

## Mini-Review

# Nutrition in Pancreatic Cancer: A Review

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## Key Words

Enteral nutrition · L-Carnitine · Omega-3 fatty acids · Pancreatic cancer · Parenteral nutrition

## Abstract

**Background:** Pancreatic cancer is the fourth leading cause of cancer-related mortality in both genders. More than 80% of patients suffer from significant weight loss at diagnosis and over time develop severe cachexia. Early nutritional support is therefore essential. **Summary:** This review evaluates the different nutritional therapies, such as enteral nutrition, parenteral nutrition and special nutritional supplements, on nutritional status, quality of life and survival. **Key Message:** Due to the high prevalence of malnutrition and the rapid development of anorexia-cachexia-syndrome, early nutritional intervention is crucial and supported by clinical data. **Practical Implications:** Enteral nutrition should be preferred over parenteral nutrition. Omega-3 fatty acids and L-carnitine are promising substances for the prevention of severe cachexia, but further randomized controlled trials are needed to establish generally accepted guidelines on nutrition in pancreatic cancer.

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## Introduction

### *Incidence and Prevalence of Pancreatic Cancer*

Pancreatic cancer (PC) is the fourth leading cause of cancer-related mortality in both genders, leading to an all-cause mortality rate of 7% worldwide [1]. Given that PC is burdened with an aggressive tumor biology, most of the patients are diagnosed in a metastasized stage with a poor prognosis. With 95% of PC, ductal adenocarcinoma is the most frequent subtype. Due to the late occurrence of clinical symptoms, incidence equals mortality. The 5-year

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survival rate is 8% with a median survival of 5 months [2, 3]. Several risk factors for PC such as age, sex, family history, history of chronic pancreatitis, diabetes, insulin resistance, obesity and cigarette smoking have been identified [4–7].

#### *Nutrition-Related Symptoms*

More than one third of PC patients experience a significant weight loss of >10% of their initial body weight prior to diagnosis [8–10]. The greater number of patients suffer from abdominal pain, anorexia, early satiety, nausea, vomiting and diarrhea or constipation [9]. In addition, patients experience changes in metabolism due to increased protein catabolism and increased energy expenditure [11].

#### *Incidence of Malnutrition at the Date of Diagnosis*

Malnutrition characterized by weight loss and decreased dietary intake is common among PC patients. More than 80% of patients with PC suffer from significant weight loss at diagnosis [12] and over time develop severe cachexia [13]. Cachexia is a multifactorial syndrome with ongoing loss of skeletal muscle mass with or without fat mass accompanied by impaired body function [14].

#### *Influence of Malnutrition on Survival*

Cachexia is recognized as a major cause of reduced quality of life (QoL), decreased survival and treatment failure in patients with PC [14]. Weight stabilization in case of unresectable PC is thus associated with improved survival and QoL [8]. Patients maintaining stable weight and body composition have a better prognosis [15, 16]. Various studies have revealed that malnutrition leads to skeletal muscle wasting and fat degradation, longer hospital stay, increased risk of complications as well as reduced response to treatment, shorter survival time, reduced QoL and increased morbidity and mortality [17–19]. If oral nutritional intake is not sufficient, additional nutritional therapy is absolutely essential for PC patients to stabilize body weight and composition. This review evaluates the different nutritional therapies, such as enteral nutrition (EN), parenteral nutrition (PN) and special nutritional supplements, on nutritional status, QoL and survival.

## **Methods**

#### *Search Strategy and Selection Criteria*

A PubMed search was performed for publications from January 1980 through October 2015, using the following key words: 'pancreatic cancer' OR 'nutrition' OR 'enteral nutrition' OR 'parenteral nutrition' OR 'dietary factors' OR 'nutritional supplements' OR 'quality' OR 'life' OR 'survival' OR 'antioxidants' OR 'omega-3 fatty acids' OR 'L-carnitine' and combinations of these terms. We restricted our search to studies in English and those reporting human studies.

We excluded case reports, review articles and studies not providing primary data on nutritional support in patients with PC. The application of these criteria resulted in 11 studies concerning enteral and PN and 8 studies on supplementation of omega-3 fatty acids (n-3 FAs) or L-carnitine shown in table 1.

