


Developments & Potential of Nanotechnology for the Detection and Treatment of Pancreatic Cancer

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Abstract: Pancreatic cancer is projected to become the second leading cause of cancer death by 2030 with a dismal 5-year survival rate compared to other cancers (12%). Due to the absence of clear early symptoms, diagnosis is often delayed resulting in many patients presenting with advanced disease and limited treatment options. Surgery remains the only potential curative option. However, only about 20% of cases are detected early enough for surgery. Consequently, most patients rely on chemotherapy, immunotherapy and radiotherapy. Among these, chemotherapy offers the best chance of tumor shrinkage, it comes with many problems such as harsh side effects which kill healthy cells and cancer cells, leaving the patient sometimes too ill to continue treatment. With immuno- and radiotherapy, it offers limited success in the treatment of pancreatic cancer despite its success in treating other forms of cancer. Nanotechnology offers promising opportunities for more effective diagnosis and less aggressive treatment. Fortunately, there has been some success for pancreatic cancer with two nano formulations currently approved by the Food and Drug Agency (Onivyde and Abraxane) offering greater survival rates and reduced side effects compared to traditional chemotherapy. Unfortunately, progress in nanotechnology-based diagnostics for pancreatic cancer remains limited. However, numerous different types of nanoparticles are under investigation in preclinical and clinical studies showing positive results. This review gives an overview of the potential of nanotechnology within this area looking at harnessing its potential in more effective diagnosis strategies and for more efficient therapy.

Keywords: pancreatic cancer, drug delivery, cancer nanomedicine, diagnostics, theranostics, nanotechnology

Introduction

Pancreatic cancer (PC) is a highly fatal disease with 511,000 new cases and 467,000 deaths globally, in 2022 alone, ranking it as the 6th leading cause of cancer death and the 12th most prevalent cancer.¹ PC has the worst 5-year survival rate compared to other common cancers, with only 12% of patients surviving, and as such in the UK, the cancer has been officially designated as a cancer of unmet need. Unfortunately, giving the rising numbers of cases annually, the mortality to incidence ratio is expected to increase, with PC projected to become the second leading cause of cancer death by 2030 in the United States.^{1–3}

Pancreatic ductal adenocarcinoma (PDAC) is the most common form of exocrine PC and accounts for ~90% of all pancreatic malignancies.⁴ With ~60–70% of PDAC occurring at the head of the pancreas, 15% residing within the body and the remainder in the tail (15%). Conventional treatment for PC includes surgery, chemo- and radiotherapy, with surgery being the most favourable option.⁵ However, due to a multitude of challenges such as the asymptomatic early stages, lack of known biomarkers resulting in lack of early detection/screening methods, PC is typically diagnosed at much later stages than the other cancers, with ~70–80% of cases being diagnosed at the locally advanced (LA) or metastatic stage.^{6–8} As a result, surgical resection is only feasible in fewer than 20% of patients, underscoring the urgent need for improved therapeutic and early diagnostic approaches.⁵



Graphical Abstract



Nanotechnology sits at the forefront of innovation in the 21st century with applications spanning a vast array of sectors including electronics, food, cosmetics and most promisingly in medicinal detection and therapeutics.⁹ Nanomaterials possess many unique properties that make them highly versatile such as optical properties, enhanced permeation, ease of synthesis and purification. Their high surface area to volume ratios allows them to be easily tailored and surface engineered for their intended application. In the pharmaceutical industry various nanocarriers, such as solid lipid nanoparticles (SLNs), liposomes, polymeric micelles and polymeric drug conjugate (PDU) have shown to improve stability, control drug release and offer targeted drug delivery. Additionally, nanotechnology has been shown to increase solubility and bioavailability, a vital advantage due to the increase in highly hydrophobic drugs arriving on the market. Nanocarriers can be functionalized with ligands, proteins or antibodies to target specific cells/tissues. Alternatively, nanocarriers can be engineered to respond to external (light) or internal stimuli (pH, enzymes), leaving a wide range of opportunities for as therapeutics. Aside from drug delivery, the inorganic nanoparticles have been developed as diagnostic agents, usually as tracer molecules used as an aid in illuminating tumor tissue, with some of these combining this powerful diagnostic tool with triggered drug delivery, acting as theranostic molecules.

This review focuses on the current climate of PC research up to late 2025, highlighting recent success in preclinical and clinical therapeutic and diagnosis studies, addressing the challenges associated and the critical need to address the

knowledge gap, analysing the advances which nanotechnology has made to date, and its future potential in the diagnosis and treatment of PC.

Challenges in Pancreatic Cancer

PC remains one of the most lethal malignancies, with limited progress over the last few decades. The common treatment options for PC are summarized in Figure 1A with the associated challenges in treating pancreatic cancer in Figure 1B.

Late Diagnosis and Lack of Biomarkers

There are many factors which are challenging for the diagnosis and treatment of PC, including the lack of known, reliable biomarkers at the early stages of cancer, meaning it is incredibly hard to detect, and no large-scale screening technique is used, which often results in the tumor being undetected until it is too late.¹⁰ PC forms extremely solid (cartilage like) tumors, surrounded by a dense stroma, this hostile rapidly growing body has been designed by the microenvironment (TME) to hinder penetration – including therapeutics.¹¹ Often large drug doses are required to exert any effect on the tumor size or rate of proliferation, however, given such low quantities of chemotherapy penetrate the tumor, resistance often rapidly develops.

Unlike in other cancers, such as breast cancer (BRCA gene), biomarkers have been identified in body fluids which are used to definitively diagnose a disease at an early, curable stage.¹² PC only has one biomarker currently approved by the Food and Drug Agency (FDA), cancer antigen 19–9 (CA19-9).⁴ However, it is only used to monitor treatment response and to detect recurrence – as it is not accurate in diagnosing the disease in the general population due to its low predictive value. Carcinoembryonic agent (CEA) is another traditional biomarker, which has been investigated for use in early-stage diagnostics, as it is present in PC, however, CEA have proven to be less effective than CA19-9.⁵ However, when the two biomarkers are used in combination, diagnostic accuracy increased. A newer potential biomarker, cell migration-inducing hyaluronan binding protein (CEMIP) has been observed in multiple cancers, including PC, and when combined with CA19-9, is better at identifying PC than CA19-9 alone.

