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INTEGRATIVE CARE (M FRENKEL, SECTION EDITOR)

Complementary and Integrative Medicine in Pancreatic Cancer

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Abstract

Purpose of Review Pancreatic cancer has high mortality and morbidity rates, associated with the issues of typically late diagnosis and the limited effectiveness of current treatments. Patients tend to experience multiple symptoms that can include anxiety, fear, depression, fatigue, weakness, peripheral neuropathy, and abdominal pain, which reduce quality of life (QoL) and may compromise the treatment continuum. Many of those symptoms are amenable to complementary and integrative medicine (CIM) therapies as a part of supportive and palliative care. This article reviews research findings on the beneficial effect of use of CIM modalities in regard to pancreatic cancer, with emphasis on pancreatic ductal adenocarcinoma (PDAC).

Recent Findings Given the often-poor prognosis of the disease, patients with PDAC often seek integrative therapies to help manage the disease itself, to provide support through cancer treatment and its symptoms, and to provide emotional stress relief. Data is accumulating in the past few years on the potential benefits of CIM to the management of pancreatic cancer symptoms and treatment side effects, in order to augment supportive care. This data reveal that nutrition counselling; digestive enzyme therapy; microbiome support; dietary supplements; lifestyle interventions (physical activity and circadian health/sleep hygiene) appear to improve QoL of these patients through reduced symptom burden and meeting psychological needs, such as distress and fatigue. Acupuncture, mindfulness, yoga, reflexology, massage, and homeopathy may also contribute to symptom reduction, both physical and psychological, in all stages of the disease.

Summary There is supporting evidence that some CIM modalities may alleviate side effects and symptoms related to pancreatic cancer and its treatment, suggesting that practitioners might consider integrating these modalities in certain situations encountered in the treatment of pancreatic cancer. Further investigation is needed to define the optimal integration of CIM into the treatment and supportive care of patients affected by pancreatic cancer.

Keywords Pancreatic cancer · Pancreatic ductal adenocarcinoma · Complementary medicine · Integrative medicine · Touch therapies · Nutrition · Nutritional supplements · Physical activity · Acupuncture · Reflexology · Homeopathy · Curcumin · Mind–body medicine · Dietary supplements

Introduction

Pancreatic cancer is the seventh leading cause of global cancer deaths [1]. Pancreatic cancer has high mortality and morbidity rates with poor prognosis. The 5-year survival rate is approximately 11%, rising to 42% among the operable population [2]. While the only current curative treatment is surgery, more than 80% of patients have inoperable metastatic disease at diagnosis [1, 2]. The disease is strongly associated with epigenetic etiologies, such as smoking, obesity, and diabetes. More than 90% of cases are pancreatic ductal adenocarcinoma (PDAC) [2, 3], on which this review will focus.

Because pancreatic cancer is frequently diagnosed at an advanced stage, patients suffer from a high symptom burden,

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including digestive enzyme degradation, appetite alterations, weight loss, epigastric abdominal pain, and diarrhea. Insulin secretion alterations and type 2 diabetes may also occur. Due to the proximity of the hepatic portal vein, metastasis to the liver and bile organs is common and may cause jaundice, pain, and progression to hepatic failure [1–3]. Patients also typically suffer profound stress and depression due to a poor prognosis [4]. Typical side effects of anticancer treatments include myelosuppressive effect, peripheral neuropathy, anxiety, depression, gastrointestinal complaints, and fatigue, which additionally reduce the patients' quality of life (QoL) and endanger the treatment continuum [5, 6].

Given the often-poor prognosis of the disease, patients with PDAC often seek integrative therapies to help manage the disease itself, to provide support through cancer treatment and its symptoms, and to provide emotional stress relief. Established guidelines emphasize the importance of supportive care for people with pancreatic cancer to maintain the best QoL for as long as possible, addressing nutritional requirements, psychosocial needs, pain, and other severe symptoms [6, 7] using various treatment options, including integrative modalities [8]. The close connection to epigenetic factors in the incidence and progression of the disease adds to the rationale of incorporating integrative methods that aim to improve physiological homeostasis as an adjunct to standard-of-care treatments.

