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Primer

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Pancreatic cancer

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Abstract

Pancreatic ductal adenocarcinoma remains one of the deadliest malignancies, characterized by late diagnosis, aggressive biology and limited therapeutic success. Advances in multiagent chemotherapy have improved outcomes across disease stages, whereas precision medicine approaches are reshaping treatment paradigms. Personalized RNA vaccines and oncogenic KRAS-directed agents represent emerging immunological and molecular frontiers. Multimodal treatment regimens and surgical innovations, including vessel-oriented and minimally invasive techniques, have enhanced complete resection rates and enabled conversion of initially unresectable locally advanced pancreatic cancer into resectable disease. Increasingly, multidisciplinary, biology-guided strategies define resectability and the sequence of systemic and local therapies. The tumour microenvironment's complex stromal and immune ecology remains central to therapeutic resistance but also offers opportunities for rational combination therapy. Early detection and risk-adapted surveillance for high-risk individuals are advancing, as are artificial intelligence-assisted imaging and liquid biopsy approaches. Despite persistent challenges, the convergence of mechanistic insights, precision therapeutics and supportive care provides a framework for transforming pancreatic ductal adenocarcinoma from an inevitably lethal disease towards a better manageable condition.

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Introduction

Pancreatic cancer can arise from two cell types in the pancreas — exocrine cells and neuroendocrine cells. Pancreatic ductal adenocarcinoma (PDAC) is the dominant subtype of pancreatic cancer, accounting for ~85–90% of cases, and therefore is the focus of this Primer[1]. Pancreatic cancer ranks among the leading causes of cancer-related mortality worldwide, with a mortality rate that closely parallels its incidence[2]. PDAC is histologically characterized by infiltrating ductal structures within abundant desmoplastic stroma.

This hypovascular, fibrotic and immunosuppressive tumour microenvironment (TME) drives disease progression, impedes drug delivery and constrains antitumour immunity, thereby shaping clinical outcomes[3–6]. Clinically, PDAC is categorized as resectable, borderline resectable, locally advanced or (oligo)metastatic, which guides multimodal management[7]. Even when the tumour is anatomically resectable, pancreatectomy is technically challenging, and relapses remain common despite modern adjuvant and neoadjuvant therapy. Since 2010, outcomes have improved with multiagent chemotherapy backbones — FOLFIRINOX (folinic acid (leucovorin (LV)), 5-fluorouracil, irinotecan and oxaliplatin) and gemcitabine plus nab-paclitaxel (GnP) are established first-line standards for metastatic disease, and NALIRIFOX (nanoliposomal irinotecan, 5-fluorouracil, LV and oxaliplatin) provides an alternative option[8–10]. Precision strategies for biomarker-defined subsets and refinements in surgical techniques have further shaped clinical practice, although durable control remains uncommon. Personalized RNA neoantigen and driver oncogene vaccines in the adjuvant setting have induced robust and durable $CD8^+$ and $CD4^+$ T cell responses that correlate with delayed recurrence in a selected subset of patients following resection[11–14]. Early clinical and translational findings from KRAS-directed agents — including selective KRAS-G12D inhibitors and pan-RAS(ON) inhibitors — are reshaping the investigational landscape[15].

Despite these advances, PDAC remains one of the most lethal human malignancies, with survival gains over the past decades remaining modest. Beyond its high mortality, the disease imposes a profound burden on patients' health-related quality of life owing to pain, cachexia, pancreatic insufficiency and treatment-related toxicities. These realities underscore a central unmet need in the field: earlier detection and more effective, biology-informed therapies capable of overcoming the profound therapeutic resistance that characterizes PDAC.

In this Primer, we review the epidemiology, pathophysiology and diagnosis of PDAC. In addition, we focus on management — modern surgery (including conversion strategies), systemic therapy across disease stages, immunotherapy and supportive or geriatric care with attention to quality of life. Early detection, screening and primary prevention, which are critical to lowering disease burden, are referenced but are not covered in depth to maintain emphasis on therapeutic paradigms and current clinical challenges.

Epidemiology

Pancreatic cancer remains a relatively uncommon malignancy globally; however, it is a disproportionate cause of cancer-related mortality. In 2022, an estimated 510,992 new cases (age-standardized rate (ASR) 5.5 per 100,000 men and ASR 4.0 per 100,000 women) and 467,409 deaths (ASR 5.0 per 100,000 men and ASR 3.5 per 100,000 women) were recorded worldwide, with a lifetime risk of ~0.53% (both sexes, world average)[2]. Since 2000, the 5-year survival rate has increased from 4% to 13% in the USA. According to Cancer Statistics in the USA, 17% of patients are diagnosed with localized disease, 26% of patients are diagnosed with regional disease (that is, the tumour has spread beyond the primary site to nearby lymph nodes or adjacent organs and tissues) and 46% of patients are diagnosed with distant metastatic disease (10% of patients were not staged)[16]. Incidence and mortality are highest in countries with a very high human development index, reflecting differences in age distribution, smoking, prevalence of obesity or type 2 diabetes mellitus (T2DM) and diagnostic capacity[2,17] (Fig. 1). Age is a dominant risk factor for pancreatic cancer — the age-specific incidence rate climbs steeply after 50 years of age, peaking in the age range 70–79 years[2,17]. However, between 2001 and 2018 there has been an increase in the average annual percentage change in pancreatic cancer incidence rate of 1.29% among individuals <55 years of age[18]. The incidence rates of pancreatic cancer are slightly higher in men than in women across most regions[2] (SEER database). Furthermore, the incidence rates of pancreatic cancer also vary according to race and ethnicity; for example, in the USA, the incidence rate is higher in non-Hispanic Black populations than in non-Hispanic white, Hispanic and Asian–Pacific Islander populations (SEER database).

From 1990 to 2017, the age-standardized incidence rate has risen modestly, whereas absolute case counts have more than doubled, largely owing to population ageing, improved ascertainment and shifts in modifiable risks[17,19,20]. Multiple modifiable and non-modifiable factors contributed to this risk (Table 1). Cigarette smoking remains the most established risk factor (~1.7–2-fold increase in current smokers; risk attenuates after smoking cessation)[21]. Heavy alcohol intake (that is, three or more drinks per day) is associated with a small but significant increase in risk (~1.1–1.3-fold)[22,23]. Furthermore, data from pooled cohort studies indicate that obesity (BMI ≥30 kg/m^2) correlates with a 1.47-fold increase in risk[24]. In addition, diabetes mellitus displays a complex association — long-standing T2DM is associated with about a twofold increase in risk[25], whereas new-onset T2DM in adults ≥50 years might be an early warning sign of occult PDAC (~0.3–1.0% develop PDAC within 3 years)[26,27]. Pancreatitis increases the risk (overall OR ~2.1), with the strongest association with pancreatitis occurring near the time of cancer diagnosis (OR >20 within 2 years)[28].

Familial aggregation (familial pancreatic cancer) and germline susceptibility (hereditary pancreatic cancer) are also important risk factors. Heritability estimates range from 21% to 36%[29,30]. Approximately 5–10% of unselected patients with PDAC harbour pathogenic germline variants in genes involved in DNA repair or cancer predisposition (for example, *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *CDKN2A*, *PRSS1*, *TP53* and mismatch-repair genes) with clinical implications[31–33]. As detailed in subsequent sections, some of these genetic alterations are directly targetable including by PARP inhibitors in pancreatic cancers deficient in *BRCA1*, *BRCA2* and *PALB2* and by immunotherapy in microsatellite instability-high (MSI-H; mismatch repair-deficient (dMMR)) cancers. For these reasons, the National Comprehensive Cancer Network (NCCN) guidelines as well as many other professional societies recommend that all newly diagnosed individuals with pancreatic cancer or those with a history of pancreatic cancer in a first-degree relative should undergo germline genetic testing[34]. Common genetic variants are individually associated with a modest (<1.4-fold)[35–39] increase in the risk, and high-penetrance pathogenic variants are associated with a more than threefold increase in the risk of pancreatic cancer (Table 2).

Mechanisms/pathophysiology

Overview of physiological functions

The healthy pancreas is a predominantly stroma-poor yet highly secretory organ in which exocrine acinar cells and ductal cells and endocrine islets coordinate digestion and glucose homeostasis through

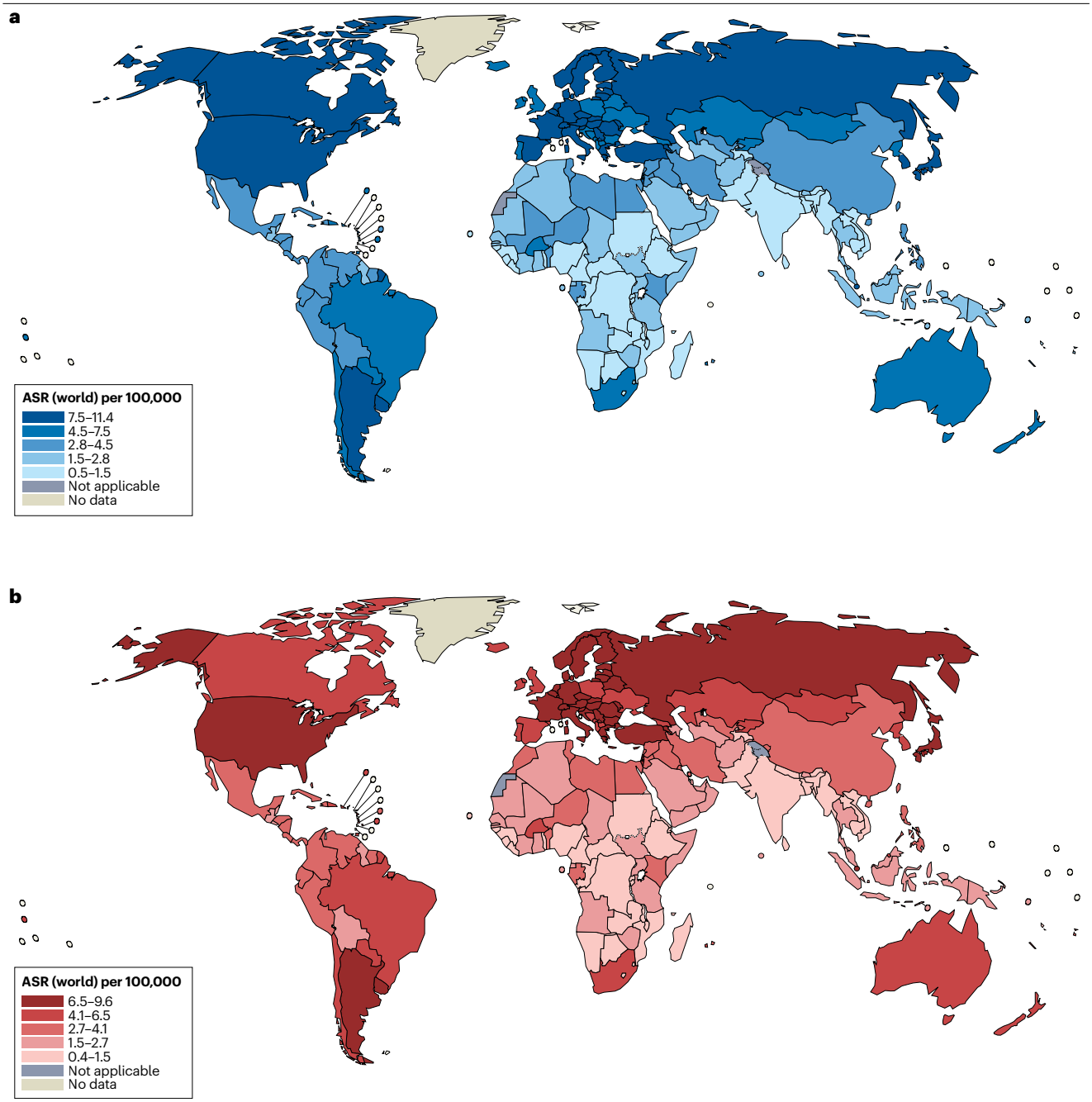


Fig. 1 | Global incidence and mortality rates of pancreatic cancer. Estimated age-standardized rates (ASRs) of incidence (part **a**) and mortality (part **b**) for both sexes (per 100,000 persons) in 2022. Created using ref. 315, courtesy of IARC/WHO.

dense autonomic innervation and sensory innervation, establishing circuits co-opted during malignant transformation[40,41]. Single-cell atlases identify discrete acinar and ductal states — ranging from digestive enzyme-rich to stress-response programmes — that map onto injury and regeneration trajectories, thereby defining the plasticity landscape available to neoplastic evolution[41]. These physiological programmes set constraints and opportunities: high biosynthetic load, injury-induced plasticity of exocrine cells and neuronal modulation collectively generate selection pressures that PDAC cells exploit for growth, immune evasion and therapy resistance[40,41].

