World Journal of Pharmaceutical Science and Research

www.wjpsronline.com

Review Article

ISSN: 2583-6579
SJIF Impact Factor: 6.916
Year - 2026
Volume: 5; Issue: 5
Page: 566-578

ADVANCES IN THE MULTIMODAL TREATMENT OF PANCREATIC CANCER: CONVENTIONAL THERAPIES AND EMERGING NANOTECHNOLOGY-BASED APPROACHES

Dr. Shweta Chahal*, Kartikey Kaushik, Pushkar Mehta, Subah Sharma, Dr. Dharinder Tayal

Anovus Institute of Clinical Research, Chandigarh.

Article Received: 18 March 2026 | | ***Article Revised: 9 April 2026*** | | ***Article Accepted: 29 April 2026***

***Corresponding Author: Dr. Shweta Chahal**
Anovus Institute of Clinical Research, Chandigarh.
DOI: https://doi.org/10.5281/zenodo.19997682

How to cite this Article: Dr. Shweta Chahal, Kartikey Kaushik, Pushkar Mehta, Subah Sharma, Dr. Dharinder Tayal (2026) ADVANCES IN THE MULTIMODAL TREATMENT OF PANCREATIC CANCER: CONVENTIONAL THERAPIES AND EMERGING NANOTECHNOLOGY-BASED APPROACHES. World Journal of Pharmaceutical Science and Research, 5(5), 566-578.

ABSTRACT

Pancreatic cancer remains one of the most aggressive malignancies, with a persistently low five-year survival rate despite significant therapeutic advancements. Over recent decades, surgical techniques have evolved toward extended resections and minimally invasive approaches, improving safety and resectability in selected patients. In parallel, systemic chemotherapy regimens, including combination therapies, have demonstrated modest survival benefits. Nevertheless, treatment efficacy is frequently limited by late diagnosis, therapeutic resistance, and the dense tumor microenvironment characteristic of pancreatic ductal adenocarcinoma. Recent progress in nanotechnology and image-guided interventions has introduced novel therapeutic strategies beyond conventional modalities. Among these, photothermal therapy (PTT), particularly when combined with molecular targeted therapy, gene therapy, immunotherapy, and nano-enzyme–based systems, has shown promising preclinical outcomes. Nanotechnology-enabled drug delivery systems offer improved tumor targeting, enhanced drug penetration, and reduced systemic toxicity, addressing key limitations of standard treatments. This review provides a comprehensive overview of current and emerging treatment approaches for pancreatic cancer, encompassing surgical innovations, chemotherapy, radiotherapy, molecular targeted therapy, photothermal therapy, and nanotechnology-based drug delivery systems. Emphasis is placed on combination therapeutic strategies and their potential to enhance treatment efficacy. Additionally, the challenges associated with clinical translation and future research directions are discussed, with the aim of supporting the development of more effective and personalized therapeutic interventions for pancreatic cancer.

KEYWORDS: Pancreatic cancer; nanomedicine; photothermal therapy; molecular targeted therapy; drug delivery systems; combination therapy.

INTRODUCTION

One type of tumor that affects the GI tract is carcinoma of the pancreas, which has been more common recently, & 5-yr survival rate of almost 10%. PDAC or Pancreatic Ductal Adenocarcinoma is currently the third-biggest cancer killer in America.[1-3] Cancer linked symptoms, such as pain, fatigue, anorexia, depression, & anxiety, are highly prevalent in PC patients and tend to worsen as the end-of-life (EoL) approach.[4,5] Obesity and diabetes have long been recognized as risk factors for this condition, and diabetes that has either developed recently or gotten worse may be a sign of PDAC.

Smoking cigarettes continues to be one of the most important and controllable risk factors for PC.[6] Smoking is a contributing factor in 16.1% of female and 25.9% of male PC deaths.[7]

Furthermore, genetic alterations were an important variable in the development of PDAC.[8,9] Currently, the mainstay of care for pancreatic cancer patients is surgery. Individuals with pancreatic cancer who did not qualify for surgical resection may be treated with chemotherapy, radiotherapy, and immunotherapy. However, due to medication resistance, their effectiveness was not up to par.[10,11] It is imperative that new, more focused treatments be developed.

Advances in science have made nanoparticles ideal for drug delivery due to their unique physical and chemical characteristics, including high surface area, tunable pore size, high drug-carryng capacity, and favorable biocompatibility, which collectively enable more efficient and targeted delivery to tumor tissues.[12,13] Gemcitabine and cisplatin co-delivery via nanoparticles may have a synergistic effect on PDAC.[14] The PDAC matrix consists of the extracellular environment, the circulatory network, and tumor-related support cells. These components can combine to form a dense tumor mesenchyme that obstructs the delivery of drugs.[15] Nano-drug delivery systems have been investigated for their potential to improve drug penetration across the tumor–interstitial barrier; however, their clinical effectiveness remains under evaluation.[16]

The most often overexpressed genes in pancreatic cancer, including SMAD4, TP53, CDKN2A, and KRAS, have been found to be viable targets for molecular targeted treatment.[17] Recent studies have explored molecular targeted therapies for pancreatic cancer, although clinical outcomes have remained modest due to therapeutic resistance. These approaches include epidermal growth factor receptor inhibitors; however, their clinical benefit has been limited, largely due to the rapid development of resistance mechanisms.[18,19] Even though there are now a lot of treatments for pancreatic cancer, the tumour’s cure would inevitably present enormous obstacles. Thus, the development of novel and potent treatments for this illness is essential. This review aimed to provide new insights into the treatment of pancreatic cancer by describing recent developments in combination drug administration strategies, molecular targeted therapy, photothermal therapies, and nano-drug delivery systems.