In this article, we review the data on the potential benefits of implementing an evidence-based integrative clinical approach to the management of pancreatic cancer symptoms and treatment side effects in order to augment supportive care. We also assess data on the significance of integrative modalities in reducing pancreatic cancer risk and improving patient outcomes. We discuss nutrition, digestive enzyme therapy, microbiome support, dietary supplements, lifestyle interventions (physical activity and circadian health/sleep hygiene), complementary therapies (acupuncture, touch therapies including massage therapy, and homeopathy), and mind–body therapies. Table 1 summarizes the known effects of these CIM therapies.

Nutrition

One of the main unmet needs that patients with cancer and their families mention through the whole cancer trajectory is nutritional advice that addresses their common question of "what to eat". Unfortunately, there is a major shortage of dieticians, and other healthcare providers do not have the training in addressing patients' needs related to nutrition. As a result, this common question is not adequately being answered [9••].

In a recent publication, authors suggest a simple approach to address some of those unmet needs, which can be implemented in integrative oncology settings in most common situations, while more complicated conditions, such as underweight patients, patients with malnutrition, patients with diabetes and patients with more complicated dietary circumstances, are being referred to the registered oncology dietician [9••]. This approach involves a focused attention to healthy nutrition based on the American Cancer Society (ACS) and the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) guidelines [9••].

A few issues in nutrition are specific to pancreatic cancer and probably need to be discussed in addition to the generic healthy nutrition recommendations. The pancreas is a hormonal-secreting (e.g., insulin) and a hormonal-responsive gland; thus, it is highly sensitive to the body's biochemistry and to chemical balance disruption. Some of these issues are mentioned below:

Carbohydrates and Fat

Obesity and diabetes are among the main risk factors for pancreatic cancer, and high carbohydrate and fat intake as early as adolescence is associated with pancreatic cancer occurrence [3, 10••].

Meat, Vegetables, Fruits, Grains

In a 2018 report from the WCRF/ AICR, ongoing project for analysis of research on cancer prevention and survival, a link was suggested between pancreatic cancer occurrence and consumption of red and processed meat, alcohol, fructose-containing beverages, and saturated fatty acids [10••]. In accordance with these findings, a 2017 meta-analysis found a positive correlation between a diet based on vegetables, fruits, whole grains, olive oil, fish, soy, poultry, and low-fat dairy and a reduced incidence of PDAC (odds ratio [OR] = 0.85; 95% confidence interval [CI]: 0.77–0.95; $p = 0.004$) [11]. In that study, the western-style diet (rich in red and processed meat, refined grains, sweets, and high-fat dairy products, together with low intake of fruits and vegetables) was associated with an increased risk of pancreatic cancer (OR = 1.24; 95% CI: 1.06–1.45; $p = 0.008$) [11]. Adherence to the WCRF/AICR recommendations for nutrition and physical activity was associated with lower pancreatic cancer risk in a population-based prospective trial of 95,962 U.S. participants [12].

Moreover, a significant inverse association between a vegetarian diet and pancreatic cancer mortality (relative risk [RR] = 0.44; 95% CI: 0.26–0.76) has also been reported [13]. Specifically, the International Agency for Research on Cancer (IARC) classified red meat as "probably carcinogenic to humans," pointing to an increased risk of pancreatic cancer with excess meat consumption [14]. This correlation

Table 1 Impact of integrative interventions on pancreatic cancer, as evaluated in clinical trials

Intervention	Effects	References	Comments
Nutrition			
Maintenance of a normal body mass index	↓ Risk for cancer development ↓ Chemoresistance ↑ OS	[3, 23, 52]	
Decreased carbohydrates, especially fructose-containing beverages and alcohol	↓ Risk for cancer development ↓ Chemoresistance	[3, 10••, 12]	
Low-glycemic-index diet			
Decreased meat and saturated fatty acids	↓ Risk for cancer development	[10••, 11, 12, 14, 15]	
Increased fruits and vegetables, especially carotenes and cruciferous	↓ Risk for cancer development ↓ Disease progression ↓ Chemoresistance ↓ Mortality	[11, 13, 15, 16, 31, 35, 39, 52]	
Increased edible mushrooms	↓ Risk for cancer development ↑ QoL ↓ Radiation and Chemotherapy-related adverse effects	[18, 19]	
Intermittent fasting	↑ Response to gemcitabine	[22]	Caution in face of changing metabolic demands
Supplements			
Whey protein	↑ Weight stabilization ↓ Chemotherapy-related adverse effects	[26]	
Digestive enzymes	↑ Weight stabilization ↑ OS ↓ Pain and gastrointestinal symptoms ↑ QoL	[24, 27, 29, 30]	
Metformin	↓ Risk ↓ Disease progression[a] ↑ OS	[6, 21]	In prediabetic and type 2 diabetic patients
Probiotics	↑ Gut microbioe restoration ↑ Response to gemcitabine and 5-FU[a] ↓ Post–Whipple surgery complications	[31, 35–37]	Specific beneficial microbiota strains are indicated in the article body
Omega-3 fatty acids	↑ Weight stabilization ↑ OS ↑ Response to chemotherapy ↑ Post-surgery recovery	[38, 39, 40, 42]	
AHCC	↑ Weight stabilization ↓ Chemotherapy-related adverse effects	[45–47]	
Curcumin	↑ Response to 5-FU and oxaliplatin[a] ↑ QoL	[48–53]	Possible GI discomfort
Modified citrus pectin	↑ Response to gemcitabine and cisplatin[a] ↑ Pancreatic β-cells' anti-stress protection[a] ↓ Cancer metastasis	[55–59]	Rare GI discomfort
Vitamin D3	↓ Risk for cancer development ↓ Possible mortality reduction (currently being tested in clinical trials)	[60–63]	