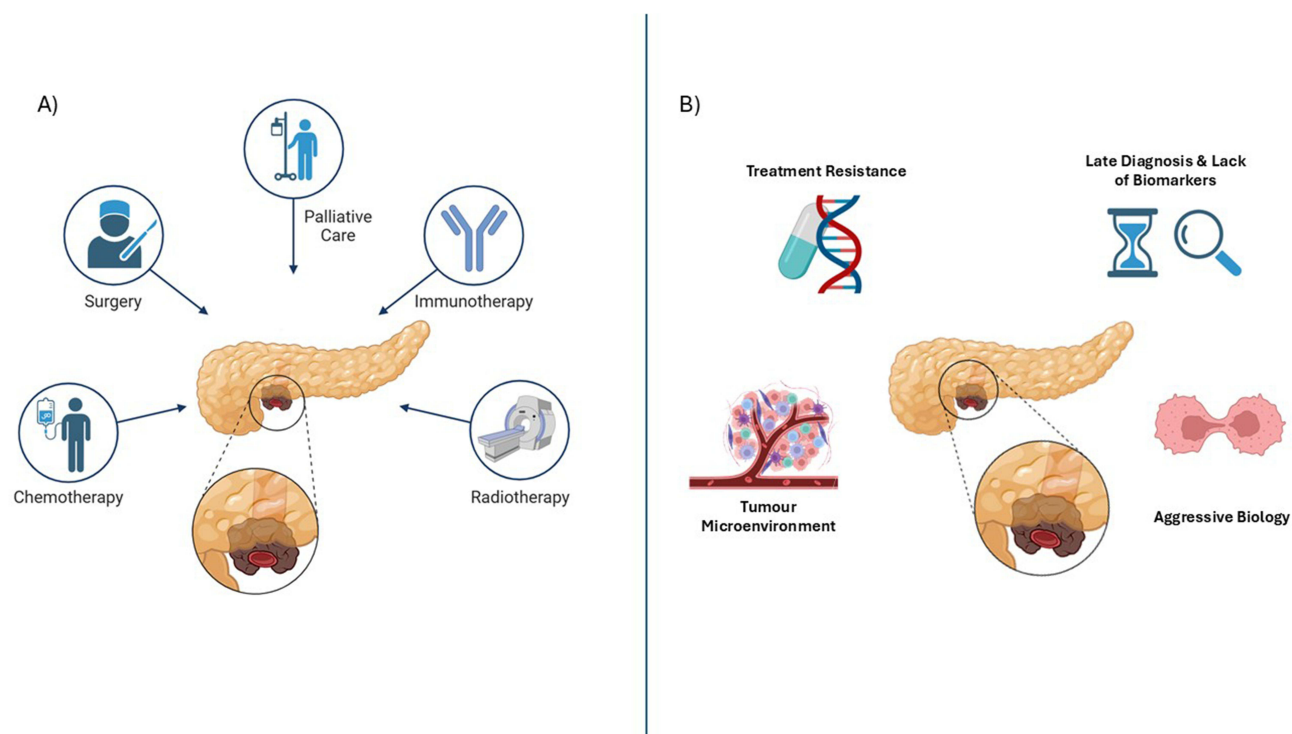


Figure 1 (A) Summary of common treatment options for pancreatic cancer (B) Summary of the major challenges in treating pancreatic cancer created with BioRender.com.

Cost-effective screening remains challenging due to its low incidence rate, typically asymptotic early stages and lack of definitive biomarkers.^{10,12} Diagnosis currently relies on imaging modalities, such as, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and endoscopic ultrasound (EUS). However, none of these techniques are perfect and come with their own issues.

Tumor Microenvironment (TME)

The TME severely hinders delivery of therapeutics to their intended site of need. Desmoplasia, a key feature in many cancers, is especially prominent in PC.^{13,14} It is a buildup of dense fibrous tissue around the tumor, caused by rapid proliferation of fibroblasts. They secrete large amounts of extracellular matrix (ECM), which are proteins which form a thick and rigid structure around the tumor. The continued overproduction of ECM increases the pressure within the TME, resulting in the blood vessels being restricted, forming a hypoxic environment and blocking the delivery of chemotherapies/immunotherapies into the tumor. Additionally, certain ECM components, such as, hyaluronan and tenascin-C interact with the toll-like receptors (TLRs) on immune cells, confusing the immune system resulting in chronic, non-productive inflammation, which further fuels tumor growth. Within the TME, the tumor will continue growing undetected due to the secretion of immunosuppressive cytokines. All these components, help PC tumors form an impenetrable wall, making therapeutic interventions very difficult and ineffective.

Resistance to Therapeutic/Chemo Side Effects

Chemotherapy can be administered as a neoadjuvant therapy (before surgery), to shrink the tumor, increasing access to the tumor site, reducing surgical complications particularly with the surrounding vasculature and increases chances of complete resection.^{15–17} Otherwise, they are administered as adjuvant therapies (after surgery) to kill residual cancer cells and reduce recurrence risk. However, in PC, the prognosis for those patients receiving adjuvant care remains poor and ultimately surgery with neoadjuvant care is the best option. In many PC cases, the tumor is too advanced to allow for surgical intervention, in these cases radiation therapy or chemotherapy are used as the first-line treatments to shrink or reduce the rate of tumor growth.

Gemcitabine (GEM) demonstrated its effectiveness as a first-line chemotherapy for PC in 1997, overtaking 5-fluorouracil (5-FU) as the most frequently used drug.¹⁸ Before this discovery, 5-FU had exceptionally low survival rates with 5.51 months and a 2% one-year survival probability. GEM offered an increase in this survival rate to 5.56 months and 18%, respectively. Although this does not seem substantial, any increase in survival chances in PC is a major breakthrough. However, GEM was not effective in all patients, huge interpatient variability was observed and ultimately, many patients who responded well to GEM treatment, ultimately developed resistance at later stages of their recovery journey.¹⁹ In recent years, new evidence has emerged that poor penetration and resistance may not be the only mechanism behind the poor GEM performance, with Geller et al reporting in 2017 that intertumoral bacterial in PC tumors had been shown to be degrading GEM before it could even enter the cells and carry out its activity.²⁰ As a result, GEM is now administered in combination with other chemotherapies clinically to enhance its performance.

Other chemotherapies used in PC include paclitaxel, irinotecan or capecitabine (cap) (oral 5-FU drug).²¹ Platinum drugs have been incorporated such as cisplatin or oxaliplatin. Additionally, these drugs can be used in combinations, such as FOLFIRINOX (folinic acid/leucovorin (LV), 5-FU, irinotecan and oxaliplatin), GemCap, nab paclitaxel/Abraxane + GEM or OFF (LV, 5-FU and oxaliplatin).²²

Unfortunately, although chemotherapy is arguably the second-best treatment action, it is accompanied by a host of negative side effects. Henry et al conducted a cross-sectional national survey in the United States to analyse side effects affected by chemo and/or radiotherapy.²³ Notably, the most common side effects reported were fatigue, pain, nausea and/or vomiting, anxiety and insomnia. With patients also showing moderate-to-high levels of depression and an average time of 4.5 hours spent on visits to professionals to treat side effects. In the study, 43% of patients were still employed and of those patients, 78% were still working and the remainder on medical leave. Patients were reported to miss an average of 26 days of work due to receiving treatment and a further 18 days for side effects experienced. Another well-known and most common side effect is hair loss which can negatively affect the patient's mental health. Others include low platelet and white blood cell counts, changes in appetite, diarrhea, skin rashes and “chemo brain” – affecting concentration levels

and focus. Unfortunately, due to the late-stage diagnosis, some patients are simply too ill to take chemotherapy due to these unforgiving off target effects, and PC ultimately is their death sentence.

Chemoresistance remains a major barrier in the effective treatment of PC, contributed by multiple factors, such as the TME, dense stroma and genetic mutations, limiting effective drug delivery.²⁴ As a result, common chemotherapy drugs such as GEM and FOLFIRINOX achieve subpar results, further highlighting the importance of finding more reliant and effective therapeutic drugs.

While essential, chemotherapy is extremely harsh and non-discriminatory, high doses are required to combat PC, leading to significant side effects. It is critical to discover alternative treatment to increase efficacy, reduce hospital visits and minimise harsh side effects.