LITERATURE SEARCH METHODOLOGY

This narrative review was conducted using literature retrieved from PubMed, Scopus, and Web of Science databases. Articles published in English up to 2024 were included. Relevant keywords included “pancreatic cancer,” “nanoparticles,” “photothermal therapy,” “molecular targeted therapy,” and “drug delivery systems.” Preclinical and clinical studies relevant to therapeutic advancements were considered.

Epidemiological data

There is no doubt that PC usage is rising globally. Between 1990 and 2017, there was 2.3 - fold rise in the number of deaths for both genders, and the age-standardized rate of death increased from 5.0 per 100,000 person-years to 5.7 per 100,000 person-years.[7] The population who was 70 years of age or older and between 50 and 69 yrs of age was the main contributor to the annual number of new cases.[20] The male-to-female ratio was 1.0:1.1, with 458,918 registered PC cases[21] in Globocan 2018 and 495,773 cases in 2020. Western Europe had the highest incidence rate (8.6/100,000), while South-Central Asia had the lowest (1.2/100,000).

The most recent Globocan data shows that although the incidence rate of PC is 4.9/100,000 worldwide, it is 8.6/100,000 in Western Europe, 8.0/100,000 in North America, and significantly higher than the global average in the pan-European region.[22] Although Asia's pancreatic cancer cases were generally lower than those of Western nations, some Asian regions—such as China—reported comparatively higher rates. South-Eastern and South-Central Asia had far lower PC incidences than the global average, while Eastern and Western Asia had slightly higher incidences.[23]

Differences in PC incidence were also observed between individuals of rural and urban areas. Numerous factors may contribute to the higher PC incidence rate in urban areas, including: a greater number of medical facilities and specialists, which raised diagnostic rates, as well as a greater incidence of obesity and tobacco use.[24] On the other hand, reduced incidence rates from rural areas may be brought on by fewer healthcare providers, a lower population density, and distinct lifestyle choices.[25]

In conclusion, a complex interaction between genetic, environmental, and lifestyle factors was reflected in the regional differences in PC incidence. It is imperative to acknowledge and tackle these variations in order to customize efficacious prevention and early detection initiatives.

Treatment approaches

Surgery: Even though surgical resection presents a chance for curative therapy, only 20% of patients have tumors that can be surgically removed.[26] Depending on where the tumor is located in the pancreas, the surgical treatment option for tumors in the pancreas varies. A majority of tumors of the pancreas are found in the head of the pancreas and require a pancreaticoduodenectomy for complete resection, which is also called as artery first approach, although tumors closer to the pancreatic head can typically be treated with a distal pancreatectomy.[27] When treating resectable pancreatic carcinoma surgically, the traditional &pancreatoduodenectomy (PD) using the Kausch-Whipple technique or+the pylorus^preserving PD using the Traverso)Longmire technique are considered the standard surgical treatments.[28]

In cases of resectable pancreatic carcinoma, the standard surgical approach involves either the pylorus-preserving Traverso-Longmire mobilization of the downcast duodenum by incision of the peritoneum along the lateral side of the duodenal fold, or conventional PD via the Kausch-Whipple procedure. After that, the Cattell-Brascha maneuver is carried out, which entails activating the caecum&the right half of the colon and the hepatic flexures from the right side in a medial direction, and mobilizing the small intestine's posterior appendices in a cranial direction. Large retroperitoneal space vessels, such as the inferior vena cava and aorta, are thus beautifully displayed. The remaining portion of the preparation is done cranially until the upper mesenteric artery and left renal vein are visible.[29] Criteria

for pancreatic cancer respectability according to the National Comprehensive Cancer$Network version 2.2017@are shown in **Table 1.**

The most crucial procedure in terms of the oncological PD stage is the technical separation of the pancreatic head from the mesenteric artery, which is also the most challenging.[30] Using the classical method, the superior mesenteric vein and portal vein combination is divided from the pancreatic neck. Afterwards, a cut along the venous plane is made to remove the pancreas. Subsequently, the surrounding tissues make it simple to dissect the pancreatic head and the uncinate process. The pancreatic head and the mesenteric artery can only be attempted to be separated at this point in the surgical procedure.

Pancreaticoduodenectomy has been additionally carried out via laparoscopy; multiple case series have shown the viability, safety, and effectiveness of this procedure in comparison to open surgery.[31] Additionally, the use of the robotic platform in pancreatic surgery is growing. This method gets around some of the drawbacks of laparoscopy, like poor ergonomics, dexterity, and two-dimensional visualization. Zureikat et al.[32] reported a total pancreatic fistula rate of027% & a 90-d Clavien5grade=III-IV complication rate of 23% in a series of 30 patients going through robot-assisted major pancreatectomy and reconstruction. After conducting research, they concluded that conventional pancreatectomy and robotic surgery can both be executed safely and with comparable rates of postoperative complications. Larger, controlled trials and more experience are required to precisely define potential advantages and clarify the long-term oncologic results of minimally invasive pancreaticoduodenectomy.