Table 1 (continued)

Intervention	Effects	References	Comments
Lifestyle interventions			
Physical activity	↓ Risk for cancer development ↑ QoL	[65, 66]	
Circadian health	↑ Sleep efficiency enhancement ↓ Risk for cancer development ↑ QoL	[70–73]	
Melatonin supplementation	- ↑ Pancreatic enzyme secretion[a] ↑ PDAC cell apoptosis[a]	[74–76]	
Complementary therapies			
Acupuncture and acupressure	↓ Pain	[78, 79, 81, 82••, 85]	
Touch therapies (including massage therapy)	↓ Pain ↓ Anxiety and depression ↓ Fatigue	[72, 78, 82••, 83–85]	
Homeopathy	↓ Pain ↓ Anxiety and depression ↓ Fatigue ↓ Sleep disturbance ↑ QoL ↑ OS	[72, 86–88]	
Mind–body therapies	↓ Distress ↓ Fatigue ↓ Sleep disturbance ↑ QoL	[78, 85, 89–92]	

[a]Preclinical trials only.

is sex-dependent, with a more significant impact on men, alongside a non-significant correlation in women [10••].

Among vegetables, consumption of cruciferous vegetables and carotenoids from dark, leafy greens and yellow to orange fruit and vegetables is also inversely correlated with pancreatic cancer risk [15, 16].

Mushrooms

Consuming edible mushrooms, such as *Ganoderma lucidum*, *Agaricus blazei*, *Lentinula edodes Coriolus versicolor*, and oyster mushrooms (*Pleurotus*), which are rich in polysaccharides, fiber, micronutrients, and antioxidant precursors, reduces systemic inflammation, increases vitamin D levels, and improves immunity [15, 17, 18, 19]. In a recent study, which was a systematic review, researchers found a lower risk of developing cancer among individuals with higher mushroom consumption [17]. In relation to pancreatic cancer, there is an in-vitro study with hot water extract of *Agaricus blazei,* which revealed a significant inhibition of the proliferation of cultured pancreatic cancer cells through the induction of G0/G1 cell cycle arrest. Authors suggest that this mushroom might be a useful treatment to add in pancreatic cancer care in the future, if additional studies will support these findings [18]. Another study reviewed 135 clinical trials in China that used lentinan, a mushroom polysaccharide obtained from *Lentinula edodes* (Shitake mushroom), for treating different type of cancers including pancreatic cancer. *Lentinula edodes* is one of the most popular edible mushroom in Asia, which has been used traditionally to improve general health, with immunostimulatory effect. In the review, over 9474 reported lentinan-associated cancer treatment cases were evaluated, and authors concluded that the clinical data showed that lentinan addition, improved quality of life and the efficacy of radiation therapy and chemotherapy [19].

Sugar and Metformin

The question of whether sugar intake increases risk of pancreatic cancer is a complex issue. Among diabetic or prediabetic patients with PDAC, a low-glycemic-index diet is of high importance [20]. Evidence suggests that the main culprit in pancreatic cancer risk is fructose and not other sugars. In its 2018 report, the WCRF/AICR found a statistically significant 22% increase in risk of pancreatic cancer per 25 g of fructose consumed per day [10••]. In contrast, for other exposures such as total carbohydrates, sucrose, and soft drinks, there was no clear association with increased pancreatic cancer risk [10••].

