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Review Article

Pancreatic Cancer: Early Detection and Novel Therapies

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Abstract

Pancreatic cancer encompasses a heterogeneous group of malignancies, primarily divided into endocrine and exocrine types, with pancreatic ductal adenocarcinoma representing approximately 90% of cases. While the incidence of pancreatic cancer is relatively low, accounting for about 3% of all cancers in the United States, it has a disproportionately high mortality rate, responsible for around 7% of cancer-related deaths. In 2024, it is estimated that there will be 66,440 new diagnoses and 51,750 fatalities associated with this disease. The overall five-year survival rate remains alarmingly low at just 13%, primarily due to late-stage diagnosis; over 80% of pancreatic ductal adenocarcinoma patients present with unresectable tumors and metastases at the time of diagnosis. This review aims to highlight recent advancements in imaging and laboratory tests that are paving the way for innovative screening and diagnostic approaches. Some of the modalities discussed in detail include endoscopic ultrasound (EUS) and its modifications, such as EUS elastography, EUS contrast-enhanced, and EUS Fine Needle Aspiration, as well as multi-detector computed tomography scans, magnetic resonance imaging, and positron emission tomography scans. Furthermore, laboratory tests, such as multi-marker analysis and circulating tumor DNA, alongside traditional markers like carcinoembryonic antigen, carbohydrate antigen 19-9, and carbohydrate antigen 125, are explored. The role of radiomics and proteomics in the early detection of pancreatic cancer is also discussed. These developments hold the promise of improving early detection, which is crucial for enhancing patient outcomes in pancreatic cancer. On the treatment front, conventional therapies, including platinum-based therapies and monoclonal antibodies, are reviewed, alongside innovative therapies such as immunotherapies, chimeric antigen receptor T-cell therapy, and cancer vaccines. It has been increasingly recognized that the intricate patho-mechanisms underlying tumorigenesis in pancreatic cancers necessitate a deeper understanding to facilitate targeted therapeutic strategies. We also explore various newer therapies currently in clinical trials, assessing their practicality and effectiveness in real-world settings.

Introduction

Pancreatic cancer (PC) encompasses a group of heterogeneous diseases, including cancers of the endocrine pancreas (such as islet cell carcinoma, neuroendocrine carcinoma, and carcinoid tumors) and the exocrine pancreas (such as pancreatic ductal adenocarcinoma and acinar carcinoma). Among these, pancreatic ductal adenocarcinoma (PDAC) accounts for approximately 90% of all cases. Unfortunately, more than 80% of patients with PDAC are diagnosed with an unresectable primary tumor and distant metastases at the time of diagnosis.[1]

Pancreatic cancer accounts for about 3% of all cancers in the United States and approximately 7% of all cancer deaths. According to the American Cancer Society, it is estimated that 66,440 new cases of pancreatic cancer will be diagnosed in 2024, with 51,750 deaths expected. Pancreatic cancer has a much lower incidence compared to more common cancers like lung, breast, and colorectal cancers, but the five-year survival rate for all stages of pancreatic cancer continues to remain as low as 13%.[2]

The pancreas, located deep in the retroperitoneal space, cannot be palpated or visually examined during routine physical exams. Pancreatic cancer often progresses without symptoms; when symptoms do appear, they are usually nonspecific, such as nausea, jaundice, weight loss, and abdominal pain, making early detection particularly challenging.[3] Three benign lesions—pancreatic intraepithelial neoplasm, intraductal papillary mucinous neoplasms, and mucinous cystic neoplasms—have been identified as premalignant precursors to PDAC, indicating a potential opportunity to

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screen for pancreatic cancer. However, due to the lack of diagnostic accuracy, screening is limited to high-risk populations.[4]

The limited number of high-penetrance risk factors further complicates the early diagnosis of pancreatic cancer. For years, risk assessment has relied on family history, behavioral, and clinical risk factors. However, more recently, advances in genomics and radiomics have led to new modalities for screening (Fig. 1) risk factors and early diagnosis, offering better identification of PDAC.[5]

Pancreatic cancer remains a challenging neoplasm to treat and often requires multimodal management targeting various pathways of tumorigenesis. We have elaborated on the various therapeutic approaches used in the management of pancreatic cancer, including targeting the homologous recombination deficiency (HRD) pathway, immunotherapeutic approaches like immune checkpoint inhibitors, using engineered viruses to infect the cancer cells and activate the body's immune response, vaccines to induce immune responses against cancer cells, and engineering T-cells to help kill the cancer cells.

Strategies to target claudin 18.2 and the tumor microenvironment have also been discussed at length, along with conventional chemotherapy. Many of these therapeutic modalities are still in nascent stages of development and offer potent ways to target the neoplasm.

In this article, we will first elucidate the diagnostic modalities, including imaging, serum markers, tissue markers, radiomics, proteomics, and multi-marker analysis, followed by treatment approaches for pancreatic cancers, which include traditional therapies like chemotherapy and newer immunotherapeutic approaches, such as oncolytic virus therapy, engineered T-cells to destroy cancer cells, and cancer vaccines, among others.

Imaging techniques for the diagnosis of pancreatic cancer

Imaging techniques have been crucial for staging pancreatic cancer, including assessing local, perineural, and vascular invasion, as well as distant metastasis. Historically, imaging has served as a central screening tool for familial pancreatic cancer due to the limited availability of reliable biomarkers. It also plays a key role in guiding clinical management, post-surgical follow-up, and monitoring after chemotherapy.[1]

We will begin with conventional imaging modalities, such as ultrasound, and then move into more sophisticated techniques, such as positron emission tomography (PET), later in this section.

Abdominal ultrasound (US)

US is the initial non-invasive imaging test for pancreatic evaluation, despite its limitations due to body habitus and gas interference. It assesses the size, location, and echogenicity of pancreatic lesions, with a sensitivity of 75% and an accuracy of 50–70%. Most focal lesions appear hypoechoic, and the "double duct sign"—dilation of both the common bile and pancreatic ducts—suggests a mass in the pancreatic head, even in the absence of a visible tumor.[6]

Endoscopic ultrasound (EUS)

EUS is considered the most sensitive non-operative imaging test for detecting malignant pancreatic lesions, with reported sensitivity ranging from 87% to 100%.[7] In a study by Agarwal *et al*., EUS demonstrated 100% sensitivity in diagnosing pancreatic cancer, outperforming multidetector computed tomography (MDCT), which showed 86% sensitivity in PDAC.[8] Overall, EUS is superior to conventional computed tomography (CT) and MDCT, although

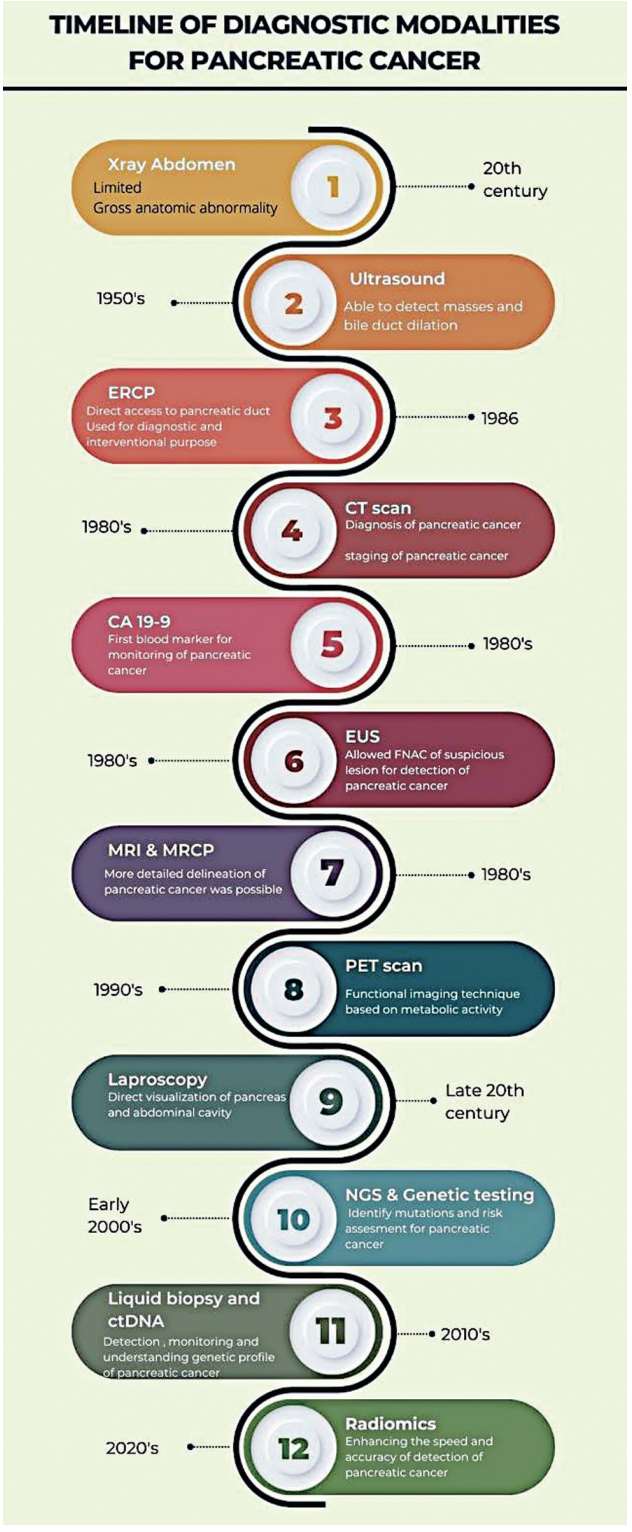

Fig. 1. Timeline of pancreatic cancer diagnostic modalities. Figure made with Canva online (www.canva.com). ERCP, endoscopic retrograde cholangiopancreatography; CT, computed tomography; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; PET, positron emission tomography; NGS, next generation sequencing; ctDNA, circulating tumor deoxyribonucleic acid.

