CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.6487415

Available online at: http://www.iajps.com *Review Article*

CURATIVE TREATMENT OF PANCREATIC CANCER: A REVIEW

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Article Received: March 2022 **Accepted:** March 2022 **Published:** April 2022

Abstract:

Pancreatic cancer is the second most common digestive cancer in the United States, with roughly 44,000 new cases diagnosed each year. It is the sixth most common cancer in Europe, accounting for 2.8 percent of male malignancies and 3.2 percent of female cancers. It is the fifth biggest cause of cancer-related death, with a five-year survival rate of fewer than 10%. Nonetheless, the most important factors of ultimate prognosis are tumour biology and adjuvant therapy. As a result, many surgeons believe that less invasive treatments (such as the pylorus-preserving pancreatoduodenectomy), which are associated with a shorter surgical time, less blood loss, and an equally long but higher quality of survival, are the best option. The current research examines cost-effectiveness studies on pancreatic cancer treatment that have been published.

Key words: *Pancreatic cancer, Treatment, Epidemiology Symptom*

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Please cite this article in press Megha Shrivastava et al, ***Curative Treatment Of Pancreatic Cancer: A Review.,*** *Indo Am. J. P. Sci, 2022; 09(04)*

INTRODUCTION:

Pancreatic cancer is associated with a very poor prognosis, highlighted by the close parallel between disease incidence and mortality.[1] 5-year survival in patients with pancreatic cancer remains as low as 6% in the USA.2 The low survival rate is attributed to several factors, of which perhaps the most important is the late stage at which most patients are diagnosed. Most patients with pancreatic cancer are asymptomatic until the disease develops to an advanced stage. Up to 20% of patients are eligible for initial resection. [2] Even after potential curative resection, most patients will eventually have recurrence, and 5-year survival of completely resected patients is only up to 25%.

Tumour biology of pancreatic cancer contributes to early recurrence and metastasis, and resistance to chemotherapy and radiotherapy. Autopsy series have shown that about 90% of cases of pancreatic cancer are complicated by distant metastasis. [3] To improve prognosis, a screening programme for early diagnosis of pancreatic cancer is needed. Several risk factors for pancreatic cancer, such as a family history of pancreatic cancer, as well as personal history of cigarette smoking, chronic pancreatitis, and diabetes mellitus [4] have been identifi ed, but there is currently no standard programme for screening patients at high risk.

Epidemiology and risk factors:

The American Cancer Society estimates that in 2015, about 49 000 people will be diagnosed with pancreatic cancer in the USA and 41 000 will die of the disease. Pancreatic cancer is the fourth leading cause of cancer death in the USA. Worldwide, pancreatic cancer accounts for more than 200 000 deaths every year. Total deaths from pancreatic cancer are currently increasing and are predicted to be the second leading cause of cancer death in the USA by 2030. Increases in pancreatic cancer mortality have also been reported in European populations, highlighting the worldwide nature of the disease. [5]

The study of geographical variation in the incidence of pancreatic cancer is complicated by substantial variation in clinical diagnostic approaches and access to care. Incidence is lowest among populations in India, Africa, and southeast Asia, but underdiagnosis in regions with poorer access to care might bias these estimates. [6]

Pancreatic cancer is a disease of older adults, with most cases occurring in patients between 60 and 80 years of age. About 10% of cases of pancreatic cancer have a familial basis, and family history of pancreatic cancer substantially increases an individual's risk of developing the disease. [7]

However, the genetic basis for most familial pancreatic cancer remains unknown. Pancreatic cancer is a feature of several genetic syndromes, but these account for a few cases of familial pancreatic cancer .Germline mutations in BRCA2 cause increased risk of breast, ovarian, and pancreatic cancer, whereas the role of BRCA1 mutations in familial pancreatic cancer remains.