Chemotherapy: There aren't many efficient chemotherapy choices for pancreatic cancer that has spread. Although many different agents have been studied alone or in combination with gemcitabine, few have shown a positive effect on survival in patients with advanced disease. Gemcitabine has been the standard agent of choice since the 1990s.[33-36]

More recently, regimens consisting of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin, or FOLFIRINOX, as well as gemcitabine + nab-Paclitaxel, have been found to result in greater levels of response than gemcitabine alone. 342 patients with metastatic pancreatic cancer were randomly allocated to receive either FOLFIRINOX7or single@agent gemcitabine as first-line4treatment for pancreatic=cancer in the Actions Concertées dans9les Cancer Colo-Rectaux et Digestifs (ACCORD) 11 trial.[37]

Following the discovery of high levels of the albumin-binding protein+SPARC (secreted7protein acidic and rich-in cysteine)5in pancreatic tumors through molecular profiling, the role of nab-paclitaxel in pancreatic cancer was examined.[38] In breast and lung cancers, nab-paclitaxel has shown anti-tumor activity, especially in tissues with high levels of SPARC expression.[38] Tumors with elevated SPARC levels in patients with pancreatic cancer are thought to act as albumin-binding sites, sequestering nab-paclitaxel and concentrating drug levels intramuscularly.[39] Another theory is that paclitaxel enters the tumoral interstitial area via endothelial cells' gp60 albumin receptor. In breast cancer and lung tumors, nab-paclitaxel has shown anti-tumor activity, especially in tissues with elevated levels of SPARC expression.

Additionally, erlotinib, along with gemcitabine, is a multidrug regimen that has demonstrated enhanced overall and progression-free survival.[40,41] However, FOLFIRINOX and gemcitabine + nab-paclitaxel are the recommended

treatment options for individuals with an appropriate level of performance because of their greater chance for improved results.

Radiation therapy: Pancreatic cancer (PC) remains a challenging disease for oncologists despite advancements in surgical management, chemotherapy, and chemoradiation therapy (CRT) techniques. A key factor in classifying locally advanced PC is whether or not there is vascular involvement. This spectrum runs from resectable to locally advanced.

Prospective evaluation using imaging studies—mostly CT scans, but also MRIs and endoscopic ultrasounds are required to determine resectability. Despite conflicting data supporting its effectiveness, an adjuvant radiation treatment (RT) is frequently used. The first randomized trial to compare@adjuvant chemo radiation (40=Gy in a split5course with weekly bolus of@5-FU) to observation in 43 patients (22 vs 21) with negative margins following a PDAC removal was the GITSG study, which was carried out in 1985.[42] Their findings indicated that CRT prolonged overall survival (average of 205months@vs. 11 months), but the trial's early closure was caused by low patient enrolment (it was meant tosenrol 100 patients). Thus, CRT was adopted as the new adjuvant treatment norm. Nonetheless, subsequent randomized trials cast doubt on the survival advantage of CRT in the adjuvant setting.[43-45] Neoadjuvant radiation offers some theoretical benefits as well, much like chemotherapy. Increasing the effectiveness of the neoadjuvant strategy for radiation treatment makes sense, considering the high morbidity following PDAC procedure and the early systemic recurrence. Research on neoadjuvant radiation since the 1980s has only been able to find a slight benefit. Numerous small-scale trials have been conducted to determine the efficacy and security of the treatments. Its capacity to enhance local control and survival when given in combination with either gemcitabine or 5-FU as radiosensitizers has been restricted to cases of resectable disease[46,47] and borderline resectable/locally advanced disease.[48,49] Better evidence for neoadjuvant chemoradiation for individuals with marginally resectable conditions was presented by the 2018 PREOPANC-1 study. A randomization process was used to assign 246 patients with PDAC who were on the verge of surgery or neoadjuvant gemcitabine + 36 Gy radiation given in between two cycles of gemcitabine, with adjuvant chemotherapy offered to both groups. The R0 resection rate (65% vs.31%), disease-free survival (median 11.2 vs. 7.9 months), and overall survival (median 17.1 vs. 13.3 months) were all noticeably higher in the chemotherapy-radiation group of patients, despite the fact that fewer of them underwent resection (62% vs. 122%). Additional evidence for the advantages of neoadjuvant chemoradiation comes from patient data from the Observation, &Epidemiology, and End=Results (SEER) registry as well as a 2018 meta-analysis.[50,51]

Nano drug delivery: The size and distinct surface characteristics of nanoparticles play a critical role in controlling drug release, suggesting that a nano=drug*delivery system for pancreatic cancer might reduce side effects and increase therapeutic efficacy.[52] The=treatment of pancreatic cancer5has made extensive use of nanoscale drug delivery systems like liposomes. Recently, Raza et al. conducted an extensive evaluation of some of the most recent developments in liposome-based pancreatic cancer detection and therapy, offering a new avenue for pancreatic cancer treatment.[53]

This section covered the following topics: albumin, natural polymers such as poly (lactic-co-glycolic acid), mesoporous silica, and exosome-mediated nano-drug delivery systems.