To complicate this issue, a 2014 systematic review and meta-analysis found that the use of metformin, a common medication used to lower high blood glucose, was associated with a significantly lower risk of pancreatic

cancer (RR = 0.63; 95% CI: 0.46–0.86, $p = 0.003$) [21]. Metformin's main anti-cancer mechanisms of action rely on activation of the LKB1/AMPK/mTOR signaling pathway and the blockage of insulin-induced tumor growth by decreasing its circulating levels. In vivo and in vitro studies have demonstrated that metformin inhibits cancer cell proliferation, migration, and invasion and preferentially kills cancer stem cells [21]. The 2022 National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma, in reviewing prior research on diabetes and cancer, note that studies have provided support that metformin use reduces pancreatic cancer risk, and in addition, metformin is associated with increased overall survival (OS) among patients with non-metastatic PDAC [6].

Intermittent Fasting

Intermittent fasting, an eating pattern that restricts intake for regular periods, seems to play a possible additional role in limiting PDAC development. Recent in vivo and in vitro studies showed that intermittent fasting encouraged improved response of pancreatic cancer cells to the chemotherapeutic agent gemcitabine, with a differential response between normal and cancerous cells that might potentially lead to a reduction in adverse events associated with chemotherapy [22]. Nevertheless, attention should be paid to the typical projected weight loss associated with intermittent fasting, by adjusting nutritional components and dietary regimens.

Malnutrition and Sarcopenia

Malnutrition occurs in 70% of patients with PDAC and is correlated with poor prognosis at all stages of the disease. More than 80% of PDAC patients report significant weight loss at the time of diagnosis, and 70–80% of patients will experience cachexia symptoms due to skeletal muscle wasting and loss of adipose tissue [23]. Sarcopenia at diagnosis and skeletal muscle depletion during chemotherapy are both independently predictors of poor survival in PDAC patients. Malnutrition can have multiple causes including exocrine pancreatic insufficiency, anxiety/depression, complication of surgery, as well as adverse effects of chemotherapy or radiotherapy, which might result in vomiting, diarrhea, or loss of appetite [23]. Weight stabilization in patients with PDAC improves QoL and OS [23]. Therefore, malnutrition management is crucial, preferably with a multidisciplinary approach, combining adequate nutrition, micronutrient supplementation, and symptom management [24].

Protein and Whey Protein

Decreased morbidity and mortality have been found in PDAC patients with improved nutrition. Nutritional support via counselling with emphasis on increasing energy and protein content in the diet should be considered a first step [25].

Protein supplementation is a feasible way to utilize protein optimization. An effective way is enhancing the diet with whey protein. Whey protein, consisting of soluble bovine dairy proteins, is rich in glutathione-synthesis substrates and essential amino acids. In malnourished patients with advanced cancer who were undergoing chemotherapy ($n = 166$), including 33 pancreatic cancer patients, 3-month supplementation with whey protein resulted in improved body composition, body weight, and muscle strength and reduced chemotherapy toxicity [26].

Digestive Enzyme Therapy

Pancreatic exocrine insufficiency (PEI), though sometimes subclinical, might lead to deficiencies in vitamins (A, D, E, K, B12) and minerals (zinc, selenium, magnesium, calcium, iron) and lipid maldigestion [27], aggravate the tendency towards cachexia, induce extended hospital stays, and increase the risk of complications, morbidity, and mortality [28]. Related symptoms include pain, diarrhea, and bloating. Digestive enzyme therapy or pancreatic enzyme replacement therapy (PERT) is a safe and effective therapy for PEI, facilitating nutritional improvement, weight gain, and longer OS [29, 30]. A 2019 study of PERT administration in patients with advanced pancreatic cancer found improvement in pancreatic and hepatic pain and diarrhea within 1 week of PERT initiation and improvement in bloating/gas symptoms and general QoL scores within 3 weeks [30]. PERT is recommended after pancreaticoduodenectomy or in pancreatic cancer patients experiencing symptoms or signs of maldigestion, malabsorption, and malnutrition [24]. Recommended dosages are 50,000–75,000 IU of pancreatic lipase with main meals and 25,000–50,000 IU with snacks [27].

