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\textsuperscript{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\textsuperscript{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\textsuperscript{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%\textsuperscript{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.
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%. For example, differential access to health care, including advanced radiological tools, can influence the accuracy of reported pancreatic cancer rates. In 2015, an estimated 367,000 new cases of pancreatic cancer were diagnosed worldwide, >50% of which occurred in high-income countries. 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 whites (12–15 cases per 100,000 men and 8–10 cases per 100,000 women). Mortality rates closely parallel incidence rates, which are probably influenced by under-diagnoses are most affected, with an >30% excess, 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, 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. Use of smokeless tobacco products can also increase the risk.

Obesity and low physical activity are also linked to pancreatic cancer. 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. However, other dietary factors remain undefined and unquantified. Reports of an association between coffee consumption and pancreatic cancer risk 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. 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. 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 (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.

10% of patients have a family history of pancreatic cancer. 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, 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)\textsuperscript{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 (HGF; also known as MET) — activate multiple pathways that enhance pancreatic cancer cell mitogenic self-sufficiency and promote migration and invasion\textsuperscript{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\textsuperscript{30}. Genes that are normally active during development, such as WNT, SHH and NOTCH, are also reactivated in some pancreatic cancers\textsuperscript{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 HGF α and EGFR, increased expression of neurofibromin 1, CD44 expression and β1 integrin, and is aggravated by the ability of HGF α to form heterodimers with EGFR\textsuperscript{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\textsuperscript{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\textsuperscript{34} (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, ML3 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%\textsuperscript{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\textsuperscript{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\textsuperscript{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.
Whole-genome sequencing has revealed patterns in mutational mechanisms occurring during tumour development, including the effects of toxins such as tobacco exposure\(^4\). 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\(^4\), suggesting that tobacco causes different patterns of mutation when cells are not directly exposed to smoke.

Analyses of epigenetic\(^4\), transcriptomic\(^4\) and metabolomic\(^6\) 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

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**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.
classifications depending on the input material and the assumptions made. Microdissected epithelium from tumours classifies them into three subgroups⁴⁴, which becomes four when bulk tissue containing the tumour microenvironment is assessed and includes an additional ‘immunogenic’ subgroup based on stromal immune cell populations⁹⁶. Others find two epithelial groups when transcripts from presumed normal pancreas are excluded from the analysis⁶⁰. 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 prognoses⁹⁶. Two stroma subtypes (normal and activated) of tumours, based on mRNA expression profiles⁶⁰, might explain the disparate findings concerning the role of the stroma⁹⁷ (see Microenvironment, below) and might provide insight into potential immuno-regulatory therapeutic strategies and into predicting outcomes⁹⁶,⁹⁷. 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 development⁹⁶.

**Microenvironment**

Pancreatic cancers characteristically have an abundant and dense collagenous stroma (desmoplasia)⁶⁰, resulting in a considerable hypoxic environment for cancer cells (see Pathology, below). This stroma is composed of extra-cellular 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, peristin 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 cells⁸¹. Overall, the immune cell infiltration suggests an immunosuppressive phenotype, even at the earliest stages of pancreatic cancer (PanINs and IPMNs)⁸².⁸³. 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 cancer⁸⁴ (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 outcome⁶⁵, but this finding was not corroborated by two subsequent, smaller studies⁶⁶,⁶⁷. 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 survival⁶⁹.

Notably, an active bidirectional interaction between stromal stellate cells and cancer cells has been demonstrated by both in vitro and in vivo approaches⁵⁹, 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 disease⁶⁰. 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 cells⁶¹.

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

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

† Familial adenomatous polyposis (caused by mutations in the APC gene) is associated with ampullary and duodenal cancer but not with pancreatic cancer⁴⁸. *Calculated against non-mutation controls. †The p16 gene product is affected, not the p14ARF gene product. In which ≥2 first-degree relatives are affected.
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 (ERBB2; 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\(^\text{265}\). 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\(^\text{266}\). Moreover, increased levels of β1 integrin in pancreatic cancer can enhance EGFR signalling\(^\text{267}\). Both HGF 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\(^\text{268,269}\). 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\(^\text{270,271}\). 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.
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\(^{69,71}\) 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
on MITF/TFE transcription factors to activate the autophagy–lysosome system to maintain intracellular amino acid levels. Genetic or pharmacological inhibition of autophagy substantially delays tumour development in genetically engineered mutant mice (GEMM) and in xenograft models of pancreatic cancer, and KRAS-driven pancreatic cancers respond to autophagy inhibition probably independently of TP53 status. Macropinocytosis (a distinct pathway of endocytosis) is an important way in which extracellular proteins are transported into KRAS-transformed pancreatic cancer cells. 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, thereby reducing the dependence on free extracellular glutamine. Blockade of macropinocytosis reduces pancreatic cancer cell growth in a KRAS-transformed xenograft model.