With their approval by the FDA, mesoporous silica nanoparticles (MSNs) have garnered significant interest as a drug delivery mediator. Their large5surface area, high drug5loading, and capacity to regulate the release of bioactive

substances were their distinguishing features. Furthermore, functional groups and ligands may be better able to target if they were altered.[54-56]

Targeting the 5folic acid receptors5on tumor5cells specifically could enhance the curative effect of folic acid-modified mesoporous silica nanoparticles.[57,58] Delivery of5irinotecan via MSNs elicited a more potent anti-tumor antibody response7in an in-situ K-Ras-dependent=pancreatic cancer model than either irinotecan alone or the liposomal formulation Onivyde. Additionally, concurrent anti-PD-1 therapy may considerably raise pancreatic cancer patients' chances of survival.[59] One protease that was found to be highly expressed in PDAC was ADAM9. Paclitaxel delivery can be efficiently targeted, toxic reactions may be greatly decreased, and therapeutic efficacy may be enhanced by a mesoporous00silica-modified@ADAM9-mediated drug6delivery system.[60] MSNs are a promising nano-drug delivery platform that reduces toxic effects as they stimulate the accumulation of drugs in cancer cells.[61] Therefore, a very promising method for treating pancreatic cancer was the MSNs-mediated nano-drug delivery system.

Albumin nanoparticles were utilized for the=targeted therapy of#PDAC by delivering6pre-drug β-lap, nab-(pro-β-lap),4with experimental results demonstrating its high safety and anti-tumor efficacy.[62] A combination of polycaprolactone, or PCL, and bovine serum albumin (BSA) was used to link albendazole into 100 nm-diameter nanoparticles. BSA-PCL nanoparticles, which have the potential to be used as targeted delivery vectors for albendazole for the management of pancreatic cancer, were demonstrated in studies to be able to precisely and efficiently deliver the drug to pancreatic multicellular tumor spheroids.[63] Studies showed that these nanoparticles could enter mouse xenograft models' tumor tissues, accumulate inside the tumors, and gradually harden to dramatically slow the growth of tumors in nude mice.[64] Furthermore, heat-and fibrosis matrix-sensitive liposomes with size-adjustable capabilities were used to encapsulate immune checkpoint inhibitor-containing smaller albumin nanoparticles (HSA-BMS@CAP-ILTSL). The combined therapeutic approach improved immunotherapeutic responses in experimental pancreatic cancer models.[65] As an outcome, the use of albumin-based nanoparticles offered a very promising method of targeted medication delivery.[66,67]

Exosomes were nanovesicles made of cells that ranged in diameter from 30 to 150 nm.@Exosomes have been broadly used as=nanocarrier platforms for*delivering nucleic acids and chemotherapy medications because of their robustness, low immunogenicity, good biocompatibility, and other qualities. Exosomes can carry molecules into target cells and initiate pathways of signaling as a way of intercellular communication.[68-70]

Because of its superior surface modification capabilities, controlled release properties, biodegradability, and biocompatibility, poly (lactic-co-glycolic acid) (PLGA) has received FDA approval.[71] PLGA nanoparticles could contain chemotherapy medications that precisely target tumor cells when they are created as specific targeting molecules.[72,73]

A naturally occurring chemical with anti-inflammatory and tumor-fighting properties that was extracted from the ginger plant is called curcumin. Constructing chitosan &(polyethylene glycol (PEG) coated PLGA=nanoparticles enriched+with curcumin, as opposed to single curcumin, could improve cellular uptake and trigger apoptosis in pancreatic cancer cells,[74,75] according to in-vivo & in=vitro experiments.

Molecular targeted therapy: Targeting the epidermal5growth factor=receptor, human=epidermal growth factor#receptor 2, trophoblast&cell-surface antigen 2, and the vascular=endothelial growth factor=was the primary strategy used in molecular targeted treatment for cancer of the pancreas.[76]

A member5of the ERBB familypof cell surfaceureceptor tyrosinelkinases is the epidermalYgrowth factor receptorI(EGFR).[77] It functions as an intracellular tyrosine Kinase domain, a transmembrane domain, along with a domain that is extracellular, specific to ligands. After attaching itself to its particular ligand,@EGF,*EGFR can assemble into homologous%or heterodimeric_complexes that auto-phosphorylate the receptor'sgtyrosinekkinase, thereby initiating downstream signaling pathways.[78,79]. Inhibitors of Tyrosine kinase that are small molecules, like gefitinib and erlotinib, have the ability to bind only toooverexpressed proteinsoin tumor cells. Theyhcan specifically target the EGFR dimer'sgintracellular protein structural domain, which will interfere with ATPHbinding and further prevent the downstreamKtyrosine kinase from being phosphorylated.

In the long run, this stops tumor cells from growing.[80,81] The only small-moleculehtargeted therapyhinhibitor that is authorized for the treatment of PDAC is erlotinib, as shown in **Figure 1**. The clinical trials demonstrated that either erlotinib used as a monotherapy on its own or in conjunction with gemcitabine produced insufficient outcomes.[40]

Canertinib is an additional irreversible EGFR inhibitor that lowers the proliferation, survival, and migration of pancreatic cancer cells by influencing EGFR familyuproteins & consequently downregulating the MUC4 mucins. It also prevents the phosphorylation of tyrosine and increases ubiquitination.[82]

Photothermal therapy alone or in combination with Gene Therapy: Nanotechnology-based photothermal therapy (PTT) offers treatment options for pancreatic cancer that show promise. Pancreatic cancer frequently has the K-Ras mutation.[83] A gene-targeting K-Ras G12V alteration was combined with a synergistic therapy that used reducedyoxidized graphene=@gold nano stars crosslinked with~folic@acid. The outcome demonstrated that photothermal and gene therapy together exhibited a strong anti-tumour effect in pancreatic cancer tumour-bearing mice.[84] Combining near-infrared photo-hyperthermia with multifunctional single-layer oxidized graphene nanosheets could significantly reduce the risk of cancer of the pancreas by delivering both K-Ras and HDAC1 siRNAs that trigger gene silencing.[85] When biodegradable imposed polyesters vectors and quantum dots of graphene were employed to co-carry doxorubicin and siRNA, a photothermal effect caused by laser irradiation may cause the release of both agents. This nano-complex would have considerably enhanced its ability to fight cancer.[86]