Immunotherapy Limitations

Given the remarkable success of several FDA approved immunotherapies in other malignancies, such as non-small cell lung cancer (NSCLC), non-Hodgkin's lymphoma and tumors with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR), there was great hope that similar immunotherapies could hold promise in PC treatment.^{25–29} Unfortunately, its impact in PC has been disappointing despite early optimism. Immunotherapy utilizes the body's own natural immune system to eliminate cancer cells.³⁰ Immune checkpoint inhibitors (ICI) are a type of immunotherapy which work by blocking the T cells which the cancer cells use to evade detection.²⁵ By blocking these cells, they remain active and attack cancer cells. Despite success in other cancers, they have shown poor performance with PC, even when combined with chemotherapy.^{25,31} Perhaps, like the chemotherapies, this is due to the dense stroma hindering their entrance into the TME to exert their effect. Although this lack of promise, one ICI, pembrolizumab has been recommended as a second line therapy for patients with dMMR or MSI-H, including certain PC types; however, not all patients are eligible. It is speculated that due to the TME actively suppressing immune responses through cells like myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), tumor cells possess poor antigenicity and even when presented, they remain “invisible” and can evade the immune system. This landscape makes ICI largely ineffective in PC treatment compared to other cancers.

Radiotherapy Limitations

Radiotherapy uses high doses of radiation (X-rays, gamma rays, or particle beams) to irreversibly damage cancerous tissue or cells, resulting in tumor shrinkage. Radiotherapy may be used after and occasionally before surgery to eliminate the cancer.³² Stereotactic body radiotherapy (SBRT) delivers higher focussed doses of radiation directly to the tumor in only a few treatment fractions. Since the tumor core exists in a higher hypoxic environment than the tumor periphery or boundary, it experiences a greater extent of radio resistance. In SBRT a hotspot in this radioresistant area allows for a high-dose distribution, resulting in dose escalation. This phenomenon has proved beneficial to PC patients, as it is rapid and generally better tolerated than conventional radiotherapy.³³

Primarily in PC, radiotherapy it is used as an intervention which can slow tumor growth, but it is not curative as it is not effective enough to eliminate the tumor completely. Therefore, it is common practice for it to be used in combination with chemotherapy³⁴ or immunotherapy.³⁵ As radiotherapy is a focussed therapy, it targets only the localized disease; therefore, it is not helpful in cases of metastasis. In PC specifically, it is also problematic given the location of the organ, which hinders the dose that can be safely delivered without risk of adverse off target radiation damage.

Cancer Nanotechnology

With cancer as the leading cause of death globally, with approximately 10 million deaths in 2020 alone, an effective treatment/early diagnosis is vital to decrease the ever-growing mortality and incidence rates.³⁶ Nanotechnology offers opportunities in this area due to its versatility, functionality and ability to precision target sites of need. Targeted delivery is believed to occur in two ways, either through passive or active mechanisms.³⁷ Passive targeting utilizes the TME through the enhanced permeability and retention (EPR) effect, where the leaky vasculature and the impaired lymphatic drainage of tumors allow for the accumulation of nanoparticles. However, the EPR effect remains controversial, as it is often significantly overestimated in animal models compared to human models.³⁷ Whilst debate rages on about whether

the EPR effect exists in a helpful manner for many cancers, consensus is that for PC, the harsh TME does not allow for EPR to occur. Therefore, a different targeting mechanism is employed. Active targeting involves modifying the surface of the nanoparticle with ligands/antibodies which specifically bind to biomarkers on certain cells or tissues.^{38,39} Due to the size of nanoparticles (10–100 nm), they can move in the body without triggering strong immune responses.⁴⁰ There is a wealth of studies using various types of nanoparticles in a range of cancers, summarised in Figure 2.

Liposomes were among the first clinically successful nanoparticles in oncology with poly(ethylene glycol) functionalised (PEGylated) liposomal doxorubicin (Doxil) approved by the FDA in 1995 for the treatment of ovarian cancer, AIDS related Kaposi's sarcoma.⁴¹ Doxil altered doxorubicin pharmacokinetics and reduced cardiotoxicity compared to the free drug. Following this success, several other liposome-based products were approved for the management of various cancers: Depocyt, Myocet, Mepact and Marqibo. More recently, lipid nanoparticles gained significant interest due to rapid and scalable production, high precision and favourable safety profile.⁴² There are multiple mRNA vaccines in animal and human trials for several types of cancers.^{43,44}

Metallic nanoparticles (MNPs) offer unique properties such as optical, magnetic, electrical characteristics which increase their capabilities to be used for diagnosis.^{43–45} With studies highlighting improved imaging and the ability to detect prostate cancer biomarkers in blood and urine with high sensitivity and specificity.^{46,47} Currently, only one MNP-based formulation is approved for glioblastoma or prostate cancer, NanoTherm.

Clinical Success of Cancer Nanotechnology for PC

The FDA approved two nanotechnologies for use in PC, both licensed for drug delivery. These are Abraxane and Onyvide. Abraxane/nab-paclitaxel is an albumin-bound drug formulation, where paclitaxel, the well-known microtubule stabilizing chemotherapy, is bound to human serum albumin. In the case of paclitaxel, its aqueous solubility severely hinders its clinical use, despite its promising potency.⁴⁸ The drug itself is highly toxic and often cannot be tolerated as the off-target effects are too extensive. However, the Abraxane formulation allows the active to travel systemically for longer, enhancing accumulation within the pancreas, reducing off target effects. Effectively, allowing patients, which would not be able to tolerate paclitaxel, to undertake this regime. Abraxane gained significant traction in the MPACT trial which demonstrated that providing it in combination with GEM, significantly improved response, overall survival and progression free (OS and PF respectively) survival rates compared to GEM alone (8.5 vs 6.7 OS months with survival

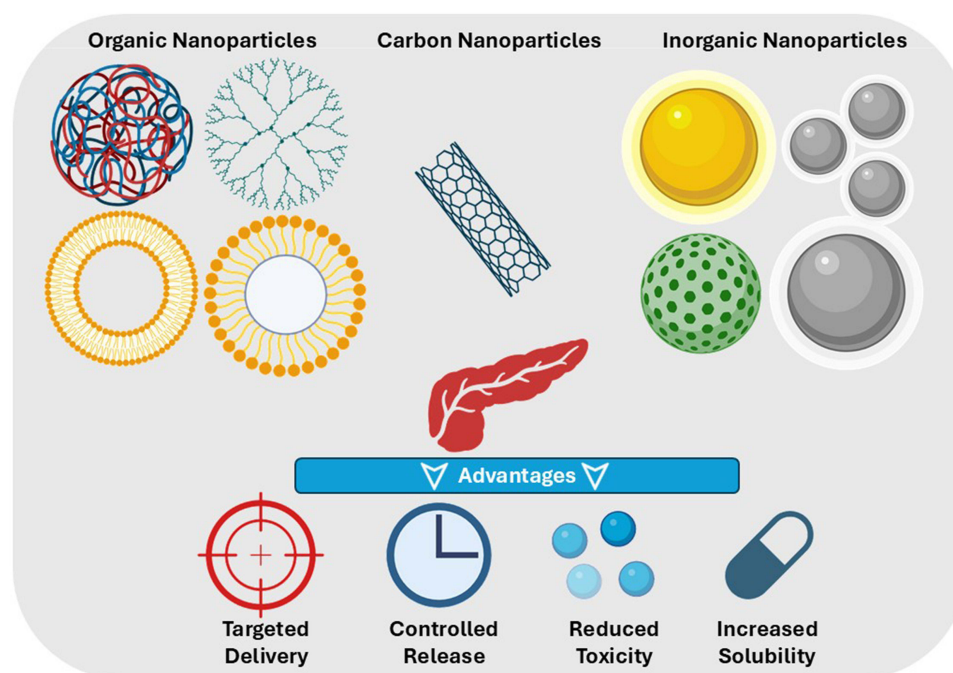


Figure 2 Types of nanoparticles (NP) used in cancer, created with BioRender.com.

rates of 35% vs 22% at year one and 9% vs 4% at year two) in patients with metastatic PDAC.⁴⁹ A follow up report investigated the long term survival of patients receiving Abraxane and GEM in a combination therapy regimen, further demonstrating that Abraxane and GEM delivered sustained survival rates over GEM alone (median OS: 8.7 vs 6.6 months) with a small positive >3% year survival in only the combination arm.⁵⁰ However, neurotoxicity and myelosuppression were higher in the combination than GEM alone, though these were observed to be manageable.