Histopathology and molecular pathology

Pancreatic ductal adenocarcinoma is by far the most common pancreatic neoplasm. It is an invasive mucin-producing gland-forming neoplasm that elicits an intense stromal desmoplastic reaction. Several histological features can help to diagnose pancreatic ductal adenocarcinoma: haphazard arrangement of glands, nuclear pleomorphism, incomplete glandular lumina, luminal necrosis, neoplastic glands immediately adjacent to muscular vessels, perineural invasion, and lymphovascular invasion. Pancreatic ductal adenocarcinomas are divided into three grades (well, moderately, and poorly differentiated) on the basis of their degree of differentiation. In addition to the morphology of pancreatic ductal adenocarcinoma, several morphological variants have unique features. [8]

Clinical presentation, signs, and symptoms

Most pancreatic cancers have no symptoms in the early stage. A large case-control study comparing the incidence of early pancreatic cancer symptoms suggested that pancreatic cancer is associated with 12 alarm symptoms: weight loss, abdominal pain, nausea and vomiting, bloating, dyspepsia, new-onset diabetes, changes in bowel habit, pruritus, lethargy, back pain, shoulder pain, and jaundice. Back pain (odds ratio [OR] 1·33 [95% CI 1·18–1·49]), lethargy (OR 1·42 [1·25–1·62]), and new-onset diabetes (OR 2·46 [2·16–2·80) were identifi ed as unique features of pancreatic cancers.Five symptoms have been shown to occur more than 6 months before diagnosis: back pain, shoulder pain, dysphagia, changes in bowel habit, and lethargy. Regarding lethargy, one systematic review described depressive symptoms as the fi rst symptoms in about 38–45% of patients with pancreatic cancer. [9]

A recent systematic review has reported nine presenting symptoms of advanced pancreatic cancer. Of these symptoms, diabetes (97%) and abdominal pain (78–82%), which is caused by cancernerve interaction, are frequently reported in advanced pancreatic cancer.Although several investigators have reported that 25% of patients have upper abdominal

discomfort up to 6 months before their diagnosis, [10] early detection of pancreatic cancer still seems diffi cult even if symptoms raise clinicians' suspicion.

Diagnostic investigations Serum tumour markers The combination of serum carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) has been reported to decrease sensitivity to 37%, but increase specifi city to 84% compared with CA19-9 alone, for diagnosis of pancreatic cancer.A recent study has shown that a serum protein biomarker panel consisting of CA125, CA19-9, and laminin γC (LAMC2) can signifi cantly improve performance in detecting pancreatic cancer compared with CA19-9 alone under several conditions (ie, all pancreatic cancer and benign conditions, p<0·005; early-stage pancreatic cancer and benign conditions, p<0·05; and early-stage pancreatic cancer and chronic pancreatitis, p<0·05). [11]

CA19-9 and CA125 have encouraging sensitivities for detecting preclinical pancreatic cancer because at a 95% specifi city, CA19-9 has a sensitivity of 68% for up to 1 year and 53% for up to 2 years before diagnosis. The combination of CA19-9 and CA125 improved sensitivity because the concentration of CA125 was raised in about 20% of CA19-9-negative cases. Transabdominal ultrasonography Diagnostic ability of ultrasonography greatly depends on the operator's experience and the patient's condition in terms of obesity and bowel gas. Thus, the sensitivity and specifi city of ultrasound for pancreatic cancer range from 75% to 89% and from 90% to 99%, respectively . [12]

Studies have reported that the sensitivity of ultrasonography or contrast-enhanced ultrasonography in diagnosing pancreatic cancer is not statistically diff erent from that of multidetector-row CT (MDCT).However, contrast-enhanced ultrasonography has a higher sensitivity than MDCT for small or medium lesions.CT MDCT with contrast medium is now routinely performed for the diagnosis of suspicious pancreatic lesions, assessment of resectability, assessment of vascular invasion,and diagnosis of metastatic lesions . The following CT findings aid in the diagnosis of pancreatic cancer: hypoattenuation (sensitivity 75% and specifi city 84%); ductal dilatation (50% and 78%); ductal interruption (45% and 82%); distal pancreatic atrophy (45% and 96%); [13]

Therapy for resectable disease

The limited progress in the adjuvant setting In 1985, the results of the GITSG trial,14 a multi-institutional, randomized study, demonstrated a survival benefit for adjuvant 5-FU-based chemotherapy plus radiotherapy followed by 2 years of 5-FU compared with observation only (median 21 months versus 10 months; P = 0.03;). Nearly three decades later, updated data from the CONKO-001 trial15 also showed an improve- ment in survival with 6 months of gemcitabine chemo- therapy versus only observation after upfront surgery (median 22.8 months versus 20.2 months; P = 0.01). Although the GITSG trial included only patients with negative margins (R0) after resection, the poor survival of patients included in the control arm suggest a substan- tial number of patients in fact had positive margins (R1 resections). [14]