Combined Administration Strategy for Pancreatic Cancer: Experimental studies have demonstrated enhanced anti-tumor activity with nanoparticle-based combination therapies, although most evidence remains preclinical.[87,88]

Varlitinib was conjugated with¥pegylated@gold nanoparticles in a controlled-release delivery system, which improved the drug's effectiveness against pancreatic malignancies while decreasing its harmful side effects.[89] Target cells may be able to absorb more medication when EGFR ligands and nanoparticles are coupled, possibly inducing apoptosis.[90]

Targeting EGFR, the GE11 peptide mixed micellar system delivered gemcitabine and OMe-PS-miR-519c to pancreatic tumor cells with precision and efficaciously inhibited the growth of the tumors.[91]

Nucleic acid delivery via nanoparticles has the potential to overcome resistance to drugs in different tumors by triggering cell apoptosis.[92] PL-1/miR-9 nanoparticles have the ability to deliver miR-9 selectively, suppress eIF5A2 expression, and cause PDAC cells to undergo apoptosis.[93] The combination therapy demonstrated improved therapeuticueffects, includingymatrix depletion, decreasedyimmunosuppression, and inhibition of metastasis. Anti-miR-210 and siKRASG12D were given via polymeric nanoparticles involving CXCR4 antagonist.[94] Gemcitabine and microRNA (miR-345) were co-delivered using a polymerzdual-deliveryznanoscale device, leading to a combination therapy that inhibited tumorzgrowth & metastasis to distant organs.[95] C225-GEM/MAN, a combination of the novel cetuximab (C225) and a magnetic albumin nanosphere containing gemcitabine, was utilized as an MRI molecular probe. According to the findings, this dual-targeted thermochemical therapy on AsPC-1 cells in the pancreas illustrated the greatest targeted killing efficiency.[96]

CONCLUSION

Treatment for pancreatic cancer is extremely difficult because it is a highly malignant tumor. Although surgical resection is still the most common method, its effectiveness hasynot increased over_time. The first-lineytreatment for pancreatic cancer is chemotherapy. Therapy outcomes are, however, frequently constrained by drug resistance, heterogeneity, and dense tumor interstitial media. Modern medicine is using **nanomaterials** (tiny, engineered particles) to solve a major problem: getting drugs past the body's natural defenses and directly into cancer cells. These particles can be designed to target specific areas, like the oxygen-starved ("hypoxic") parts of a tumor, to release medicine exactly where it is needed., immunotherapy, and nanoenzyme-based approaches has expanded the scope of experimental therapeutic strategies, though clinical translation remains limited.

REFERENCES

1. Siegel, R.L., et al., *Cancer statistics, 2021*. Ca Cancer J Clin, 2021; 71(1): p. 7-33.
2. Park, W., A. Chawla, and E.M. O'Reilly, *Pancreatic cancer: a review.* Jama, 2021; 326(9): p. 851-862.
3. Rahib, L., et al., *Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States.* Cancer research, 2014; 74(11): p. 2913-2921.
4. Lelond, S., et al., *Symptom burden of patients with advanced pancreatic cancer (APC): A provincial cancer institute observational study.* Current Oncology, 2021; 28(4): p. 2789-2800.
5. Tang, C.-C., D. Von Ah, and J.S. Fulton, *The symptom experience of patients with advanced pancreatic cancer: an integrative review.* Cancer nursing, 2018; 41(1): p. 33-44.
6. Yuan, C., et al., *Cigarette smoking and pancreatic cancer survival.* Journal of Clinical Oncology, 2017; 35(16): p. 1822.
7. Pourshams, A., et al., *The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017*. The lancet Gastroenterology & hepatology, 2019; 4(12): p. 934-947.
8. Aslanian, H.R., J.H. Lee, and M.I. Canto, *AGA clinical practice update on pancreas cancer screening in high-risk individuals: expert review.* Gastroenterology, 2020; 159(1): p. 358-362.
9. Klein, A.P., *Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors.* Nature reviews Gastroenterology & hepatology, 2021; 18(7): p. 493-502.
10. Neoptolemos, J.P., et al., *Therapeutic developments in pancreatic cancer: current and future perspectives.* Nature reviews Gastroenterology & hepatology, 2018; 15(6): p. 333-348.