## **Results**

#### *Enteral versus Total Parenteral Nutrition in Patients Undergoing Pancreaticoduodenectomy*

The six studies identified are listed in table 1. All these trials randomized patients after pancreaticoduodenectomy to receive different treatment regimens of postoperative nutritional support. Three studies compared EN with total parenteral nutrition (TPN). They

**Table 1.** Studies identified by the PubMed search

Reference	Design	Participants	Nutritional status	Comparison details	Outcome	Length of study	Results
Pelzer et al., 2010 [25]	prospective intervention trial	32	>5% weight loss in previous 4 weeks or BMI <19	additional PN of about 25 kcal/kg daily on 5 days of week	phase angle, ECM/BCM, BMI	median 18 (8–35) weeks	improved nutritional status: phase angle improved; ECM/BCM dropped; BMI increased slightly
Park et al., 2012 [35]	open randomized single-center parallel-group trial	38	PO nutritional status of patients who had undergone PD	early EN in comparison to TPN	change in weight, LOS, index, rates of delayed gastric emptying, pancreatic fistula	90 days (7, 14, 21, 90)	bowel movement and time to take normal diet shorter in early EN than TPN; no significant difference between two groups in serum albumin, total protein and patient-generated SGA; BW decreased until PO day 90 in TPN group
Nagata et al., 2009 [36]	prospective randomized single-center trial	17	PO nutritional status of patients who had undergone PD	EN in comparison to EN + PN	weight loss, symptoms like jaundice, diabetes, prealbumin, transferrin, IgG, IgM, IgA	14 PO days	EN combined with PN is more adequate for patients after pancreatic surgery
Liu et al., 2011 [37]	prospective randomized trial	60	PO nutritional status of patients who had undergone PD	EN in comparison to TPN	influence on clinical and biochemical parameters	14 PO days	EN is superior to TPN in improving nutritional status, liver and kidney functions and reducing PO complications
Gianotti et al., 2000 [21]	prospective randomized trial	212	PO nutritional status of patients who had undergone PD	SEN (control group) vs. EN enriched with arginine, n-3 FAs (immunonutrition group) vs. TPN (parenteral group)	effect of PO nutritional support on immunometabolic response and outcome	until 800 kcal orally was achieved	rate of PO complications was lower in immunonutrition group (p < 0.005); LOS shorter in immunonutrition group (p < 0.02); early PO EN choice to nourish patients after PD
Di Carlo et al., 1999 [22]	prospective randomized trial	100	PO outcome of patients who had undergone PD	SEN vs. immunonutrition enriched with arginine, n-3 FAs vs. TPN	effect of PO nutritional support on outcome of patients undergoing PD	LOS	PO complications lower in IMEN (p < 0.05); infectious complications lower in IMEN group; LOS shorter in IMEN; nutritional goal can be obtained by EN; immunonutrition seems to improve outcome
Brennan et al., 1994 [23]	prospective randomized trial	117	patients who had undergone major pancreatic resection	randomization to either receive PN and control group with standard dextrose-containing salt solution	PO complications	LOS	no benefit by use of PN; complications were greater in group receiving TPN (p < 0.05)
Bauer et al., 2005 [26]	multicenter randomized double-blind trial	200	weight loss >5% in previous 6 months, life expectancy >2 months and Karnofsky performance score of 60, untreated PC patients	consume two cans per day of either a protein- and energy-dense, n-3 FAs ONS or an isocaloric, isonitrogenous control supplement without n-3 FAs	dietary intake, weight, LBM and QoL	8 weeks	compliance with prescription of 1.5 cans of a protein- and energy-dense, ONS n-3 FAs improved nutrition-related outcomes
Vashi et al., 2014 [24]	longitudinal unrandomized clinical trial	52 (14 PC)	significant cancer cachexia, no HPN therapy prior to hospital admission, anticipated survival >90 days	HPN using 25–30 kcal/kg for BMI <30 and 22–25 kcal/kg of ideal BW for BMI ≥30; protein needs were estimated using 1.5–2 g/kg for BMI <30 and 2–2.5 g/kg of ideal BW for BMI ≥30	QoL, functional status, SGA, weight, serum albumin	1, 2, 3 months	HPN is associated with improvement in QoL, Karnofsky performance status and nutritional status; greatest benefit in patients with 3 months of HPN
Davidson et al., 2004 [8]	multicenter trial	107	weight loss of at least 5% over the previous 6 months, expected survival of at least 2 months and no chemotherapy, radiotherapy or surgery during the study or for 4 weeks prior to baseline	237 ml cans per day of supplement, weekly contact by phone	weight, survival, QoL	8 weeks	weight stabilization was associated with improved survival duration and QoL