Onivyde, is a liposomal formulation of irinotecan (nal-IRI) approved to PC. Irinotecan is a topoisomerase inhibitor, which disturbs the cancer cell ability to replicate DNA, leading to cell death. The drug molecules are encapsulated within the liposome macromolecular structure, which protects it on its journey to the PC, prolongs drug circulation times, enhances ability to accumulate and in effect increases drug exposure, increasing therapeutic effectiveness. Onivyde is mainly used in combination with other drugs, with the NAPOLI-1 Phase III trial highlighting the importance of the liposomal formulation.⁵¹ The trial consisted of 417 patients with metastatic PC previously treated with GEM-based therapy, who were randomly grouped and administered Onivyde with or without 5-FU/LV or 5-FU & LV. Results demonstrated that OS of Onivyde in combination with 5-FU and LV was 6.1 months vs 4.1 months with 5-FU and LV alone. No difference was observed in Onivyde alone with 5-FU and LV (4.9 vs 4.2 months). Additionally, it was noted that Onivyde alone presented more side effects than 5-FU and LV. This study led to the approval of Onivyde in combination with 5-FU/LV for metastatic PC patients whose disease has progressed after GEM-based therapy. More recently, the FDA approved another combination chemotherapy treatment for metastatic PC using Onivyde along with 5-FU, LV and oxaliplatin (NALIRIFOX).⁵² The NAPOLI 3 trial consisted of 770 patients with metastatic PC, who were randomly assigned NALIRIFOX on days 1 and 25 or Abraxane and GEM on days 1, 8 and 15 of a 28-day cycle. NALIRIFOX median OS was significantly greater than standard chemotherapy (11.1 vs 9.2 months) with PF at 7.4 vs 5.6 months.

While some success has been made in improving treatment for PDAC patients with two FDA nano formulations approved for use, there is still demanded to strive for better. Prescribing Onivyde on its own was determined not to be effective as a single agent and resulted in more adverse events. Its strength is demonstrated when it is used as a combination therapy with a slight improvement in OS.^{51,52} The liposomal formulation alters irinotecan's pharmacokinetics, extending circulation time and shown to accumulate in tumour cells through the EPR effect.⁵³ Similarly, this is observed with Abraxane with the nanoparticle formulation disrupting the tumor stroma, improving penetration of both paclitaxel and GEM.⁴⁸

There is no diagnostic technique or nanotechnology which has been approved specifically for PC. The existing contrast agents are predominantly nanotechnology based where inorganic nanoparticles such as Dotarem, Clariscan and Primovist which are all Gadolinium-based or Feridex which is iron oxide based are used combined with magnetic resonance imaging. Other imaging modalities under investigation with the use of nanoparticle tracers, such as CT scanning, will be discussed later.

Nanotechnologies Undergoing Clinical Trial for PC

Beyond metastatic settings, Abraxane is used in ongoing studies investigating its effectiveness in neoadjuvant, adjuvant and combination strategies to further improve outcomes in PC, some examples are shown in Table 1 below with other clinical trials involving other common chemotherapy drugs.

NCT03496662 evaluated the safety and efficacy of combining the CCR2/5 inhibitor immunotherapy, BMS-813160 with nivolumab, GEM and Abraxane in patients with borderline resectable (BR) and locally advanced (LA) PDAC.^{54,55} The regimen consisted of four 28-day cycles of patients receiving chemo or combination treatment. Generally, treatment was well tolerated with only one instance of each Grade 3 diarrhea and QTc prolongation, which increases the risk of developing dangerous arrhythmias. The objective response rate (ORR) was 42% in BR and 20% in LA with 0% in chemotherapy control group. Importantly, meaningful surgical conversion rates were observed at 83% of BR and 20% of LA after treatment. Additionally, survival outcomes with median progression and overall survival for BR and LA was 11.9 and 18.2 months and 14.7 and 17.0 months, respectively.

The NEOLAP (NCT02125136) study was a multicentre randomized phased 2 trial evaluating conversion rate to resectability in LA PDAC with intensified neoadjuvant chemotherapy.^{56,57} Initially, all patients received two rounds of

Table 1 Clinical Trials Involving Nanoparticles for the Treatment of PC

Trial Number	Treatment Type	Compound	Year	Phase	Cohorts	Status	Median OS	Ref
NCT03496662	Chemo-	BMS-813160, nivolumab, GEM and Abraxane	2018-2024	I/2	23 BR +12 LA	Completed	BR: 18.2 LA: 17.0	[54,55]
NCT02125136	Chemo-	GEM, Abraxane vs GEM, Abraxane and FOLFIRINOX	2014-2018	2	130 LA	Completed	18.5 in GEM/ Abraxane 20.7 in FOLFIRINOX	[56,57]
NCT05630183	Chemo-	Abraxane, GEM and botensilimab	2023-2026	2	81 meta	Active, not recruiting	Not yet reported	[58]
NCT06261359	Chemo-	Abraxane, GEM and CEND-1 vs same chemotherapy with placebo	2024-2026	2	~120 meta/LA	Recruiting	No yet reported	[59]
NCT06361030	Chemo-	Abraxane, GEM + surufatinib	2024-2027	2	~40 LA	Not yet recruiting	Not yet reported	[60]
NCT06467565	Chemo-	NALIRIFOX	2023-2025	2	20 LA	Recruiting	Not yet reported	[61]
NCT04662112	Chemo-	NASOX	2021-2024	I	40 LA/ meta	Completed	11.4	[62,63]
NCT06821997	Chemo-	NALIRIFOX	2025-2027	2	20 BR	Recruiting	Not yet reported	[64]
NCT04752696	Chemo-	Onvansertib, Nal-IRI, LV 5-FU	2021-2024	2	43 meta	Completed	Not yet reported	[65]
NCT04484909	Radio-	Hafnium-oxide nanoparticles	2020-2026	I	24 LA/ BR	Recruiting	Not yet reported	[66,67]
NCT04161755	Immuno-	Lipoplex	2019-2026	I	24	Active, not recruiting	Not yet reported	[68,69]

Abbreviations: Where BR, borderline resectable; LA, locally advanced, meta = metastatic.

Abraxane and GEM as neoadjuvant chemotherapy and were restaged. Patients without disease progression were randomised into a 1:1 trial and received either two further rounds of Abraxane and GEM or four rounds of FOLFIRINOX. All patients without progression underwent exploratory laparotomy, while those with resectable tumors underwent curative surgery followed by three rounds of adjuvant chemotherapy. Among 130 patients, resection rates were comparable with Abraxane/GEM at 36% and 44% with FOLFIRINOX and median OS rates similar at 18.5 vs 20.7 months, respectively. It is important to note that FOLFIRINOX produced significant nodal downstaging, suggesting deeper pathological response. Both regimens had manageable toxicity with grade 3 adverse effects in ~55% of patients and no treatment-related induction deaths.