11. Strobel, O., et al., *Optimizing the outcomes of pancreatic cancer surgery.* Nature reviews Clinical oncology, 2019; 16(1): p. 11-26.
12. Li, T., et al., *Recent advancements in mesoporous silica nanoparticles towards therapeutic applications for cancer.* Acta biomaterialia, 2019; 89: p. 1-13.
13. Raj, S., et al. *Specific targeting of cancer cells with nanoparticles and drug delivery in cancer therapy*. in *Seminars in cancer biology*. 2021. Elsevier.
14. Tarannum, M., et al., *Advanced Nanoengineering Approach for Target-Specific, Spatiotemporal, and Ratiometric Delivery of Gemcitabine–Cisplatin Combination for Improved Therapeutic Outcome in Pancreatic Cancer.* Small, 2022; 18(2): p. 2104449.
15. Hosein, A.N., R.A. Brekken, and A. Maitra, *Pancreatic cancer stroma: an update on therapeutic targeting strategies.* Nature Reviews Gastroenterology & Hepatology, 2020; 17(8): p. 487-505.
16. Kashkooli, F.M., M. Soltani, and M. Souri, *Controlled anti-cancer drug release through advanced nano-drug delivery systems: Static and dynamic targeting strategies.* Journal of Controlled Release, 2020; 327: p. 316-349.
17. Hayashi, A., J. Hong, and C.A. Iacobuzio-Donahue, *The pancreatic cancer genome revisited.* Nature reviews Gastroenterology & hepatology, 2021; 18(7): p. 469-481.
18. Roskoski Jr, R., *ErbB/HER protein-tyrosine kinases: Structures and small molecule inhibitors.* Pharmacological research, 2014; 87: p. 42-59.
19. Vaquero, J., et al., *Genetic alterations shaping tumor response to anti-EGFR therapies.* Drug Resistance Updates, 2022: p. 100863.
20. Ilic, I. and M. Ilic, *International patterns in incidence and mortality trends of pancreatic cancer in the last three decades: a joinpoint regression analysis.* World Journal of Gastroenterology, 2022; 28(32): p. 4698.
21. Ferlay, J., et al., *Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods.* International journal of cancer, 2019; 144(8): p. 1941-1953.
22. Lortet-Tieulent, J., et al., *Profiling global cancer incidence and mortality by socioeconomic development.* International Journal of Cancer, 2020; 147(11): p. 3029-3036.
23. Zhao, C., et al., *The distributional characteristic and growing trend of pancreatic cancer in China.* Pancreas, 2019; 48(3): p. 309-314.
24. Rawla, P., T. Sunkara, and V. Gaduputi, *Epidemiology of pancreatic cancer: global trends, etiology, and risk factors.* World journal of oncology, 2019; 10(1): p. 10.
25. Arnold, M., et al., *Global burden of 5 major types of gastrointestinal cancer.* Gastroenterology, 2020. 159(1): p. 335-349. e15.
26. Li, D., et al., *Pancreatic cancer.* The Lancet, 2004; 363(9414): p. 1049-1057.
27. Sohn, T.A., et al., *Resected adenocarcinoma of the pancreas—616 patients: results, outcomes, and prognostic indicators.* Journal of Gastrointestinal Surgery, 2000; 4(6): p. 567-579.
28. Masiak-Segit, W., et al., *Surgical treatment of pancreatic cancer.* Polish Journal of Surgery, 2018; 90(2): p. 45-53.
29. Del Chiaro, M., et al., *Cattell-Braasch maneuver combined with artery-first approach for superior mesenteric-portal vein resection during pancreatectomy.* Journal of Gastrointestinal Surgery, 2015; 19: p. 2264-2268.
30. Inoue, Y., et al., *Pancreatoduodenectomy with systematic mesopancreas dissection using a supracolic anterior artery-first approach.* Annals of Surgery, 2015; 262(6): p. 1092-1101.

31. Kendrick, M.L. and D. Cusati, *Total laparoscopic pancreaticoduodenectomy: feasibility and outcome in an early experience*. Archives of Surgery, 2010; 145(1): p. 19-23.
32. Zureikat, A.H., et al., *Robotic-assisted major pancreatic resection and reconstruction.* Archives of Surgery, 2011; 146(3): p. 256-261.
33. Burris, H.r., et al., *Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreatic cancer: a randomized trial.* Journal of Clinical Oncology, 1997; 15(6): p. 2403-2413.
34. Hertel, L.W., et al., *Evaluation of the antitumor activity of gemcitabine (2', 2'-difluoro-2'-deoxycytidine).* Cancer research, 1990; 50(14): p. 4417-4422.
35. Cullinan, S.A., et al., *A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma: fluorouracil vs fluorouracil and doxorubicin vs fluorouracil, doxorubicin, and mitomycin.* Jama, 1985; 253(14): p. 2061-2067.
36. Conroy, T., C. Gavoille, and A. Adenis, *Metastatic pancreatic cancer: old drugs, new paradigms.* Current opinion in oncology, 2011; 23(4): p. 390-395.
37. Conroy, T., et al., *FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer.* New England journal of medicine, 2011; 364(19): p. 1817-1825.
38. Neuzillet, C., et al., *Stromal expression of SPARC in pancreatic adenocarcinoma*. Cancer and Metastasis Reviews, 2013; 32: p. 585-602.
39. Desai, N.P., et al., *Improved effectiveness of nanoparticle albumin-bound (nab) paclitaxel versus polysorbate-based docetaxel in multiple xenografts as a function of HER2 and SPARC status.* Anti-cancer drugs, 2008; 19(9): p. 899-909.
40. Moore, M.J., et al., *Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group.* Journal of clinical oncology, 2007; 25(15): p. 1960-1966.
41. Yang, Z.-Y., et al., *Gemcitabine plus erlotinib for advanced pancreatic cancer: a systematic review with meta-analysis.* PloS one, 2013; 8(3): p. e57528.
42. Kaiser, M.H. and S.S. Ellenberg, *Pancreatic cancer: adjuvant combined radiation and chemotherapy following curative resection*. Archives of surgery, 1985; 120(8): p. 899-903.
43. Klinkenbijl, J.H., et al., *Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group.* Annals of surgery, 1999; 230(6): p. 776.
44. Neoptolemos, J.P., et al., *A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer.* New England Journal of Medicine, 2004; 350(12): p. 1200-1210.
45. Smeenk, H.G., et al., *Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891*. 2007, LWW.
46. Kim, E.J., et al., *A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer.* Cancer, 2013; 119(15): p. 2692-2700.
47. Shroff, R.T., et al., *Updated survival analysis of preoperative gemcitabine (gem) plus bevacizumab (bev)-based chemoradiation for resectable pancreatic adenocarcinoma*. 2012, American Society of Clinical Oncology.
48. Epelbaum, R., et al., *Phase II study of gemcitabine combined with radiation therapy in patients with localized, unresectable pancreatic cancer.* Journal of surgical oncology, 2002; 81(3): p. 138-143.