Table 1 | Principal risk factors for pancreatic cancer (illustrative effect sizes)

Risk factor	Typical effect size	Notes or population	Key sources
Current cigarette smoking	~1.7–2.0×	Risk declines after cessation; near-baseline ~20 years after quitting	17,21
High alcohol intake (three or more drinks per day)	~1.1–1.3×	Dose–response; heavier use associated with higher risk	22,23
Obesity (BMI ≥30 kg/m^2)	1.47× (95% CI 1.23–1.75×)	Pooled analysis of 14 cohorts	24
Long-standing type 2 diabetes	Up to ~2.0×	Association attenuates with duration and therapy	25
New-onset diabetes ≥50 years	0.3–1.0% develop PDAC within 3 years	Early warning subset; consider surveillance context	26,27
History of pancreatitis	OR ~2.1 overall; ~23× within 2 years of PDAC	Reverse causality near diagnosis drives peak	28
Family history of pancreatic cancer	4.5×	Kindred with at least two first-degree relatives with pancreatic cancer and all >50 years of age at diagnosis	294,295
	6.9×	Kindred with at least two first-degree relatives with pancreatic cancer and at least one relative with pancreatic cancer before 50 years of age	
	2.5×	One first-degree relative	

PDAC, pancreatic ductal adenocarcinoma.

Core drivers and precursors

Approximately 85–95% of PDACs harbour activating *KRAS* mutations, predominantly codon 12 substitutions, G12D (34–47%), G12V (27–36%) and G12R (10–17%), which together account for ~90% of *KRAS*-mutant tumours, whereas 8–13% of tumours are *KRAS* wild-type. These alleles are biologically and clinically distinct, with G12D associated with inferior survival and G12R enriched in early-stage disease[16,42,43]. Cooperative inactivation of *TP53* (~50–81%), *CDKN2A* (~16–95%) and *SMAD4* (~20–60%) defines the canonical tumour suppressor landscape, with loss of *SMAD4* correlating with metastatic propensity and absence among long-term survivors[44]. PDAC genomes can be categorized as 'stable', 'scattered' and 'unstable' structural classes, with the unstable subset enriched with DNA repair defects that may be exploitable therapeutically[45]. Precursor lesions follow distinct trajectories — pancreatic intraepithelial neoplasia (PanIN) typically harbour *KRAS* mutations, which are followed by *CDKN2A* and *TP53* inactivation (Fig. 2), whereas intraductal papillary mucinous neoplasms (IPMNs), cystic neoplasms of the pancreas that have the potential to become malignant, more often carry *GNAS* and *RNF43* alterations with subsequent convergent pathways to invasion[46,47]. A striking paradox of PDAC is that its earliest precursors (PanIN) are remarkably common, yet their progression into cancer is rare. Autopsy and organ donor studies have detected low-grade PanINs in 75–85% of adult pancreata, beginning in young adulthood and increasing with age[48–50]. These lesions almost universally harbour activating *KRAS* mutations[51,52], but only very few progress to invasive adenocarcinoma[53]. Progression requires sequential inactivation of tumour-suppressor genes (for example, *CDKN2A*, *TP53* and *SMAD4*)[54], unfolds over decades[53,55], and is restrained by immune surveillance and a non-permissive stromal microenvironment[56,57]. This multi-hit process explains why most *KRAS*-mutant PanINs remain indolent throughout life, highlighting that oncogenic *KRAS* is necessary but not sufficient for PDAC development (Fig. 2). This composite scenario supports a multistep clonal selection model in which oncogenic signalling, cell-cycle deregulation and TGFβ pathway disruption cooperate to drive invasion and metastasis[46,58]. At the same time, the tissue organization field perspective emphasizes that evolving stroma and architectural shifts facilitate malignant fitness, cautioning against exclusively cell-intrinsic mechanisms for progression and therapy resistance[59].

Cell of origin, plasticity and inflammatory memory

Genetically engineered mouse models (GEMMs) demonstrate that ductal cancers can arise from either ductal or acinar compartments when oncogenic *Kras* is activated, with acinar-to-ductal metaplasia creating a plastic intermediate that stabilizes inflammation[60–62]. Acinar-to-ductal metaplasia is not merely a histological curiosity, but is rather characterized by transcriptional and chromatin reprogramming that locks cells into progenitor-like states, from which oncogenic signalling more easily induces malignant transformation[60,61]. Current lineage-tracing studies in mice have identified a rare acinar subpopulation capable of pancreatic renewal and particularly susceptible to *Kras*-driven clonal expansion, transdifferentiation and PanIN formation by activating the RAS–MAPK–ERK signalling pathway, with parallel phospho-ERK-positive acinar foci observed in human neoplasms harbouring *KRAS* mutations[63]. Transient injury events create an epigenetic scar, which reduces activity of the acinar programme and primes *KRAS* oncogenesis, mechanistically linking recurrent pancreatitis and other forms of tissue damage to elevated PDAC risk[64,65]. Studies including human donors and investigating early lesions have shown multifocal neoplastic fields with 3D genome remodelling, supporting the concept of widespread pre-neoplastic susceptibility; nevertheless,

Table 2 | High-risk pancreatic cancer inherited susceptibility genes

Gene	Relative risk of pancreatic cancer	Prevalence in patients with pancreatic cancer (%)	Key sources
BRCA2	2–10	2–7	296–299
PALB2	2.3 or higher	<0.5	299–301
BRCA1	2–9	0.6–2.2	32,297,302–304
ATM	6.5	2.3	32,297,299,305,306
STK11	76–140[a]	<1	307
CDKN2A	39–52[a]	<1–2.5	32,297,299,308–310
Hereditary pancreatitis	More than tenfold, up to 40% lifetime risk[a]	<1	31–33,311
Mismatch repair: *MLH1*, *MSH2*, *MSH6* and *PMS2*	0.7–6.7	<1	312–314

[a]Risk estimates include data from individuals with associated hereditary syndromes.

the cells of origin in humans remain undefined, underscoring the need for careful translation of murine lineage findings[49,66,67]. Clinically, these data rationalize surveillance of high-risk pancreatitis cohorts and argue that anti-inflammatory or acinar identity-preserving strategies could be preventative in selected settings[64,67].

Transcriptional phenotypes

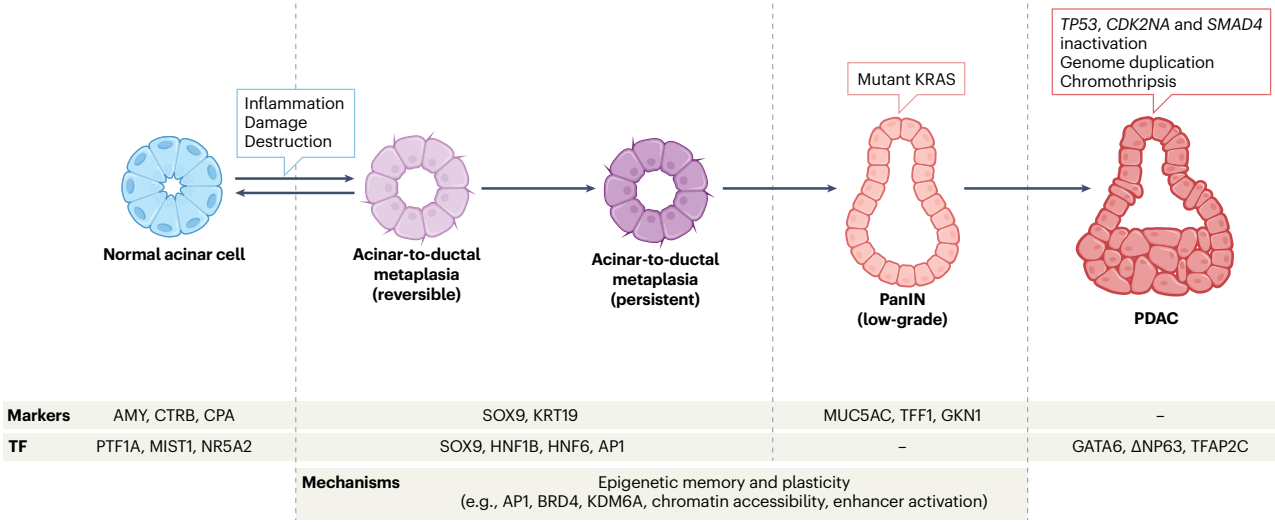
A number of independent studies over the last decade[46,47,68–70] have converged on the notion that the PDAC epithelium mainly comprises two transcriptional subtypes (that is, classic and basal-like). Basal-like PDAC exhibits a less differentiated histology, a poor prognosis and inferior response to chemotherapy[46,68,70], particularly 5-fluorouracil-based regimens[71,72]. The clinical utility of PDAC molecular subtypes, along with suitable biomarkers, is currently under intense investigation. In addition, new studies have indicated that different subtypes can coexist within individual tumours, explaining why bulk sequencing yields inconsistent clinical associations and therefore motivating spatially aware biomarkers and sampling strategies[69,73]. Although their aetiology is not fully resolved, studies have identified several regulators of a highly aggressive basal-like subtype (for example, *KRAS* dosage[69], TP63 (ref. 74) and TME factors[75–77]). For example, macrophage-derived TNF can drive lineage reprogramming of classic tumour cells towards a more aggressive basal-like phenotype, and basal-like tumours are enriched with specific tumour-associated macrophage populations, particularly C1QC$^+$ macrophages, whereas classic tumours show greater immune infiltration with enrichment of inflammatory FCN1$^+$ monocyte-like and SPP1$^+$ macrophage subsets[75–77]. GEMMs further suggest that the cell of origin contributes to subtype identity, with acinar-derived tumours preferentially aligning with classic signatures and ductal-derived tumours with basal-like programmes[78].