it yields results similar to magnetic resonance imaging (MRI). However, there is a lack of studies directly comparing high Telsa MRI with EUS.[7] Another advantage of EUS is its ability to provide ultra-high-resolution images for detecting small pancreatic head tumors, especially those smaller than 2 cm, making it widely regarded as the most sensitive method for tumor detection.[9]

A few limitations of EUS include challenges in distinguishing a true pancreatic mass in cases of chronic pancreatitis, recent acute pancreatitis (less than four weeks), diffusely infiltrating carcinoma, and potential image quality reduction due to acoustic shadowing from biliary or pancreatic stents.[10] On a positive note, a retrospective study by Ranney *et al*. found no significant difference in the diagnostic yield or technical difficulty of EUS-fine needle aspiration (FNA) for visualized pancreatic masses, regardless of the presence of a biliary stent (plastic or metal).[11]

EUS-FNA is a safe and highly accurate procedure for diagnosing malignancy, with two meta-analyses[12] reporting pooled sensitivities of 85% and 89%, and specificities of 98% and 99%.[13] Complications include pain (0.38%), bleeding (0.10%), fever (0.08%), and infection (0.02%) as shown by Wang *et al*.[14] Additionally, chronic pancreatitis can complicate cytological interpretation, further decreasing EUS-FNA sensitivity.[15]

Contrast-enhanced EUS is a technique in which intravenous contrast agents like Levovist and Sonovue are administered, enabling visualization of microbubbles in the microvasculature of pancreatic tumors in real-time. PDAC has a hypoenhancing appearance, while other conditions, such as neuroendocrine tumors and chronic pancreatitis, appear iso- or hyper-enhancing.[16]

Another emerging technology used to differentiate benign from malignant masses is EUS elastography. This technique provides real-time evaluation of tissue stiffness, based on the premise that harder tissues show less strain when compressed compared to softer tissues.[17] In a meta-analysis conducted by Hu DM *et al*.[18] and Mei M *et al*,[19] EUS elastography was found to have high sensitivity but low specificity. Despite the lower specificity, EUS elastography serves as an excellent adjunct to EUS-FNA and helps endosonographers improve targeting for FNA. Limitations of EUS elastography include limited availability, challenges in controlling tissue compression by the endosonographer, the presence of motion artifacts, and the lack of clear stiffness cut-off values for pancreatic masses. Săftoiu *et al*. demonstrated that combining elastography with contrast-enhanced imaging achieved 75.8% sensitivity, 95.2% specificity, and 83.3% accuracy in differentiating hypovascular hard pancreatic masses as either chronic pancreatitis or PDAC.[20] The limitations of this modality include its availability, low sensitivity, difficult operation, and increased costs.

MDCT

MDCT is the primary imaging modality for pancreatic tumors, with sensitivity ranging from 76% to 92% for diagnosing pancreatic cancer. It has an accuracy of 85–95% for tumor detection, a positive predictive value of 89–100% for unresectability, and a negative predictive value of 45–79% for resectability.[21] MDCT effectively assesses tumor morphology, ductal anatomy, and relationships with surrounding organs and vascular structures, aiding in surgical planning. High-resolution techniques, such as multiplanar reconstructions and curved reformations, enhance the evaluation of pancreatic duct anatomy. The "double duct sign" is easily identifiable on CT. Although tumors may be isoattenuating and not visible in about 10% of cases, indirect signs such as abrupt cut-off of the pancreatic duct and mass effects on the parenchyma are important indicators of tumors. Quantitative analysis during triphasic MDCT improves tumor detection compared to visual analysis.

Standard CT protocols typically involve non-contrast imaging followed by pancreatic parenchymal and portal venous phases after intravenous contrast. The pancreatic parenchymal phase (40–45 seconds post-contrast) is most sensitive for evaluating pancreatic lesions, while the portal venous phase (70 seconds post-contrast) is optimal for detecting liver metastases.[22]

Although multiphase CT exposes patients to high radiation doses, the split-bolus CT protocol combines the arterial and portal venous phases, optimizing pancreatic enhancement, improving tumor conspicuity, and reducing radiation exposure while also allowing for lymph node and focal liver lesion assessment.[23]

MRI

MRI and CT have similar sensitivity and specificity (89%) in diagnosing and staging pancreatic cancer, making MRI less frequently used as a primary imaging tool due to cost and availability. However, MRI is beneficial in:

- Differentiating isoattenuating pancreatic lesions, which may not be clearly visible on CT
- Providing better characterization of indeterminate liver lesions identified on previous CT scans
- Offering an alternative for patients with impaired renal function or sensitivities to iodinated contrast used in CT
- Differentiating pancreatic tumors from mass-forming pancreatitis
- Detecting tumors smaller than 2 cm
- Identifying abnormalities in cases of hypertrophied pancreatic head or focal fatty infiltration of the pancreatic parenchyma.[24]

PET

PET has been shown to be more effective than CT, US, and EUS in accurately diagnosing pancreatic cancer due to its higher sensitivity and specificity. While PET is well-established in the advanced stages of pancreatic cancer, the limited spatial resolution of FDG-PET restricts its effectiveness in the local staging of pancreatic cancer. Elevated glucose metabolism has been observed in precursor lesions, providing a window of opportunity to detect early changes and improve patient outcomes.[25]

In a retrospective study led by Keiichi Okano *et al*., the role of FDG-PET with dual-time-point evaluation in small pancreatic cancers (<2 cm) demonstrated higher standardized uptake values in the delayed phase compared to the early phase, suggesting malignancy in the lesions.[26]

In a small study led by Rakesh Kumar *et al*.,[27] the diagnostic performance of dual-time-point PET/CT was compared against CECT and EUS with FNA in diagnosing PDAC, particularly in the context of concomitant chronic pancreatitis (CP). These results are depicted in Table 1. In conclusion, in patients without concomitant CP and with larger lesions, PET/CT and CECT are equivalent as screening modalities, with no benefit from dual-time-point PET/CT acquisitions. However, in patients with concomitant CP and smaller lesions, dual-time-point PET/CT is better, with sensitivity comparable to EUS + FNA.

While imaging modalities, such as those discussed above, provide valuable insights into the location, size, and potential spread of pancreatic masses, they are often not definitive in confirming the nature of these lesions. To achieve a more definitive diagnosis, especially for identifying cancerous tissues at the molecular level, blood and tissue-based diagnostic tests become essential. These tests, though more invasive, offer greater specificity and sensitivity in confirming pancreatic cancer and are crucial in guiding treat-

Table 1. Diagnostic performance of various imaging modalities in patients with or without concomitant chronic pancreatitis

Diagnostic modality	Sensitivity	Specificity	Accuracy
With concomitant chronic pancreatitis			
Standard-Acquisition-PET/CT	97.4%	83.3%	94.0%
Dual-Time-Point-PET/CT	97.4%	75%	92%
CECT	94.6%	66.7%	87.8%
EUS + FNA	92.6%	88.9%	91.7%
Without concomitant chronic pancreatitis			
Standard-Acquisition-PET/CT	88.9%	57.1%	80%
Dual-Time-Point-PET/CT	100%	57.1%	88%
CECT	82.4%	57.1%	75%
EUS + FNA	100%	100%	100%

PET/CT, positron emission tomography/computed tomography; CECT, contrast-enhanced computed tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration.

ment decisions. In the following section, we will explore some of the key blood and tissue-based diagnostic approaches, focusing on biomarkers and molecular testing that aid in the accurate diagnosis of pancreatic cancer.

Blood and tissue-based tests for the diagnosis of pancreatic cancer

In this section, we delve into blood and tissue-based diagnostic strategies for pancreatic cancer, which remains one of the most challenging cancers to diagnose, especially in the early stages when it is often asymptomatic. Advancements in blood and tissue-based diagnostic tests have provided promising avenues for improved detection and monitoring. Key biomarkers such as carbohydrate antigen (CA) 19-9, a widely used glycoprotein, and microRNAs (miRNAs), which regulate gene expression, have shown potential in identifying pancreatic cancer. Innovative techniques like methylation on beads, which detect epigenetic changes, and circulating tumor DNA (ctDNA), which reflects tumor-specific mutations, offer non-invasive methods for early diagnosis. Additionally, autoantibodies produced in response to tumor-associated antigens, along with cytokines and chemokines that modulate the tumor microenvironment, are being explored for their diagnostic and prognostic value.

Beyond these markers, the integration of -omics technologies—such as proteomics, which analyzes protein expression patterns, and radiomics, which extracts quantitative features from imaging data—has further enhanced diagnostic precision. Multimarker analysis, combining multiple biomarkers and -omics approaches, holds particular promise for improving the accuracy and reliability of pancreatic cancer diagnostics, paving the way for personalized and targeted therapeutic strategies.

CA 19-9

To date, the serum CA 19-9 has been used as a biochemical marker for assessing clinical treatment efficacy in pancreatic cancer.