49. Small Jr, W., et al., *Full-dose gemcitabine with concurrent radiation therapy in patients with nonmetastatic pancreatic cancer: a multicenter phase II trial.* Journal of Clinical Oncology, 2008; 26(6): p. 942-947.
50. Versteijne, E., et al., *Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer.* Journal of British Surgery, 2018; 105(8): p. 946-958.
51. Stessin, A.M., J.E. Meyer, and D.L. Sherr, *Neoadjuvant radiation is associated with improved survival in patients with resectable pancreatic cancer: an analysis of data from the surveillance, epidemiology, and end results (SEER) registry.* International Journal of Radiation Oncology* Biology* Physics, 2008; 72(4): p. 1128-1133.
52. Liu, L., et al., *Nanocarriers for pancreatic cancer imaging, treatments, and immunotherapies.* Theranostics, 2022; 12(3): p. 1030.
53. Raza, F., et al., *Liposome-based diagnostic and therapeutic applications for pancreatic cancer.* Acta Biomaterialia, 2023; 157: p. 1-23.
54. Su, J., et al., *Enhanced blood suspensibility and laser-activated tumor-specific drug release of theranostic mesoporous silica nanoparticles by functionalizing with erythrocyte membranes.* Theranostics, 2017; 7(3): p. 523.
55. Thi, T.T.H., et al., *Functionalized mesoporous silica nanoparticles and biomedical applications.* Materials Science and Engineering: C, 2019; 99: p. 631-656.
56. Kankala, R.K., et al., *Nanoarchitectured structure and surface biofunctionality of mesoporous silica nanoparticles.* Advanced materials, 2020; 32(23): p. 1907035.
57. Yin, F., et al., *Folic acid-conjugated organically modified silica nanoparticles for enhanced targeted delivery in cancer cells and tumor in vivo.* Journal of Materials Chemistry B, 2015; 3(29): p. 6081-6093.
58. Wang, C.E., et al., *Polymer nanostructures synthesized by controlled living polymerization for tumor-targeted drug delivery.* Journal of Controlled Release, 2015; 219: p. 345-354.
59. Liu, X., et al., *Combination Chemo-Immunotherapy for Pancreatic Cancer Using the Immunogenic Effects of an Irinotecan Silicasome Nanocarrier Plus Anti-PD-1.* Advanced Science, 2021; 8(6): p. 2002147.
60. Slapak, E.J., et al., *ADAM9-Responsive mesoporous silica nanoparticles for targeted drug delivery in pancreatic cancer.* Cancers, 2021; 13(13): p. 3321.
61. Asefa, T. and Z. Tao, *Biocompatibility of mesoporous silica nanoparticles.* Chemical research in toxicology, 2012; 25(11): p. 2265-2284.
62. Dou, L., et al., *Albumin binding revitalizes NQO1 bioactivatable drugs as novel therapeutics for pancreatic cancer.* Journal of Controlled Release, 2022; 349: p. 876-889.
63. Lu, H., et al., *Penetration and drug delivery of albumin nanoparticles into pancreatic multicellular tumor spheroids.* Journal of Materials Chemistry B, 2017; 5(48): p. 9591-9599.
64. Hu, Y., et al., *Hierarchical assembly of hyaluronan coated albumin nanoparticles for pancreatic cancer chemoimmunotherapy.* Nanoscale, 2019; 11(35): p. 16476-16487.
65. Yu, Q., et al., *Mild hyperthermia promotes immune checkpoint blockade-based immunotherapy against metastatic pancreatic cancer using size-adjustable nanoparticles.* Acta Biomaterialia, 2021; 133: p. 244-256.
66. Bhushan, B., et al., *Impact of albumin based approaches in nanomedicine: Imaging, targeting and drug delivery.* Advances in colloid and interface science, 2017; 246: p. 13-39.
67. Elzoghby, A.O., W.M. Samy, and N.A. Elgindy, *Albumin-based nanoparticles as potential controlled release drug delivery systems.* Journal of controlled release, 2012; 157(2): p. 168-182.

