non-specific and include jaundice, unexplained weight loss, epigastric pain that radiates to the back, nausea, new-onset diabetes mellitus and, rarely, migratory thrombophlebitis (inflammation of the vein wall)[143]. When a diagnosis of a pancreatic cancer is suspected, imaging must be conducted. Multidetector CT (MDCT) provides excellent resolution of the pancreas and surrounding vasculature and can be used to evaluate other organs for spread of the disease[143]. A pancreas-specific protocol with dual-phase or multi-phase dynamic contrast is usually used, including early arterial phase images (to evaluate the involvement of the coeliac trunk, the superior mesenteric artery and other arteries), pancreatic phase images (to evaluate pancreatic lesions) and portal venous phase images (to evaluate the involvement of the portal vein, the superior mesenteric vein and other veins)[144]. Most pancreatic cancers form solid hypodense lesions (FIG. 8). Cancers of the pancreas head typically obstruct both the pancreatic ducts and the bile ducts, producing upstream dilatation of both ducts (the so-called double duct sign) (FIG. 9), whereas carcinomas of the corpus and tail of the gland will only obstruct distal parts of the pancreatic duct. MDCT can define lesions in the pancreas, but is also the current gold standard to evaluate the resectability of any lesion. Involvement of the large vessels adjacent to the pancreas (such as the superior mesenteric artery and vein (FIG. 8)), might render the tumour borderline resectable, or locally advanced

and unresectable[143] (see Surgery, below). Involvement of distant organs, such as the liver, would indicate advanced-stage disease and that the patient is best treated with palliative therapy only (chemotherapy in most cases). MRI can provide excellent resolution of the pancreatic ducts (FIG. 9) and of any cysts that might be present. MRI might also be more sensitive than MDCT in detecting and evaluating liver metastases[145,146].

Given that pathology is required for establishing a diagnosis of pancreatic cancer (see Pathology, below), most patients will undergo endoscopic ultrasonography with fine-needle aspiration biopsy[147,148]. Endoscopic ultrasonography, although highly operator dependent, provides excellent resolution of the pancreas and peripancreatic vessels and lymph nodes, and can be used to obtain tissue for definitive diagnosis. PET can supplement these technologies, particularly when evaluating enlarged lymph nodes and larger masses of uncertain clinical significance, such as a persistent mass present after therapy[149].

CA19-9 levels, although not useful for screening asymptomatic individuals, can be useful in monitoring patients with an established pancreatic cancer[134]. CA19-9 levels in the thousands of IU per ml are suggestive of metastatic disease, whereas a significant decline in levels after treatment suggests a good response. However, 10–15% of the population lack the enzyme necessary to synthesize CA19-9; thus, measurement of CA19-9 levels will obviously not be useful in these individuals[134]. Other blood tests that are particularly useful in managing patients with pancreatic cancer include serum bilirubin and fasting blood glucose levels. Biliary obstruction can cause hyperbilirubinaemia, and paracrine effects by cancer and/or stellate cells — as well as destruction of pancreatic parenchyma, including the islets of Langerhans — can cause diabetes mellitus[150]. Fasting blood glucose and haemoglobin A1c levels can, therefore, be helpful in diagnosis.

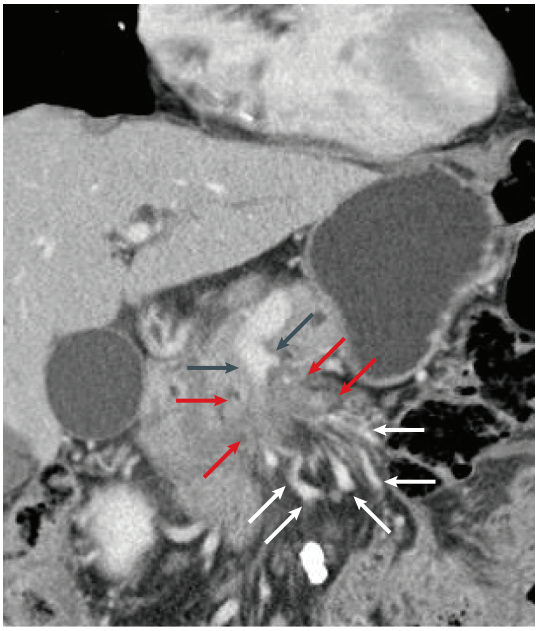

Figure 8 | **Diagnostic imaging of pancreatic cancer.** A multidetector CT scan of the abdomen demonstrating a hypodense pancreatic lesion (red arrows) obstructing and infiltrating the superior mesenteric vein (grey arrows). Note the visible dilated venous collaterals proximal of the obstruction (white arrows). Image courtesy of K. Holzapfel, Technical University of Munich, Germany.