Microbiome Support

Preclinical studies demonstrate that gut microbiota dysbiosis affects tumorigenesis and triggers PDAC occurrence and aggressiveness. It is suggested that the differential pancreatic microbiome composition and diversity in PDAC leads to treatment resistance due to reduced response to immune checkpoint blockade therapy, or through breakdown of chemotherapy into inactive metabolites. Some suggest that it might be due to induction of suppressor cells in the tumor microenvironment [31, 32, 33, 34].

The previously discussed advantages of a vegetarian or highly plant-based diet for the reduction of PDAC risk and progression might be partially attributed to the metabolic, anti-inflammatory, and immunogenic effects of microbial metabolites (i.e., short-chain fatty acids, butyrate, and propionate, or phenolic metabolites from plant polyphenols) derived from a prebiotic (fiber-rich) and phenolic-rich diet [13, 31]. Studies also demonstrate the effect of a prebiotic diet on expression of miRNAs and levels of metabolites, such as purines or amino acids that are associated with better outcomes and prolonged overall survival of patients with PDAC [31, 35].

Probiotics have also been studied as a potential approach for microbiome support.

In a clinical study, Nomura et al. showed that probiotics containing *Enterococcus faecalis*, *Clostridium butyricum*, and *Bacillus mesentericus* reduced infectious complications after pancreatoduodenectomy [35].

Additional studies suggest that probiotics might have antitumor effect specific to pancreatic cancer. In a preclinical pancreatic cancer model, *Lactobacillus* spp. demonstrated an additive antitumor effect with gemcitabine and 5-fluorouracil (5-FU), as well as downregulation of elevated aspartate transaminase (AST) and alanine transaminase (ALT) [36, 37].

In an in-vitro and in-vivo mouse xenograft model, ferrichrome, a substance derived from a probiotic bacterium, *Lactobacillus casei*, was found to have tumor-suppressive effects in pancreatic cancer. The tumor-suppressive effects were found also in 5-FU-resistant pancreatic cancer cells [37].

Dietary Supplements

Omega-3 Fatty Acids

A systematic analysis of clinical studies found that consumption of omega-3 fatty acids, usually from fatty fish, such as salmon, tuna, mackerel, and herring, modulates metabolic abnormalities in cachectic PDAC patients, resulting in body weight and lean body mass increase, along with a decrease in resting energy expenditure [38]. The outcomes were mainly attributed to the omega-3 fatty acid eicosapentaenoic acid (EPA). The authors also described an OS increase (130–259 days vs. 63–130 days) among those patients. The omega-3 fatty acid docosahexaenoic acid (DHA) has been shown to reduce β-catenin expression and decrease Akt phosphorylation in pancreatic cells, resulting in improved cancer cell death and improved effectiveness of PDAC chemotherapy [39, 40, 41]. Additional studies suggest liver protection and improved post-surgery recovery in patients with omega-3 supplementation were demonstrated, possibly due to omega-3 s' anti-inflammatory properties [39, 42].

The researched reported dosages of omega-3 s vary from 1.5 to 3 g/day of EPA via oral administration, for periods of 8 to 12 weeks. Omega-3 fatty acids are well tolerated, with no serious adverse events reported [38].

Active Hexose-Correlated Compound (AHCC)

AHCC, an alpha-glucan-rich extract derived from the mycelia of the shiitake mushroom (*Lentinula edodes*), has antioxidant, anti-inflammatory, immunomodulatory effects on both the innate and adaptive immune systems, as well as anti-proliferative properties [43, 44]. A Japanese study that examined the effect of 6.0 g/day of AHCC for 2 months, on gemcitabine-related adverse events in patients with PDAC, found improved hemoglobin and albumin levels, fewer taste disturbances, and suppressed C-reactive protein in the AHCC group compared with the control group [45]. In a more recent study [44], 1.5 g/day of AHCC was administered for 3–6 months to malnourished patients with adenocarcinoma, including PDAC, during active chemotherapy or radiotherapy. In the AHCC group, 80% of patients experienced an increase in body cell mass [44]. A dosage of 3.0 g/day of AHCC potentiated the neutrophil-to-lymphocyte ratio (NLR) and improved the prognostic nutrition index when administered to patients with PDAC receiving neoadjuvant chemotherapy from the first treatment day to a day before surgery (for 3–6 months). A phase II prospective study is ongoing, aiming to validate these results and examine the long-term impact of AHCC [46].

The researched dose for oral administration of AHCC is 3–6 g. However, AHCC induces Cytochrome P450 2D6 (CYP2D6) activity, which may decrease the activity of several drugs, though the clinical significance of this effect has not been established [47].