CA 19-9, initially identified as a tumor-specific antigen for colon cancer, also reacts with a glycoprotein present in pancreatic and biliary tract cancers, making it a biomarker for these malignancies.[28] However, its specificity is limited, as it can be elevated in benign conditions like pancreatitis, cholangitis, cirrhosis, and gastric cancer. Sensitivity (69–98%) and specificity (46–98%) for pancreatic cancer are moderate, and only 65% of patients with resectable pancreatic cancer show elevated levels.[29]

miRNAs

miRNAs are small, non-coding RNA molecules that play a vital role in regulating gene expression after transcription by binding to target messenger RNAs (mRNAs). This interaction can result in the degradation of the mRNA, destabilization through poly(A) tail shortening, or inhibition of protein translation. The dysregulation of miRNAs is linked to various cancers, as they can function as oncogenes or tumor suppressors, affecting cancer development and progression. Furthermore, miRNAs are released into extracellular fluids, acting as signaling molecules, making them valuable biomarkers for cancer diagnosis.[30]

In a study by Vicentini *et al*., MiR-1290 was found to be elevated in patients with resectable pancreatic cancer, effectively distinguishing them from control subjects. It showed superior diagnostic performance compared to the CA 19-9 marker, particularly in identifying low-stage pancreatic cancer. Additionally, miR-1290 levels were increased in patients with non-invasive intraductal papillary mucinous neoplasms (IPMNs), suggesting its potential as a marker for monitoring individuals at risk of developing invasive IPMNs.[31]

In the study led by Abue *et al*., miRNA-483-3p and miRNA-21 were significantly higher in PDAC. The plasma expression of miRNA-483-3p was considerably higher compared to intraductal papillary mucinous neoplasm ($p < 0.05$), and the expression of miRNA-21 was linked to advanced-stage disease ($p < 0.05$), with metastases in the lymph nodes and liver ($p < 0.01$). Indeed, miRNA expression correlated with a significantly reduced survival in those patients with pancreatic ductal adenocarcinoma ($p < 0.01$).[32]

A study by Yang *et al*. identified 38 miRNAs that were significantly dysregulated in pancreatic cancer patients compared to controls, leading to the development of two diagnostic panels. The first, Index I (comprising miR-145, miR-150, miR-223, and miR-636), achieved an area under the curve (AUC) of 0.86 (95% CI: 0.82–0.9), with a sensitivity of 85% and specificity of 64%. The second, Index II (including miR-26b, miR-34a, miR-122, miR-126, miR-145, miR-150, miR-223, miR-505, miR-636, and miR-885-5p), performed even better, reaching an AUC of 0.93 (95% CI: 0.90–0.96) with both sensitivity and specificity at 85%. Furthermore, combining Index I with the CA 19-9 biomarker

increased diagnostic accuracy, achieving an AUC of 0.94 (95% CI: 0.90–0.98) compared to CA 19-9 alone (AUC: 0.90, 95% CI: 0.87–0.94).[33]

MiRNAs offer promise as novel gene therapies, but their success has been limited due to the lack of consensus on testing and interpretation. miRNA levels vary between tissue and serum, where nucleases can easily degrade them. Additionally, multiple miRNAs may be implicated in a disease (as evidenced by Yang *et al*.), while the same miRNA might be implicated in multiple malignancies, making it difficult to validate in large population samples. The techniques for miRNA detection remain expensive, and significant research is required before it can be widely adopted.

Methylation on beads technique

Misregulated epigenetic mechanisms and DNA mutations are hallmarks of pancreatic cancer. Alterations in DNA promoter methylation patterns can significantly influence tumorigenesis and cancer progression. Consequently, numerous studies have explored DNA methylation analysis of specific genes for both clinical diagnostics and therapeutic purposes. It is used for early detection, prognosis assessment, prediction of therapeutic response, and as a therapeutic target.

The methylation on beads technique is a novel nanotechnology that enables the capture, retention, and bisulfite treatment of minute amounts of DNA. In a study by Yi *et al*., this method demonstrated a sensitivity of 81% and specificity of 85% for detecting pancreatic cancer using the BNC1 and ADAMTS1 gene promoters. These genes exhibited dense methylation in cancerous samples but not in normal or pancreatitis samples, suggesting a promising approach for early diagnosis.[34] Methylation rates increased with each disease stage and were higher than those of CA 19-9, except in stages III and IV, where both methylation and CA 19-9 reached 100%.[34]

A non-invasive technique that detects KRAS mutations and methylation biomarkers (such as NDRG4 and BMP3) in stool samples, delivered in a mail-in kit format similar to Cologuard for colon cancer, is currently under development for identifying DNA mutations in the digestive tract.[3] Similar to miRNAs, these biomarkers are still in the early stages of development, and further research is necessary to validate this innovative nanotechnology.

ctDNA

ctDNA is analyzed through a technique called liquid biopsy, wherein DNA shed by tumor cells into the circulation is isolated using polymerase chain reaction and next-generation sequencing to quantify and identify point mutations, epigenetic modifications, or translocations. Compared to tissue biopsy, it offers several advantages, including being non-invasive, capturing tumor heterogeneity, and complementing tissue biopsy. This technology holds promise for cancer screening, minimal residual disease detection, treatment response monitoring, and evaluation of drug resistance.

In addition to blood, liquid biopsy can use other body fluids, such as urine, saliva, and cerebrospinal fluid, and has become increasingly popular in clinical settings due to its minimally invasive nature.[35–38] The concentration of ctDNA in the blood of cancer patients ranges from 0−5 ng/mL to hover 1,000 ng/mL, while in healthy individuals, it typically ranges from 0−100 ng/mL.[39]

Lee *et al*. evaluated the prognostic role of *KRAS* ctDNA in a prospective cohort of patients with resectable PDAC. Using a polymerase chain reaction-based SafeSeq assay, the preoperative sensitivity for ctDNA detection was 62% (23 ctDNA-positive out of 37 *KRAS*-mutated tumors in tissue). Positive *KRAS* ctDNA identified a subset of patients with poorer outcomes compared to those with negative *KRAS* ctDNA [hazard ratio for recurrence-free survival: 4.1, $p = 0.002$; hazard ratio for overall survival (OS): 4.1, $p = 0.015$], consistent with findings in other tumor types.[40]

In a study by Watanabe *et al*., ctDNA was utilized to detect early recurrence of pancreatic cancer, particularly in cases with low tumor-cell content or complex tumor environments. The researchers employed molecularly barcoded ultradeep sequencing capable of detecting low-frequency mutations. Despite these advanced techniques, the ctDNA detection rate in resected patients remained modest at 39% (28 out of 71), aligning with earlier findings of a 38% detection rate in preoperative samples. However, using a tumor-informed approach, detection rates improved to 56% in treatment-naïve samples. Notably, patients with detectable KRAS and TP53 mutations in ctDNA before surgery had significantly shorter recurrence-free survival, further supporting ctDNA's role as a prognostic biomarker for PDAC.[41]

Another study by the same group reinforced the use of ctDNA as a prognostic marker and introduced a clinically feasible approach for its application. This research examined ctDNA for predicting therapeutic outcomes in patients with unresectable pancreatic cancer, emphasizing its role in identifying chemotherapy resistance. A novel regression assessment framework was developed, integrating genomic analysis of resected specimens with liquid biopsy data. This method offered critical insights into treatment efficacy and recurrence risk. Monitoring changes in ctDNA levels alongside CA 19-9 during chemotherapy provided valuable information on tumor dynamics, aiding clinical decisions and potentially minimizing unnecessary adverse effects.[42] These findings emphasize the need for larger, multicenter studies to validate the clinical utility of ctDNA and support its incorporation into personalized treatment strategies aimed at improving survival in pancreatic cancer patients.

Autoantibodies

Efforts are ongoing to harness autoantibodies as diagnostic tools for PC, despite challenges such as tumor heterogeneity and low detection rates (10–20%). A study by Tomaino *et al*.[43] screened serum samples from PC patients, chronic pancreatitis (CP) patients, individuals with non-PC tumors, and healthy controls using proteins from PC cell lines (CF-PAC-1, MiaPaCa-2, BxPC-3). They identified autoantibodies against metabolic enzymes such as triosephosphate isomerase and cytoskeletal proteins like keratin.

Additionally, Bracci *et al*. evaluated autoantibodies against CTDSP1, MAPK9, and NR2E3 in 300 PC patients and 300 controls, finding significantly higher antibody responses in PC patients for CTDSP1 ($p = 0.004$), MAPK9 ($p = 0.0002$), and NR2E3 ($p = 0.0001$). Although the combined biomarker set did not exhibit strong predictive value, the study marks progress in validating autoantibodies as potential diagnostic and prognostic markers for pancreatic cancer. Notably, the presence of these autoantibodies months to years before the onset of clinical symptoms suggests their potential utility for early detection and disease prognosis.[44]

Cytokines and chemokines

Cytokines and chemokines are used as both diagnostic and prognostic markers. Ingvarsson *et al*. utilized a recombinant antibody microarray targeting 60 serum proteins to identify differentially expressed proteins in the serum of PC patients compared to healthy controls. This platform was further optimized to differentiate between short-term (<12 months) and long-term (<24 months) survivors. The study found that IL-1α, IL-3, IL-8, and IL-11 were

upregulated in short-term survivors, while RANTES, IL-16, IL-4, and eotaxin were upregulated in long-term survivors.[45] A weak association was observed between elevated sTNF-R2 levels and pancreatic cancer (OR: 1.52), along with a strong correlation with diabetes and higher BMI. VEGF and bFGF levels were significantly elevated in the serum of pancreatic cancer patients, correlating strongly with CA19-9, tumor size, and stage, suggesting their potential as diagnostic or prognostic markers. However, this technology requires validation in large-scale human studies before it can be translated to clinical use.

While blood and tissue-based tests, as detailed above, provide valuable insights into the diagnosis and prognosis of pancreatic cancer, there is an increasing shift toward more comprehensive, molecularly detailed approaches in the form of -omics studies, especially in research settings. These advanced techniques, such as proteomics and radiomics, allow for the analysis of vast datasets and provide a deeper understanding of the biological processes underlying pancreatic cancer.

Omics studies and multimarker analysis

By investigating protein expression profiles (proteomics) or extracting quantitative features from medical imaging data (radiomics), these studies offer the potential for identifying novel biomarkers, discovering new therapeutic targets, and improving patient stratification. In the following sections, we will explore how these cutting-edge omics technologies are revolutionizing pancreatic cancer research, enabling more precise diagnoses, personalized treatment plans, and better clinical outcomes.