Desmoplasia as an ecology

The PDAC TME commonly comprises up to 80% of the tumour volume, creating hypoperfusion, hypoxia and high interstitial pressure, which physically limit drug penetration and seed immune dysfunction[3]. Cancer-associated fibroblasts (CAFs) arise from stellate cells, mesothelial cells and other mesenchymal sources, and diversify into myofibroblastic (myCAF), inflammatory (iCAF) and antigen-presenting (apCAF) states, which interconvert under TGFβ, IL-1 and other cytokines, thereby controlling extracellular matrix (ECM) composition, cytokine tone and antigen processing[79–81]. Distinct LRRC15-positive and endoglin (also known as CD105)-positive CAF subsets are associated with T cell exclusion or immunotherapy responsiveness, arguing for marker-guided stromal normalization rather than unselective depletion of CAFs, which has previously been shown to worsen outcomes[4,82,83]. Mechanistically, fibroblasts function as units with their self-deposited ECM to control tissue mechanics and growth factor bioavailability, so perturbing adhesions and matrix architecture can have non-intuitive, system-level effects[83,84]. Early enthusiasm for stromal ablation was thus tempered by clinical trials of Hedgehog blockade and enzymatic hyaluronan degradation, which did not confer clinical benefit and instead emphasized the complex, context-dependent roles of CAFs in PDAC pathophysiology[85]. Contemporary strategies, therefore, prioritize normalizing ECM crosslinking, interrupting CAF–tumour crosstalk, or selectively targeting protumour CAF states while preserving or enhancing antitumour fibroblast functions[4,86] (Fig. 3).

Immune circuitry and therapeutic combination

The PDAC immune landscape is typically myeloid-dominated with sparse, dysfunctional effector T cells, aligning with minimal responses to single-agent checkpoint blockade in most patients[5,6]. Oncogenic KRAS induces granulocyte–macrophage colony-stimulating factor



Markers	AMY, CTRB, CPA	SOX9, KRT19	MUC5AC, TFF1, GKN1	–
TF	PTF1A, MIST1, NR5A2	SOX9, HNF1B, HNF6, AP1	–	GATA6, ΔNP63, TFAP2C
Mechanisms	Epigenetic memory and plasticity (e.g., AP1, BRD4, KDM6A, chromatin accessibility, enhancer activation)			

Fig. 2 | The roads to PDAC. Genetically engineered mouse models have underscored that acinar cells, the most abundant cells of the exocrine pancreas, can undergo transcriptional and epigenetic changes that herald plasticity and the acquisition of ductal-like features (either in a reversible or persistent mode). *KRAS* mutations drive persistent acinar-to-ductal metaplasia and herald progression to low-grade pancreatic intraepithelial neoplasia (PanIN), which can, at very low frequency, progress to pancreatic ductal adenocarcinoma (PDAC) through the acquisition of additional genetic changes, leading to the inactivation of key genes such as *CDKN2A*, *TP53* and *SMAD4*. *KRAS* can also drive PDAC development when activated in ductal cells, via a pathway that appears to bypass PanIN and instead involves intraductal papillary mucinous neoplasm (not shown). Understanding the mechanisms involved may provide key clues to preventing PDAC. This model does not preclude the possibility that PDAC can also arise from genetic alterations occurring in ductal cells. TF, transcription factor.

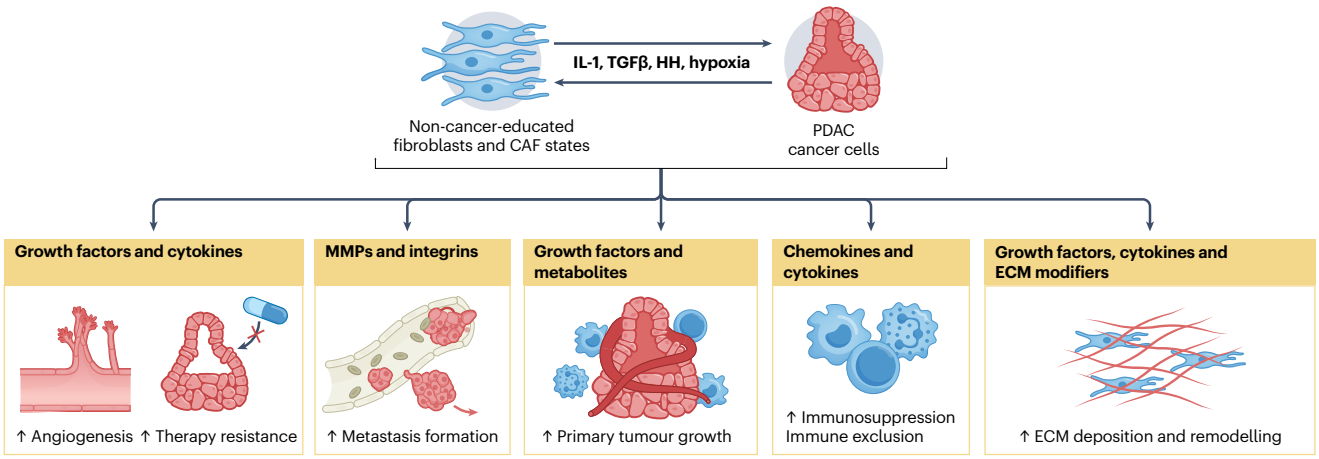


Fig. 3 | Tumour-promoting functional heterogeneity of cancer-associated fibroblasts in PDAC primary tumours. Cancer-associated fibroblasts (CAFs) from pancreatic ductal adenocarcinoma (PDAC) have several roles, including promoting tumour growth, angiogenesis and metastasis formation, depositing extracellular matrix (ECM), increasing therapy resistance and establishing an immunosuppressive microenvironment. Non-exhaustive examples of mediators of these functions are shown. HH, Hedgehog; MMP, matrix metalloproteinase.

expression in epithelial cells, recruiting suppressive myeloid populations and directly coupling tumour genotype to an immunosuppressive microenvironment[87,88]. Independent studies have described opposite outcomes following regulatory T cell depletion, ranging from collapse of myCAFs and unleashed compensatory myeloid infiltration with accelerated carcinogenesis[89] to induction of an effective antitumour immune response[90]. This finding highlights how single-node immune manipulation without systems-level design, particularly in settings where such manipulation triggers pancreatitis, can induce ecosystem recoil rather than selective release of antitumour immunity. Spatial analyses reveal co-existing hot but suppressed and cold and excluded regions within the same tumour[3,5], implying that response heterogeneity may reflect sampling location rather than biology alone. Early combination strategies, such as CD40 agonism with chemotherapy, 4-1BB–LAG3 co-stimulation and CXCR1–CXCR2 blockade to remodel myeloid trafficking, have demonstrated safety and durable benefit in mice, overall supporting multinode, stroma-aware immunotherapy design[91,92]. Integrating genotype (for example, *SMAD4* and *KRAS* status) with TME features improves predictive modelling of therapeutic response, and should guide biomarker development[91,92].

Metabolic reprogramming, systemic consequences

KRAS-mutant PDAC rewires metabolism to support growth under hypoxia and nutrient stress, via upregulating glycolysis and the hexosamine biosynthesis pathway and by adopting a non-canonical glutamine circuit to fuel redox balance and anaplerosis[93–95]. Tumours also scavenge extracellular substrates, including uridine-derived ribose under glucose restriction, unveiling salvage pathways as context-dependent vulnerabilities for therapy[96]. Approximately 70–90% of newly diagnosed patients with PDAC present with pancreatic exocrine insufficiency, which is associated with malabsorption and weight loss. Pancreatic exocrine insufficiency requires pancreatic enzyme replacement therapy in almost all patients following pancreatoduodenectomy and in up to 80% of patients following distal pancreatectomy[97,98]. Systemically, up to ~80% of patients develop cancer-associated cachexia, driven by inflammatory cytokines such as IL-6, LIF and TNF and by GDF15, which together reprogramme appetite, increase circulating glucocorticoid levels, muscle proteolysis and adipose lipolysis to worsen treatment tolerance and survival[99–101]. Preclinical data suggest that early neutrophilia can transiently support host energetics but mask emerging cachexia, implying that proactive, mechanism-based supportive care — nutrition, exercise and anti-inflammatory interventions — should be integrated with systemic therapy following diagnosis[99,102]. These insights suggest that metabolic biomarkers and inflammatory biomarkers should be included as stratification and pharmacodynamic end points in trials in patients with PDAC to avoid confounding therapeutic signals with patient frailty[99,100,102].

Metastasis, organotropism and stromal niches

PDAC preferentially metastasizes to the liver, with frequent peritoneal and lung spread[103]. Loss of SMAD4 is associated with widespread metastatic disease and worse survival, suggesting that adjuvant strategies and clinical trial stratification should be tailored to molecular failure risks in addition to tumour stage alone[104]. Myeloid cells and CAFs promote intravasation and seeding, and chemotherapy can paradoxically enhance metastasis through neutrophil infiltration and GAS6–AXL signalling, underscoring the need to monitor regimen-specific microenvironmental effects[105]. Newly identified EGFR-activated myofibroblasts act as prometastatic effectors, strengthening the rationale for combined epithelial–stromal targeting in advanced disease[106]. Premetastatic niches form before circulating tumour cells arrive, with tumour-conditioned hepatocytes and stromal cells depositing ECM and chemokines, which enable seeding and immune escape[107,108]. Metastatic CAFs differ transcriptionally and functionally from primary-site CAFs and cooperate with liver-resident macrophages via JAK–STAT circuits[109].

PDAC behaves as an evolving ecosystem in which genotype, cellular plasticity, stromal states, immune suppression and metabolic symbiosis cooperate across space and time, explaining the historical failure of single-node interventions. This systems view prioritizes combination and normalization strategies with stromal and/or immune pharmacodynamic readouts, spatially resolved sampling and state-aware biomarker development to align therapy with the dominant liabilities of a given tumour at a given time[3,69,83].

Disease models

Disease models are critical for studying PDAC pathogenesis, progression and therapeutic responses[110,111]. GEMMs replicate the molecular profile of human tumours by, for example, using activating oncogenic *Kras* and inactivating tumour suppressors such as *Trp53*, *Cdkn2a* and *Smad4* in a spatial-temporal fashion within a natural immune environment[112,113]. They capture the histological, molecular, genetic and clinical hallmarks of human PDAC, including precursor lesions, tumour heterogeneity, stroma composition and spontaneous metastasis formation[112–114]. These models are instrumental for the mechanistic understanding of the drivers of tumour initiation, progression and metastatic spread, and for studying tumour–stroma interactions and immune evasion. However, multi-allelic breeding is time-intensive and resource-intensive; tumour onset can be variable and commonly used pancreas-specific developmental promoters can show off-target activity. Furthermore, conditional models often activate multiple genetic events simultaneously during development, which can be overcome by using inducible systems[113,115]. GEMMs, as well as syngeneic orthotopic allografts of GEMM-derived cell or organoid cultures, are widely used as preclinical platforms to identify and validate therapeutic targets, test the efficacy of novel drugs, including RAS inhibitors, and explore resistance mechanisms[116,117].

Patient-derived xenografts are generated by implanting human tumours into immunocompromised mice. The xenografts preserve the genetic and histopathological features of the original tumour, aiding drug testing and precision medicine approaches. However, immunocompromised mice lack a functional immune system that limits their suitability for studying immune interactions and immunotherapy responses, which humanized patient-derived xenograft models address by incorporating human immune cells[118].

In vitro models, including 3D spheroids and patient-derived organoids, provide a more physiological architectural configuration than traditional 2D cell cultures, capturing genetic heterogeneity valuable for personalized treatment studies[119,120]. Although patient-derived organoids lack full TME interactions, a growing body of evidence supports their predictive value for therapy response[121,122]. Co-culture systems with stroma, their self-generated ECM and immune cells enable exploration of tumour–stroma dynamics, whereas advanced organ-on-chip systems and tissue slice cultures closely recapitulate tissue structure and mechanical properties of PDAC[111,123]. Although promising for drug testing, these technologies are still in early stages and not yet broadly accessible for large-scale high-throughput studies. Each of these models has unique strengths and limitations, and a combination is needed to capture the complexity of PDAC and support clinical translation.