Curcumin

Preclinical studies have demonstrated that curcumin, the active ingredient of turmeric (*Curcuma longa*), has potential therapeutic effects for both the prevention and treatment of PDAC through more than 30 molecular targets, potentiating inhibition of oxidative stress and angiogenesis and the induction of apoptosis, as well as reduction of PDAC cell motility [48, 49, 50, 51, 52]. Preclinical studies have also demonstrated that curcumin enhanced the cytotoxic effect of gemcitabine, 5-fluorouracil, and oxaliplatin [51, 53].

Despite the promising preclinical therapeutic effects, only a few phase II clinical trials have been conducted to date to assess the efficacy of curcumin in patients with PDAC. A single-arm study of oral curcumin in 21 patients with gemcitabine-resistant PDAC reported a median survival time

of 5.4 months and a 19% 1-year survival rate [53]. These outcomes are an improvement compared to the 10-week reported median survival time in PDAC patients who received only best supportive care after failure of first-line gemcitabine therapy [53].

For dosages, a daily oral dose of 500–3000 mg has been used in most clinical trials, while a maximum dose of 8 g was safe and feasible [49]. Notably, one study from 2010 reported gastrointestinal pain in patients with advanced pancreatic cancer receiving a dose of 8 g, within 2 weeks of administration [54]

Modified Citrus Pectin

Modified citrus pectin (MCP) is a pH-modified soluble β-galactosyl-containing polysaccharide obtained from the peel of citrus fruits. MCP affects multiple paths in cancer metastasis, mainly through blockade of galectin-3, which is highly expressed in PDAC [58, 59]. Galectin-3 is a protein with various roles in tumor cell adhesion, proliferation, differentiation, angiogenesis, metastasis, and apoptosis [55, 56, 57, 58]. Specifically, MCP protects pancreatic β-cells against oxidative and inflammatory stress [57]. In vitro and in vivo studies have shown that MCP sensitizes PDAC cells to gemcitabine and cisplatin [58].

The customary dose of MCP is 15 g/day, in two to three divided doses, mixed with cold water before meals. Though there are usually no side effects, mild gastrointestinal complaints might occur, resolving after a short period [59].

Vitamin D

1,25-dihydroxy vitamin D3 [1,25$(OH)_2$D3], the active form of vitamin D, is generated by exposure to sunlight. A higher incidence of PDAC in northern latitudes (3 to 4 times higher than in areas closer to the equator) is attributed to reduced sunlight exposure [60]. Vitamin D deficiency is prevalent among patients with PDAC (as is the case with various types of cancer) and is associated with both PDAC risk and worse outcomes. A recent review of meta-analyses found an inverse association between vitamin D levels and pancreatic cancer risk (pooled RR = 0.91; 95% CI: 0.57–1.46) [61]. Liu et al. [62] found that vitamin D supplementation of 400 IU (10 µg/d) was correlated with reduced PDAC occurrence by 25% (RR = 0.75; 95% CI: 0.60–0.93) [62].

Accumulating evidence suggests that vitamin D supplementation might correlate with reduced PDAC mortality risk by inhibiting cell proliferation, inducing apoptosis and differentiation, and potentiating chemotherapy or radiotherapy [60, 61]. The latter is partially explained by vitamin D's reported ability to regulate the PDAC tumor microenvironment, typically characterized by a highly fibrotic and hypoxic stroma. Specifically, vitamin D pancreatic receptor variant rs2853564 increased pancreatic cancer's susceptibility to gemcitabine [60]. Nevertheless, although vitamin D supplementation presented a positive effect in meta-analyses in terms of OS of patients with cancer in general, there is no conclusive up-to-date research on its positive effect on OS of patients with PDAC [60]. Several phase I and II clinical studies are enrolling patients now based on these data [63].

Daily supplementation recommended doses are 1000–4000 IU, according to deficiency levels.

Lifestyle Interventions

Physical Activity

Physical activity (PA) assists body weight regulation, improves insulin sensitivity, and decreases chronic inflammation, all of which are correlated with PDAC risk. It may also improve anticancer immune function and stimulate gastrointestinal motility, and limit the time that carcinogens remain in the intestinal tract [64]. A statistically significant reduction in PDAC risk has been found, especially for consistent PA over time (RR = 0.86; 95% CI: 0.76–0.97) [65]. This inverse association was not attenuated even when data were adjusted for smoking, body mass index, and alcohol consumption [64]. A history of inactivity prior to PDAC diagnosis is associated with increased mortality rate [52].