Proteomics

Proteomics is the large-scale study of proteins, particularly their functions and structures. It involves analyzing the entire complement of proteins produced by a cell, tissue, or organism at a specific time, often under defined conditions. In the context of cancer liquid biopsies, proteomics plays a crucial role in identifying protein biomarkers that can aid in cancer detection, diagnosis, and treatment monitoring. Unlike nucleic acid analysis, which focuses on DNA or RNA, proteomics offers insights into the functional state of cells, as proteins are the primary executors of cellular processes and often serve as direct drug targets in many cancer therapies.[46] Given the dynamic nature of the proteome, influenced by factors such as post-translational modifications and cellular responses to stimuli, proteomics provides valuable information that can enhance the accuracy of cancer diagnostics and therapeutic strategies. Advances in high-plex proteomic technologies have significantly improved the ability to analyze numerous protein targets simultaneously from liquid biopsy samples, paving the way for a better understanding of tumor biology and personalized cancer treatment.[47]

Proteomics approaches have been employed to identify protein markers associated with pancreatic cancer.[48,49] Several research groups, using surface-enhanced laser desorption ionization, have identified protein fragments in serum that appear to serve as diagnostic markers with comparable effectiveness to serum CA19-9.[50,51] Another mass spectrometry technique, matrix-assisted laser desorption ionization, has also revealed pancreatic cancer-related proteins in serum.[52] Key proteins linked to pancreatic tumor development, including galectin-1, gelsolin, lumican, 14-3-3 protein sigma, cathepsin D, cofilin, moesin, and plectin-1, have been uncovered through proteomics studies.[48,53] Notably, gelsolin and lumican were tested as composite biomarkers in plasma, demonstrating 80% sensitivity and 95% specificity in distinguishing early-stage pancreatic cancer patients (stages I and II) from healthy controls and patients with chronic pancreatitis, utilizing targeted proteomics assays based on selected reaction monitoring.[54] Although proteomics is still an evolving and challenging field in pancreatic cancer research, it has already provided essential insights into disease mechanisms and holds the potential for advancing early detection of pancreatic cancer.

Radiomics

Radiomics is an advanced analytical approach that uses computer software to extract and analyze both quantitative and qualitative features from medical images (DICOM), such as CT, MRI, and PET scans. This process involves several steps, including image acquisition, dataset creation, export of DICOM studies, segmentation to identify the volume of interest, feature extraction, and the development of predictive models. It enables precise tumor delineation and assessment of the tumor microenvironment.

The integration of radiomic features with genomic and molecular data—referred to as radiogenomics—can improve diagnosis and help stratify patients based on their individual tumor biology. The incorporation of convolutional neural networks into radiomic analyses enhances performance compared to traditional machine learning algorithms, further improving the utility of deep learning in medical image analysis.

Attiyeh *et al*.[55] explored the relationship between radiomic variables and tumor genotype in pancreatic cancer, focusing on genes such as KRAS, TP53, CDKN2A, and SMAD4. Among 35 patients, 34 had KRAS mutations, 29 exhibited CDKN2A mutations, 16 showed SMAD4 alterations, and 29 had TP53 expression. The number of altered genes was predictive of OS (p = 0.016), with significant separation between tumors with and without SMAD4 alterations. A higher mutation count was associated with increased imaging heterogeneity. The study revealed that radiomic features from CT scans were linked to genotype and stromal content, which could be useful in developing survival prediction tools.

Sandrasegaran *et al*.[56] examined texture analysis for prognostic prediction in 70 patients with unresectable pancreatic cancer, evaluating features such as mean, kurtosis, entropy, skewness, and tumor characteristics in relation to OS and progression-free survival. They reported a median survival of 13.3 months and progression-free survival of 7.8 months, concluding that OS was associated with texture features, particularly in patients undergoing curative-intent surgical resection.

Another study led by Ren S *et al*. evaluated the CT imaging features, specifically texture analysis, from arterial and portal phase CT images, to differentiate mass-forming pancreatitis (MFP) from PDAC.[57] The group found that arterial CT attenuation, along with arterial and portal enhancement ratios, were significantly higher in MFP than in PDAC. In multivariate analyses, arterial CT attenuation and the pancreatic duct penetrating sign were identified as independent predictors of distinguishing MFP from PDAC. While this study was conducted on a small group of 30 patients, it highlights the potential of radiomics as a promising non-invasive tool for diagnosing pancreatic tumors and differentiating them from non-malignant conditions.

In patients undergoing neoadjuvant therapy for pancreatic cancer, radiomics can contribute to a more accurate definition of lesions for radiotherapy and facilitate the assessment of treatment response. This approach offers more reliable and reproducible tumor measurements compared to traditional methods. The integration of radiomics with genomic data also holds significant potential for

future advancements. However, there are several limitations that can influence the results of radiomic analysis. Factors such as CT acquisition protocols, reconstruction methods, kernel selection, tube currents, slice thickness, voxel size, gray level, and contrast enhancement timing can all impact outcomes. Standardization of image acquisition protocols and radiomic analysis systems is essential, as is the establishment of validation cohorts. Continued research is crucial to strengthen the existing data.[58]

Multimarker analysis

Various individual biomarkers have been explored for diagnosing PDAC, as utilizing a single marker simplifies the development and application of diagnostic assays in clinical settings. However, these biomarkers often exhibit limited sensitivity and specificity. Given the significant variability among patients and the heterogeneity of tumors, employing a multimarker panel may offer additional benefits and generally performs better than single biomarkers.[59]

Several studies have documented the good performance of PDAC-specific multimarker panels for detecting early-stage PDAC.[60] However, for these markers to be used in screening high-risk groups, their sensitivity and specificity need to be higher to reduce false positives and false negatives. Achieving high sensitivity in detecting PDAC presents significant challenges, particularly due to the overlap of biomarkers and mutations, such as RAS mutations, with other malignancies (e.g., colorectal cancer), benign pancreatic conditions (e.g., pancreatitis), and precancerous lesions like IPMN.[61] These alternative conditions are more prevalent in the general population than PDAC itself, which complicates diagnostic accuracy. To reduce false positives and improve understanding of the molecular mechanisms behind PDAC tumorigenesis, it is essential to include individuals with precancerous conditions, pancreatitis, and pancreatic cysts in research studies. Given these factors, a strategy for screening PDAC should be integrated into broader pan-cancer screening initiatives rather than pursued as a standalone diagnostic approach.

A panel of multiple biomarkers can facilitate simultaneous screening for various cancer types, allowing for broader application across diverse populations. Two notable multimarker tests, CancerSEEK and Galleri (developed by GRAIL),[62,63] have been designed to detect early-stage tumors, including PDAC. The CancerSEEK panel combines ctDNA with eight specific proteins—CA-125, carcinoembryonic antigen (CEA), CA 19-9, PRL, HGF, OPN, MPO, and TIMP-1—enabling detection of ovarian, liver, stomach, pancreatic, esophageal, colorectal, lung, and breast cancers. Currently, CancerSEEK is utilized exclusively in clinical trials (NCT04213326). In contrast, the Galleri test, which is commercially available, analyzes whole-genome methylation patterns of cell-free DNA to identify over 50 different cancer types. In an independent validation study involving 4,077 participants, the Galleri test demonstrated the ability to correctly identify 35 out of 41 patients with early-stage pancreatic cancer, achieving a sensitivity of approximately 60% and a specificity of 99.5%.[64]

A prospective study with 6,662 participants utilizing the Galleri test identified suspicious cancer signals in 92 cases. Follow-up after 12 months confirmed that 35 of these 92 participants (38%) were diagnosed with cancer, while 6,235 of the remaining 6,549 individuals were correctly identified as true negatives. This highlights the potential of multicancer early detection testing. Notably, this study by Schrag *et al*. provides significant insights into the clinical applicability of multicancer early detection tests, even among individuals not considered high-risk.[65]

Furthermore, another study (THUNDER), which focused on the methylation patterns of cell-free DNA, reported high sensitivity for detecting advanced-stage pancreatic tumors. However, it showed a sensitivity of only around 35% for stages I and II, despite achieving a specificity of 98.9% in identifying pancreatic malignancies.[66]

Although the specificity of these diagnostic tests is satisfactory, their sensitivity for detecting early-stage PDAC is inferior to that of PDAC-specific biomarker panels. This indicates that individuals in high-risk groups may require a specialized PDAC screening approach to improve early detection. False-negative results could lead to unnecessary additional diagnostic procedures, increasing healthcare costs and causing psychological distress for patients. For advanced-stage cancers, however, the sensitivity of these tests is relatively high, ranging from 80% to 100%. Consequently, prioritizing research focused on early-stage cancer detection is critical for developing a reliable multicancer diagnostic tool, which would significantly improve the overall efficacy of cancer screening programs.

Having established the crucial role of early and accurate diagnosis in pancreatic cancer, it is equally important to explore available treatment options. Once a diagnosis is confirmed, the choice of treatment depends on several factors, including the stage of the disease, the patient's overall health, and the types of markers expressed by the underlying malignancy. In the following section, we will explore both conventional and advanced treatment options, examining their main advantages and disadvantages.

Treatment approaches

Pancreatic cancer is difficult to treat due to its rapid growth and the limited availability of effective treatments. The pathomechanisms governing the growth and spread of this cancer involve several key pathways in the body, including the phosphoinositide 3-kinase/protein kinase B pathway, RAS, Janus kinase/signal transducer and activator of transcription, NF-κB, Hippo/Yes-kinase-associated protein, and Wingless/int1 pathways.