The potential of neoadjuvant therapy

Significant improvements in surgical technique in the past decade have resulted in decreased perioperative morbidity and mortality after pancreatic cancer resection.In this regard, referral of patients to large volume centres is important, as not only surgeon experience, but also medical and nursing expertise have been shown to be key factors that influence the risk of death following surgery. Unfortunately, despite improvements in surgery, the 5-year survival rate for patients with resectable pan- creatic cancer is less than 20%.[15]

Treatment of unresectable disease

Contemporary therapy for locally advanced PDAC Early administration of chemotherapy is favoured for patients with locally advanced unresectable pancreatic cancer and an adequate performance status; the role of chemoradiotherapy in these patients, other than for pal- liation, is controversial. The Eastern Cooperative Oncology Group (ECOG) 4201 trial demonstrated an improve- ment in survival with chemoradiotherapy compared with gemcitabine chemotherapy, but at the cost of substan- tially increased toxicity. However, the 2000-01 Fédération Francophone de Cancérologie Digestive (FFCD)/Société Française de Radiothérapie Oncologique (SFRO) study suggested a detrimental effect of chemoradiotherapy on overall survival, compared with gemcitabine therapy. Intriguingly, co-culturing cancer cells with irradiated fibroblasts promoted invasiveness through activation of the MET and MAPK signalling pathways, [16]

Advances in therapy for metastatic disease

In the metastatic setting, during the past decade, single- agent gemcitabine therapy has been the standard of care for patients desiring active treatment. Single-agent gemcitabine remains the standard-of-care treatment for patients with ECOG grade 2

performance status. Disappointingly, multiple randomized phase III trials have failed to show any improvement in survival with chemotherapy doublets that included gemcitabine, or with the addition of targeted therapies to gemcitabine chemotherapy. [17]

Novel treatment opportunities in PDAC

Next-generation DNA sequencing performed in patients with advanced stage cancer and used to tailor therapy according to the specific molecular profile of the tumour is an approach that is rapidly becoming wide- spread in clinical practice. However, common markers of vulner ability to therapies have rarely been reported in pancreatic cancer and, therefore, patients with this disease are often under-represented or not included in sequencing efforts. [18]

Nevertheless, some of the reported actionable mutations might predict response to DNA- damaging agents (PALB2, ATM and BRCA2 aberrations) or mTOR inhibitors (STK11 mutations). HER2 over expression, as assessed by immunohisto chemistry, has also been reported in pancreatic cancer, but clinical trials of HER2 inhibitors in patients with HER2- positive (3+ staining pattern) pancreatic tumours have reported disappointing results. [19]

These results might be due to the recent finding that HER2 amplifications, as assessed by single nucleotide polymorphism profiling and whole genome sequencing, are only present in 2% of patients with this disease. Thus, HER amplification might be a more informative biomarker than HER over expression. Given the poor clinical outcome of patients with pancreatic cancer, novel strategies are needed to introduce new treatment opportunities. The roadmap to achieving breakthroughs in this area will necessarily include initiatives, such as the National Cancer Institute (NCI) Exceptional Responders Initiative, designed to better understand exceptional responses to therapy at the molecular level. [20]

Drugs targeting pancreatic cancer cells:

Cytotoxic agents Drug delivery might be compromised in PDAC due to the desmoplastic reaction associated with this disease. To tackle this issue, novel formulations of classic cyto- toxic agents are currently being developed. Preclinical data on MM 398, a nanoliposomal formulation of irinotecan, showed that this agent had prolonged circulation in the bloodstream compared with standard irinotecan, and higher levels of SN38 the active metabolite of irinotecan—were present in tumours compared with blood samples.[21]

This agent has been evaluated in the clinic in the NAPOLI1 study, which randomly assigned patients with metastatic pancreatic cancer refractory to gemcitabine to received either MM-398 plus infusional 5-FU and folinic acid, or infusional 5-FU and folinic acid; a 2-month improvement in median survival was observed in the experimental arm (6.1 months versus 4.2 months; HR 0.67; P = 0.012).Interestingly, irinotecan had previously shown only modest activity as a second line therapy in this disease setting. [22]