Diagnosis, screening and prevention

Primary prevention

As most PDACs present late, primordial or primary prevention is critical. Smoking cessation decreases the risk of former smokers over time[21]. Healthy weight and physical activity mitigate PDAC risk, given established associations with obesity and insulin resistance[17]. Heavy alcohol intake elevates the risk in part through pancreatitis[23]. Optimal glycaemic control and metabolic health are advisable[17,25]. Occupational exposures (for example, certain pesticides or petrochemicals) have been implicated, warranting more investigation[17].

However, chemoprevention of PDAC remains to be investigated. The association between aspirin use and PDAC is controversial; metformin and statins show inconsistent hypothesis-generating associations but lack confirmatory randomized controlled trials (RCTs) for PDAC prevention, and personalized risk–benefit discussions and clinical trial participation are appropriate for high-risk individuals[124–126].

Screening

Pancreatic cancer screening of asymptomatic high-risk individuals is crucial to diagnose PDAC at very early stages and to offer patients a potentially curative treatment. The 5-year survival is substantially higher for very small tumours detected on screening, and outcomes have been reported to be better for tumours detected in surveillance cohorts than for those detected outside a screening programme[127–131]. Specifically, the Cancer of the Pancreas Screening study found that pancreatic surveillance in high-risk individuals detects most cancers at stage I, improving long-term survival compared with cancers diagnosed outside surveillance[128]. At present, structured surveillance is offered to high-risk individuals, defined by familial aggregation or hereditary cancer syndromes, altogether representing only 10% of the burden of the disease[132]. The optimal entry criteria, starting age and surveillance intervals remain under investigation[17]. Currently, population screening of asymptomatic average-risk adults is not recommended as PDAC incidence is low, current tests lack accuracy or lack cost-effectiveness at the population level, and precursor progression can occur between screening intervals[129,133]. Risk-enrichment strategies for sporadic PDAC focus on mucinous cystic precursors (for example, IPMN), and new-onset diabetes mellitus after 50 years of age (type 3c), which is associated with near-term PDAC risk and remains difficult to distinguish from T2DM[26,27,134]. Contemporary programmes (for example, the Cancer of the Pancreas Screening programme and the Pancreatic Cancer Early Detection consortium) refine multivariable risk models and harmonize protocols across centres[135,136].

Surveillance modalities include endoscopic ultrasonography (EUS) and MRI or magnetic resonance cholangiopancreatography, which are often complementary. Pancreas-protocol multiphase CT is used when indicated for staging or to address indeterminate findings[130,136,137]. EUS can detect small lesions with high sensitivity, although operator dependence is notable. The combination of imaging with blood-based or cyst-based biomarkers is under active investigation[138,139]. Emerging approaches (such as artificial intelligence-assisted imaging,

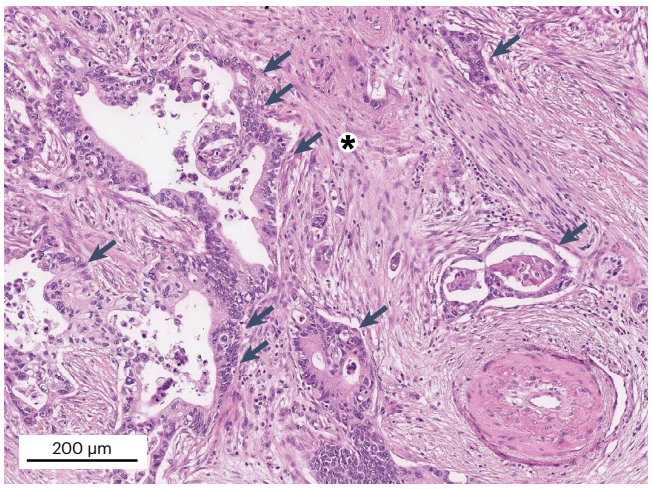


Fig. 4 | Infiltrating pancreatic ductal adenocarcinoma. Haematoxylin- and eosin-stained section of pancreatic cancer. Note the irregular glands (arrows) of varying size and shape embedded in a desmoplastic stroma (asterisk).

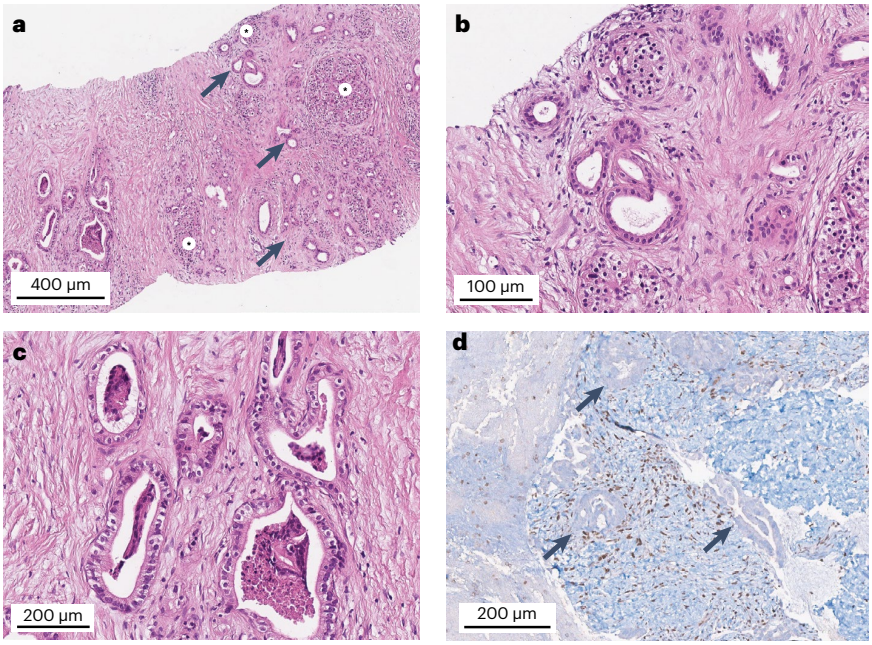


Fig. 5 | Histopathology of pancreatic ductal adenocarcinoma. a, Pancreas biopsy sample with well-differentiated pancreatic ductal adenocarcinoma (PDAC; bottom left) next to an area of acinar-to-ductal metaplasia with ductular proliferation (arrows), fibrosis and residual islets (asterisks) (haematoxylin and eosin (H&E) staining). **b**, Higher magnification of the acinar-to-ductal metaplasia area. Note the lobular arrangement of the ductuli, which show open lumina and regular nuclei (H&E staining). **c**, Higher magnification of the PDAC displaying glands with irregular shape, intraluminal detritus and polymorphic nuclei (H&E staining). **d**, SMAD4 staining is very useful for differentiating PDAC from reactive ductular proliferation. Arrows indicate PDAC glands with loss of nuclear expression, whereas the surrounding stromal cells are strongly positive.

multimodal liquid biopsy and microbiome-augmented models) have been explored but are not yet validated for routine use[140,141]. In practice, many guidelines advise beginning surveillance in individuals at 50 years of age or 10 years younger than the earliest PDAC in the family, using annual EUS and/or MRI with shorter intervals for related findings.

Diagnosis

Pathology. Resection specimens usually permit straightforward diagnosis; the presence of irregular infiltrative duct-like glandular structures in a desmoplastic stroma establishes a diagnosis (Figs. 4 and 5). However, cytology or biopsy of small lesions or highly fibrotic lesions can be challenging owing to low cellularity[142,143]. A diagnostic biopsy is warranted prior to systemic chemotherapy with neoadjuvant or palliative intent, whereas diagnostic workflow varies by region for resectable disease[144,145]. EUS-guided fine-needle biopsy and fine-needle aspiration show similar overall accuracies; fine-needle biopsy often requires fewer passes and outperforms fine-needle aspiration when rapid on-site evaluation is not available and for small lesions[146,147]. In fine-needle aspiration, cytomorphology (for example, nuclear enlargement and crowding) is key; in fine-needle biopsy, architecture adds diagnostic information owing to the irregular shape of neoplastic glands (Fig. 5). A minimal immunohistochemical panel can help a problematic differential diagnosis (for example, PDAC-related versus IPMN-related epithelium or changes related to obstruction) (Fig. 5) and fluorescent in situ hybridization or targeted molecular assays may increase the yield in equivocal cases[142,143].

Markers. Among serum markers, CA 19-9 remains the most widely used for response or recurrence monitoring, but lacks sensitivity and/or specificity for screening or early diagnosis and is uninformative in ~10–15% of individuals lacking the Lewis antigen[148,149]. Furthermore, different types of biomarkers (for example, microRNA, cell-free DNA and metabolomic profiles) have been evaluated as diagnostic and/or prognostic markers in PDAC, and biomarker panels have been shown to improve areas under the curve in meta-analyses; yet these markers have not entered routine practice[150,151]. For cystic lesions, cyst fluid molecular analysis (for example, *KRAS*, *GNAS* and copy number alterations) improves the identification of high-grade dysplasia or early cancer compared with cytology alone, with advances in liquid biopsy and multiplex platforms, but still requires broader validation before standard adoption[152,153].

Cross-sectional imaging and staging. For suspected PDAC, pancreas-protocol multiphase contrast-enhanced CT with imaging obtained during late arterial pancreatic and portal venous phases with reconstructions is the workhorse for detection, vascular mapping and staging. MRI with magnetic resonance cholangiopancreatography and diffusion-weighted imaging is a complementary problem-solving imaging modality with higher soft-tissue contrast than CT that can enhance tumour detection (Fig. 6). Guidelines recommend the clarification of indeterminate liver lesions and the detection of small hepatic metastases that alter resectability[137,154,155]. PDAC typically appears as a hypoenhancing (darker) mass on contrast-enhanced CT and MRI against the well-perfused normal pancreas parenchyma. Multiplanar reformats and maximum intensity projections (vessel-focused 3D views) of CT scans help to define tumour relationships to key arteries and veins relevant to surgical planning (Fig. 7).

Local treatment intent is commonly described as resectable, borderline resectable, locally advanced and (oligo)metastatic integrating major-vessel involvement and metastatic burden. The tumour–vessel (arterial or venous) contact angles (≤180° or >180°; that is, less than or more than half of the vessel circumference), contour irregularity and/or occlusion, and whether vascular reconstruction is feasible are central descriptors[156]. Beyond local resectability, any extrapancreatic tumour spread (liver and/or lung lesions, suspicious lymph nodes, peritoneal and/or omental nodules, or invasion in adjacent organs) must be

described (Fig. 8). For liver staging, MRI with diffusion-weighted imaging improves the detection of small or occult metastases compared with CT and is recommended when CT findings are equivocal (Fig. 9), helping to avoid non-beneficial laparotomy[137,157,158]. Formal staging should follow the American Joint Committee on Cancer eighth edition TNM system (T, tumour extent; N, nodal disease; M, metastases) for consistent reporting and multidisciplinary discussion[159].

Management

Effective care for PDAC depends on stage-appropriate treatment planning, early molecular stratification and realistic tailoring of fitness and goals of care. From the outset, the patient management plan should be discussed by a multidisciplinary board with surgery, medical and radiation oncology, radiology, pathology, genetics, nutrition and supportive care specialists. Baseline work-up must include performance status (ECOG-PS), nutritional assessment and, especially in older adults, geriatric assessment to forecast toxicity and guide dose and/or intensity decisions[160].