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, and include GEMM and organoid cultures.

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 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, and this strategy is the standard method to query the function of a potentially pathogenic allele. Furthermore, novel pancreatic cancer genes and pathways can also be discovered using transposon insertional mutagenesis strategies in sensitized mice.

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 and NRF2, 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 and loss of TP53, or both. For example, silencing of oncogenic KRAS identified new metabolic alterations in pancreatic cancer that offer therapeutic opportunities.

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, 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 dissemination73 and have identified a potent stimulatory role for pancreatic inflammation48 and myeloid cells109,110 in pancreatic cancer pathogenesis. GEMM have also demonstrated that pancreatic cancer differentiation is influenced by the juxtaposition of activated pancreatic stellate cells62,71. Finally, pathophysiological sequelae of pancreatic cancer, such as cachexia111 and pain112, and the role of obesity113 and the intestinal microbial flora114 can also be evaluated in GEMM.

Therapeutic studies using GEMM led to the realization that human pancreatic cancer contains a markedly deficient vasculature115, 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 limiting116,117, several analogous approaches using pegylated hyaluronidase118,119 and synthetic vitamin D analogues120 are under active investigation. Several factors that suppress the immune response in pancreatic cancer have also been identified, stimulating multiple clinical efforts121–124.

Finally, therapies that target the RAS pathway effectors125 and parallel pathways (such as Notch126) 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 panels129 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 chimera analysis131, and the direct intrapancreric delivery of recombinant viruses harbouring gene-editing constructs to rapidly generate pancreatic cancer models132. 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 described148. 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 studies116,117. In this regard, organoids might recapitulate the heterogeneity of human pancreatic cancer better than GEMM (FIG. 7).

**Diagnosis, screening and prevention Biomarkers**

A neoplastic cell in the pancreas can take >10 years to generate distant metastases135, providing a large window of opportunity for early detection136. 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.

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**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 cells120. Glucose uptake and use is increased, partially as a result of oncogenic KRAS-driven expression of glucose transporter 1, hexokinase 1 and hexokinase 2, nuclear factor erythroid 2-related factor 2 (NRF2), and inducible transcription factor 1a (HIF1α). 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 mechanisms82,110. 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 metabolism114. In pancreatic cancer, glutamine is necessary for synthesizing proteins and nucleic acid and for maintaining the redox state24. 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 conditions115. Increased fatty acid synthesis from glutamine-derived ketoglutarate instead of glucose-derived pyruvate is supported by hypoxia-induced enzymes involved in fatty acid synthesis117,171. Pancreatic cancer cells frequently overexpress these enzymes137. To maintain their biomass needs, pancreatic cancer cells depend on autophagy24 and rely on KRAS-dependent macropinocytosis (nonselective endocytosis)90 to transport extracellular proteins into cancer cells for energy supplies. HIF1α, hypoxia-inducible transcription factor 1a.
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. 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, 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. 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.

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. 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. 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. Thus, assaying exosome-bound adrenomedullin could help to diagnose pancreatic cancer earlier. Plasma microRNA signatures 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.

**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). 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. 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). Most pancreatic cancers form solid hypodense lesions. 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), 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), might render the tumour borderline resectable, or locally advanced.

**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.
and unresectable\textsuperscript{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\textsuperscript{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\textsuperscript{147,148}. Endoscopic ultrasonography, although highly operator dependent, provides excellent resolution of the pancreas and peri-pancreatic 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\textsuperscript{149}.

CA19-9 levels, although not useful for screening asymptomatic individuals, can be useful in monitoring patients with an established pancreatic cancer\textsuperscript{150}. 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\textsuperscript{151}. 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 hyperbilirubinemia, 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\textsuperscript{152}. Fasting blood glucose and haemoglobin A1c levels can, therefore, be helpful in diagnosis.