Pathology

Several non-neoplastic and neoplastic conditions can mimic pancreatic cancer clinically. Pathology is, therefore, the gold standard in establishing a diagnosis. Depending on how the pancreas is sampled, the materials obtained can be evaluated cytologically as smears or histologically as tissue sections[151]. As is true for other organs, the diagnosis of cancer is usually established by evaluating nuclear features such as the shape, size and intensity of staining of nuclei. In addition to establishing the diagnosis of cancer, pathology can be used to define tumour grade (an important prognostic factor) and tumour type (FIG. 1). Furthermore, immunohistochemical labelling for markers such as SMAD4 can be used to supplement, but not establish, the diagnosis of malignant cancer[152]. Precursor lesions that give rise to invasive pancreatic cancer can also be identified; these include PanIN (graded from low-grade to high-grade dysplasia[153]), IPMNs and mucinous cystic neoplasms[151].

Most pancreatic cancers are infiltrating 'tubular' ductal adenocarcinomas. These tumours are characterized by gland-forming neoplastic cells infiltrating into an intensely desmoplastic stroma[151] (FIGS 1a,10). This desmoplastic stroma is important to recognize for two reasons. First, the stroma can be so florid that small biopsy samples can miss the neoplastic glands. Accordingly, extensive sampling is needed before a diagnosis of pancreatic cancer can be ruled out. Second, as described, the desmoplastic stroma is typically hypovascular and under profound hydrostatic pressure, potentially impeding the delivery of chemotherapeutic agents to neoplastic cells[118,119].

Several distinct types of neoplasm can arise in the pancreas, some of which have clinical significance[151]. Pancreatic neuroendocrine tumours are characterized, as the name suggests, by extensive neuroendocrine differentiation (FIG. 1b). These tumours tend to be slow growing and are often best treated surgically. By contrast, adenosquamous carcinomas and undifferentiated carcinomas are usually fast growing and are often widely metastatic. However, some adenosquamous carcinomas respond to platinum-based chemotherapy[154]. Colloid carcinomas (FIG. 1c) almost always arise in association with a distinct cystic precursor lesion, an IPMN[151]. The prognosis for a patient with a colloid carcinoma is better than it is for a patient with a typical ductal adenocarcinoma (FIG. 1a), but some of the improved outcome might be because these neoplasms tend to present at an early stage. Finally, medullary carcinomas are a distinct form of cancer characterized by poor differentiation, a syncytial growth pattern and pushing borders. Medullary carcinomas are important to recognize because, despite their poor differentiation, these cancers are associated

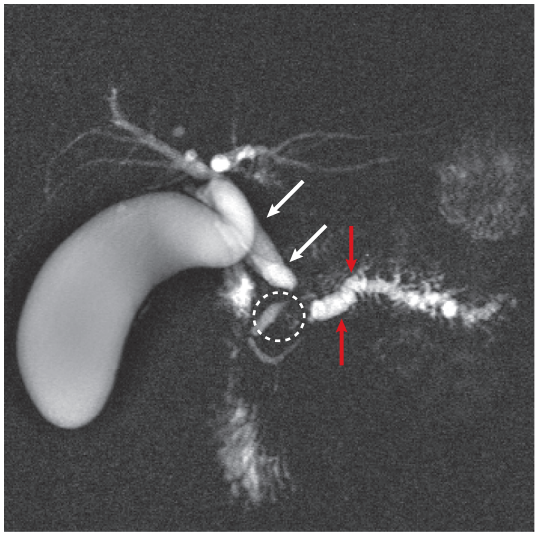

Figure 9 | **The double duct sign in pancreatic cancer.** Magnetic resonance cholangiopancreatography demonstrating a dilated bile duct (white arrows) and a pancreatic duct (red arrows) — the so-called double duct sign — caused by a suspected pancreatic head lesion (white dotted circle). Image courtesy of K. Holzapfel, Technical University of Munich, Germany.

with a good prognosis and often exhibit microsatellite instability; cancers with microsatellite instability seem to be exquisitely sensitive to some immunotherapies[155].

Screening

Earlier detection of pancreatic cancer should, in principle, lead to improved survival[133], although whether this goal can be achieved in the context of a screening programme is not yet well established. Detection and surgical resection of the histologically distinct, non-invasive, curative precursor lesions before the development of an invasive cancer gives a high probability of cure[156,157]. However, these lesions are common and, accordingly, there is a real risk of overtreatment. Improvements can also be made by identifying pancreatic cancer at an operable stage, as surgical resection is associated with an improved 5-year survival from <5% to 15–25%[158]. It has been estimated that increasing the proportion of people diagnosed with stage I or stage II disease (staging according the American Joint Committee on Cancer, 7th edition, or the Union for International Cancer Control, 7th edition) from 34% to 61%, with a concomitant reduction in the proportion of patients diagnosed with stage III or stage IV disease, would result in a doubling of 5-year survival[159].

Population-based screening is not feasible owing to the low lifetime risk of developing pancreatic cancer (~1.3% to age 70 years), but subgroups who have at least a fivefold increased risk of developing pancreatic cancer might benefit from screening. Efforts to stratify the general population on the basis of non-genetic risk factors and single-nucleotide polymorphisms have thus far failed to identify a group at sufficiently high risk to warrant screening[160]. However, the incorporation of high-risk genetic changes and prediagnostic symptoms into a risk prediction model could identify a small subgroup of the population among whom screening could be considered[161]. Diabetes mellitus (type 3c) can arise as an early symptom of pancreatic cancer and, as biomarkers and imaging improve, routine screening of adults with newly diagnosed diabetes mellitus may be appropriate, especially in those with other risk factors, such as genetic predisposition or smoking.