NCT04662112 is a completed multicentre study, which evaluated the safety and efficacy of NASOX regimen (Onivyde, S-1 and oxaliplatin) in advanced PC.^{62,63} Recommended dose consisted of receiving Onivyde and oxaliplatin on day 1 and S-1 twice daily on days 1–7, repeating every 14 days. Overall, the regimen has a manageable safety profile with most common Grade 3–4 adverse events being neutropenia (31.7%), enterocolitis (9.8%), anorexia (7.3%) and diarrhea (2.4%). The objective response rate (ORR) was 58.5% (with one complete and 23 partial responses). Additionally, two patients underwent surgery with complete resection and after a median follow up of 17.5 months,

the median progression-free survival was 6.5 months and OS at 11.4 months. Therefore, showing potential to replace current chemotherapy treatments.

NCT04752696 assessed the efficacy of immunotherapy onvansertib in combination with Onivyde, LV, 5-FU for second line treatment of metastatic PC. Treatment schedule included oral delivery of onvansertib on days 1–10 per 14-day cycle, co administered with Onivyde, LV and 5-FU. Current available results show 19% ORR, a median PFS of 5 months. However, these results are early and full data on OS and safety have yet to be published, but trial shows promising results as when compared to conventional treatment in similar patients, ORR is ~7.7% and 3.1 months PFS.

NCT05630183 is an ongoing multicentre trial due for completion in 2025 with currently 81 patients receiving intravenous care for metastatic PC. The study aims to assess if the addition of immunotherapy botensilimab to Abraxane and GEM combinations will improve the efficacy. While NCT06261359 is trial that is currently recruiting and aims to assess the safety and efficacy of CEND-1 in combination with standard chemotherapy for patients with locally advanced unresectable or metastatic PC. CEND-1 is a cyclic peptide, which will form a nanoparticle, it targets αV integrins and neuropilin-1 and enhances tumor delivery of co-administered anticancer drugs and has been hailed as a frontrunner as a new therapeutic targeting strategy in PC. NCT06361030 is an active, not yet recruiting trial looking the evaluate the safety and efficacy of surufatinib combined with standard chemotherapy in patients with locally advanced PC due to complete in 2027.

Rojas et al evaluated autogene cevumeran, an individualized mRNA neoantigen vaccine delivered in lipoplex nanoparticles, given sequentially with atezolizumab and mFOLFIRINOX.^{68,69} Primary findings show vaccine was well-tolerated and induced de novo high-magnitude neoantigen-specific T cell responses in 8 of 16 patients, including expansion of functional CD8⁺ T cells detectable in blood. Patients who showed these responses, also had longer recurrence-free survival compared with non-responders.

NCT03589339 reports for the first time an LA PDAC patient receiving a functionalized hafnium oxide crystalline nanoparticle, NBTXR3.^{66,67} The patient received EUS-guided intratumoral injection of NBTXR3 followed by intensity-modulated radiation therapy. NBTXR3 was well retained within the tumor, confirmed by daily imaging and no acute adverse events or treatment-related toxicities observed. All these studies are ongoing, but the hope is that all or most progress onto clinical success.

As observed, most clinical trials for the treatment of PC are chemotherapy or immunotherapy based. However, one radiotherapy trial is currently recruiting for LA or BR PC patients. Using NBTXR3 (hafnium-oxide nanoparticle, a radio enhancer) which will be injected into the tumor to enhance the effect of radiation therapy.

Therapeutic Nanotechnology in Pancreatic Cancer

The need for novel treatments may open new therapeutic avenues for patients with PC, some examples of other novel treatments are shown below in Table 2 which are in preclinical stages.

Prabhuraj et al designed a mesoporous silica nanoparticle loaded with curcumin and coated with PEG and targeting ligand, transferrin.⁷¹ Results showed cellular uptake was 7-fold higher than curcumin alone in pancreatic cells and 3-fold

Table 2 Preclinical Studies Involving Nanoparticles for the Treatment of PC

Treatment Strategy	Type of Nanoparticle	Compound	Ref
Immunotherapy	Polymeric nanoparticle	β -elemene (during combination studies)	[70]
Immunotherapy	Mesoporous silica nanoparticles	Curcumin	[71]
Chemotherapy	Dendrimers	Doxorubicin/GEM	[72]
Immunotherapy	Lipid-based	Monophosphoryl lipid A and cyclic diguanosine monophosphate	[73]
Chemotherapy	Solid lipid nanoparticles	Herniarin	[74]
Chemo-immunotherapy	Lipid-coated mesoporous silica nanoparticle	Activated oxaliplatin	[75]
Chemotherapy	Inorganic nanoparticles	Olaparib + Ascorbic acid	[76]
Radiotherapy	Gold nanoparticles	Docetaxel	[77]

higher cytotoxicity in MIA PaCa-2. The *in vivo* studies showed significant tumor growth inhibition and reduced metastasis in a pancreatic cancer xenograft model. Additionally, it was observed that the nanoparticles sensitized the cancer cells to GEM, boosting GEM's ability to kill cancer cells.

Responsive nanoparticles are an emerging class of smart materials engineered to change their behavior in relation to a specific internal or external stimuli.⁷⁸ These nanoparticles are designed to have built-in “triggers”, some examples include changes in pH, temperature, light, magnetic fields, enzymes, redox conditions or mechanical stress. This change causes a change in structure, surface chemistry or release of encapsulated cargo. A few approaches have been explored in recent years with examples summarized in Table 3 and Figure 3 summarizing the external and internal stimulus.

Nedelcu et al investigated using silver nanoparticles functionalized with immunoglobulin G (IgG) for phototherapy.⁸³ Under 808 nm laser exposure, the functionalized nanoparticle converted laser irradiation to localised heat, producing significant dose-dependent cytotoxicity in PANC-1 cells with silver nanoparticles or laser exposure alone showing minimal effect. Treatment induced Golgi apparatus disruption, leading to the activation of caspase 3 apoptosis, confirming cell death. Xin et al developed reactive oxygen species (ROS) responsive polymeric micelle to co-deliver PLK1 inhibitor, volasertib and tumor suppressor microRNA, miR-34a.⁸⁴ Results demonstrated synergistic cytotoxic effects with reduced IC₅₀ by 2–4.5-fold compared to volasertib alone. Additionally, the combination treatment induced greater G₂/M cell-cycle arrest, increased apoptosis (~55% in one assay), reduced colony formation. In an orthotopic pancreatic tumor model (NSG mice), it was observed that the micelles accumulated in tumors, resulting in significantly reduced tumor volume with negligible systemic toxicity in major organs.

Diaz-Riascos et al developed iron oxide magnetic nanoparticles for localised magnetic hyperthermia.⁸⁵ The formulation, termed NTT agent generated heat under an alternating magnetic field designed to be injected along with GEM + Abraxane. In PDAC cell lines and xenograft models, the combined treatment produced synergistic cytotoxicity, significantly reduced tumor growth inhibition and enhanced intratumoral drug penetration.