Localized resectable disease

The role of adjuvant chemotherapy was established in RCTs and upfront resection followed by adjuvant chemotherapy is the gold standard for patients with resectable PDAC. Fluorouracil plus folinic acid and gemcitabine have both been shown to improve overall survival (OS) compared with observation[161,162]. However, multiagent regimens such as modified FOLFIRINOX (mFOLFIRINOX; that is, dose-reduced FOLFIRINOX) and gemcitabine plus capecitabine have established a survival benefit over single-agent gemcitabine. Long-term follow-up confirmed a durable benefit, with 5-year OS rates favouring mFOLFIRINOX. Completion rates and toxicity underscore the need for careful patient selection and proactive supportive care[163,164]. In patients not eligible for mFOLFIRINOX, gemcitabine plus capecitabine is a validated alternative according to the ESPAC-4 trial, which showed a modest but significant OS advantage over gemcitabine alone, albeit with a lower dose intensity in routine practice and different toxicity trade-offs[165]. Owing to evidence for the efficacy of adjuvant oral fluoropyrimidine S-1 in Japanese patients, S-1 is the preferred adjuvant therapy in some regions in Asia[166]. Adjuvant therapy should be initiated within 6–12 weeks of surgery. Completing the planned course correlates with improved outcomes and requires active management of postoperative complications and nutrition to stay on schedule[164,165,167]. In the real-world setting, in up to 30% of patients who undergo curative resection adjuvant chemotherapy is not initiated, mainly owing to early postoperative complications, early recurrence, prolonged recovery, patient declining adjuvant therapy or advanced age.

Neoadjuvant approaches

Both induction chemotherapy and preoperative chemoradiation have been evaluated against upfront surgery in a limited number of phase III RCTs in borderline resectable PDAC. Evidence from these trials supports the use of induction therapy to improve R0 resection rates and OS[168,169]. Modern practice generally favours chemotherapy-first regimens (commonly mFOLFIRINOX) in multidisciplinary programmes[156,168,169]. However, results from contemporary RCTs do not show a consistent survival advantage of adding routine preoperative radiation to a mFOLFIRINOX backbone, although local-control end points can improve in selected scenarios (for an overview see ref. 170). For anatomically resectable disease, the PREOPANC RCT, using gemcitabine-based chemoradiation, demonstrated higher R0 rates and a long-term OS signal than upfront surgery, but these results do not indicate better performance than modern adjuvant mFOLFIRINOX, and should be contextualized as specific to that regimen era[171–173]. When induction therapy is chosen (for example, in the presence of very high CA19-9, borderline anatomy or high-risk biology), prehabilitation and clear surgical re-staging rules should be specified up front.

In upfront resectable PDAC, a small number of phase III RCTs have compared neoadjuvant chemotherapy and preoperative

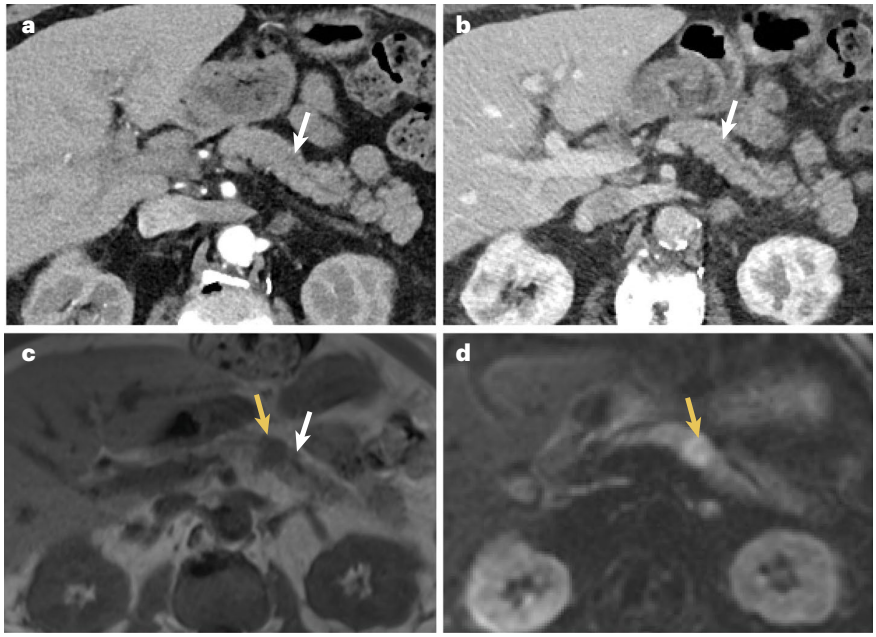


Fig. 6 | CT and MRI imaging for pancreatic cancer staging. CT scans during arterial (panel **a**) and portal venous (panel **b**) phase show dilation of the pancreatic main duct in the pancreatic tail with duct interruption (white arrows), but no lesion is visible. On MRI images (on both the native T1-weighted image (panel **c**) and the diffusion-weighted image ($b = 800$) (panel **d**)) the causing tumour can be clearly delineated (yellow arrows; hypointense on the T1-weighted image, hyperintense on the diffusion-weighted image).

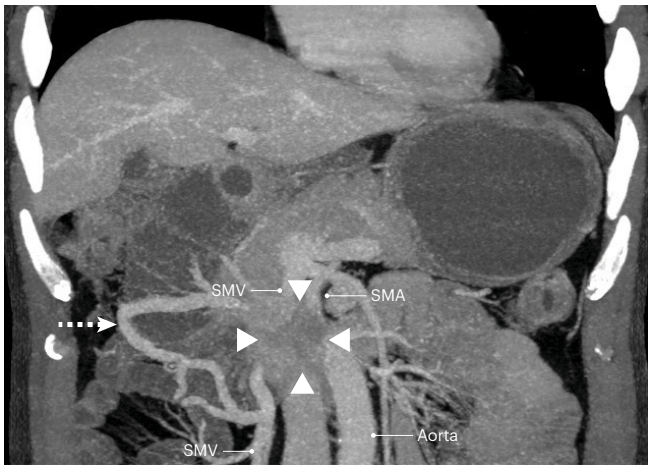


Fig. 7 | Diagnostic imaging of pancreatic cancer. Coronal maximum intensity projection (portal venous phase CT) image demonstrates a hypodense pancreatic lesion (arrowheads) and displays the relevant blood vessels vividly showing occlusion of the superior mesenteric vein (SMV) with venous collateral (broken arrow) and ≤180° tumour contact with the superior mesenteric artery (SMA).

chemoradiation with surgery followed by standard adjuvant chemotherapy. Feasibility of neoadjuvant therapy remains challenging owing to the need for histological confirmation and biliary stenting for tumours in the pancreatic head, and treatment-related complications. Resectability was assessed by imaging without CA19-9 thresholds, leading to heterogeneous populations that included both resectable and borderline resectable PDAC[169,172–175], with no significant survival benefit observed in upfront resectable disease[172,175]. The only RCT showing clearly positive chemotherapy results in both populations investigated the combination of gemcitabine and the oral fluoropyrimidine S-1, the availability of which is limited to a small number of Asian countries[174]. Furthermore, differences in chemotherapy duration[174] and compliance[175,176], omission of adjuvant therapy[173], or use of different chemotherapy regimens[175] complicate trial interpretation.

The optimal neoadjuvant regimen and duration remain uncertain. The CASSANDRA phase III RCT showed improved event-free survival with PAXG (cisplatin, nab-paclitaxel, capecitabine and gemcitabine) compared with mFOLFIRINOX[169], whereas the NORPACT-1 RCT[176] found no survival benefit for neoadjuvant FOLFIRINOX, probably owing to the influence by poor treatment completion. To date, there is no definitive evidence supporting neoadjuvant therapy in resectable PDAC.

Larger RCTs are needed to clarify the effectiveness and appropriate length of treatment of neoadjuvant therapy. Ongoing phase III RCTs, including ALLIANCE A021806 (ref. 177) (NCT04340141) and PREOPANC-3 (ref. 178) (NCT04927780), are expected to provide helpful answers.

Locally-advanced pancreatic cancer

At diagnosis, 30% of patients have locally-advanced pancreatic cancer. Induction systemic therapy with mFOLFIRINOX or GnP is the appropriate first step, aiming to downstage a subset of patients to resection and to control occult systemic disease[34,179]. Randomized evidence does not establish one induction regimen as superior, but series from expert centres show that secondary resection is consistently performed in a subset of patients when intensive induction achieves durable disease control[180,181]. The optimal use of radiotherapy in locally advanced pancreatic cancer is still controversial. The randomized LAP07 trial found that consolidative chemoradiation after gemcitabine-based induction did not improve OS compared with continued chemotherapy[182]. Similarly, the CONKO-007 RCT did not show differences in median OS or resection rates between chemotherapy followed by chemoradiotherapy and chemotherapy alone in locally advanced, inoperable pancreatic cancer[183]. Local ablative treatments, including radiofrequency ablation, stereotactic ablative radiotherapy, irreversible electroporation and heavy ion (carbon ion) radiotherapy, have been evaluated. Early-phase clinical trials have shown encouraging results showing local control with heavy ion radiotherapy[184–186], but randomized evidence demonstrating a survival advantage over contemporary systemic therapy is currently lacking. Overall, RCTs of local ablative approaches have not demonstrated clear survival benefit over chemotherapy, and their use remains limited by small study sizes and lack of standardized protocols[187–189]. Emerging technologies, such as tumour treating fields have demonstrated an OS advantage in locally advanced pancreatic cancer when combined with GnP[190].

Surgical intervention

Surgery is decisive for a cure, and the resection margin status is a major determinant of patient prognosis[191–193], with outcomes superior in high-volume centres[194–196]. A tumour-free margin of ≥1 mm is increasingly regarded as clinically relevant[193]. Importantly, R0 definitions differ internationally, substantially affecting reported R0 rates, as outer surfaces cannot always be further dissected despite no true margin invasion. Despite curative-intent surgery, recurrence remains common, occurring in ~70–80% of patients with a median recurrence-free survival of 12 months. Most relapses are distant rather than local, and nodal burden strongly predicts distant recurrence[197]. Pancreatic resections aiming to achieve radical local tumour removal are tailored to location and extent. For tumours in the pancreatic head, the standard procedure is a partial pancreatoduodenectomy. For tumours in the body and tail, a distal pancreatectomy with splenectomy is typically performed. Total pancreatectomy, resulting in complete exocrine and endocrine insufficiency, including brittle diabetes (characterized by glycaemic instability resulting from the complete loss of pancreatic endocrine function, including both insulin and glucagon secretion), is rarely indicated and reserved for extensive, central disease or technical necessity. Both standard and advanced pancreatic resections, including complex procedures such as arterial reconstructions, should be performed in high-volume centres by experienced pancreatic surgeons, as surgical volume strongly correlates with perioperative outcomes and long-term survival[194–196,198].

Traditionally, assessment of resectability for achieving an R0 resection focused on anatomical criteria, particularly the tumour's relationship to major visceral vessels such as the superior mesenteric vein, portal vein, superior mesenteric artery, coeliac axis and common hepatic artery[7]. Since 2017, the International Association of Pancreatology has recommended a more comprehensive approach by including not only anatomical factors but also biological factors (for example, CA 19-9) and physiological factors (for example, performance status) in guiding the evaluation of resectability[7]. Yet, the assessment of technical resectability depends on surgical expertise, and varies among multidisciplinary teams[179,199]. Especially after neoadjuvant therapy, the concept of resectability is debated. Imaging often overestimates tumour extent owing to desmoplastic reactions and poorly predicts

resectability. Notably, arterial involvement seen on imaging rarely equates to histological invasion: only 15% of resected arteries show histological infiltration[200]. Radiological downstaging is rare and not linked to survival or margin status[201,202]. In contrast, post-treatment CA19-9 normalization correlates with better outcomes and may guide resection decisions[203,204]. Thus, in the absence of disease progression, surgical exploration may not be precluded regardless of imaging findings (NCCN guidelines, 2025 (ref. 156)). Although no RCT data are available yet, resection of oligometastases together with the primary tumour in selected patients seems to improve survival compared with palliative chemotherapy, especially after neoadjuvant treatment[205].