Current screening investigations are limited to people with family histories, those who have up to a 32-fold increased risk depending on the number of relatives affected[162] and to people with inherited mutations in genes known to increase risk (TABLE 1). The yield of potentially actionable lesions identified in high-risk cohorts varies considerably according to the inclusion criteria for the study, the screening methods used and the definition of an abnormal lesion; in the largest series to date ($n = 262$), with a mean follow-up of 4.2 years, the yield of pancreatic cancer, IPMN or high-grade PanIN was 7.3%[163].

Although the general consensus is that high-risk individuals should be enrolled in a screening trial, there is a paucity of evidence on the age at which screening should commence and which patients should be discharged from the screening programme, the screening interval and the optimal imaging modality. Current suggestions are that patients should begin screening at 50 years of age or at 10 years younger than the age at which the youngest family member was diagnosed. At a summit held by the International Cancer of the Pancreas Screening Consortium, ~75% of experts agreed that MRI or endoscopic ultrasonography should be used preferentially over CT owing to the higher yield, but there was no consensus on screening intervals[164].

Screening carries the risk of overdiagnosis. Furthermore, apart from unambiguous solid lesions, it is currently unclear how best to manage asymptomatic cystic lesions. For screened patients who are found to have an IPMN, following the current Sendai consensus guidelines[165] for the management of these lesions in the general population is probably appropriate. PanIN is difficult to detect and imaging cannot distinguish low-grade from

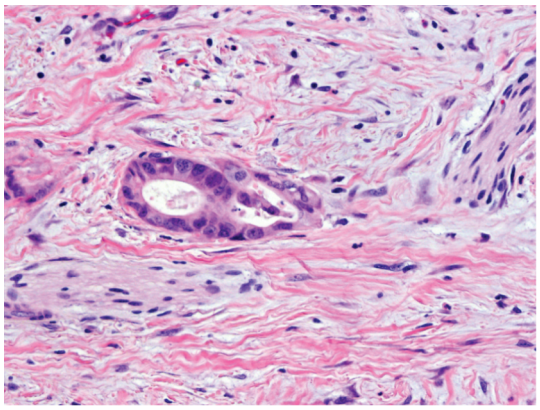

Figure 10 | **Infiltrating ductal adenocarcinoma of the pancreas.** Haematoxylin and eosin-stained image of pancreatic cancer. Note the extensive fibrosis associated with the neoplastic glands (centre).

Box 1 | **Stage-dependent treatment recommendations for pancreatic cancer**

Resectable disease

- Upfront surgery followed by adjuvant therapy (gemcitabine or 5-fluorouracil)*

Borderline resectable disease

- Neoadjuvant chemotherapy with FOLFIRINOX or gemcitabine plus albumin-bound paclitaxel with or without chemoradiation followed by surgery
- Upfront surgery followed by adjuvant therapy as above

Locally advanced disease

- Chemotherapy as for metastatic disease (see below).
- Chemoradiation is not indicated after gemcitabine monotherapy, but is often used after combination chemotherapy as above (followed by surgery in highly selected cases)

Metastatic disease (first line)

- FOLFIRINOX (for patients with an ECOG performance status of 0–1)*
- Gemcitabine plus albumin-bound paclitaxel (for patients with an ECOG performance status of 0–2)*
- Gemcitabine monotherapy or best supportive care (for patients with an ECOG performance status of >2)
- Radiotherapy can be used in selected circumstances for palliation of pain and the prevention of pathological fractures

Metastatic disease (second line)

- Following gemcitabine-based first-line therapy, 5-fluorouracil-based chemotherapy (5-fluorouracil and oxaliplatin or 5-fluorouracil and liposomal irinotecan)*
- Following 5-fluorouracil-based first-line therapy, gemcitabine monotherapy or gemcitabine plus albumin-bound paclitaxel
- Radiotherapy can be used in selected circumstances for palliation of pain and the prevention of pathological fractures

ECOG, Eastern Cooperative Oncology Group; FOLFIRINOX, folinic acid (leucovorin), 5-fluorouracil, irinotecan and oxaliplatin. *Supported by data from randomized controlled trials.

high-grade PanIN, making management of patients with these lesions challenging. Biomarkers based on mutation profiles might overcome this problem in the future.

Clinical trial evidence regarding the benefits of screening high-risk cohorts for pancreatic cancer will be challenging to obtain owing to the relatively low incidence of familial pancreatic cancer. However, a mathematical model found that, depending on assumptions regarding the age of screening and the characteristics of the screening test, screening could save lives in cohorts with a risk of developing pancreatic cancer of at least 2.5 times that of the general population[166].

Prevention

Given that general screening is currently not available on a clinical level, primary prevention is important. In this regard avoidance of smoking is the major practicable way for reducing the number of cases. In developed countries, tobacco control efforts are likely to result in future decreases in the incidence of pancreatic cancer, whereas in developing countries, incidence might rise owing to increasing consumption of tobacco products. Control of obesity is another possible preventive measure; thus, integrated efforts to address the international obesity epidemic may result in avoidance of a large number of pancreatic cancer cases. Importantly, however, known risk factors for pancreatic cancer are able to explain only one-quarter to one-third of cases[5].