**Table 1** (continued)

Reference	Design	Participants	Nutritional status	Comparison details	Outcome	Length of study	Results
Klek et al., 2011 [20]	randomized double-blind trial	305	patients undergoing resection for PC or gastric cancer, malnutrition (weight loss by at least 10% or BMI <18), Karnofsky performance score >80	preoperative: 14 days of PN, PO; IMEN or standard oligopeptide diet	PO complications, LOS, function of immune system, assessment of liver and kidney function	LOS	shorter LOS in IMEN group; more infectious complications in SEN group; mortality and morbidity were greater in SEN group; no differences in kidney and liver function
Wignmore et al., 2000 [27]	prospective intervention trial	26	weight loss 13%/4 months, BMI 23.2, advanced PC patients	oral EPA (week 1: 1 g, week 2: 2 g, week 3: 4 g, weeks 4–12: 6 g)	weight loss, body composition, hematologic and clinical chemistry variables, performance status	12 weeks (0, 4, 8, 12 weeks)	weight loss decreased ( $p < 0.005$ vs. week 0) under EPA supplementation; no change in anthropometric and body composition; no change in performance status, nutritional intake and acute-phase protein response
Heller et al., 2004 [32]	double-blind prospective randomized single-center pilot trial	44	mean BMI = $24.5 \pm 4.1$ (SO group); mean BMI = $25.2 \pm 4.4$ (SO + FO group)	TPN supplemented with SO (1.0 g/kg BW) or FO + SO (FO 0.2 + SO 0.8 g/kg BW)	liver and pancreas blood parameters; days of ICU stay and weight loss	5 days	FO significantly reduced ALAT, ASAT, bilirubin, LDH, lipase; shorter ICU stay with FO; absence of weight loss with FO (SO 1.1 ± 2.2 kg)
Fearon et al., 2003 [28]	double-blind randomized multicenter trial	200	weight loss 3.3 kg/month; advanced PC patients	ONS vs. ONS + EPA and antioxidants (480 ml, 620 kcal, 32 g protein ± 2.2 g EPA)	weight, LBM, dietary intake, QoL	8 weeks	loss of weight and LBM was stopped in both groups; dose response relationship: weight gain and increase in LBM only in ONS + EPA group; improved QoL only in ONS + EPA group
Barber et al., 1999 [29]	prospective intervention trial	20	weight loss 2.9 kg/month; advanced PC patients	ONS + EPA (620 kcal, 32.2 g protein and 2.2 g EPA)	weight, body composition, dietary intake, REE and performance status	7 weeks (0, 3, 7 weeks)	significant weight gain at both 3 weeks (median 1 kg; $p = 0.024$ ) and 7 weeks (median 2 kg; $p = 0.033$ ); dietary intake increased; performance status and appetite improved
Barber et al., 2001 [30]	prospective intervention trial	20	weight loss 2.9 kg/month; advanced PC patients	ONS + EPA (620 kcal, 32.2 g protein and 2.2 g EPA)	weight, proinflammatory cytokines, hormones and tumor-derived products	3 weeks	significant decline in IL-6 production; rise in serum insulin concentration; fall in the cortisol to insulin ratio; decrease in PIF; weight gain (median 1 kg)
Barber et al., 2000 [31]	case-control trial	16 cases 6 controls	weight-losing patients; advanced PC patients	ONS + EPA (620 kcal, 32.2 g protein and 2.2 g EPA)	indirect calorimetry, body composition, weight	3 weeks	after 3 weeks ONS + EPA: BW increased; energy expenditure in response to feeding rose (no difference to healthy controls); fasting fat oxidation decreased (no difference to healthy controls)
Arshad et al., 2015 [33]	single-arm phase II clinical trial, two-stage design	50	advanced PC patients	gemcitabine 1,000 mg/m <sup>3</sup> weekly followed by up to 100 g (200 mg/ml) of n-3 FAs-rich lipid emulsion for 3 weeks followed by a rest week	response rate, overall and progression-free survival, QoL scores and adverse events	min. 4 weeks up to max. 24 weeks	intravenous n-3 FAs in combination with gemcitabine show evidence of improved activity and benefit to QoL in patients with advanced PC
Kraft et al., 2012 [34]	prospective multicenter placebo-controlled randomized double-blind trial	72	weight loss 11% in 6 months	oral l-carnitine (4 g) or placebo for 12 weeks	weight loss, BMI, nutritional status, QoL, survival, LOS	12 weeks	weight loss decreased; BMI increased; nutritional status and QoL improved

BW = Body weight; ECM/BCM = extracellular mass/body cell mass; FO = fish oil; HPN = home PN; ICU = intensive care unit; IMEN = immunomodulating EN; LOS = length of hospital stay; ONS = oral nutritional supplement; PD = pancreaticoduodenectomy; PIF = proteolysis-inducing factor; PO = postoperative; SEN = standard EN; SO = soy oil.

revealed that EN is superior in improving the nutritional status compared to PN. TPN is associated with an increased rate of complications, loss of body weight, longer duration to first bowel movement and a longer time period until normal diet is tolerated. EN is superior to TPN in improving nutritional status. Three studies [20–22] showed that especially immunomodulating EN is associated with lower postoperative complications, shorter length of hospital stay and lower mortality and morbidity compared to standard EN and TPN.

The effect of PN compared to standard dextrose-containing solution was examined in one study [23]. The authors could not show a benefit by the use of PN and complications were significantly greater in the TPN group.