These pathways are involved in many cellular functions that are critical for pancreatic cancer, such as cell death, blood vessel formation, cell differentiation, immune system regulation, metabolism, cell movement, and cell growth. Additionally, modifications in histone regulation are crucial for the process of epithelial-to-mesenchymal transition, which is associated with this cancer. Understanding and targeting these pathways could help develop new treatments for pancreatic cancer.

Targeting HRD pathways

Defects in DNA damage response genes that lead to HRD highlight a significant subgroup of patients with PDAC, with important implications for treatment and prevention.[67]

Recent nonrandomized clinical trials suggest that HRD may be a useful biomarker for predicting response to platinum-based chemotherapy in patients with advanced PDAC.[68] In those with HRD, inherited mutations in BRCA1 and BRCA2 predict increased progression-free survival for patients with platinum-sensitive metastatic PDAC treated with the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib as maintenance therapy.[69] Beyond BRCA mutations, accumulating preclinical and phase II nonrandomized trial evidence suggests that other non-BRCA HRD mutations may also predict sensitivity to PARP inhibitors. Other DNA damage response-targeting treatments are being explored in clinical trials, including immunotherapy and inhibitors of ATM, ATR, and WEE1.[70]

Table 2. Other forms of therapy targeting claudin 18.2 (CLDN 18.2)

Type of therapy	Mechanism	Examples
Bispecific antibodies	These can bind two different epitopes on the same or different antigens and therefore enhance therapeutic potential. They also have more efficacy and less off-site toxicity as compared to some monoclonal antibodies	AZD 5863 (NCT06005493)
Antibody-Drug conjugates	Have strong anti-cancer efficacy through antibody-dependent cellular cytotoxicity and endocytosis	CMG901, LM-302
CAR T-cell therapy	It is like administering a living drug to the patient, and these therapies are customized to meet each patient's specific needs. The process involves collecting T cells from the patient and modifying them in the laboratory to produce CARs on their surfaces. These CARs can recognize and bind to tumor antigens, found on the surface of cancer cells, and kill them	CT041, LY011 (NCT04977193, NCT04966143), LB1908 (NCT05539430), HEC-016 (NCT05277987), KD-496 (NCT05583201), and CT048 (NCT05393986)

CAR, Chimeric antigen receptor.

Platinum-based therapy

Numerous studies have consistently shown that patients with PDAC and HRD benefit from platinum-based chemotherapy combinations.[71] A retrospective analysis from the PanCan Know Your Tumor registry found that PDAC patients with actionable molecular alterations had significant advantages from genomically matched therapies.[72] Specifically, the median overall survival for these patients receiving matched therapies was about one year longer than for those receiving unmatched therapies or those without actionable alterations, with HRD mutations being the most frequently observed.[72] Other retrospective studies and prospective trials have confirmed these findings, thus establishing platinum chemotherapy as a standard practice for this patient group.[71]

PARP inhibitors

Using olaparib as maintenance therapy after at least four months of frontline platinum-based chemotherapy is now a recognized standard for patients with germline BRCA1/2 mutations in PDAC.[69] However, resistance to PARP inhibitors remains a significant challenge. Ongoing trials aim to build on the findings from the POLO trial by exploring combinations of PARP inhibitors with immunotherapy.[73] Recent prospective trials have expanded the eligibility for PARP inhibitors to include patients with somatic BRCA2 mutations and germline PALB2 mutations.[71] A crucial unmet need is developing strategies to induce HRD or overcome resistance to HRD-targeted therapies, thus increasing the number of patients who could benefit from these treatments.

Immune checkpoint inhibitors (ICIs)

ICIs have shown effectiveness in a selected group of patients with pancreatic adenocarcinoma. A recent report by Terrero *et al*. detailed a group of 12 patients with pathogenic germline variants in BRCA1/2 or RAD51C/D, with some achieving long-lasting complete responses to combined PD-1 and CTLA-4 inhibition. The overall response rate was 42%, including four patients who had complete responses lasting 24 to 48 months, along with one patient showing a partial response.[74] Terrero *et al*. measured archival tumor samples using the Nanostring platform and found that tumors from responders had significantly higher expression levels of CCL4, CCL5, and CXCL10 compared with non-responders. These co-regulated chemokines are responsible for the migration of immune cells into the tumor microenvironment, which has been associated with a T-cell-inflamed phenotype in PDAC. Cumulatively, these preclinical and translational data suggest that this may be one of the few exceptions to the general rule of PDAC's unresponsiveness to ICI therapies.

Reiss *et al*. found that the combination of ipilimumab and niraparib was superior in maintaining treatment response compared to nivolumab and niraparib in metastatic PDAC patients who responded to initial platinum therapy, emphasizing the importance of CTLA-4 inhibition for this subgroup.[75]

CLDN18.2 as a treatment target

Claudin18.2 is highly expressed in both pancreatic adenocarcinoma and its metastases, with patients showing elevated levels of this marker often experiencing better survival outcomes.[76] Current research on therapies targeting claudin18.2—including monoclonal antibodies, bispecific antibodies, antibody-drug conjugates, and chimeric antigen receptor (CAR) T-cell treatments—is advancing rapidly, offering promising new options for pancreatic cancer treatment.

Monoclonal antibodies—the emerging potential of claudin 18.2

Zolbetuximab (IMAB362)

Zolbetuximab (IMAB362) is a monoclonal antibody specifically targeting claudin18.2. It induces antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity by binding to tumor cell surfaces, potentially leading to cell death.[77]

The effectiveness of Zolbetuximab correlates with claudin18.2 expression levels. An ongoing study (NCT03816163) is evaluating the safety and efficacy of combining Zolbetuximab with nab-paclitaxel and gemcitabine in claudin18.2-positive metastatic pancreatic adenocarcinoma patients.[76] Zolbetuximab has already been approved for first-line treatment of metastatic pancreatic cancer in China and could become the world's first marketed monoclonal antibody targeting claudin18.2.

TST001

TST001, developed after IMAB362, is another monoclonal antibody targeting claudin18.2. It shows enhanced affinity and binding activity, resulting in improved natural killer cell-mediated ADCC.[78] Preclinical studies suggest that TST001 exhibits strong anti-tumor effects and works synergistically with immune checkpoint inhibitors.[79] An ongoing trial (NCT04396821) is investigating the safety and tolerability of TST001 in patients with advanced or metastatic solid tumors, including pancreatic adenocarcinoma. Other monoclonal antibodies targeting claudin18.2, such as ASKB589, M108, MIL93, NBL-015, and ZL-1211, are also being evaluated in clinical trials.[76]

Table 2 provides further details on additional therapies being developed to target claudin18.2.[80–82]

Role of immunotherapy

Pancreatic cancer is considered non-immunogenic and immunologically "cold" because it does not respond well to common ICIs like anti-PD-1 and anti-CTLA-4. This resistance is largely due to the immunosuppressive environment of the tumor microenvironment (TME). While immune checkpoint blockade (ICB) has been highly successful in other cancers, PDAC has shown minimal responses to ICB alone, with overall response rates of 0% for ICB monotherapy and only 3% when combined with anti-PD-1 and anti-CTLA-4 antibodies.[83]

In light of this, several promising immunotherapeutic approaches, including non-checkpoint-directed therapies, are being explored. Many of these therapies are still in clinical trials and are not yet widely available.

Oncolytic virus therapy

Oncolytic virus therapy uses specially engineered viruses that infect and destroy cancer cells, triggering an immune response by releasing tumor antigens into the bloodstream. These oncolytic viruses have unique properties that make them an attractive treatment option for pancreatic cancer. Current research is focused on applying various oncolytic DNA and RNA viruses to specifically target and invade cancer cells.[84]

1. Talimogene laherparepvec (T-VEC or OncoVEXGMCSF) is the first oncolytic virus approved by the United States Food and Drug Administration (hereinafter referred to as FDA) for melanoma treatment. This virus is derived from Herpes simplex virus (HSV) and contains the GM-CSF gene in its genome. T-VEC has demonstrated potent lytic activity against various tumor cell lines, including those from pancreatic cancer.[85]
2. HF10, originating from HSV-1 and undergoing an unexpected mutation, can effectively attack tumors while sparing healthy tissue. It can be safely administered via direct injection for the treatment of locally advanced pancreatic cancer, especially when combined with erlotinib and gemcitabine.[86]
3. VCN-01, an oncolytic adenovirus, is engineered to replicate within cancer cells with a defective RB1 pathway. The virus produces hyaluronidase, which helps it spread through the tumor and facilitates the delivery of chemotherapy drugs and immune cells into the cancerous tissue.[87] In animal models of PDAC, VCN-01 demonstrated enhanced anti-cancer activity when combined with chemotherapy. Clinical studies have shown that VCN-01 can be safely administered intravenously to PDAC patients, with manageable adverse events, highlighting its positive tolerability profile.[88] These findings lay a strong foundation for the future application of oncolytic virus therapy in pancreatic cancer treatment.
4. Two other HSV-derived oncolytic viruses, NV1020 (r7020) and G207, have also shown effectiveness in attacking and destroying human pancreatic cancer cells both *in vitro* and *in vivo*.[89]
5. ONCOTECH is a promising new technology that combines oncolytic adenoviruses (OAs) with T cells to improve the delivery of these viruses to tumors. The engineered OAs specifically target the immune checkpoint protein PD-L1. In mouse models of PDAC, ONCOTECH significantly increased the presence of OAs within tumor cells, leading to a reduction in PD-L1 expression and improved survival rates. This strategy of combining virotherapy and cell therapy shows great promise in cancer treatment.[90]

Additionally, multiple clinical trials are investigating the effectiveness of various oncolytic virus therapies for pancreatic cancer. For example, a Phase I/II trial found that combining intratumoral injections of LOAd703, an oncolytic adenovirus with transgenes for CD40L and 4-1BB ligand, with standard nab-paclitaxel/gemcitabine chemotherapy was both safe and feasible. The treatment achieved an overall response rate of 44% and a disease control rate of 94% in patients with unresectable or metastatic PDAC.[89]

Adoptive cell transfer therapy

Adoptive cell transfer therapy is a promising form of immunotherapy with significant potential for cancer treatment. This approach involves using the patient's own immune cells, particularly T cells, to combat the disease. These cells are often collected, expanded, and modified to enhance their ability to target and fight cancer.[91] The FDA's approval of CAR T-cell therapy for certain blood cancers has greatly advanced research in this field. Modified T cells are engineered to specifically recognize tumor cells based on their distinct molecular characteristics.