Management

Systemic therapies

Optimizing therapy for patients with pancreatic cancer is a formidable challenge (BOXES 1,2). The majority of patients present with locally advanced and technically unresectable disease because of vascular involvement or with widespread metastatic disease, generally to the liver and peritoneum. Fewer than 20% of patients have resectable disease and, for those who undergo resection followed by adjuvant therapy, ~80% will relapse and ultimately die of their disease. Druggable mutations are unusual in pancreatic cancer but this may change as our knowledge improves. Approximately 7% of patients have mutations involving DNA repair genes (for example, *BRCA2* and *PALB2*), raising hope that PARP inhibitors could be useful in this subset of patients[37].

For these reasons, discovering effective drug therapies for affected patients is of paramount importance. Historically, very few effective drugs have been identified. As described, this disease is associated with profound desmoplastic stroma, which, in preclinical systems, has been shown to impede drug delivery[115]. In addition, almost all cases are driven by *KRAS* activation, a poor prognostic factor in cancer in general and one that is often associated with treatment resistance. Nonetheless, some progress has been made that is positively influencing the therapeutic landscape.

In 1997, gemcitabine, a nucleoside analogue, was approved by the US FDA for therapy of pancreatic cancer based on a randomized trial comparing gemcitabine with bolus 5-fluorouracil[167]. The primary end point was clinical benefit as measured by symptom control and the survival advantage was relatively modest. In 2005, erlotinib, a tyrosine kinase inhibitor of EGFR, in combination with gemcitabine was approved by the FDA, again based on a randomized trial that showed significant but minimal improvement over gemcitabine alone[168]. However, in 2011, a combination of folinic acid (leucovorin), 5-fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) demonstrated robust activity compared with gemcitabine monotherapy[169]. However, this regimen has significant toxicities of diarrhoea, nausea, fatigue, myelosuppression and neuropathy, which are only partially controlled with antidiarrhoeal and anti-emetic drugs. Thus, FOLFIRINOX is usually reserved for patients ≤76 years of age who have an excellent performance status (BOX 1). In 2012, the regimen of gemcitabine and albumin-bound paclitaxel was introduced, again showing improved efficacy[170] in a randomized trial compared with gemcitabine alone, leading to FDA approval of albumin-bound paclitaxel for pancreatic cancer treatment. Toxicities with this therapy are also considerable: alopecia, myelosuppression, nausea, fatigue and neuropathy. However, this regimen can be safely given to patients who are somewhat older or who have a slightly worse performance status (BOX 1).

The National Comprehensive Cancer Network guidelines list several other combinations that are supported by relatively lower levels of evidence. These regimens include pharmacokinetic optimization of gemcitabine by fixed-dose rate delivery[171], gemcitabine and cisplatin (for patients with germline DNA repair mutations)[172],

gemcitabine and capecitabine (based on a study showing significant improvement in progression-free survival)[173], and fixed-dose rate gemcitabine, taxotere and capecitabine (GTX, an active regimen that has never been compared with gemcitabine monotherapy)[174].

The choice of second-line therapy depends primarily on which regimen was used initially; a gemcitabine-based regimen is selected if FOLFIRINOX was initially used or a fluorinated pyrimidine-based regimen is selected if gemcitabine and albumin-bound paclitaxel were initially used. The FDA has approved liposomal irinotecan to be used in combination with 5-fluorouracil and leucovorin following first-line therapy with gemcitabine[175] (BOX 1).

Locally advanced, unresectable disease (local extension usually around large vessels but without metastatic disease) has traditionally been treated with chemoradiation. However, a pivotal trial of systemic therapy with gemcitabine monotherapy followed by chemoradiation or continued chemotherapy failed to show a survival benefit for the inclusion of radiation[176]. Whether this result is true following more-active regimens awaits testing.

Box 2 | **Treatment options for complications**

Pain*

- Follow the WHO's cancer pain ladder[252]
- Coeliac plexus neurolysis (commonly ultrasonography-guided, rarely transcutaneous or intraoperative)[253]
- Thoracoscopic splanchnicectomy in individual cases[254]

Biliary obstruction*

- Covered self-expandable metal stents[255,256]
- Percutaneous drainage (used in selected patients with low performance status or after failure of an endoscopic stent)
- Surgical bypass (used in selected patients with good performance status when a stent fails or is not feasible)

Gastric outlet obstruction*

- Self-expandable metal stents[257,258]
- Percutaneous endoscopic gastrostomy (rarely in patients with low performance status and after failure of an endoscopic stent)
- Surgical bypass (used in selected patients with good performance status when a stent fails or is not feasible)

Cachexia and anorexia*

- Increased caloric intake
- Symptom management (for example, of depression and gastric outlet obstruction)
- Pharmacological intervention (for example, corticosteroids, cannabinoids and other orexigenics)‡

Exocrine insufficiency

- Empirical treatment with pancreatic enzymes
- Proton pump inhibitors for increased efficacy

Depression

- Regular screening[259]
- Antidepressant medications in combination with psychotherapy

*Multidisciplinary approach. ‡Sparse evidence, reviewed in REF. 261. Adapted with permission from REF. 260, Cancer Network.