68. Channon, L.M., et al., *Small extracellular vesicles (exosomes) and their cargo in pancreatic cancer: key roles in the hallmarks of cancer.* Biochimica et Biophysica Acta (BBA)-Reviews on Cancer, 2022; 1877(3): p. 188728.
69. Mc Namee, N. and L. O'Driscoll, *Extracellular vesicles and anti-cancer drug resistance.* Biochimica et Biophysica Acta (BBA)-Reviews on Cancer, 2018; 1870(2): p. 123-136.
70. H. Rashed, M., et al., *Exosomes: from garbage bins to promising therapeutic targets.* International journal of molecular sciences, 2017; 18(3): p. 538.
71. Patra, A., S. Satpathy, and M.D. Hussain, *Nanodelivery and anticancer effect of a limonoid, nimbolide, in breast and pancreatic cancer cells.* International journal of nanomedicine, 2019: p. 8095-8104.
72. Mir, M., N. Ahmed, and A. ur Rehman, *Recent applications of PLGA based nanostructures in drug delivery.* Colloids and Surfaces B: Biointerfaces, 2017; 159: p. 217-231.
73. 73. da Silva Feltrin, F., et al., *Curcumin encapsulation in functional PLGA nanoparticles: A promising strategy for cancer therapies.* Advances in Colloid and Interface Science, 2022; 300: p. 102582.
74. Wang, Q., et al., *Combined delivery of salinomycin and docetaxel by dual-targeting gelatinase nanoparticles effectively inhibits cervical cancer cells and cancer stem cells.* Drug Delivery, 2021; 28(1): p. 510-519.
75. Tomeh, M.A., R. Hadianamrei, and X. Zhao, *A review of curcumin and its derivatives as anticancer agents.* International journal of molecular sciences, 2019; 20(5): p. 1033.
76. Duan, H., L. Li, and S. He, *Advances and prospects in the treatment of pancreatic cancer.* International Journal of Nanomedicine, 2023: p. 3973-3988.
77. Roskoski Jr, R., *The ErbB/HER family of protein-tyrosine kinases and cancer.* Pharmacological research, 2014; 79: p. 34-74.
78. Hynes, N.E. and H.A. Lane, *ERBB receptors and cancer: the complexity of targeted inhibitors.* Nature Reviews Cancer, 2005; 5(5): p. 341-354.
79. Eser, S., et al., *Oncogenic KRAS signalling in pancreatic cancer.* British journal of cancer, 2014; 111(5): p. 817-822.
80. Lakkakula, B.V.K.S., et al. *Small molecule tyrosine kinase inhibitors and pancreatic cancer—Trials and troubles*. in *Seminars in cancer biology*, 2019. Elsevier.
81. Wu, P., T.E. Nielsen, and M.H. Clausen, *FDA-approved small-molecule kinase inhibitors.* Trends in pharmacological sciences, 2015; 36(7): p. 422-439.
82. Seshacharyulu, P., et al., *Targeting EGF-receptor (s)-STAT1 axis attenuates tumor growth and metastasis through downregulation of MUC4 mucin in human pancreatic cancer.* Oncotarget, 2015; 6(7): p. 5164.
83. Lin, G., et al., *Biodegradable nanocapsules as siRNA carriers for mutant K-Ras gene silencing of human pancreatic carcinoma cells.* Small, 2013; 9(16): p. 2757-2763.
84. Jia, X., et al., *Functionalized Graphene@ Gold Nanostar/Lipid for Pancreatic Cancer Gene and Photothermal Synergistic Therapy under Photoacoustic/Photothermal Imaging Dual-Modal Guidance.* Small, 2020; 16(39): p. 2003707.
85. Yin, F., et al., *SiRNA delivery with PEGylated graphene oxide nanosheets for combined photothermal and genetherapy for pancreatic cancer.* Theranostics, 2017; 7(5): p. 1133.
86. Yang, C., et al., *Biodegradable polymer-coated multifunctional graphene quantum dots for light-triggered synergetic therapy of pancreatic cancer.* ACS applied materials & interfaces, 2018; 11(3): p. 2768-2781.

87. Yang, A., et al., *Hydrogel/nanoparticles-mediated cooperative combination of antiangiogenesis and immunotherapy.* Acta Biomaterialia, 2022; 153: p. 124-138.
88. Wang, M. and M. Thanou, *Targeting nanoparticles to cancer.* Pharmacological research, 2010; 62(2): p. 90-99.
89. Coelho, S.C., et al., *Gold nanoparticles for targeting varlitinib to human pancreatic cancer cells.* Pharmaceutics, 2018; 10(3): p. 91.
90. Grapa, C.M., et al., *Epidermal growth factor receptor and its role in pancreatic cancer treatment mediated by nanoparticles.* International Journal of Nanomedicine, 2019: p. 9693-9706.
91. Xin, X., et al., *Redox-responsive nanoplatform for codelivery of miR-519c and gemcitabine for pancreatic cancer therapy.* Science advances, 2020; 6(46): p. eabd6764.
92. Vaughan, H.J., J.J. Green, and S.Y. Tzeng, *Cancer-targeting nanoparticles for combinatorial nucleic acid delivery.* Advanced Materials, 2020; 32(13): p. 1901081.
93. Wu, Y., et al., *Chimeric peptide supramolecular nanoparticles for plectin-1 targeted miRNA-9 delivery in pancreatic cancer.* Theranostics, 2020; 10(3): p. 1151.
94. Xie, Y., et al., *Stromal modulation and treatment of metastatic pancreatic cancer with local intraperitoneal triple miRNA/siRNA nanotherapy.* ACS nano, 2020; 14(1): p. 255-271.
95. Uz, M., et al., *Dual delivery nanoscale device for miR-345 and gemcitabine co-delivery to treat pancreatic cancer.* Journal of Controlled Release, 2019; 294: p. 237-246.
96. Wang, L., et al., *GEM-loaded magnetic albumin nanospheres modified with cetuximab for simultaneous targeting, magnetic resonance imaging, and double-targeted thermochemotherapy of pancreatic cancer cells.* International journal of nanomedicine, 2015: p. 2507-2519.