**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\textsuperscript{153}. 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\textsuperscript{154}. Precursor lesions that give rise to invasive pancreatic cancer can also be identified; these include PanIN (graded from low-grade to high-grade dysplasia\textsuperscript{155}), IPMNs and mucinous cystic neoplasms\textsuperscript{156}.

Most pancreatic cancers are infiltrating ‘tubular’ ductal adenocarcinomas. These tumours are characterized by gland-forming neoplastic cells infiltrating into an intensely desmoplastic stroma\textsuperscript{157} (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\textsuperscript{158,159}.

Several distinct types of neoplasm can arise in the pancreas, some of which have clinical significance\textsuperscript{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\textsuperscript{154}. Colloid carcinomas (FIG. 1c) almost always arise in association with a distinct cystic precursor lesion, an IPMN\textsuperscript{157}. 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...
high-risk genetic changes and prediagnostic symptoms warrant screening far failed to identify a group at sufficiently high risk to factors and single-nucleotide polymorphisms have thus in the general population on the basis of non-genetic risk cancer might benefit from screening. Efforts to stratify least a fivefold increased risk of developing pancreatic (~1.3% to age 70 years), but subgroups who have at the low lifetime risk of developing pancreatic 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\(^ {160}\) 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 range.
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.

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.

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. 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. 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. However, in 2011, a combination of folic acid (leucovorin), 5-fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) demonstrated robust activity compared with gemcitabine monotherapy. However, this regimen has significant toxicities of diarrhoea, nausea, fatigue, myelosuppression and neuropathy, which are only partially controlled with anti-diarrhoeal 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 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.

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, gemcitabine and cisplatin (for patients with germline DNA repair mutations), and neoadjuvant chemotherapy with FOLFIRINOX or gemcitabine plus albumin-bound paclitaxel with or without chemoradiation followed by surgery.

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.

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.

Prevention
gemcitabine and capecitabine (based on a study showing significant improvement in progression-free survival)\textsuperscript{173}, and fixed-dose rate gemcitabine, taxotere and capecitabine (GTX, an active regimen that has never been compared with gemcitabine monotherapy)\textsuperscript{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 and albumin-bound paclitaxel. However, a pivotal trial of systemic therapy with gemcitabine monotherapy followed by chemoradiation or radiation. 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\textsuperscript{72}
- Coeliac plexus neurolysis (commonly ultrasonography-guided, rarely transcutaneous or intraoperative)\textsuperscript{511}
- Thoracoscopic splanchnicectomy in individual cases\textsuperscript{514}

**Biliary obstruction**
- Covered self-expandable metal stents\textsuperscript{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\textsuperscript{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)\textsuperscript{9}

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

**Depression**
- Regular screening\textsuperscript{259}
- Antidepressant medications in combination with psychotherapy

*Multidisciplinary approach. \textsuperscript{5}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\textsuperscript{377}, especially at medical centres with low patient volumes\textsuperscript{178}. Furthermore, the benefit of surgery to patients in terms of overall survival was questioned\textsuperscript{179,180}. These factors led to (surgical) therapeutic nihilism and an underutilization of pancreatic cancer surgery\textsuperscript{181}. Today, with increasing experience, further centralization of patient care to high-volume centres\textsuperscript{182,183} and better perioperative management, pancreatic cancer surgery can be performed safely in high patient volume centres with acceptable mortality rates of <5\textdegree\textsuperscript{144}. Furthermore, macroscopic complete tumour resection and adjuvant therapies results in robust 5-year survival rates of 20\% (15–25\%)\textsuperscript{185–187}, with ≥40\% overall survival in selected subgroups\textsuperscript{184,188}.