Surgery

Surgery remains the only potentially curative option for pancreatic cancer. A few decades ago, surgical resection of a pancreatic tumour was associated with unacceptably high morbidity and mortality rates[177], especially at medical centres with low patient volumes[178]. Furthermore, the benefit of surgery to patients in terms of overall survival was questioned[179,180]. These factors led to (surgical) therapeutic nihilism and an underutilization of pancreatic cancer surgery[181]. Today, with increasing experience, further centralization of patient care to high-volume centres[182,183] and better perioperative management, pancreatic cancer surgery can be performed safely in high patient volume centres with acceptable mortality rates of <5%[184]. Furthermore, macroscopic complete tumour resection and adjuvant therapies results in robust 5-year survival rates of 20% (15–25%)[185–187], with ≥40% overall survival in selected subgroups[184,188].

For cancers of the pancreatic head, a partial pancreaticoduodenectomy (the so-called Whipple procedure) is usually required with or without partial resection of the distal stomach[189]. For tumours of the pancreatic tail, distal pancreatectomy with splenectomy is carried out. A total pancreatectomy with resulting exocrine and endocrine insufficiency (brittle diabetes mellitus) is rarely required except for tumours involving the entire length of the organ, centrally located tumours or for other technical reasons[190]. Pancreatic cancer surgery has traditionally been carried out as an open procedure, but laparoscopic and even robotically assisted resections are increasingly being performed. Although high-quality evidence is lacking, laparoscopic distal pancreatectomy is increasingly considered a safe and effective option[191]. By contrast, laparoscopic pancreaticoduodenectomy is a demanding and complex procedure that is not considered standard at present[192], with increased mortality being a potential issue in low patient volume hospitals[193]. Robotic or computer-assisted resections are feasible and safe in few specialized centres[194,195]. The steep learning curve, training aspects and high costs of robotic surgery remain barriers to its widespread adoption.

At diagnosis, ~10–20% of patients present with resectable tumours, 30–40% present with borderline resectable pancreatic cancer (BRPC) or locally advanced/unresectable pancreatic cancer (LAPC), and 50–60% present with metastatic or systemic disease. Clear definitions of BRPC and LAPC had been lacking in the past, which hampered the comparison of clinical trials and reliable outcome analysis. In 2014, the International Study Group for Pancreatic Surgery[196] improved the definitions of BRPC and LAPC, and these definitions were subsequently adopted by the National Comprehensive Cancer Network[197]. Classification of resectability depends on the involvement of major arteries (the coeliac trunk, the hepatic artery and the superior mesenteric artery) and veins (the portal vein and the superior mesenteric vein) (FIG. 11).

With the aim of achieving complete tumour resection, technical aspects have been thoroughly addressed. Thus, pancreatic cancer resection, including venous resection, can be performed safely — although with

slightly increased morbidity and mortality — with survival comparable to resection without venous involvement[198–200]. By contrast, arterial resections are associated with increased morbidity and mortality and a disputable survival benefit[201], although in selected patients, special procedures such as the Appleby procedure might be indicated[202–204]. Multivisceral resections (that is, removing additional tumour-infiltrated organs) also increase morbidity, but might be necessary to achieve complete tumour resection and can provide survival rates comparable to standard resections[205]. The International Study Group of Pancreatic Surgery advises a defined standard lymphadenectomy for accurate staging and to achieve clearance of tumour-affected lymph nodes[206]. By contrast, more-extended lymphadenectomies increase morbidity and do not increase survival and are, therefore, not advised[207,208] (FIG. 12).

Concomitant resection of the primary tumour and distant metastases is currently not indicated; small series did not show a consistent survival benefit[209,210], although a subgroup of patients with lung metastases did have increased survival[211]. Tumour debulking (R2 resection) is also currently not indicated because it substantially increases morbidity and mortality without providing a survival benefit[212]. Microscopic clearance (R0 resections) has been a matter of debate owing to different definitions and protocols[213–215]. R0 resections are rare owing to the close proximity of tumours to major intra-abdominal vessels, and high rates of R1 resections (that is, tumour cells in or at close proximity to the resection margin) reflect tumour growth patterns rather than surgical expertise[213–216].

Perioperative and adjuvant therapies

Given that surgery alone is not sufficient to achieve long-term survival[217], adjuvant therapy is standard following tumour resection[185,187] (BOX 1). Postoperative therapy with either gemcitabine[187] or 5-fluorouracil and leucovorin[185] has demonstrated significant improvement in overall and 5-year survival compared with observation. Many adjuvant studies have included radiotherapy, usually chemoradiotherapy, in addition to a course of systemic chemotherapy[218], but the true benefit of the addition of radiotherapy is unknown. More-active regimens, such as FOLFIRINOX and gemcitabine plus albumin-bound paclitaxel, are now being studied in the adjuvant setting.