Several immunotherapeutic approaches are associated with adoptive cell transfer therapy, including:

Tumor-infiltrating lymphocyte (TIL) therapy

TILs are immune cells that naturally migrate to the tumor microenvironment. TIL therapy is an exciting strategy in which a patient's TILs are collected after surgical tumor removal, expanded outside the body, and then reinfused into the patient.[92,93]

Techniques to enhance the production and activity of TILs include inhibiting the PD-1 receptor, activating the CD137 receptor, and boosting the levels of $CD8^+$ T cells. Research has shown that functionally expanded TILs from pancreatic tumors can recognize tumor-associated antigens specific to pancreatic cancer.[94] A meta-analysis indicates that long-term outcomes for patients with PDAC are strongly associated with specific TIL types, particularly $CD8^+$ T cells.[95]

Currently, two clinical trials are recruiting participants to investigate TIL therapy for metastatic PDAC (NCT03935893 and NCT01174121). The first trial will assess the effectiveness of autologous TILs combined with fludarabine and cyclophosphamide, while the second trial will explore the efficacy of young TILs combined with aldesleukin (recombinant IL-2), pembrolizumab, cyclophosphamide, and fludarabine. The young-TIL approach involves minimal *in vitro* culturing and does not require pre-selection for tumor recognition before rapidly expanding and infusing the TILs into patients. This method has shown response rates similar to those of screened TILs, without adding extra toxicities.[96]

Genetically modified T-cell therapy

1. *T-cell receptor (TCR)-engineered T-cell therapy.* TCR-engineered T-cell therapy involves modifying T cells outside the body to express TCRs that can recognize specific tumor antigens, including hard-to-target intracellular driver mutations such as KRAS. TCRs can identify peptides presented by both MHC class I and II molecules.[97] A phase I clinical trial (NCT04809766) is currently investigating the safety and effectiveness of autologous mesothelin (MSLN)-specific TCR T cells in patients with stage IV pancreatic cancer. In this trial, patients receive autologous MSLN-specific TCR T cells alongside treatments like bendamustine, cyclophosphamide, and fludarabine. After undergoing leukapheresis, patients receive three infusions of TCR-MSLN cells every 21 days, with the primary focus on assessing safety and identifying any dose-limiting toxicities.
2. *CAR T-cell therapy.* CAR T-cell therapy can be thought of as a living drug administered to patients. These therapies are customized to meet each patient's specific needs. The process in-

volves collecting T cells from the patient and modifying them in the laboratory to produce CARs on their surfaces. These CARs can recognize and bind to specific proteins, known as tumor antigens, found on the surface of cancer cells. While CAR T-cell therapy has shown impressive results in treating certain types of B-cell leukemia and lymphoma, it faces several challenges that hinder its broader application in treating solid tumors. Key issues include life-threatening toxicities, cytokine release syndrome (CRS), limited anti-tumor effectiveness, antigen escape, and difficulties with T-cell trafficking.[98,99]

A significant barrier to the effective use of CAR T-cell therapy for PDAC is the scarcity of suitable tumor-specific antigens. Research by Schäfer *et al*. identified CD318, TSPAN8, and CD66c as potential target molecules for CAR T-cell immunotherapy in PDAC, based on an analysis of 371 antigens.[100]

The various therapeutic targets for CAR T-cell therapy under study in pancreatic cancer include B7H3 (CD276), fibroblast activation protein, human epidermal growth factor receptor 2, MSLN, CD22, CD70, CEA, and epidermal growth factor receptor (EGFR).[89]

3. *CAR-natural killer (NK) cell therapy.* CAR-NK cell therapy is an emerging approach in cancer treatment that aims to enhance the anti-cancer capabilities of NK cells. In this therapy, NK cells are engineered to express CARs that specifically recognize antigens on cancer cells, allowing them to more effectively target and eliminate these cells.[101] Compared to CAR T cells, CAR NK cells offer several advantages. Their shorter lifespan reduces the risk of inadvertently damaging healthy cells, known as on-target/off-tumor toxicity. Additionally, the specific cytokines they produce lower the risk of CRS and neurotoxicity. Their decreased likelihood of alloreactivity also enables the creation of off-the-shelf allogeneic CAR NK cells sourced from NK cell lines.[102]

   However, some challenges limit the widespread use of CAR NK cell therapy in clinical settings. Key issues include difficulties in selecting appropriate antigens, the variability of antigens among tumors, choosing suitable donors, designing effective CARs, and the complexities of producing and storing CAR NK cells. Furthermore, considerations regarding the ability of NK cells to infiltrate tumors and their short lifespan are also important factors to address.[102,103]

   When targeting ROBO1, CAR-NK cell immunotherapy combined with radiation therapy demonstrates enhanced effectiveness in treating human PDAC in an orthotopic mouse model.[104] Research has shown that a novel NK cell-based immunotherapy targeting PSCA effectively inhibits PSCA+ pancreatic cancer both *in vitro* and *in vivo*, producing promising results without systemic toxicity. Additionally, a fusion of CAR-NK cells aimed at MSLN, combined with cGAMP (a STING agonist), resulted in reduced tumor growth and improved survival.[105]

   Two clinical trials have been registered to test ROBO1 and mucin 1-specific CAR NK cells in patients with pancreatic cancer (NCT03941457 and NCT02839954), focusing on safety and overall response rates. PSCA has emerged as a notable target in pancreatic cancer immunotherapy, with CAR-NK cells targeting this antigen showing significant efficacy against advanced PDAC while avoiding harmful systemic effects. These encouraging results support the continuation of clinical trials.

   Recent advancements in genetic engineering have significantly enhanced the therapeutic efficacy of NK cells by improving their cytotoxic potential, persistence, and tumor infiltration. CRISPR/Cas9-mediated genome editing has facilitated precise modifications, such as the knockout of inhibitory receptors that dampen NK cell activation and the integration of CAR constructs into optimal genomic loci to enhance functionality.[106] Additionally, the deletion of cytokine-inducible SH2-containing protein has been shown to improve NK cell metabolic fitness, leading to prolonged survival and increased anti-tumor activity.[107] Furthermore, engineering strategies aimed at enhancing tumor infiltration have focused on overexpressing chemokine receptors, such as CXCR2, CXCR4, and CCR7, which direct NK cells to tumor sites expressing corresponding ligands. Efforts to reduce fratricide among CAR NK cells have led to the development of inhibitory CAR receptors that prevent self-targeting, while allogeneic applications have been optimized through beta-2 microglobulin knockout strategies to evade immune rejection. These advancements collectively contribute to the development of more robust and persistent NK cell therapies.[108]

   In parallel, innovative approaches in NK cell sourcing have addressed the challenges of scalability and clinical applicability, ensuring a consistent and functional cell supply for therapeutic use. Induced pluripotent stem cell (iPSC)-derived NK cells have emerged as a renewable and standardized source, allowing for precise genetic modifications at the pluripotent stage before differentiation. These cells have demonstrated enhanced ADCC when engineered with high-affinity, non-cleavable CD16 receptors, making them highly effective in combination therapies.[109] Additionally, umbilical cord blood-derived NK cells offer a highly proliferative alternative, with *ex vivo* expansion strategies utilizing optimized cytokine cocktails to maintain cytotoxic potential.[110] These advancements in NK cell sourcing are critical to the broader clinical application of NK cell-based immunotherapies.

   In the context of pancreatic cancer, engineered NK cell therapies have been developed to counteract the highly immunosuppressive TME that limits NK cell infiltration and function. One approach involves the use of chimeric antigen receptor-modified NK cells designed to target tumor-associated antigens specifically expressed in pancreatic cancer, thereby enhancing cytotoxicity. Additionally, strategies aimed at reversing immune suppression within the TME, such as the inhibition of transforming growth factor-beta signaling, have been explored to enhance the persistence and efficacy of adoptively transferred NK cells.[108] These efforts collectively aim to improve NK cell-based therapeutic responses in pancreatic cancer, a malignancy that has historically been challenging to treat with immunotherapy.

4. *Cytokine-induced killer (CIK) cell therapy.* CIK cells are a diverse group of $CD8^+$ T cells derived from lymphocytes collected from human peripheral blood. They are expanded *ex vivo* using an anti-CD3 antibody, IFN-γ, and IL-2. CIK cells can kill cancer cells through mechanisms involving FasL and perforin. They are categorized into two main subsets based on the presence of the CD56 surface molecule: one subset expresses both CD3 and CD56, while the other expresses CD3 but lacks CD56.[111] The use of CIK cells in cancer treatment has been shown to be both effective and safe, resulting in improved survival rates for patients with various tumors. When combined with chemotherapy, CIK cell therapy further enhances the prevention of cancer recurrence and boosts patient prognosis.