Up to 60% of initially unresectable locally advanced pancreatic cancers can be converted to resectable disease using neoadjuvant regimens and advanced surgical techniques[181] (Fig. 10). In locally advanced pancreatic cancer, survival outcomes in patients undergoing resection seem to compare favourably to those achieved with non-surgical approaches[180,181,198,206]. Vessel-oriented pancreatic cancer surgery techniques have been developed to ensure optimal removal of all potentially tumour-infiltrated soft tissue around critical vascular structures to increase R0 rates and reduce local recurrence. Even in complex resections involving major visceral arteries, outcomes are comparable to those following standard resections[181,200].

Key techniques include the artery-first approach that allows early evaluation of arterial involvement before any irreversible surgical steps are taken[207–209], and the uncinate-first approach for pancreatic head tumours, in which dissection is begun caudocranially, targeting the uncinate process and focusing on early exposure of the superior mesenteric artery and the superior mesenteric vein[210]. These vessel-guided approaches can reduce blood loss and may improve R0 rates when combined with radical soft-tissue clearance[210,211].

The so-called triangle operation was developed to address frequent local recurrences near the aorta by removing the soft tissue between the superior mesenteric vein, coeliac axis and portal vein[212]. Evidence comes primarily from single-centre retrospective series, suggesting that it can be performed without substantially increasing perioperative risk and may improve local control[212,213], but data

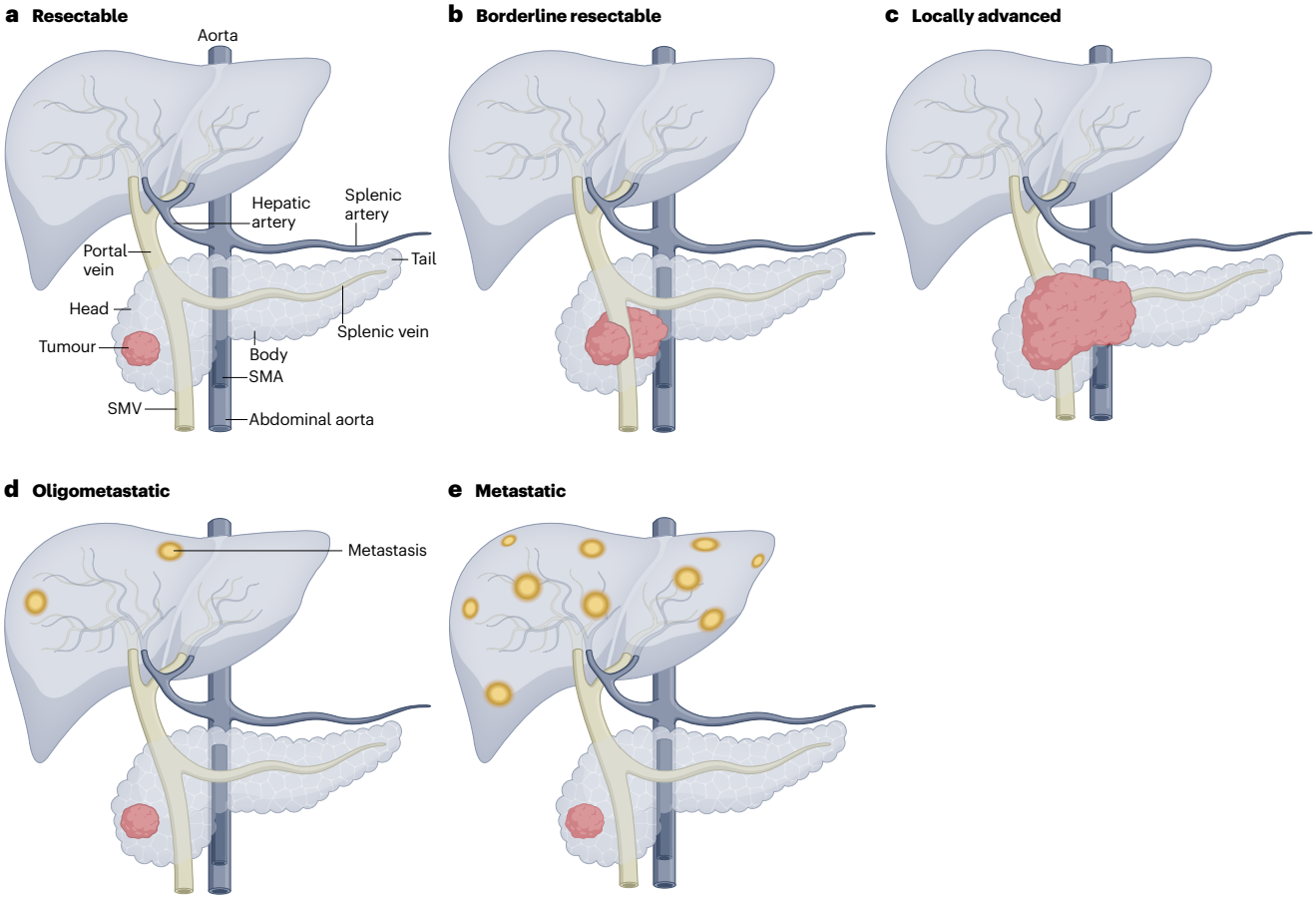


Fig. 8 | Pancreatic cancer stages. a, Resectable. The tumour is separated from the superior mesenteric artery (SMA) by fat or normal tissue, may abut but not occlude the superior mesenteric vein (SMV). **b**, Borderline resectable. The tumour is in contact with <50% of the SMA circumference; the SMV may be occluded but remains technically reconstructable. **c**, Locally advanced. The tumour encases the SMA and/or involves an unreconstructable SMV. **d**, Oligometastatic. Limited distant metastases (typically fewer than three to five). **e**, Metastatic. Extensive metastatic disease beyond the primary tumour site. Adapted from ref. 316, Springer Nature Limited.

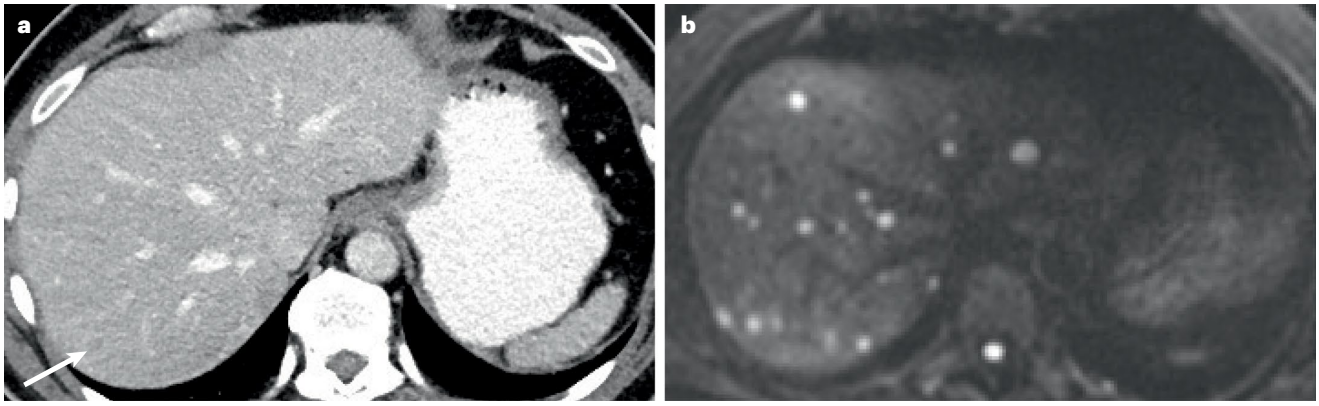


Fig. 9 | Detection of liver metastasis on CT and MRI imaging. a, CT image obtained during the portal venous phase with one indeterminate liver lesion in segment VII (arrow) in a patient with pancreatic cancer. **b**, MRI diffusion-weighted image (b = 800) reveals diffuse metastatic spread with small liver lesions in both lobes (multiple hyperintense lesions in both right and left lobes).

from randomized studies are lacking, and its true oncological benefit remains to be confirmed in prospective studies. For tumours in the pancreatic body and tail, radical antegrade modular pancreatosplenectomy follows three main principles: systematic N1 lymph node dissection, a modular posterior plane of dissection to maximize the chance of achieving negative posterior margins, and right-to-left dissection for early vascular control, with the posterior depth set by imaging, always behind the anterior renal fascia and variably including the adrenal gland[214]. Venous resections are now routine in major centres for localized but advanced pancreatic tumours. Current studies show comparable outcomes with standard surgery when adjusted for tumour stage and adjuvant therapy[215,216]. In cases of portal vein thrombosis, a bypass graft-first approach helps control bleeding and allows safer dissection[217]. After neoadjuvant therapy, tumour remnants in pancreatic cancer often spare the arterial wall[218], making arterial divestment, dissecting tumour tissue from the artery without resection, a feasible, lower-risk option[198]. When tumour infiltration extends beyond the adventitial layer, arterial resection and reconstruction may be necessary[198,219]. For tumours in the pancreatic body involving the coeliac axis, distal pancreatectomy with coeliac axis resection — a modified Appleby procedure — allows complete tumour removal by relying on collateral blood flow from the superior mesenteric and gastroduodenal arteries to maintain liver perfusion. Once controversial, arterial resections are now considered viable in selected patients, with specialized centres reporting acceptable morbidity (~50%), low mortality (3–5%) and encouraging survival outcomes[198,220].

Minimally invasive pancreatic surgical procedures, including laparoscopic and robot-assisted approaches, are increasingly used. Evidence suggests that minimally invasive distal pancreatectomy offers advantages such as reduced blood loss, faster recovery and shorter hospital stays compared with open distal pancreatectomy, whereas R0 resection rates and long-term survival appear comparable[221–224]. In contrast, for pancreatoduodenectomy, a laparoscopic approach has not demonstrated clear benefits over open surgery[225,226]. However, studies have shown that robot-assisted partial pancreatoduodenectomy provides equivalent 90-day mortality and survival outcomes to open procedures, along with less blood loss and shorter hospital stays[227,228]. Robot-assisted pancreatic surgery is considered safe and feasible in expert hands and offers certain perioperative advantages, particularly regarding blood loss and recovery time. Although oncological outcomes seem comparable to those following open surgery, high-level evidence from RCTs is still lacking.