Recent advances in nanomedicines have explored stimulus-responsive prodrug formulations to improve therapeutic precision. Cho et al developed a light-activated MMAE prodrug nanoparticle for photo-chemotherapy treatment.⁸⁷ MMAE is conjugated to the photosensitizer Ce6 via a caspase-3-cleavable linker. Upon light irradiation, Ce6 produces ROS that induced apoptosis and elevates caspases-3 levels which cleave the linker to release active MMAE within tumor tissue. This produced enhanced cytotoxicity *in vitro* compared with monotherapies while remaining inactive without light exposure. In orthotopic PDAC models, treatment with the prodrug nanoparticle and irradiation resulted in substantial

Table 3 Stimuli Responsive Nanoparticles in Preclinical Studies for the Treatment of Pancreatic Cancer

Nanoparticle Type	Compound	Stimuli Response	Ref
Liposome/microbubble	Irinotecan and oxaliplatin	Ultrasound	[79,80]
Mesoporous silica	Paclitaxel ADAM9	Enzyme	[81]
Semiconducting polymeric nanoparticles	¹⁷⁷ Lu and glucose dependant insulinotropic polypeptide	Photo	[80]
Gold nanoparticles	Gold nanorods	Thermal	[82]
Silver nanoparticles	Immunoglobulin G	Photo	[83]
Polymeric micelle	PLK1, volasertib and miR-34a	Reactive oxygen species (ROS)	[84]
Magnetic nanoparticles	Iron oxide	Hyperthermia	[85]
Quantum dots	RGD peptide	Photo	[86]
Prodrug nanoparticle	Chlorin e6 (Ce6), caspase-3-cleavable peptide linker and monomethyl auristatin E (AMME)	Photo	[87]

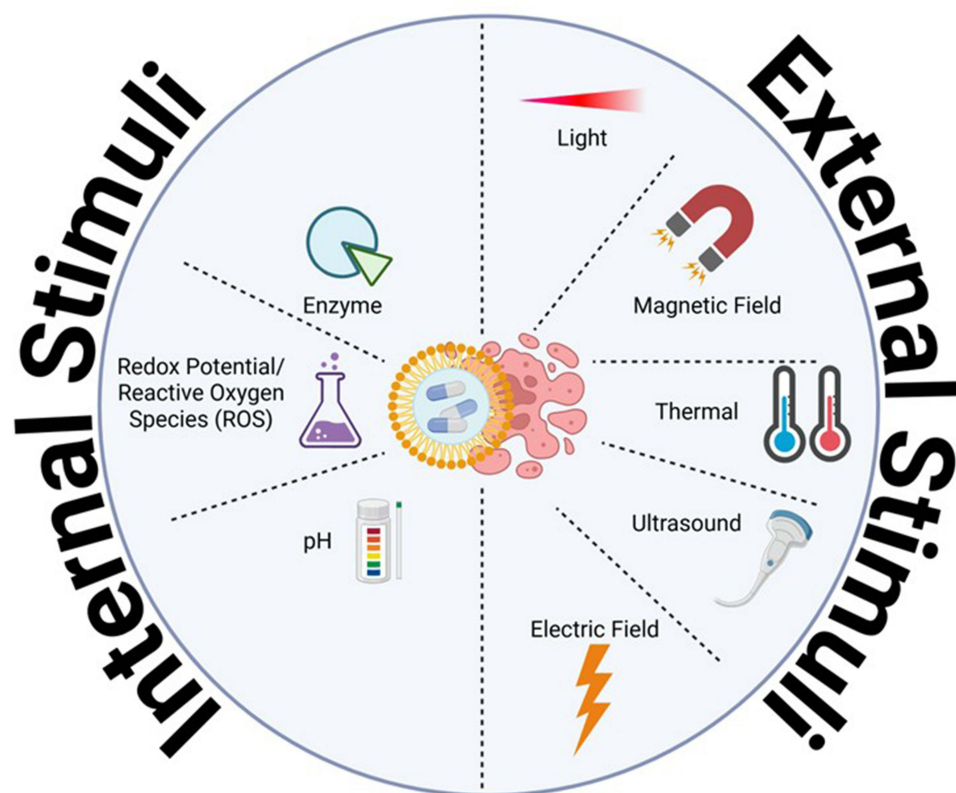


Figure 3 External and internal stimuli nanoparticles used in pancreatic cancer, created with BioRender.com.

tumor growth suppression with improved survival (Figure 4). Additionally, reduced systemic toxicity relative to free MMAE was observed.⁸⁷

Nanoparticles as Radiation Enhancers in PC

Nanoparticle-enhanced radiotherapy (NERT) uses biocompatible nanoparticles functionalized for tumor targeting. In NERT, the nanoparticles act as radiosensitizers or radiation enhancers, thereby, increasing the local radiation dose experienced within the tumor tissue, whilst reducing the overall dose requirement, which minimizes the off-target effects. Park et al reported the fabrication of a docetaxel-contained polymeric nanoparticle (DTX-PNP) to act as a radiosensitizer for PC.⁸⁸ The novel DTX-PNP was tested *in vitro* and *in vivo* in AsPC-1 or BxPC-3 cell lines or xenografts. The combined DTX-PNP administration and radiation therapy DTX-PNP in combination with IR possessed a high level of cytotoxicity in the cell lines. *In vivo* radiotherapeutic efficacy of the DTX-PNP nanoplatfrom was compared to the standard chemoradiation agent Gemzar. The data showed that in both PC xenograft models, the DTX-PNP combined with radiotherapy showed a significant enhancement in tumor retardation compared with the radiotherapy alone, an improvement when compared with the Gemzar and IR. This combined approach for chemoradiation plus radiosensitization holds promise for further therapeutics in PC. Other organic nanoparticles coupled with drugs which act as radiosensitizer such as albumin encapsulating paclitaxel have shown to possess enhanced therapeutic outcomes in PC when used in combination.⁸⁹

Colloidal gold (nanoparticles, nanospheres, rods etc) is well known to act as radiation enhancers. The high atomic number of gold leads to a greater absorption of X-rays and gamma rays compared to the biological tissue. The focused radiation absorption by the gold nanoparticle enhances the local damage within the tumor microenvironment. Aliru et al created gold nanospheres (AuNSs) which were surface decorated with a nuclear localization sequence (NLS) peptide to promote accumulation within the nucleus in PC cells.⁹⁰ *In vitro* radiosensitization studies were carried out in Panc-1 cells,