   Recent research has explored CIK cells as a potential second-line treatment for advanced pancreatic cancer, yielding positive results whether used alone or in combination with other therapies. In a phase II clinical trial, patients with gemcitabine-refractory advanced pancreatic cancer who received CIK cell

therapy had a median overall survival of 6.2 months.[112] Additionally, gemcitabine-resistant patients treated with CIK cells alongside S-1, an oral fluoropyrimidine derivative, achieved a median overall survival of 6.6 months, outperforming the 6.1 months seen in those treated with S-1 alone.[113]

5. *Immune checkpoint-oriented immunotherapy.* Immunotherapy has emerged as a key component of cancer treatment, largely due to the success of ICB, highlighted by the approval of ipilimumab in 2011. By targeting specific inhibitory immune checkpoints such as CTLA-4, PD-1, and PD-L1, ICB effectively interrupts or reverses the acquired peripheral tolerance to cancer antigens, thereby restoring T-cell activation.[114]

Inhibitory immune checkpoints

1. *PD-1/PD-L1 axis.* The PD-1/PD-L1 axis has been explored in pancreatic cancer following successful anti-PD-1/PD-L1 treatments in melanoma. PD-1, a member of the B7-CD28 protein family, is linked to T-cell exhaustion, while its ligands, PD-L1 and PD-L2, are expressed by various cells, including tumor cells and immune-suppressive cells. When PD-1 binds to PD-L1, it inhibits T-cell activation, leading to exhaustion.[115,116] Some cancers have shown positive responses to PD-1/PD-L1 inhibitors, but responses can vary significantly among patients, suggesting that other ligands, like PD-L2, may also influence treatment efficacy, particularly in pancreatic cancer. Research indicates that PD-L2 is upregulated in chemotherapy-induced senescent cancer cells, helping them evade the immune system. Blocking PD-L2 in combination with chemotherapy has led to tumor regression in mice, indicating a potential therapeutic avenue.[117,118]

   Additionally, combination therapies targeting both PD-L1 and CCL5 have demonstrated benefits in pancreatic cancer by reducing regulatory T cell and tumor-associated macrophage infiltration, activating $CD8^+$ T cells, and enhancing overall survival.[119] Further combinations, such as anti-TNFR2 with PD-L1 antibodies, have shown promise by diminishing regulatory T cell (Treg) and macrophage infiltration while boosting $CD8^+$ T cell activation.[120] Novel approaches, such as a bispecific immunocytokine targeting PD-1 and IL-2Rβγ, have also been effective in reducing tumor progression when combined with radiotherapy.[121]
2. *CTLA-4 (CD152).* CTLA-4, primarily found on Tregs, inhibits T-cell activation by suppressing co-stimulatory signals and removing CD80 and CD86 from antigen-presenting cells. This interaction regulates T-cell entry into the pancreatic cancer microenvironment.[115] Blocking CTLA-4 can facilitate the infiltration of $CD4^+$ and $CD8^+$ T cells into tumors, leading to tumor regression via a mechanism dependent on T cells and CXCR3.[122]
3. *LAG-3.* The LAG-3 signaling pathway allows cancer cells to evade immune detection by diminishing T-cell functionality and hindering the activation of dendritic cells that promote T-cell growth. LAG-3 also regulates T-cell proliferation and can enhance immunosuppression via Tregs. Patients with pancreatic cancer exhibiting LAG-3 on tumor-infiltrating lymphocytes tend to have poorer disease-free survival rates.[123] Targeting LAG-3, alongside other checkpoints, may enhance antitumor immunity.
4. *T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain (TIGIT).* TIGIT is expressed on immune cells and inhibits T-cell activation by binding to CD155 and CD112, generating suppressive signals. It can also compete with activating receptors, further dampening T-cell responses. Increased expression of PD-1 and TIGIT has been observed in tumor-infiltrating T cells. To boost $CD8^+$ T-cell responses against tumors, co-blocking the TIGIT and PD-1 pathways may be necessary.[124] Co-blockade has been shown to rejuvenate tissue-resident memory T cells in pancreatic cancer and enhance the effectiveness of vaccinations.[125] Moreover, the CD155/TIGIT axis plays a crucial role in immune evasion in pancreatic cancer, and combining TIGIT and PD-1 blockade may provide a promising therapeutic strategy.

Cancer vaccines

Cancer vaccines are being actively studied in the context of pancreatic cancer, though many remain in pre-clinical stages. These vaccines include whole tumor cell vaccines, DNA vaccines, dendritic cell vaccines, mRNA vaccines, and peptide vaccines. While conventional immunotherapies are often effective against cancers with identifiable surface antigens, cancer vaccines have the advantage of targeting a broader range of intracellular antigens.[89]

Whole tumor cell vaccines

Whole tumor cell vaccines are a direct approach to tumor immunotherapy, incorporating both $CD4^+$ helper T-cell and cytotoxic T lymphocyte (CTL) epitopes. One example is Algenpantucel-L (NLG0205), which demonstrated an 86% one-year survival rate, 51% at two years, and 42% at three years when combined with gemcitabine and 5-fluorouracil in a phase II study.[126] However, another study found that Algenpantucel did not provide significant benefits for patients with advanced PDAC when combined with standard care protocols, including neo-adjuvant chemotherapy and chemoradiation.[127]

To stimulate T-cell responses against various tumor antigens, scientists have developed the GVAX vaccine. This allogeneic vaccine consists of human GM-CSF-secreting whole tumor cells.[128,129] Research has shown that both neo-adjuvant and adjuvant GVAX, with or without the addition of nivolumab (an anti-PD-1 monoclonal antibody) and urelumab (an anti-CD137 agonist), safely increase the number of activated effector T cells infiltrating tumors, significantly enhancing disease-free survival compared to GVAX alone.[130] However, a phase II study of 82 patients found no improvement in OS when GVAX was combined with nivolumab, suggesting that further refinement of this therapeutic approach is necessary.[131]

Dendritic cell (DC) vaccines

DC vaccines are created by isolating DCs from a patient's blood and loading them with tumor-associated antigens (TAAs) or tumor-derived mRNA. Once administered, these modified DCs travel to lymph nodes, where they present antigens to T lymphocytes and provide co-stimulatory signals.[132] In one study, DCs pulsed with the mucin 1 peptide demonstrated safety and efficacy in eliciting an immune response in patients with advanced pancreatic cancer.[133]

Many pancreatic cancer cells overexpress Wilms' tumor 1, prompting studies that evaluate the use of DCs pulsed with Wilms' tumor 1 peptides alongside chemotherapy.[134,135] A multicenter analysis of 255 patients indicated that those receiving a DC vaccine had improved survival rates, especially if a positive erythema reaction occurred at the injection site.[136]

Additionally, research using mesothelioma lysate-loaded DCs combined with FGK45 (a CD40 agonist) in mouse models of PDAC showed significant transcriptomic changes and improved survival. The addition of lymphokine-activated killer cell therapy

to DC-based immunotherapy and gemcitabine notably increased survival in advanced pancreatic cancer patients.[137] However, standalone DC vaccination increased cancer antigen-targeting CTLs while reducing Tregs.

Peptide vaccines

GV1001, a peptide vaccine derived from a portion of telomerase (hTERT), has demonstrated significant cell-penetrating capabilities. In a phase II trial, most patients with advanced pancreatic cancer exhibited immune responses that resulted in improved median survival compared to non-responders.[138] However, a later phase III trial combining GV1001 with chemotherapy failed to show significant improvements in OS.[139]

Another peptide vaccine, KIF20A-66, evaluated in a phase I/II trial, was well-tolerated, with a median OS of 142 days and a median progression-free survival of 56 days.[140] More recently, a phase I study of ELI-002 2P, aimed at KRAS-mutated pancreatic cancer, yielded promising results. This vaccine targets lymph nodes and includes modified long peptides for G12D and G12R mutations in KRAS, along with the TLR9 agonist CpG-7909 DNA. It was well-tolerated, induced strong T-cell responses, cleared biomarkers, and improved relapse-free survival, suggesting its potential for treating KRAS-mutant tumors resistant to other immunotherapies.[141]

DNA vaccines

Several studies have shown that DNA vaccines targeting TAAs can significantly extend survival in mice with PDAC. One effective example is a DNA vaccine targeting α-enolase.[142] Combining this DNA vaccine with chemotherapy (gemcitabine) improved efficacy against multiple TAAs, including enolase, glyceraldehyde-3-phosphate dehydrogenase, keratin type II cytoskeletal 8, and far upstream binding protein 1.[143] Additionally, a DNA vaccine targeting mucin 1-variable number tandem repeat showed strong cytotoxic effects in both *in vivo* and *in vitro* studies.[144]

Another DNA vaccine targeting fibroblast activation protein alpha and survivin reduced immunosuppressive cells and increased TILs, creating a more favorable tumor microenvironment for immune responses against pancreatic tumors.[145]

mRNA vaccines

mRNA-based personalized cancer vaccines are designed to include specific tumor-specific antigens and TAAs. After administration, antigen-presenting cells take up the mRNA and present the corresponding peptide antigens, triggering immune responses from CTLs and memory T cells. One such mRNA vaccine, RO7198457 (also known as BNT122), targets tumor neo-antigens to stimulate T-cell responses. Several clinical trials are planned for various cancers, including pancreatic cancer (NCT04161755 and NCT05968326), solid tumors (NCT03289962), melanoma (NCT03815058), and colon cancer (NCT04486378), though results from many of these studies are still pending.

A clinical trial led by Memorial Sloan Kettering Cancer Center (NCT04161755) investigated an mRNA vaccine called autogene cevumeran, delivered via uridine mRNA-lipoplex nanoparticles. After surgery, patients received a combination of the mRNA vaccine (targeting up to 20 neo-antigens per patient), atezolizumab, and chemotherapy. The findings revealed that vaccine-enhanced T cells accounted for up to 10% of the total T cells in the bloodstream and re-expanded after a booster. These re-expanded cells included long-lasting, multifunctional $CD8^+$ T cells that specifically targeted pancreatic cancer neo-antigens. After a median follow-up of 18 months, patients with vaccine-enhanced T cells showed significantly longer median recurrence-free survival compared to the control group.[146] The vaccine is now being further evaluated in a phase II randomized trial (NCT05968326) comparing its effectiveness to standard chemotherapy (FOLFIRINOX).