For cancers of the pancreatic head, a partial pancreatocoduodenectomy (the so-called Whipple procedure) is usually required with or without partial resection of the distal stomach\textsuperscript{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\textsuperscript{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\textsuperscript{191}. By contrast, laparoscopic pancreatocoduodenectomy is a demanding and complex procedure that is not considered standard at present\textsuperscript{192}, with increased mortality being a potential issue in low patient volume hospitals\textsuperscript{193}. Robotic or computer-assisted resections are feasible and safe in few specialized centres\textsuperscript{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\textsuperscript{196} improved the definitions of BRPC and LAPC, and these definitions were subsequently adopted by the National Comprehensive Cancer Network\textsuperscript{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
Perioperative and adjuvant therapies

Given that surgery alone is not sufficient to achieve long-term survival, adjuvant therapy is standard following tumour resection \[185,187\] (BOX 1). Postoperative therapy with either gemcitabine \[188\] or 5-fluorouracil and leucovorin \[189\] 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 \[191\], but the true benefit of the addition of radiotherapy is unknown. More-active regimens, such as FOLFIRINOX and gemcitabine plus albumin-bound paclitaxel \[192\] 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 \[193,194\] 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 \[194,195\] (BOX 1). Importantly, these patients should be discussed by specialized multidisciplinary teams \[196\] 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...
or emotional distress, and to medical communication or information regarding specific treatments, the potential benefits and the risks.

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 months232,233. Common problems after pancreatectomy include weight loss, abdominal pain, fatigue, foul stools and diabetes mellitus, but long-term QOL is good in most domains234.

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 groups235. 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 trial236 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 cancer237. 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.

**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 medicine238 (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 as has been described in colorectal cancer. 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 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. 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, 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. Clinical trials are mandatory to analyse different treatment options; however, these trials require considerable effort from all involved stakeholders 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), ruxolitinib and momelotinib (inhibitors of Janus kinase (JAK) and STAT), ibritinib (an inhibitor of the tyrosine-protein kinase BTK), 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 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 — less commonly — their low immunogenicity due to the expression of the immune checkpoints PD-L1 and PD-L2. Indeed, immune checkpoint blockade to activate T cell function 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 and of postoperative complications in general as well as for specific complications have been proposed and are now widely accepted, as are definitions of adverse events following chemotherapy, radiotherapy and targeted therapy, 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, 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%, 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, 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.
Tobacco-attributable cancer burden | 2016
Ann. Oncol.
Pancreatic Cancer Case–Control Consortium (PanC4).
association with diagnosis of cancer.
Pancreatic Cancer: a systematic review and meta-
analyses.
Smoking and cancer.
Pancreatic Cancer: a pooled analysis in the
International Pancreatic Cancer Case–Control
Consortium (PanC4).

This comprehensive study defines four subtypes depending on patterns of structural variation:
stable, locally rearranged, scattered and unstable.

This work demonstrates that pancreatic cancer is a major neoplasm without favourable incidence
trends over the past decades, and its prognosis remains dismal.


This comprehensive study defines four subtypes of pancreatic cancer based on expression profile:
squamous, pancreatic-endocrine-like, and two immunogenic subtypes.

This is the first study to demonstrate that pancreatic stellate cells can migrate from the primary tumour site to distant sites where they probably facilitate seeding and survival of metastatic cancer cells.


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This paper describes the original GEMM model for the genetic evolution of pancreatic cancer. Cancer Cell 1, 437–450 (2002).


This paper demonstrates that mutant DNA shed from early-stage (surgically resectable) pancreatic cancers can be detected in blood, suggesting that circulating tumor DNA might be a useful approach for the early detection of pancreatic cancers.


Together with reference 135, this paper shows that advances in analytical technologies and detection capabilities will yield sensitive and specific non-invasive diagnostic tests for early-stage pancreatic cancer, thereby increasing pancreatic cancer resection rates.


Hruba, R. H., Pitman, M. B. & Rimmasa, D. S. Tumors of the exocrine pancreas (American Registry of Pathology and Armed Forces Institute of Pathology, 2007).


This registry-based study quantifies pancreatic cancer risk in families and demonstrates that an increased risk begins as early as 45 years of age.

Pancreatic cancer: surgery alone is not enough.  


Xiao, Y. & Freeman, G. J. The microsateellite instable subset of colorectal cancer is a particularly good candidate for checkpoint blockade immunotherapy. Cancer Discov. 5, 16–18 (2015)

Khaled, Y. S., Wright, K., Melcher, A. & Jayne, D. Antibodies that target the cancer cell niche are particularly effective with targeted therapy in human pancreatic cancer cell lines. Lancet 385, 556 (2015)


Together with reference 25, this paper demonstrates that pancreatic cancer cells are characterized by multiple aberrant signalling pathways that enhance protumoric signalling, underscoring the need for combinatorial therapies.