Metastatic disease

In fit patients (ECOG-PS 0 or 1), FOLFIRINOX improved OS and response rates versus gemcitabine in the landmark PRODIGE-4/ACCORD 11 RCT (11.1 months versus 6.8 months), at the cost of greater haematological, gastrointestinal and neuropathic toxicity — underscoring the need for careful selection and dose management[8]. GnP offers broader use, including in cohorts of older patients; the MPACT RCT showed an extended median survival of ~8.5 months versus 6.7 months with gemcitabine alone and improved response rates with a manageable toxicity profile and different neuropathy risks[9]. In addition, the phase III NAPOLI-3 RCT established NALIRIFOX as another active first-line option, achieving longer OS than GnP (11.1 months versus 9.2 months; HR 0.83) with a distinct toxicity spectrum (more diarrhoea and neutropenia; relatively less severe neuropathy) and practical considerations around central access and infusion time[10]. There has been much debate as to whether the NALIRIFOX regimen represents an advance over FOLFIRINOX, and cross-trial comparisons acknowledging the inherent limitations do not suggest a major difference, noting that FOLFIRINOX was bench-marked against single-agent gemcitabine and NALIRIFOX against the more potent GnP combination. In practice, the choice of FOLFIRINOX or mFOLFIRINOX, GnP and NALIRIFOX turns on fitness, comorbidity, baseline neuropathy, biliary stents, patient preferences, access and logistics, all of which require early supportive care (pancreatic enzyme replacement therapy, nutrition and pain control) to maintain dose intensity and quality of life[8–10].

Second-line chemotherapy for metastatic PDAC is generally recommended for patients who maintain a sufficient performance status (ECOG-PS ≤2) after progression following first-line treatment [34,149]. Second-line therapy depends on first-line treatment and platinum exposure. After first-line GnP, the only regimen with phase III survival benefit is nanoliposomal irinotecan plus 5-fluorouracil plus LV, as established in the NAPOLI-1 trial; median OS was longer than with 5-fluorouracil plus LV alone, with expected irinotecan-class toxicities[229].

Oxaliplatin-based (oxaliplatin, LV and fluorouracil) regimens show conflicting results (positive with the OFF protocol in the CONKO-003 trial[230], negative with the mFOLFOX6 protocol in the PANCREOX trial[231]); therefore, decisions should be individualized and trial participation prioritized where available. After first-line FOLFIRINOX, gemcitabine–taxane combinations are commonly used based on the results of phase III and retrospective studies[232]. Early palliative care integration, neuropathy mitigation, antiemetics, pancreatic enzyme replacement and proactive nutrition are not adjuncts, but integral to delivering benefits across lines.

Biomarker-directed therapy

For germline *BRCA1*, *BRCA2* and other DNA damage repair alterations, platinum sensitivity can be exploited up front, and PARP inhibitor maintenance is an option after disease control. In the POLO RCT, olaparib maintenance significantly prolonged progression-free survival compared with placebo in patients with metastatic PDAC with germline *BRCA* mutations that had not progressed on platinum[233]. Gene fusions (for example, *NTRK* and *NRG1*) are rare, but actionable; when identified, TRK inhibitors can yield meaningful responses and should be considered[234,235]. Studies have shown benefits with HER2 and HER3 inhibitors in the small subgroup for NRG1 fusion-positive PDAC[236]. The *KRAS*-mutant majority has only entered the plausibly 'druggable' era. Although *KRAS* mutations are present in most PDAC, the $KRAS^{G12C}$ variant occurs in only ~1–3% of tumours[43]. Accordingly, FDA-approved KRAS-G12C inhibitors (sotorasib and adagrasib) have shown limited and often short-lived activity in PDAC, underscoring the need for broader approaches. Next-generation strategies aim to target additional *KRAS* alleles (for example, G12D and G12V) and the active RAS state more comprehensively[237]. Pan-RAS(ON) inhibitors represent a promising class in this context. The oral agent daraxonrasib (RMC-6236) has shown encouraging early clinical activity in *RAS*-mutant

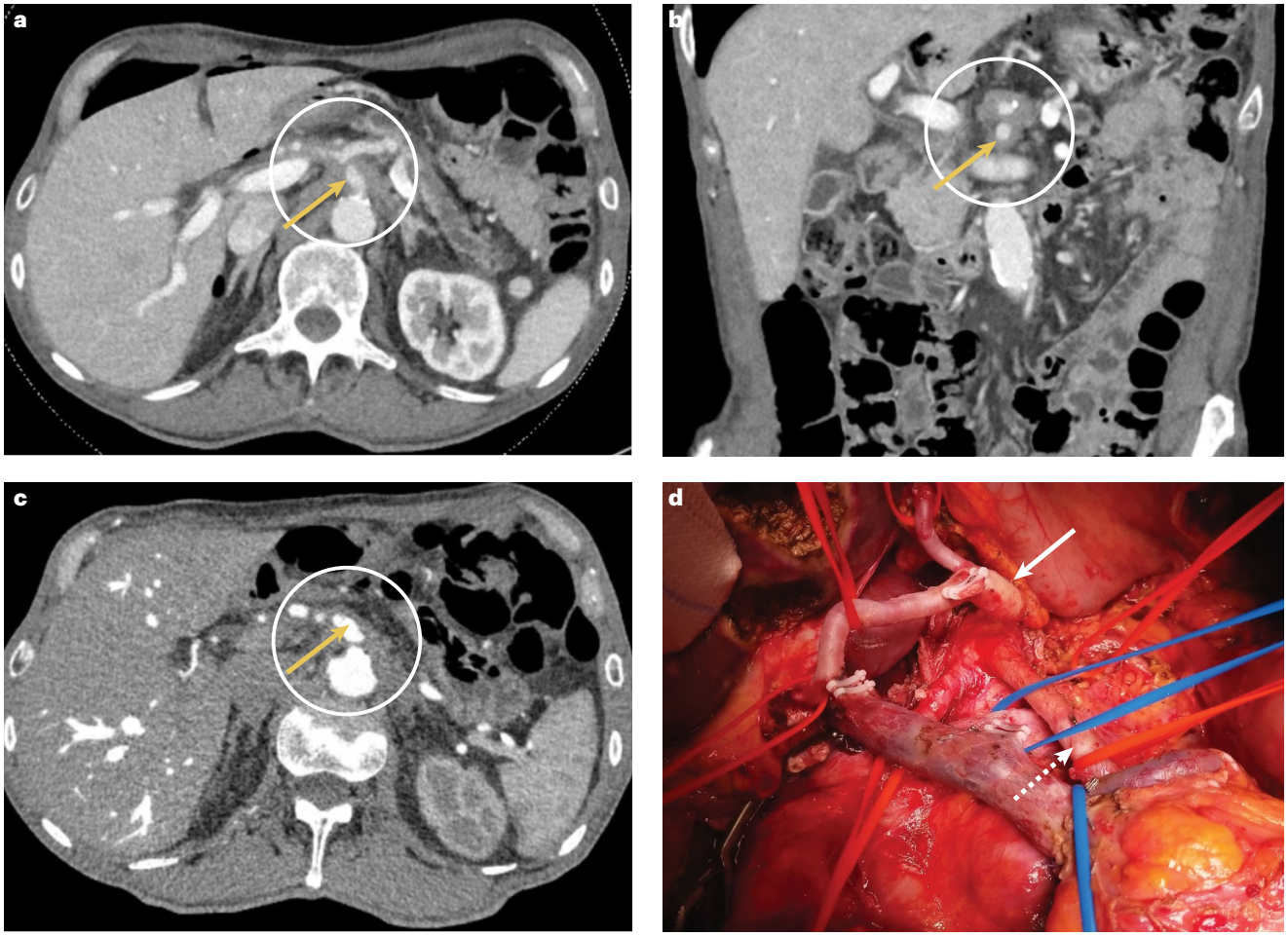


Fig. 10 | Resection of locally advanced pancreatic cancer after neoadjuvant therapy. Axial (panel **a**) and coronal (panel **b**) CT images in a patient with locally advanced pancreatic ductal adenocarcinoma (PDAC), demonstrating 360° encasement of the coeliac axis and superior mesenteric artery (yellow arrows), with aortic contact (white circles). The post-induction chemotherapy (mFOLFIRINOX) CT image (panel **c**) shows persistent 360° coeliac axis encasement (yellow arrow), with no significant radiological response. Intraoperative view (panel **d**) following total pancreatoduodenectomy with arterial divestment of the coeliac axis (solid white arrow) and superior mesenteric artery (broken white arrow). Final histopathology: PDAC ypT3, pN0, R0 (negative circumferential resection margin).

Box 1 | Key points on immunotherapy in PDAC

- Pancreatic ductal adenocarcinoma (PDAC) is largely resistant to immunotherapy approaches and has historically been viewed as 'immunologically invisible' owing to low neoantigen load and a highly suppressive tumour microenvironment.
- Immune checkpoint inhibitors are ineffective in unselected PDAC, except in 1–2% of tumours with mismatch repair deficiency (mismatch repair-deficient or microsatellite instability-high).
- Neoantigen-targeting is a promising strategy, supported by evidence of natural T cell responses in long-term survivors of PDAC and the presence of immunogenic neoantigens in most PDACs.
- A phase I trial of personalized RNA neoantigen vaccines (with atezolizumab and mFOLFIRINOX) showed strong T cell responses and correlated with delayed recurrence after surgery. These vaccine-induced $CD8^+$ T cells demonstrated cytotoxicity, memory formation and durability — hallmarks of effective antitumour immunity.
- Early-phase studies suggest that CD40 agonists with chemotherapy with or without PD1 blockade and other co-stimulatory and/or chemokine axis combinations show promising activity in PDAC, but remain investigational, highlighting the need for biomarker-driven validation in randomized controlled trials.
- Barriers to success include antigen heterogeneity, low baseline immunogenicity and the hostile tumour microenvironment.

PDAC and manageable toxicity. Early data from a phase I–II clinical trial of daraxonrasib plus GnP in metastatic PDAC (NCT05379985) show objective response rates of ~55% for the combination, and phase III RCTs (for example, the RASolute-302 and RASolute-303 trials) are ongoing[238]. Parallel preclinical development of other pan-RAS inhibitors further supports this strategy[237]. Together, these findings suggest that pan-RAS targeting may expand effective biomarker-directed therapy beyond rare *KRAS* subtypes, although definitive randomized evidence is pending. KRAS targeting in PDAC thus represents a highly promising frontier, with its therapeutic role being defined through ongoing clinical trials. These advances underscore the critical importance of molecular testing, expanding access and continued development of targeted therapies for PDAC.

Immunotherapy and rational combinations

PDAC has long been regarded as among the most 'immunologically invisible' tumours owing to few presumed neoantigens[239] and a TME inconducive to immunotherapies[240] (Box 1). Although immune checkpoint inhibitors are nearly completely ineffective in unselected patients with PDAC, they produce durable responses in those with MSI-H or dMMR PDAC (~1–2%, mostly colloid and medullary subtypes[241]), which justifies routine microsatellite instability and/or mismatch-repair testing in all patients[242,243]. This observation suggests that not all PDACs are immunologically invisible, and illuminates that deploying T cells against somatically mutated neoantigens in PDAC could be one path to induce a clinically relevant immunological response. Several studies have revealed that neoantigens are indeed present in the majority of primary PDAC and metastatic PDAC[244–247] and may be therapeutically targetable beyond the dMMR or MSI-H context. Definitive proof, however, arose from a landmark clinical trial of adjuvant RNA vaccines targeting somatic mutation-derived neoantigens in patients with surgically resectable PDAC[11]. Although this was a phase I trial of limited sample size, it demonstrated that treatment with sequential immune checkpoint inhibitors (anti-PDL1, atezolizumab), personalized RNA neoantigen vaccines (autogene cevumeran) and chemotherapy (mFOLFIRINOX) after resection induced robust $CD8^+$ T cell responses in a subset of patients and was correlated with delayed recurrence in a small, single-arm study[11]. Follow-up analyses further revealed that vaccine-induced $CD8^+$ T cells have exceptional longevity, durable function and transition to memory $CD8^+$ T cells[12], requisite features of an effective antitumour immune response. Randomized testing of adjuvant RNA neoantigen vaccines for PDAC (IMCODE003 trial) is ongoing and necessary before routine adoption[11]. In addition, other clinical trials are similarly testing additional vaccination strategies in PDAC[248], including vaccines that target other antigen classes, such as mutated driver oncogenes (*KRAS*)[13,14].