Viral and bacterial vector-based vaccines

Viral and bacterial vectors have been used to deliver genetic material encoding tumor antigens into human cells, which then produce the tumor antigens and activate the immune response. For example, bacterial vectors have been explored in the treatment of castration-resistant prostate cancer, showing promising anti-tumor effects in clinical trials.[147] A notable example is CRS207, a live attenuated strain of *Listeria monocytogenes* engineered to express MSLN. In patients with metastatic pancreatic cancer, CRS207 has demonstrated promising results, including prolonged survival with minimal adverse effects.[148]

Another approach uses Salmonella as a vector for delivering exogenous immunization antigens, redirecting $CD8^+$ T cells to target cancer cells within tumors. This method has shown complete eradication of pancreatic tumors, enhanced anti-tumor immunity, and significant improvements in survival rates in mouse models of PDAC.[149] Additionally, the vascular endothelial growth factor receptor-2 (VEGFR-2), a key target for anti-angiogenic therapies, is found on tumor blood vessels. VXM01, an oral tumor vaccine using attenuated Salmonella carrying a VEGFR-2 expression plasmid, was evaluated in a phase I trial with advanced pancreatic cancer patients. The vaccine was well-tolerated, with no dose-limiting toxicities, and led to significant increases in VEGFR-2-specific T effector responses. Patients receiving the vaccine experienced reduced tumor perfusion and higher serum levels of biomarkers associated with anti-angiogenic activity, correlating with their pre-existing levels of VEGFR-2-specific T cells.[150]

Stem cell-based vaccines

Due to the similarities in cellular and molecular characteristics between cancer cells and embryonic tissues, iPSCs hold potential for cancer vaccine development. iPSCs exhibit gene expression profiles resembling those of tumor cells. Research indicates that iPSC-based vaccines can effectively inhibit tumor growth in various murine models, including breast cancer, mesothelioma, and melanoma.[89] In PDAC mouse models, iPSC-derived cancer vaccines have been shown to provoke a robust immune response. This includes enhanced activity of $CD8^+$ effector and memory T cells against tumor cells, the production of antibodies targeting cancer cells, and a reduction in immunosuppressive Tregs comprised of $CD4^+$ T cells.[151]

CRISPR/Cas9 and pancreatic cancer immunotherapy

CRISPR/Cas9 is a precise gene-editing tool that is transforming cancer research and treatment. Combining CRISPR/Cas9 with cancer immunotherapy holds the potential to expand the effectiveness of immunotherapy to a broader range of patients. Current clinical trials are exploring the use of CRISPR/Cas9 in immune cells for targeted genome modifications. This technology enables highly efficient, site-specific gene knockouts, helping to address persistent challenges in cancer treatment, such as T-cell exhaustion and the immunosuppressive TME.[152]

In pancreatic cancer research, many studies employ CRISPR/Cas9 for gene knockout purposes. For instance, disrupting the CD73 gene in both human and mouse models of pancreatic cancer inhibited cell proliferation and migration, effectively arresting the cells in the G1 phase of the cell cycle. This knockout also affected

the ERK/signal transducer and activator of transcription 3 signaling pathway and activated the E-cadherin pathway.[153]

Another study revealed that mesenchymal-like pancreatic cancer cells are more resistant to immune cell attacks than their epithelial-like counterparts. Using CRISPR/Cas9 knockout screens, researchers identified several mesenchymal-specific genes, such as Egfr and Mfge8, that contribute to immune resistance.[154] Moreover, applying CRISPR/Cas9 to induce targeted BRCA1/2 mutations restored sensitivity to the drug olaparib in pancreatic cancer cells.[155]

Despite challenges such as off-target effects and immunogenicity, these studies underscore the promising applications of CRISPR/Cas9 in pancreatic cancer immunotherapy.

Having examined the role of cytotoxic and immunotherapeutic strategies in treating pancreatic neoplasms, we now turn to emerging targeted therapies that offer new avenues for more precise and effective treatment.

Future directions

Targeting epigenetic changes and the tumor microenvironment represents a novel approach to overcoming tumor defenses and improving immune infiltration in these "cold" tumors. However, these modalities require extensive clinical testing before they can be translated into improved patient outcomes.

Costimulatory molecule agonists

Activating CD40 with agonistic antibodies is a promising strategy in cancer immunotherapy. Several anti-CD40 antibodies, such as SGN-40 and selicrelumab, are currently in clinical trials.[156] In a phase I trial combining an anti-CD40 antibody with gemcitabine for pancreatic cancer, safety was confirmed, although efficacy was minimal.[157] However, this combination may enhance $CD8^+$ T cell accumulation against tumors. Selicrelumab treatment significantly altered the TME by increasing T cell presence and reducing tumor fibrosis and M2-like TAMs.[158] Additionally, using a drug-eluting device for sustained CD40 monoclonal antibody delivery showed positive effects on the TME and tumor size in mouse models.[159]

Neutralizing tumor acidity

Tumor acidosis is a major immunosuppressive factor in pancreatic cancer. A study investigated L-DOS47, a urease immunoconjugate designed to neutralize tumor acidity and improve immunotherapy responses. L-DOS47 binds to CEACAM6 and raises local pH by converting urea into ammonia and carbon dioxide. In mouse models, L-DOS47 increased extracellular pH and, when combined with anti-PD-1 therapy, significantly reduced tumor growth.[160]

Targeting desmoplastic barriers

Desmoplastic barriers, such as hyaluronan in the stroma, hinder effective immunotherapy in pancreatic cancer. Targeting these barriers can improve drug delivery and chemotherapy efficacy. For example, removing hyaluronan in mouse models enhanced vascular permeability and improved outcomes when combined with gemcitabine.[161] Combining PEGPH20 (a hyaluronidase) with a focal adhesion kinase inhibitor and anti-PD-1 therapy increased survival rates and T cell infiltration, altering the tumor immune landscape.[162]

Innate immune activation

Stimulating the innate immune system is a promising strategy against pancreatic cancer. A genetically modified strain of Listeria monocytogenes expressing MSLN, combined with the GVAX vaccine, improved survival rates in patients. This approach increased T cell infiltration and helped convert cold tumors into hot tumors with elevated immune activity. Activation of innate immune pathways such as cGAS and STING enhances type I interferon production, crucial for $CD8^+$ T cell development. STING activation has shown promise in reversing immune suppression and shrinking tumors in preclinical studies, potentially improving responses to PD-1 and CTLA-4 therapies.[163]

TME-modulating agents

Effective immunotherapy for pancreatic cancer often requires multifaceted strategies to promote T cell infiltration and activity within a hostile TME. Current research aimed to enhance the TME in PDAC, stimulate immune responses, and improve T cell therapy outcomes.[164] ADH-503, a small molecule that binds CD11b, enhances myeloid cell adhesion, shifts TAM polarization toward an anti-tumor phenotype, and improves survival in PDAC models. Although well tolerated in trials, ADH-503 did not yield significant clinical responses in pancreatic cancer patients.[165] Inhibiting the CCL2/CCR2 pathway has also shown early signs of efficacy, though results have been mixed.

Inhibition of the CXCR4/CXCL12 axis also modulates the TME. CXCR4 knockdown reduced pancreatic cancer cell invasiveness, and its blockade combined with PD-1 inhibition enhanced tumor cell death and lymphocyte expansion.[166] The CXCR4 inhibitor AMD3100 increased T cell presence in tumors and boosted the efficacy of PD-L1 therapy. Other CXCR4 antagonists, such as motixafortide, have shown promise in combination with pembrolizumab by increasing $CD8^+$ T cell infiltration and reducing immune suppressor cells.[167]

Pharmacologic inhibition of the A2A adenosine receptor is being explored to enhance anti-PD-1 therapy efficacy, reflecting the need for a multifaceted approach in pancreatic cancer immunotherapy.[168]

Several therapeutics targeting CD73 and adenosine receptors have been developed. Oleclumab (MEDI9447), a monoclonal antibody against CD73, slowed tumor growth and enhanced immune cell infiltration in colon cancer models. When combined with anti-PD-1 treatment, it achieved complete tumor elimination in 60% of animal subjects.[169] Clinical trials of oleclumab, alone or with durvalumab, in patients with advanced pancreatic cancer who were unresponsive to anti-PD-L1 therapies, showed good tolerability and some partial responses lasting 22 to 28 months (two of 73 patients; NCT02503774). Additionally, a study of quemliclustat, a small-molecule CD73 inhibitor, combined with standard treatments and zimberelimab in patients with metastatic pancreatic cancer reported a safety profile similar to that of single agents, with no new toxicities. Some patients experienced extended partial responses (NCT04104672).

Conclusions

Although pancreatic cancer is relatively rare compared to other solid tumors, it remains the third leading cause of cancer-related mortality in the United States. Early diagnosis continues to elude most patients, as current screening is largely limited to high-risk populations due to insufficient diagnostic accuracy, and the broad applicability of early detection remains limited. Treatment options are still predominantly based on decades-old chemotherapeutic regimens, and newer immunologically targeted therapies have yet to become standardized.

As the landscape of pancreatic cancer research evolves, there is renewed hope for both patients and healthcare providers. By harnessing advancements in diagnostics and treatment, we anticipate a future where early detection and personalized therapies can significantly improve survival rates and quality of life for those affected by this challenging disease. Collectively, these efforts represent a critical step toward transforming pancreatic cancer from a typically fatal diagnosis into a more manageable and treatable condition.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Contributed to study concept and design (DR), resource acquisition (AVM, AN), drafting of the manuscript (AVM, AN), visualization (AN), critical revision of the manuscript (DR), and supervision (DR). All authors have approved the final version and publication of the manuscript.

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