RAS-pathway inhibitors:

Activating KRAS mutations are found in >90% of PDACs.RAS proteins undergo a number of post translational modifications, including the addition of a farnesyl moiety by a farnesyltransferase enzyme. The mature, farnesylated RAS protein must also be transported from the endoplasmic reticulum/golgi apparatus to the cell membrane, where it can bind to GTP and become activated, and this relocation involves a RAS shuttle protein, cyclic-GMP phosphodiesterase δ (PDEδ). [23]

Thus, inhibition of oncogenic RAS signalling could potentially be achieved by multiple mecha- nisms: blocking farnesylation; abrogating RAS protein transport to the cell membrane; as well as by inhibiting oncogenic RAS activity directly, or indirectly by targeting d ownstream c omponents of the pathway. Different farnesyltransferase inhibitors have been tested in the clinic in the past decade with disappointing results.[24]

Furthermore, oncogenic RAS proteins have an extremely high affinity for GTP and, therefore, were traditionally considered undruggable, owing to restricted access to the ‘active site’ resulting from GTP occupancy.

Nevertheless, in 2013, the NCI allocated US$10 million per year to expedite development of RAS inhibitors,and such efforts have identified novel small allosteric inhibitors of RAS isoforms commonly found in NSCLC (KRAS G12C) with activity in vitro. [25]

These compounds lock KRAS G12C in the GDP-bound (inactive) state and thereby block downstream signalling. Similarly, inhibitors against the KRAS mutations most commonly associated with PDAC (G12D) might be identified in the near future. Indeed, a small interfering RNA targeting KRASG12D (siG12D) encapsulated in a local drug eluter (LODER) could be locally injected into cancer cell line derived xenografts and suppress KRAS expression, which resulted in tumour growth

inhibition and increased s urvival in this mouse model. [26]

Janus kinase inhibitors:
The Janus kinases (JAK) family comprises four different tyrosine kinases (JAK1, JAK2, JAK3, and TYK2). JAK signalling has a critical role in haematopoiesis; JAK2 is activated after binding to dimerized cytokine receptors, and recruits and activates signal transducer and activator of transcription (STAT) transcription factors as well as various signalling pathways (such as the Src, RAS and PI3K–AKT pathways).Upon activation, STAT dimers translocate to the nucleus to initiate transcription of genes involved in cell proliferation.Activating JAK2 V617F mutations have been reported in 50% of patients with myelofibrosis.In that disease, ruxolitinib (a JAK1/2 inhibitor) therapy improved survival and gained FDA approval in 2011. [27]

Drugs targeting tumour metabolism:
The flow of oxygen and nutrients to pancreatic cancer cells is limited by the dense desmoplastic reaction that surrounds these tumours. To survive in this hostile microenvironment, cancer cells reprogramme metabolic pathways to metabolize 10 times more glucose than the levels consumed by normal cells. Indeed, to meet their demand for energy, cancer cells process glucose not only via a comparatively low rate of cytosolic glycolysis followed by aerobic mitochondrial metabolism of pyruvate, but also through an high rate of glycolysis and anaerobic conversion of pyruvate to lactate in the cytosol (Warburg effect). Nutrient deprivation also activates autophagy, enabling cancer cells to use internal fuel sources. Among other activities, hydroxyl chloroquine is an autophagy inhibitor approved by the FDA for the treatment of malaria, but is also commonly used in the treatment of rheumatic diseases, particu- larly systemic lupus erythematosus. As a single agent, hydroxychloro quine is not active in pancreatic cancer however, the combination of hydroxychloroquine with nab-paclitaxel plus gemcitabine chemotherapy is currently undergoing evaluation both in the neoadjuvant setting (NCT01978184) as well as in advanced stage disease (NCT01506973). [28]

PI3K–mTOR pathway inhibitors:
Mutations in PIK3CA, which encodes the p110α catalytic subunit of PI3K, have rarely been reported in PDAC, and two phase II trials failed to demonstrate therapeutic activity of rapalogues, which target mTOR (a downstream effector of PI3K–AKT signalling), in gemcitabine resistant metastatic pancreatic cancer. [29]