Accumulating data suggest that PA reduces disease and treatment-induced symptoms, such as pain, fatigue, anxiety, and depression, and improves physical fitness and muscle function, showing an elevation in QoL [27, 66]. The assessment of treatable contributing factors in the 2022 NCCN guidelines on cancer-related fatigue [67] and a meta-analysis of 113 studies [68] report that exercise improves cancer-related fatigue, a frequent symptom in PDAC patients that has a pronounced influence on patients' QoL.

A recent review that screened PA modalities among PDAC patients at various stages of disease and treatment found PA to be safe and feasible [66]. However, there are no specific guidelines for optimal PA programs or modalities in patients with pancreatic cancer. PA implementation requires an individualized program for each patient [66].

Circadian Health and Sleep Hygiene

Circadian rhythm regulation has been proposed as a target for oncology interventions, as the human circadian rhythm governs several potential cancer targets, such as cell proliferation and apoptosis, and drug-metabolizing enzymes [69]. Circadian rhythm disruption may play a role in PDAC etiology; night-shift work has been linked to a more than two-fold increase in PDAC risk in men (OR = 2.31; 95% CI: 1.48–3.61). Light at night is linked to obesity and diabetes,

two PDAC risk factors. A large ($n = 464{,}371$) epidemiological study based on data from the NIH-AARP Diet and Health Study found a 27% increase in PDAC risk in the highest versus lowest environmental light-at-night exposure among the trial participants [70].

Sleep disturbances, known to lead to circadian rhythm disruption, are reported among patients at all stages of pancreatic cancer and are correlated with reduced QoL and poorer treatment outcomes [69, 71]. Circadian rhythm regulation interventions in cancer patients include cool and dark bedrooms at night, exposure to early morning sunlight, and insomnia improvement through various methodologies, such as massage therapy, aromatherapy, cognitive behavioral therapy, and melatonin supplementation [72, 73].

Above sleep regulation, in vitro and in vivo studies suggest that melatonin supplementation can contribute to pancreatic health through mediation of inflammation and oxidative stress. In neoplastic disease, melatonin progressive deficiency is associated with disease progression [74]. Conceptually, melatonin may induce apoptosis in pancreatic cancer cells by regulating several molecular pathways, including the oxidative stress, heat-shock proteins, and vascular endothelial growth factor pathways [74, 75, 76, 77]. Moreover, melatonin receptors in the pancreas stimulate pancreatic enzyme secretion [75, 76]. Despite clinical research on melatonin's positive role in several types of cancer treatment, clinical studies that evaluate the efficacy of melatonin administration in PDAC are scarce [77]. Lissoni et al. demonstrated prolonged OS in patients with advanced PDAC receiving 20 mg/day of melatonin compared to supportive care only (median OS: 5 vs. 10 months; $p < 0.001$) [74]. The study reported no serious adverse effects with this dose [74].

The daily recommended melatonin dose for sleep regulation is 0.5–5 mg, in the evening before bedtime.

Complementary Therapies

Pain, especially abdominal and back pain, is a common symptom among PDAC patients, with a multifactorial etiology, including gastrointestinal dysfunction resulting from digestive enzyme deficiency or a direct mass obstruction, mass effect on nerves in the celiac plexus, sleep disturbances, procedure-related pain, and anxiety. The 2022 NCCN guidelines for adult cancer pain management recommend that patients at all pain levels receive complementary therapies, such as acupuncture, massage, and relaxation techniques [78]. Unfortunately, pain is only one symptom among the common symptoms that patients with PDAC suffer from. Multiple studies describe beneficial effect of multiple modalities such as acupuncture, massage therapy, meditation/mindfulness, hypnosis, Reiki, yoga, tai chi, homeopathy, music, and art therapy, as effective for reducing symptom burden among these patients [79, 80, 81, 82••, 83, 84, 85, 86, 87, 88].