Despite progress in the adjuvant setting, challenges remain in metastatic PDAC. Current immunotherapy approaches being explored include cell therapies (for example, chimeric antigen receptor T cells[249] and other cellular therapies[250]), in vivo immune activation through combination therapies with immune checkpoint inhibitors[92,251], direct cancer cell targeting using antibody–drug conjugates[252], and emerging strategies, such as combining immune checkpoint inhibitors with KRAS inhibitors[253] or inducing tertiary lymphoid structures[254,255]. However, barriers such as antigen heterogeneity[256], low immunogenicity[257,258] and possible microenvironment features, which may challenge therapeutics, remain[259]. Accordingly, no dominant approach has emerged.

Box 2 | Limitations and future challenges in PDAC

Despite remarkable advances, several critical gaps have hindered real-world translation.

- The benefit of biomarker-guided neoadjuvant therapy remains elusive. Validated predictors of response (for example, CA19-9 kinetics and circulating tumour DNA) are promising but not yet standardized, risking over-treatment or delayed surgery.
- Access disparities to targeted therapies persist — although *KRAS* is nearly universally mutated in pancreatic ductal adenocarcinoma (PDAC) (~95%) and current breakthrough treatments target G12D or G12V variants, access remains limited to trial patients and clinical efficacy data are still emerging.
- Research funding remains misaligned; PDAC receives disproportionately low research investment relative to its mortality burden, limiting innovation and clinical implementation.
- Equity in global care delivery is inadequate, with many populations lacking access to multidisciplinary care, molecular testing and clinical trials.
- Translational caution is essential — genetically engineered mouse models, although foundational, differ from human stromal biology, immunogenicity and metastatic potential, challenging the interpretation of preclinical findings.
- Health-related quality of life data are variable and under-powered, which calls for robust, longitudinal and disease stage-specific study designs.

Developing future immunotherapies for advanced PDAC may require the reversal of traditional drug development paradigms with forward translation of lessons from the adjuvant setting to guide application in metastatic disease. Until such data mature, clinicians should counsel patients that immunotherapy outside MSI-H should be pursued in a trial.

Older adults

Chronological age alone should not preclude disease-modifying therapy. A holistic evaluation using geriatric assessment is essential to capture comorbidities, polypharmacy, nutrition, functional status, cognition and psychosocial concerns that influence treatment tolerance and outcomes. Frailty and geriatric assessment findings correlate with survival in older adults with PDAC. The optimal care of older adults remains poorly defined owing to limited prospective data and under-representation in trials[260,261]. Two studies showed geriatric assessment-driven interventions reduce grade ≥3 toxicities[262,263]. Accordingly, NCCN and the American Society of Clinical Oncology recommend the routine use of geriatric assessment, supported by practical tools and brief screening instruments such as G8 or Vulnerable Elders Survey-13 (refs. 264–266). Chemotherapy toxicity prediction models (for example, CARG (Cancer and Aging Research Group chemotherapy toxicity score) and CRASH (Chemotherapy Risk Assessment Scale for High-Age patients)) further guide shared decision-making[267,268].

Older adults are less likely to receive surgery, perioperative therapy or palliative chemotherapy than young adults[269–271]. Nevertheless, fit patients achieve outcomes comparable to those in younger cohorts. Surgical resection is feasible in selected older adults, although with higher complication rates and longer hospital stays than in younger patients[270]. Systemic therapy poses added challenges in frail patients. Triplet regimens (FOLFIRINOX and NALIRIFOX) provide survival benefit in patients >65 years of age, but evidence for those >75 years of age is scarce[8,10]. Retrospective data suggest tolerability in carefully selected individuals >70 years of age[272,273]. GnP shows comparable benefit in older patients and those with poor performance status (ECOG-PS 2)[9,274]. The GIANT RCT in vulnerable older adults demonstrated poor outcomes with reduced-dose doublets, with a median OS of <5 months overall, and 8 months only in those tolerating ≥4 weeks of therapy[275,276]. These findings highlight the importance of tailoring therapy and, for frail patients, considering best supportive care.

Quality of life

Health-related quality of life (HRQoL) profoundly shapes outcomes in PDAC, where symptom burden, including pain, anorexia, fatigue, anxiety and/or depression, and cachexia, dramatically affects both patients and care-givers[277,278]. The most robust patient-reported outcome instruments include the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30), QLQ-PAN26 (Quality of Life Questionnaire Pancreatic Cancer Module, 26 items) and FACT-Hep (Functional Assessment of Cancer Therapy – Hepatobiliary), which collectively capture dimensions across physical, emotional, social and functional domains[279–281].

In addition, a validation study with QLQ-PAN26 has refined the interpretation of clinically relevant changes, and minimal important differences for various scales were determined via both distribution-based and anchor-based methods, with minimal important difference values ranging from ~8 to 17 points, an essential advance for assessing therapeutic impact in trials[282]. Moreover, ongoing international efforts are underway to update the QLQ-PAN26 content for modern treatments and evolving patient priorities, with phase I completed across centres in Europe, India and the Middle East.

Longitudinal studies have demonstrated nuanced postoperative recovery trajectories – patients report temporary declines in physical and social function immediately after resection, but global health scores typically rebound by 3–6 months after surgery. Persistent symptoms include pain, insomnia, flatulence and health-related anxiety[283]. In locally advanced PDAC, HRQoL often remains stable during the first year among patients receiving tumour-directed treatment[284]. Therapy-related quality of life varies according to the regimen. For instance, FOLFIRINOX yields better emotional functioning and reduced distressing symptoms (pain, anorexia, insomnia) than gemcitabine, albeit with higher toxicity – a trade-off that underscores the importance of personalized decision-making[279,285]. Integrating early palliative care improves HRQoL and anxiety, reinforcing its role as foundational therapy[286].

In summary, an updated psychometric understanding of HRQoL tools, paired with longitudinal genomics and intervention data,

Box 3 | Priorities in PDAC for the next 5–10 years

- Early detection: artificial intelligence deployment and biomarker screening in populations and enriched high-risk cohorts, facilitating the development of preventive or interceptive approaches.
- Therapy access: expand compassionate and trial access to targeted agents (for example, KRAS inhibitors, immunovaccines and restoring tumour-suppressive microenvironment protection). Scale precision therapy availability beyond limited trial settings.
- Effective combinatorial treatment design: increase worldwide collaborative efforts to move away from specialized but siloed research towards gaining a holistic understanding of the complexity of the pancreatic ductal adenocarcinoma (PDAC) primary and metastatic microenvironments, as well as macroenvironment.
- Trial and funding equity: advocate for equitable allocation of resources and establish global trial networks. Reform public and philanthropic funding to better reflect PDAC's disproportionate burden.
- Biomarker validation: standardize analytic workflows for neoadjuvant predictors and circulating tumour DNA response markers. Advance biomarker-guided therapy validation to reduce over-treatment or treatment delay.
- Patient stratification: identify groups of patients with PDAC with shared features (for example, mutational profiles, risk factors and co-morbidities) and related therapeutic vulnerabilities.
- Global policy integration: embed PDAC into non-communicable disease frameworks (for example, the Sustainable Development Goals target for non-communicable diseases), elevate awareness and expand genetic testing for familial risk.
- Standardized care pathways: harmonize molecular testing, early palliative integration and patient-reported outcome collection in clinical trials.

Box 4 | Call to action

Pancreatic ductal adenocarcinoma (PDAC) stands at a crossroads: on one path, it remains immutable with dismal outcomes; on the other hand, emerging biology, precision tools and advocacy align to create the first inflexion point in decades. However, numbers alone — progression-free survival, objective response rate and hazard ratio — mean little unless they translate into real-world access, especially for patients traditionally under-served by the system. Herein lies our collective responsibility: to move beyond incrementalism, to transform PDAC not through fleeting novelty but through integration — of imaging and molecular diagnostics, of therapeutics and socioeconomic accessibility, and of supportive care and global equity. This integration involves boosting cross-laboratory collaborations, institutionalizing reflex molecular testing, funding multiregional registries, energizing early detection programmes and embedding health-related quality of life and patient-reported outcomes as trial and real-world standards. Every breakthrough, from KRAS inhibitors to neoantigen vaccines and others, is as powerful as its reach. Let us harness our combined momentum to evolve pancreatic cancer from a symbol of despair to a model for how complex, deadly diseases can be redirected — by science, by strategy and by the unshakable conviction that the next chapter on PDAC is one of possibilities.

demonstrates that although PDAC relentlessly challenges patients, strategic symptom management and therapy selection can meaningfully preserve or even improve quality of life during and after treatment.

Outlook

PDAC remains one of the greatest challenges in oncology, and is characterized by late detection, aggressive biology and under-investment in research. However, advances over the past decade have led to cautious optimism (Box 2).

Early detection and artificial intelligence-assisted imaging

New artificial intelligence-driven modalities have improved early detection. The deep learning model PANDA demonstrates high accuracy in detecting PDAC lesions on non-contrast CT scans, indicating its potential for opportunistic screening[140]. Moreover, models leveraging liquid biopsy and radiomics can detect features months to years before clinical presentation, offering a prediagnostic lead time[287].

Precision medicine and emerging therapies

The widespread adoption of molecular testing has enabled targeted therapy in subsets of patients with PDAC, such as PARP inhibitors for *BRCA*-mutated tumours, immune checkpoint inhibitors for MSI-H tumours, and *NTRK*-targeted therapies[288]. More widely applicable interventions, such as KRAS-targeted agents and vaccines, remain under investigation. Nonetheless, early signals from KRAS inhibitors and neoantigen mRNA and oncogene targeted vaccines suggest the existence of actionable pathways.

Public health and screening strategies

Public health priorities must include population awareness, screening of high-risk individuals, and reflex genetic and somatic tests. Pilot screening of individuals with new-onset diabetes has already yielded early-stage diagnoses, illustrating its feasibility. Frameworks such as 'Define–Enrich–Find' that integrate risk stratification, biomarker screening and imaging are emerging as translational models[289].

Health-system organization and centralization

Beyond technical advances, durable improvements in PDAC outcomes require optimized care delivery. Large contemporary analyses have demonstrated that centralization of pancreatic surgery to high-volume centres reduces perioperative mortality, largely through improved management of complications[194,290], and is associated with improved long-term survival, even in patients with advanced disease[195]. Population-level studies have further indicated that structured centralization increases resection rates and translates into measurable survival gains[196], consistent with the established volume–outcome relationship[291,292]. Strengthening referral pathways and implementing national quality standards, therefore, represent immediate, evidence-based strategies to improve outcomes independent of therapeutic innovation.

Funding gaps and advocacy

Pancreatic cancer is significantly under-funded compared to its mortality burden: one study found that global grant funding per death was only US$317 for PDAC versus nearly $3,600 for breast cancer[293]. These disparities reinforce the need for advocacy and redistribution, particularly because early diagnosis offers the greatest potential for cure.

Pancreatic cancer has long been synonymous with poor outcomes. But with technology, advocacy and precision medicine converging, the horizon is no longer dark – early detection, personalized treatment and equitable care can redefine what 'inevitable' means (Box 3). The time to act is now (Box 4).

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