Drugs targeting the stromal compartment:
A growing body of evidence indicates a rich crosstalk between malignant epithelial cells and the surround-ing stroma, resulting in cancer cell proliferation, survival, and resistance to therapy.128,129 In fact, preclinical research has shown that the pancreatic epithelial (cancer cell) compartment promotes desmoplasia by mediating paracrine signalling through Sonic hedgehog (SHH) and CXC motif chemokine receptors. Hedgehog inhibitors In genomic studies, the Hedgehog (HH) pathway was identified as one of the core signalling pathways involved in pancreatic cancer. Mutations in PTCH1and SMO— genes encoding a receptor for HH ligands and a protein that activates the intracellular HH signalling cascade, respectively— that result in constitutive activation of this pathway have been found in tumours exquisitely sensitive to SMO inhibitors (such as medulloblastoma and basal cell carcinoma). [30]

By contrast, these mutations have not been reported in pancreatic cancer. As introduced previously, preclinical models have revealed that activation of the HH pathway in pancreatic cancer occurs in the stroma, rather than in cancer cells; knocking down SMO in stroma inhibited tumour growth in mice. In the KPC mouse model of PDAC, the combination of gemcitabine and the SMO inhibitor saridegib (also known as IPI 926) enhanced delivery of gemcitabine to the tumour and prolonged survival. Unfortunately, these results could not be replicated in the clinic in a randomized, placebo-controlled trial. [31]

The clinical failure of HH pathway inhibitors in pancreatic cancer might be better understood in light of new preclinical evidence indicating that HH pathway inhibition promotes tumour progression in pancreatic cancer, by a mechanism that seems to involve release of the tumour restraining influences of the stroma. [32]

Enhancing drug delivery using hyaluronidase:
Hyaluronic acid is a glycosaminoglycan extracellular matrix component that is enriched in the stroma surrounding primary tumours, and particularly the desmoplastic, predominantly hypovascular, stroma associated with PDAC. It has been hypothesized that degradation of hyaluronic acid by treatment with hyaluronidase enzymes might overcome the physical barriers presented by this stromal factor and, therefore, enhance drug delivery to the tumour. PEGPH20 is a PEGylated form of a recombinant

human hyaluronidase (rHuPH20), which is currently being investigated in this context.

In the KPC model of PDAC, intravenous injection of PEGPH20 decreased tumour interstitial fluid pressures, was associated with remodelling and increased vascularity of the tumour stroma, and enhanced delivery of doxorubicin throughout the tumour tissues. In combination with gemcitabine, PEGPH20 prolonged the survival of the mice, compared with gemcitabine plus placebo.The researchers also noted increased expression of hyaluronic acid in metastatic sites of disease, which suggests that the stroma has a critical role, and that this therapeutic approach might also be of benefit, even in metastatic pancreatic cancer. [33]

The randomized, phase II HALO 109202 trial, which is evaluating PEGPH20 in combination with nab-paclitaxel and gemcitabine in this setting (NCT01839487;), was halted temporarily, owing to an increased rate of blood clots in the experi mental arm. The study has now reopened, and patients will receive prophylactic treatment with low molecular weight heparin. In addition, patients with a history of deep venous thrombosis or pulmonary embolism are now ineligible for participation in this study. The S1313 trial is evaluating PEGPH20 in combination with modified FOLFIRINOX, also in previously untreated patients with metastatic PDAC (NCT01959139). [34]

Drugs targeting cancer stem cells

The concept of CSCs as a subpopulation of cells driving tumour growth and proliferation remains highly controversial. In pancreatic cancer, CSCs have been characterized as CD44+CD24+ESA+ cells.Expression of CSC markers in surgical specimens from patients with PDAC was found to be associated with shorter survival.Furthermore, in patient derived xenograft models, treat- ment with drugs targeting the CSC compartment led to increased survival. As CSCs frequently represent <1% of the total tumour cell population, anti CSC drugs will probably not result in objective tumour responses, as traditionally evaluated by RECIST cri teria, in patients with advanced-stage disease and short life expectancy.

Nevertheless, several drugs that inhibit signalling pathways associated with CSCs, such as Wnt, Notch and HH, are currently undergoing clinical testing in combination with chemotherapy in advanced-stage PDAC. However, if CSCs are truly involved in chemotherapy resistance and tumour repopulation, in keeping with the CSC paradigm, then targeting CSCs in the adjuvant setting following chemo therapy will probably be a more efficient strategy for drug development.