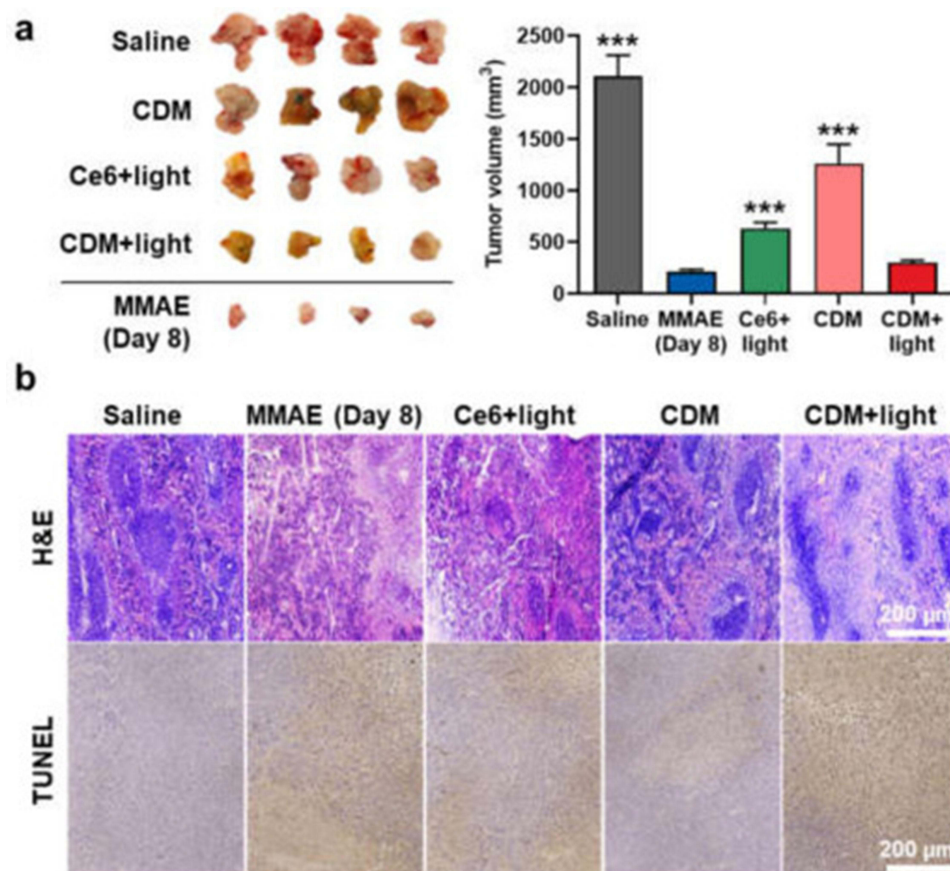


Figure 4 In vivo therapeutic efficacy of CDM in orthotopic pancreatic cancer models. (a) Optical images and volume of cancer tissues from orthotopic pancreatic cancer models after treatment with saline, MMAE, Ce6, or CDM. The tumors of Ce6- or CDM-treated mice were locally irradiated with visible light with power of 160 mW for 10 min. The 3 asterisks in Figure indicate the comparison to the CDM+light group. (b) Pancreatic cancer tissues stained with H&E or TUNEL.⁸⁷

and in vivo models. The study showed that internalization within the nucleus of the targeted particles was significantly higher than for the non-targeted particles. Clonogenic cell survival indicated a statistical significance ($p < 0.05$) in radiosensitization enhancement factors, calculated at the 10% survival fraction between the treatment groups using different types of radiation. In vivo studies showed increased tumor retardation with the AuNSs and radiation, compared with the radiation alone. Besides gold, other metallic nanoparticles such as gadolinium and hafnium oxide exert a comparative effect.^{91,92}

Nanotechnology as Diagnostics for PC

There have been promising results in this arena, ranging from improving biomarker detection, contrast enhancement, to the detection of circulating cancer cells (CTCs) and enabling multiplexed detection.

Conventional biomarkers such as CA-19 are useful but they lack the sensitivity and specificity for utilization in screening. Nanoparticles can provide signal amplification and physiochemical properties (magnetic, plasmonic, fluorescent and catalytic) which can be exploited to enhance current diagnostic tools or create more suitable methods. A recent breakthrough is the development of a protease-activated magnetic nano-sensor (PAC-MANN).⁹³ Designed to measure protease activity by monitoring the cleavage of peptides on nano-sensors. Each nano-sensor is functionalized with short peptide probes labeled with a fluorescent molecule and any change in fluorescence by protease-mediated cleavage is measured by a detector. PAC-MANN successfully identified PC at all stages with 98% specificity and 73% sensitivity in a blind trial, distinguishing 100% of non-cancer patients. When combined with CA19-9, stage one detection PC identified with 85% sensitivity and 96% specificity, a significant increase in sensitivity to CA 19-9 alone (62%).

When nanoparticles interact with a biological environment, a protein corona is formed.⁹⁴ This alters the nanoparticles' properties and influences how the body interacts with them. In a small pilot study, plasma from PC and non-cancerous patients were mixed with liposomes and analyzed by particle size and surface charge measurement. Results demonstrated that particle size and surface charge were different from the two groups, suggesting different proteins were interacting with the nanoparticle. However, no proteomics-based mass spectrometry was conducted and therefore could not pinpoint what the proteins were. Other sources have studied different nanoparticles, observing similar effects. A recent study incubated 106 samples (PC and control) with the nanosheets and then combined with CA19-9.⁹⁵ There was a significant improvement in distinguishing PC samples from non-cancerous with up to 92% accuracy and boosted PC classification by 50% relative to using CA19-9 alone. In another study, using graphene oxide consisting of 50 samples (PC and control) incubated with plasma. Additionally, a double-blind trial was performed on an independent set (10 cancer and 10 control) with sensitivity ~92% and in the independent trial, strong discrimination was replicated.⁹⁶

Gold nanoparticles (AuNP) possess unique optical properties due to their nano-size, whereby they experience a strong surface plasmon resonance when irradiated with light at resonant wavelengths. They can be fabricated to form particles of various architectures (sphere, shell, rod, star) and sizes, each with unique and exploitable optical properties. Gold nanoparticles can be used as contrast agents for MRI and CT scans. Here, the AuNPs accumulate at the tumor site, and illuminate the scan in this accumulation region, helping clinicians diagnose the presence of cancer. Sobol et al attached a 5B1 targeting antibody, onto the surface of AuNPs, before radiolabeling the particles with⁸⁸ Zr.⁹⁷ The particles were administered to a CA19.9-positive BxPC-3 orthotopic tumor model in mice. The mice had been pre-treated with clodronate liposomes for PET imaging and biodistribution studies. Their study showed that the functionalised particles increased targeted delivery to CA19.9-positive pancreatic tumors. The combination of clodronate liposomes and a functionalised AuNPs allowed for PET/CT imaging of the orthotopic xenografts, giving better resolution and tumor information.

Using another powerful imaging tool, work has been carried out investigating the use of gold nanoparticles coated PEG and functionalised with F19 monoclonal antibodies, which have been shown to be effective as labelling agents in human PC tissues using darkfield microscopy.⁹⁸ The nanoparticles were incubated with tumor stroma sections of resected human pancreatic adenocarcinoma before imaging with a darkfield microscope. The study showed that these particles could be used as a novel labeling method could provide future biopsy diagnosis of PC.

AuNPs are also utilised as signal enhancers in surface-enhanced Raman spectroscopy (SERS). Here the light used for the spectroscopic technique can be scattered more effectively from the surface of particulates with a rough surface and optical properties such as gold nanoparticles. These are often exploited in lateral flow or immunoassays. A study has shown the promise of this combination in an immunoassay for PC.⁹⁹ Here gold colloids were surface decorated with a Raman reporter and an anti-MUC4 monoclonal antibody (8G7). The SERS platform was used for detecting cancer biomarkers in a sandwich format, using the same antibody for capture and detection and the analyte was cell lysate from MUC4-expressing PC cells. The study demonstrated that the assay could distinguish between PC cells and non-PC cells, and that it demonstrated superior performance to other existing assays, being able to detect and quantify levels of MUC4 in individual serum samples. It is hoped that this may lead to advances in screening of identified patients at risk. Other nanoparticle platforms being investigated for PC detection include iron oxide based magnetic nanoparticles, and quantum dots.^{100–103}

More recently, Zhang et al reported a plectin-1-targeted multimodal nanoparticle imaging probe for detecting PDAC in orthotopic mice.¹⁰⁴ A superparamagnetic iron oxide-based probe, labeled with a targeting peptide and near-infrared dye, IRDye800CW, enabled fluorescence molecular imaging, magnetic particle imaging and MRI. Compared to non-targeted controls, it showed higher tumor accumulation and clearer tumor delineation, demonstrating its potential use in improving specificity and precision of PDAC diagnostic imaging. Similarly, by the same group, developed a fibronectin-targeting dual-modality contrast agent for MRI and near-infrared fluorescence imaging of PDAC.¹⁰⁵ In mouse models, the agent provided enhanced tumor contrast at half the clinical gadolinium dose with imaging signals correlating with chemotherapy-induced TME changes, enabling for non-invasive diagnosis and treatment monitoring.