The success of neoadjuvant (preoperative) therapy in diseases such as breast and rectal cancer and the availability of more-active regimens have stimulated interest in the application of neoadjuvant treatment for pancreatic cancer. Data from high-quality trials are lacking; however, the current evidence suggests that no benefit is imparted by neoadjuvant therapy in patients with resectable tumours (compared with resection and adjuvant therapy), although the systemic therapy used in these reports was of low effectiveness[219]. Ongoing trials analysing neoadjuvant therapy in the setting of resectable tumours will help to answer this controversy[220,221]. By contrast, evidence suggests that approximately one-third of initially BRPCs and selected LAPCs become resectable after neoadjuvant therapy — with similar outcomes to initially resectable tumours[219,222]. Traditionally, most protocols have used

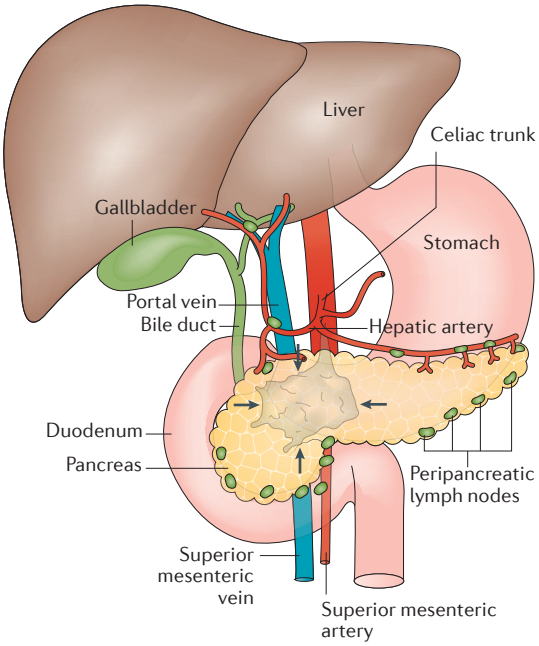

Figure 11 | **Resectability of pancreatic cancer.** The anatomical location of a pancreatic cancer (black arrows) in the organ in relation to vascular structures dictates how surgically resectable the tumour is. Here, the tumour sits in the pancreatic head and body and is in close proximity to the superior mesenteric vein and portal vein and extends towards the coeliac trunk. Image courtesy of M. Maak, University of Erlangen, Germany.

chemoradiotherapy; however, the availability of more-effective systemic therapies (such as FOLFIRINOX or gemcitabine plus albumin-bound paclitaxel[169,170]) has led to an increased interest in this approach. The first data using FOLFIRINOX in the neoadjuvant setting suggested a considerable rate of conversion of BRPCs and LAPCs to resectable tumours[222,223] but highlighted the difficulties in response evaluation; that is, imaging does not reliably predict tumour response in this setting. Prospective randomized studies are needed for this approach as well as for the other current options: gemcitabine-based chemotherapy, chemoradiotherapy or induction chemotherapy followed by treatment with chemoradiotherapy[224,225] (BOX 1). Importantly, these patients should be discussed by specialized multidisciplinary teams[226] to provide the optimal treatment strategy with input from all involved disciplines.

Quality of life

Assessment of quality of life (QOL) in patients with pancreatic cancer is important because the disease is often incurable and survival is short. The cancer commonly causes severe pain that requires opioid treatment and can obstruct the bile duct, causing jaundice, or the duodenum, causing anorexia, nausea and vomiting (BOX 2). In addition to these physical symptoms, patients with advanced-stage incurable cancer face psychological and social distress, and spiritual challenges, which are summarized as end-of-life issues. Most of these patients experience unmet needs in several areas, most of which are related to psychological

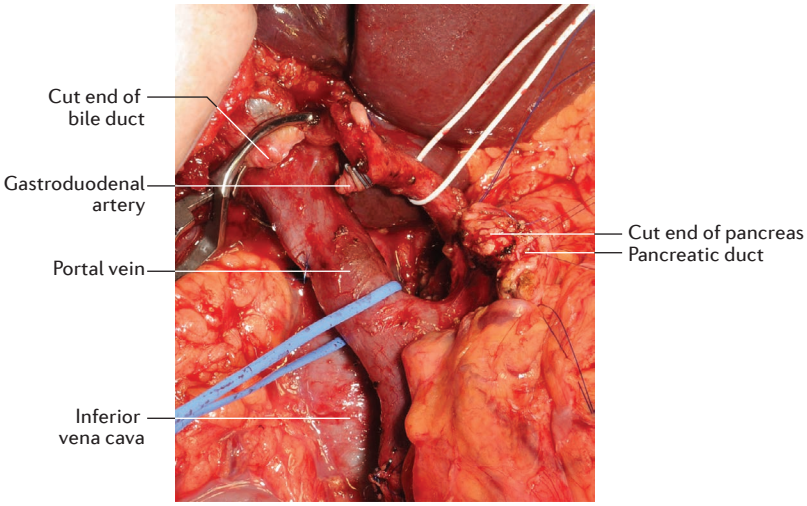

Figure 12 | **Surgical resection of pancreatic cancer.** Photograph of the intraoperative situs (surgical site) following resection of a tumour in the pancreatic head with standard lymphadenectomy as defined by the International Study Group of Pancreatic Surgery[206]. The portal vein (looped with a blue vessel loop) and the common hepatic artery (white vessel loop) are indicated. The gastroduodenal artery is clip ligated.

or emotional distress, and to medical communication or information regarding specific treatments, the potential benefits and the risks[227].