#### *Parenteral Nutrition in Patients with Cancer Cachexia*

Data on the effect of PN in patients with severe cancer cachexia were available from two studies. In the first one [24], patients with cancer cachexia received home PN over 1, 2 or 3 months. There was an improvement in global QoL (from 37.1 to 49.2;  $p = 0.02$ ), Subjective Global Assessment (SGA) and weight (from 57.6 to 60.0 kg;  $p = 0.04$ ) after 2 months and in global QoL (from 30.6 to 54.4;  $p = 0.02$ ), SGA and weight (from 61.1 to 65.9) after 3 months of treatment. In the second one, Pelzer et al. [25] showed a benefit of additional PN on parameters of body composition in patients with PC. Body mass index (BMI) increased from 19.7 to 20.5, median phase angle improved by 10% from 3.6 to 3.9 and extracellular mass/body cell mass index improved down from 1.7 to 1.5.

#### *Oral Supplementation in Patients with Pancreatic Cancer*

Weight stabilization by the use of oral supplementation was examined in two studies [8, 26]. Over an 8-week period the authors found an improvement in weight by 0.5 kg ( $p = 0.052$ ), but they did not detect a difference in lean body mass (LBM). Patients with stable weight had a higher energy intake ( $p = 0.004$ ) in comparison to patients with weight loss. Patients with stable weight had a median survival of 259 days (95% CI 229–289 days) compared to 164 days (95% CI 97–231 days) for patients who continued to lose weight. The authors also concluded that patients with stable weight reported a better QoL [8].

#### *Fish Oil Supplementation in Pancreatic Cancer Patients*

Five studies concerning oral supplementation of eicosapentaenoic acid (EPA) pure or in the form of an oral nutritional supplement and one with a supplementation to TPN were identified and are listed in table 1. All patients recruited to the studies had lost weight prior to study entry. The amount of EPA given ranged from 2.2 g in the oral supplements and was dosed from 1.0 to 6.0 g EPA daily over 4 weeks in the pure oral supplementation study of Wigmore et al. [27]. An oral supplementation of high-purity EPA was used in weight-losing advanced PC patients. Median weight loss decreased significantly after 4 weeks of EPA supplementation and remained significant after 8 and 12 weeks. There was no change in anthropometric data, body composition, nutritional intake or performance status. Fearon et al. [28] showed a dose-response relationship of EPA on weight gain and LBM gain. Increased plasma levels of EPA were associated with weight gain and LBM gain. Weight gain was also associated with an improved QoL, but only in the EPA-supplemented group. The three studies of Barber et al. [29–31] revealed an effect of EPA on weight gain, decreasing resting energy expenditure (REE) and improved performance status and appetite. They also demonstrated that this anabolism is associated with a significant decline in peripheral blood mononuclear cell IL-6 production, a rise in serum insulin concentrations, a decrease in the cortisol to insulin ratio and a decline in the proportion of patients excreting proteolysis-inducing factor. In the fasting state, cancer patients had a lower serum insulin concentration, elevated REE per unit weight and an increased rate of fat oxidation. Under EPA the fasting insulin concentration increased

and a normalization of energy expenditure, with a fall in REE per unit weight and a rise in the apparent metabolic cost of feeding, was documented. Substrate utilization was also normalized.

#### *Fish Oil and Parenteral Nutrition in Postoperative Pancreatic Cancer Patients*

In the study by Heller et al. [32], postoperative patients received TPN supplemented with fish oil versus TPN with soy oil for 5 days. The fish oil TPN improved liver and pancreas parameters in the postoperative course and patients maintained their weight in contrast to soy oil-supplemented TPN. Patients with an increased risk of developing sepsis showed a tendency for a shorter intensive care unit stay under fish oil.

#### *Fish Oil and Gemcitabine in Pancreatic Cancer Patients*

The study of Arshad et al. [33] demonstrated that intravenous n-3 FAs in combination with gemcitabine resulted in improved activity and benefit to QoL in patients with advanced PC.

#### *L-Carnitine Supplementation in Pancreatic Cancer Patients*

The study by Kraft et al. [34] revealed that supplementation with L-carnitine decreased weight loss, increased BMI and improved the nutritional status and QoL in PC patients in contrast to placebo.

### **Conclusions and Advices for Daily Practice**

Unfortunately there are only few studies on the nutritional aspects of PC, partly explained by the short survival of those patients. Because of the high prevalence of malnutrition and rapid development of the anorexia-cachexia-syndrome, early nutritional intervention is crucial as suggested by the studies discussed above. EN should be preferred in comparison to PN whenever possible. There are some investigations that examined specific nutritional supplements like fish oil and L-carnitine. The results of these studies are somehow limited due to the low number of participants and in some studies control groups are lacking. However, all studies show a positive trend for those compounds with a beneficial impact on the reduction or reversion of weight loss and tissue wasting. Further randomized controlled trials are needed to establish generally accepted guidelines for nutrition in PC.

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