Theranostic Nanotechnology in Pancreatic Cancer

Theranostics are platforms consisting of a diagnostic modality as well as a therapeutic one. They allow for rapid treatment after diagnosis, which can cut down the current lag time that can be so detrimental to PC patients' survival chances. Although, currently, there are no clinical trials for these technologies, it is believed that these are the next-generation gold standard for cancer.

The Hoskins lab focuses on the development of iron oxide core-gold shell hybrid nanoparticles and their use as theranostic entities for pancreatic cancer.^{106–110} Here, iron oxide acts as an MRI contrast agent whilst the gold shell confers biocompatibility and serves as an anchor point for other molecules such as drugs or other biomolecules. Barnett et al demonstrated the MRI contrast ability of these systems, and their acceptability to pancreatic cancer cell lines.^{111,112} Malekigorji et al immobilized a novel cytotoxic agent based on a bisnaphthalimido spermine molecule, which due to the charges in its polyamine backbone, was capable of electrostatically attaching onto the particle surface.¹⁰⁸ Oluwasanmi et al used a different method for drug conjugation onto the hybrid nanoparticle surface, instead conjugating a maleimide-GEM prodrug onto the gold surface via a thiofuran anchor, forming a Diels-Alder cycloadduct.¹⁰⁷ The optical properties of gold allow for it to absorb/scatter light within the biological NIR window with no detriment to tissue. This was exploited by irradiating the nanoparticles with 1064 nm, 10 ns pulsed laser light for 20 seconds, resulting in rapid heat generation, which was exploited as a thermal trigger for drug release. In the Malekigorji study, this temperature resulted in the threshold temperature required to break the electrostatic bonds being exceeded leading to drug release. In PC BxPC-3 xenograft models, this led to significant reduction in tumor volume after intratumoral injection once per week for four weeks.¹⁰⁸ Similarly, in the Oluwasanmi study, the heat generation was sufficient to initiate the retro Diels-Alder reaction, where the anchor furan and maleimide became uncoupled, liberating the prodrug. In the xenograft study, this resulted in a 56% tumor size reduction compared to GEM alone.¹⁰⁷ Work is currently underway in this group, to confer active targeting properties and move these studies further towards the clinic.

Qiu et al developed a theranostic nanoparticle-based platform of gold nanocages (AuNCs) modified with hyaluronic acid (HA) and conjugated with an anti-Glypican-1 antibody (anti-GPC1), anti-cancer agent oridonin, contrast agent gadolinium (Gd), and a fluorescent dye Cy7 dye.¹¹³ Their platform showed excellent MRI contrast ability as well as fluorescence. The modified AuNCs enhanced apoptosis in PC cells *in vitro*, whilst showing negligible haemolytic activity. *In vivo* trials on PC xenograft mice showed that the modified AuNCs were capable of multimodal imaging combined with targeted therapy.

Other theranostics under consideration include the combination of MRI guidance with photodynamic therapy. Khan et al coated gadolinium nanoparticles with gold nanoparticles, stabilised by a lactose-modified chitosan polymer.¹¹⁴ These particles were tested *in vitro* on MiaPaCa-2 PC cell lines. The particles were stable under physiological conditions, and non-toxic until activated. Once irradiated at 808 nm, the photothermal effect resulted in significant loss in cell viability, indicating their effectiveness as an ablation source. The MRI data showed that the particles were effective as contrast agents *in vitro* and *in vivo*. The authors concluded that these particles are suitable for diagnosis and therapy in one single platform.

Barui et al constructed a gadolinium-doped zinc oxide nanoparticle platform which possessed MRI imaging capabilities.¹¹⁵ Onto the surface of these nanocrystals, they adsorbed GEM. Surrounding the drug loaded nanoparticle was a biomimetic layer composed of extracellular vesicles to confer biocompatibility and finally a synthetic targeting peptide was anchored onto the surface (CKAAKN). This drug loaded platform was testing *in vitro* in both BxPC3 and AsPC-1 PC cells. Up to 90% of the targeted construct was internalized by the cells, showing the effectiveness of the synthetic peptide, the unloaded nanoparticle construct was not toxic to the cells, neither was the GEM treatment alone (30 µg/mL); however, once loaded onto the platform, the cytotoxic effect became evident in both cell lines. The authors concluded that the GEM-loaded nano construct enhanced the drug efficacy, without changing its mechanism of action, by simply trafficking it more effectively into cells.

Harnessing *in vivo* fluorescent tracking combined with therapeutics, Tao et al fabricated a sequence-activated construct consisting of a diblock pH sensitive copolymer nano carrier, a NIR Förster resonance energy transfer (FRET) donor (AIEgen TCM-DN) with a PDAC targeting peptide (U11) and a FRET acceptor (cyanine).¹¹⁶ This

nanotheranostic: TCM-U11&Cy@P possessed dual-channel near-infrared fluorescence outputs which allowed for in vivo tracking. The programmable targeting ability was able to break through the PDAC stroma, entering the tumor, after which in vivo behaviors were monitored via activatable dual-channel near-infrared (NIR) fluorescence, showing enhanced tumor permeability. Once inside the tumor where the microenvironment is more acidic, the block copolymer released their internalized TCM-U11 nanoparticles where they were activated and photodynamic therapy was used to ablate tumors. The 3D tissue culture in Panc-1 tumor spheroids and xenografts in vivo demonstrated that the novel thernaostic platform was successful in tumor targeting and phototoxicity, whilst real-time monitoring was achievable by exploiting the FRET-based dual-channel activatable fluorescence.

Although all these technologies are in pre-clinical stages, more interest is being attracted to this arena, with publications showing promise over a host of theranostic nanoplatforms, where imaging and therapeutic modalities are combined, most recently in the systems demonstrated by Appidi et al and Fukumitsu et al.^{117,118}

Conclusions and Future Prospective

PC remains one of the most formidable challenges in oncology, owing to its complex biology, late diagnosis and limited responsiveness to conventional therapies. Despite significant advances in nanotechnology and the clinical approval of more than 50 nanomedicines across various disease areas, only two have been approved for PC. This highlights evidence of critically low investment in a disease area often described as an unmet cancer need. Compared with other cancers that receive higher levels of funding and commercial interest.

The studies discussed in this review demonstrate that meaningful progress has been achieved through innovative nano-based strategies, including prodrug nanoparticles, combination therapy, radiation enhancers, responsive nanoparticles and using nanoparticles as an enhancement tool for diagnostics. Unfortunately, the pace of advancement has been slow. However, the growing number of preclinical and clinical evidence continues to prove the potential in nanomedicine to address key challenges such as poor drug solubility, poor drug penetration, therapeutic resistance and systemic toxicity.

Looking ahead, continued interdisciplinary collaboration between academic and industry will be critical if any change is to be done. Increased investment and earlier intervention from regulatory agencies may accelerate this process. While significant challenges remain, the ever-expanding knowledge base offers optimism that nanomedicine has more to give for more effective diagnostic and therapeutic options for patients with PC cancer and their families.

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Figures created using BioRender n.d. Available online: <https://app.biorender.com/illustrations/65ff040d4603630b1370a481> (accessed January 2026).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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