Given that diagnosis is often late, the median survival of patients is only 6–9 months for those with locally advanced disease and 3 months for those with metastatic disease. In the absence of curative treatment, the main aims of treatment are to relieve symptoms and to slow tumour progression. Even in the 10–20% who can undergo curative treatment, the effects of major pancreatic resection, chemotherapy or radiotherapy impose a considerable burden on QOL.

Two systems are available in multiple languages to assess QOL in patients with cancer: the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (REF. 228) and the Functional Assessment of Cancer Therapy (FACT)[229]. These questionnaires assess general cancer symptoms and functional impairments and have specific organ supplements. QOL issues identified by professionals and by patients as important are included in the EORTC QLQ-PAN26 (for pancreatic cancer)[230] and the FACT(Hep) (hepatobiliary and pancreatic malignancies)[231]. TABLE 2 shows the issues covered by the EORTC system. Patients with pancreatic cancer may have impairment in any of these areas at some stage in their illness. For example, pain is a major issue for many patients; good pain control improves QOL. Furthermore, digestive disturbances arise from cancer effects on the gut and from toxicities of treatment; common problems include loose stools, diarrhoea and weight loss (from nutritional malabsorption) and constipation (from taking opioids and reduced appetite).

Surgery is a major physical and psychological challenge, with obvious immediate effects on QOL. One month after surgery, QOL domains such as pain, fatigue, appetite and bowel habit are typically worse than preoperatively. However, most domains recover to preoperative values or better at 3–6 months[232,233]. Common problems after pancreatectomy include weight loss, abdominal pain, fatigue, foul stools and diabetes mellitus, but long-term QOL is good in most domains[234].

The adverse effects of chemotherapy, including gastrointestinal toxicity, taste changes and fatigue, can impair QOL, but effective therapy enhances QOL. In one randomized comparison of gemcitabine against cisplatin, epirubicin, 5-fluorouracil and gemcitabine, emotional function, fatigue, overall QOL, pain and flatulence all improved in both treatment groups[235]. However, the domains of physical function, fatigue, appetite and satisfaction with health care improved more in patients who achieved a partial response to therapy (40–46%) than in those who had stable disease (0–12%).

The SCALOP trial[236] of palliative chemoradiotherapy confirmed the improvement in most QOL domains during induction chemotherapy. During chemoradiotherapy, fatigue, appetite loss and gastrointestinal symptoms were reported. However, QOL deficits recovered within 3 weeks of completing chemoradiotherapy.

Finally, QOL issues and the end-of-life situation of patients are often not adequately considered in the design and reporting of clinical trials. For example, QOL issues or patient-reported outcomes were considered in only 4 of 25 analysed clinical trials in pancreatic cancer[237]. Indeed, most treatments adversely affect QOL, but effective treatments can lead to substantial improvement of QOL, which often justifies their use, even in the palliative setting.

Table 2 | **Scales and items in EORTC QLQ questionnaires**

Domain	QLQ-C30	QLQ-PAN26
General	• Global health and QOL status (2)	• None
Functional scales*	• Physical functioning (5) • Role functioning (2) • Emotional functioning (4) • Cognitive functioning (2) • Social functioning (2)	• Body image (2) • Satisfaction with health care (2) • Sexuality (2)
Symptom scales*	• Fatigue (3) • Nausea and vomiting (2) • Pain (2)	• Pancreatic pain (4) • Digestive symptoms (2) • Altered bowel habits (2) • Hepatic‡ (2)
Single items§	• Insomnia (1) • Appetite loss (1) • Constipation (1) • Diarrhoea (1) • Financial difficulties (1)	• Emotional (2) • Side effects (3) • Cachexia (2) • Other gastrointestinal symptoms (3)

The number of items is noted in parentheses. EORTC, European Organization for Research and Treatment of Cancer; QOL, quality of life. *Scales contain a number of related items, which are reported as one value per scale. ‡Relating to itching and jaundice. §Both questionnaires contain some single items, which are reported separately; the four groups of single items shown for the QLQ-PAN26 are not reported as scales.

Outlook

Pancreatic cancer remains a deadly disease; however, the next decade holds promise to substantially change the current dismal outlook for most patients. Key areas for basic and clinical research are advances in our understanding of the molecular pathophysiology, precision medicine[238] (that is, subgrouping patients for tailored therapies) and standardization in clinical care and research.