Immunotherapy:

Pancreatic cancers are characterized by an immune suppressive microenvironment. This dampening of anticancer immunity is orchestrated by multiple different cell types recruited to the tumour, including cancer associated fibroblasts (CAFs), myeloid derived suppressor cells (MDSCs), tumour associated macrophages (TAMs), dendritic cells (DCs) and tumor infiltrating lymphocytes (TILs). [35]

Disrupting this immuno suppressive network and promoting the tumoricidal activity of some of these cells might provide new opportunities in the treatment of this lethal disease. Monoclonal antibody immunotherapies Cancer cells are able to evade the natural immune response by modulating T cell signalling and indu cing immune tolerance. PD 1 is an immune checkpoint receptor expressed by activated T cells, and PD1 ligands (PD L1 and PD L2) can be expressed by both stroma and cancer cells. [36]

Binding of PDL1 or PDL2 to PD1 inacti vates the T cell response to the cells presenting these ligands, and this mechanism can be exploited by cancer cells to make themselves ‘invisible’ to the immune system . Early clinical trials with monoclonal anti bodies targeting either PDL1 or PD1 have shown remarkable and durable responses in patients with NSCLC, melanoma, and renal cell carcinoma. By contrast, no responses to such agents were observed in patients with pancreatic cancer, despite the fact that PDL1 expression has been associated with a poor prognosis in such patients. [37]

Cancer vaccines:

GVAX pancreas is an allogeneic whole cell cancer vaccine generated from a pancreatic cancer cell line that have been modified to express granulocyte macrophage colony stimulating factor (GM CSF).The rationale for this vaccine design is that the GM CSF released by the modified tumour cells induces chemotaxis of DCs to the injection site, which phagocytose the tumour cells and subsequently present tumour antigens to T cells, thus eliciting an immune response against the tumour.

Chimeric antigen receptor T cells:

Genetically modified T cells engineered to express chimeric antigen receptors that are recognized tumour antigens (CAR T cells) remain in their infancy. CAR T cells have established activity in

CD19 positive haemato logical malignancies. In solid tumours, however, the occurrence of 'off tumour on target' toxicities whereby recognition of noncancer cells expressing the tumour antigen provokes adverse immune mediated effects has limited clinical development of CAR T cell therapy. [38]

A first in man study has examined the safety of treatment with autologous T cells expressing anti mesothelin CARs. In these 'meso CAR T cells', the expression of the antimesothelin CAR was made transient by electro porating the cells with mRNA, rather than DNA, encod- ing the chimeric protein, with the intention of improving the toxicity profile. The use of a mouse CAR led to anaphilaxis and cardiac arrest in one of these patients.Nevertheless, evidence of clinical activity with this agent was seen in two patients: a patient with mesothelioma had a confirmed partial response according to the RECIST v1.1 criteria; and a patient with PDAC had stable disease. A phase I study is currently evaluating meso CAR T cell therapy in patients with advanced stage pancreatic cancer. [39]

Indoleamine-2,3-dioxygenase inhibitors Indoleamine 2,3 dioxygenase (IDO) is a tryptophan catabolizing enzyme; tryptophan metabolites are toxic to effector T cells and also contribute to generation of an immunosuppressive microenvironment in tumours by increasing regulatory T cell numbers. [40]

In pancreatic cancer, IDO expression is associated with poor outcomes,170 and IDO expression is increased in metastases in this disease.In addition, IDO inhibitors increased T cell responses and had synergistic anti cancer activity with chemotherapy in a preclinical study.These findings provide a rationale for targeting IDO in PDAC. In fact, an ongoing phase Ib trial is testing the IDO inhibitor indoximod in combination with nab- paclitaxel plus gemcitabine in advanced PDAC. [41]

CONCLUSION:

The current research examines cost-effectiveness studies on pancreatic cancer treatment that have been published. Present systematic review has reported nine presenting symptoms of advanced pancreatic cancer of these symptoms, diabetes (97%) and abdominal pain (78–82%), which is caused by can cernerve interaction, are frequently reported in advanced pancreatic cancer.

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