Acupuncture

Acupuncture-based therapies (e.g., acupuncture, acupressure, and electroacupuncture) are reported to reduce pain in animal models and clinical trials [79]. The most accepted mechanism of action is the rebalance of the ratios of sympathetic to parasympathetic activity [79, 80]. A systematic review and meta-analysis found a favorable association with reduced pain intensity in patients with cancer when acupuncture and acupressure were combined with analgesic therapy [80]. Chen et al. (2013) found that electro-acupuncture was significantly associated with reduced pancreatic cancer pain ($n = 60$; mean difference = –1.51 points; 95% CI: –1.8 to –1.22 points) [81]. In a new joint practice guideline of the Society of Integrative Oncology (SIO) and the American Society of Clinical Oncology (ASCO) about integrative medicine for pain management in oncology, authors emphasize the role of acupuncture and mention that it should be recommended for aromatase inhibitor–related joint pain and general cancer pain or musculoskeletal pain [82••].

Massage Therapy

The 2022 NCCN guidelines for distress management state that patients with pancreatic cancer have an increased risk for distress, and recommend relaxation, mindfulness, meditation, and creative therapies such as art and music for patients experiencing distress [83]. Anxiety and depression are common among patients with PDAC [4, 83]. The negative effect of mood disorders on QoL is well established [52]. Multiple studies suggest that massage therapy to be efficient in the reduction of pain, anxiety, depression, and cancer-related fatigue in cancer patients, including those with PDAC [72, 84, 85]. Because of this understanding, most integrative oncology settings integrate some type of touch therapy for addressing these distresses. In the new joint SIO/ ASCO practice guideline mentioned previously, related to integrative medicine for pain management in oncology, authors suggest that reflexology or acupressure may be recommended for general cancer pain or musculoskeletal pain, and massage may be recommended to patients experiencing pain during palliative or hospice care [82••].

Homeopathy

In homeopathy, highly diluted natural substances are used to treat multiple symptoms and different types of distress. Its effectiveness is controversial; nevertheless, several studies suggest that homeopathy may alleviate cancer symptoms

and treatment side effects, such as pain, fatigue, sleep disturbance, and distress, common in PDAC [72]. In a study conducted in Israel in 2018 ($n=124$) that evaluated the feasibility of a homeopathic consultation during cancer treatment, 82 (66%) of the patients adhered to the homeopathic treatment, and 73% of them reported that the homeopathic treatment was beneficial [86]. In a 2014 retrospective survey of patients with cancer ($n=538$) in Vienna, Austria, patients received homeopathic consultations in addition to conventional care. Patients had a range of cancer types, including patients with pancreatic cancer. The authors found a significantly extended OS when homeopathy was added on to conventional care as compared to conventional care alone [87].

Homeopathy is considered safe and without adverse effects, either direct (i.e., toxic effects) or indirect (i.e., interactions with conventional anticancer agents) [88].

Mind–Body Therapies

Mindfulness, meditation, guided imagery, and hypnosis have been found to reduce fatigue and stress and improve QoL in several types of cancer, as reviewed previously [52, 72].

In their 2015 study, Focan et al. [88] addressed the use of mindfulness for the treatment of malnutrition and cachexia in patients with cancer. The authors found that a mindfulness workshop ($n=53$, including six patients with GI-tract cancers) enhanced a significant weight gain. Patients also reported general QoL improvement, especially regarding emotional function, fatigue, and digestive problems.

High vagal activity, indexed by increased heart rate variability (HRV), was found to independently predict more prolonged survival of patients with PDAC, through the mediation of inflammation [90]. HRV is inversely related to insulin resistance and levels of the glucose-metabolism marker HbA1C. Yoga is both a physical activity and a mind–body intervention, and its positive effect on HRV has been well studied and established, as has its effect on inflammatory biomarkers [91, 92]. Therefore, an exploration of the impact of yoga, and its intervention methodology in terms of duration and intensity, on QoL and disease progression in is warranted in patients with pancreatic cancer.

Conclusion

Most patients with pancreatic cancer are diagnosed late in their disease process and thus have a poor prognosis and increased distress. Due to this understanding, authorities start to emphasize the importance of supportive care for people with pancreatic cancer to maintain the best QoL using various treatment options, including CIM modalities.

In the past decade, there is growing number of studies that suggest beneficial effect of CIM integration as part of supportive care for patients with PDAC. CIM modalities such as acupuncture, nutrition, mindfulness, massage, homeopathy and others, appear to contribute to symptom reduction, both physical and psychological, in all stages of the disease.

Additional studies in this field are needed to further explore the specific benefit and added value that is obtained from each CIM modality, as well as learning the best integration strategy that can be utilized, in patients with pancreatic cancer.

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Declarations

Competing Interests The authors declare no competing interests.

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• Of importance
•• Of major importance

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