Box 3 | **Immunotherapy in pancreatic cancer**

The tumour microenvironment in pancreatic cancer is remarkable for its profound desmoplasia, absence of effector T cells and its T helper 2 cell immunophenotype, which contribute to its ability to avoid immune surveillance. For these reasons, antibodies against the immune checkpoint programmed cell death protein 1 (PD-1) and its ligand PD-L1 show limited efficacy in treating pancreatic cancer. Immunotherapies including PD-1 inhibition might be effective in the small fraction (3%) of patients with hypermutated tumours and microsatellite instability[262] as has been described in colorectal cancer[263]. Strategies to modulate the tumour microenvironment to a T helper 1 cell immunophenotype include inhibition of the tyrosine-protein kinase BTK. Vaccination to induce or reinforce pre-existing immune responses[262] is being investigated with agents such as GVAX (autologous pancreatic cell lines transfected with granulocyte–macrophage colony-stimulating factor) or CRS-207 (live attenuated *Listeria monocytogenes*-expressing mesothelin) alone or with a checkpoint inhibitor or a CD40-specific antibody to — besides other effects — activate antigen-presenting cells. Other immune-based targets under study include CD47 and C-X-C chemokine receptors. Directed cytolysis using T cells expressing chimeric antigen receptors is being investigated alongside oncolytic virus therapy for the induction of inflammation, immunomodulation and cancer cell lysis[264]. Given the great promise of immune-based therapies in other malignancies, there is reason to hope that modulating the tumour microenvironment could also augment tumour control in pancreatic cancer.

Precision medicine

An in-depth understanding of the molecular pathology of pancreatic cancer through large-scale 'omics' and other approaches will be necessary for improved patient selection (that is, patient stratification to specific therapies). As we understand more about the molecular pathology of pancreatic cancer, it is becoming clear why trials of targeted therapies have mostly been unsuccessful or were associated with only incremental benefits. First, signalling in pancreatic cancer is complex, consisting of multiple nodes and aberrant pathways. Thus, targeting single alterations is often ineffective owing to redundant signalling and complex crosstalk. Second, apart from four common mutations (in *KRAS*, *CDKN2A*, *TP53* and *SMAD4*), which are not currently druggable, essentially all of the currently druggable mutations in pancreatic cancer have low prevalence (FIG. 4b). Consequently, any trial that did not select appropriate patients based on molecular subtypes would not have detected an effect. Even if one patient was captured and had an exceptional response[239], the result would be considered anecdotal and not informative.

To overcome these problems, druggable key signalling hubs first have to be identified. Second, low prevalence alterations have to be targeted, possibly in the context of grouping cancers with common alterations rather than by the cell or organ of origin. Third, for effective treatments, new multipronged approaches must be developed that not only target cancer cells but also reprogramme the cancer stroma by modulating the interactions of pancreatic stellate cells, endothelial cells, immune cells and cancer cells. Fourth, for more-effective therapy, pancreatic cancer has to be detected at earlier stages using novel biomarkers and multimodal imaging.

Large-scale 'omics' approaches will aid in achieving these goals, as will the decreasing costs of whole-genome sequencing[240]. Clinical trials are mandatory to analyse different treatment options; however, these trials require considerable effort from all involved stakeholders[241] and, with the development of personalized medicine, clinical trials increasingly need to be carried out in multicentre and/or multinational settings to provide sufficiently large patient populations to detect effects.

Emerging treatments

Despite these challenges, innovative strategies currently in clinical trials include PEGPH20 (a pegylated hyaluronidase for stromal modulation)[242], ruxolitinib and momelotinib (inhibitors of Janus kinase (JAK) and STAT)[243], ibrutinib (an inhibitor of the tyrosine-protein kinase BTK)[244], MM-141 (an IGF1R inhibitor) and palbociclib (a cyclin-dependent kinase 4 (CDK4) and CDK6 inhibitor), among others. One of the emerging interests in pancreatic cancer therapy is immunotherapy (BOX 3) because these tumours generally escape immune surveillance through various mechanisms, including the secretion of immunosuppressive factors such as TGFβ, their immunosuppressive microenvironment that is depleted of effector T cells, and — less commonly — their low immunogenicity due to the expression of the immune checkpoints PD-L1 and PD-L2 (REF. 245). Indeed, immune checkpoint blockade to activate T cell function[121,246] is being investigated in pancreatic cancer.

Standardization in clinical care and research

Progress in the clinical management of patients with pancreatic cancer had been hampered by the lack of generally accepted definitions of clinical and outcome parameters. Unified definitions and their routine use will be a challenge in the coming years. For example, definitions of resectability[196] and of postoperative complications in general[247] as well as for specific complications[248–250] have been proposed and are now widely accepted, as are definitions of adverse events following chemotherapy, radiotherapy and targeted therapy[251], and of QOL. These definitions have made comparisons of trial and cohort data easier and have greatly enhanced the clinical usefulness of the data. Indeed, in our opinion, it should be mandatory in the future to only publish data if accepted definitions of clinical and outcome parameters are used. Some heterogeneous definitions remain in other areas, such as definitions of R1 resection[215], and minimal data sets required for clinical reporting have not been established, blocking progress in these areas. Internationally accepted standards are a prerequisite, as are reduced institutional obstacles to carrying out multicentre and multinational trials.

Furthermore, the difficulties in the clinical management of pancreatic cancer are best highlighted by pancreatic cancer surgery. Although we have fortunately progressed past mortality rates as high as 20–40%[177], the current rate of <5% (a current quality mark) is still substantial — continued efforts to improve the safety of surgery are needed. The key points (especially with the emergence of new techniques) are patient selection, centralization (dedicated centres) and training. Centralization is an issue in many countries[182,183], with steady but slow progress in this area. It remains important to treat patients with pancreatic cancer in dedicated centres with transparent quality and outcome reporting.

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