Nutritional Status and Nutritional Support Before and After Pancreatectomy for Pancreatic Cancer and Chronic Pancreatitis

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Abstract Cachexia, malnutrition, significant weight loss, and reduction in food intake due to anorexia represent the most important pathophysiological consequences of pancreatic cancer. Pathophysiological consequences result also from pancreatectomy, the type and severity of which differ significantly and depend on the type of the operation performed. Nutritional intervention, either parenteral or enteral, needs to be seen as a method of support in pancreatic cancer patients aiming at the maintenance of the nutritional and functional status and the prevention or attenuation of cachexia. Oral nutrition could reduce complications while restoring quality of life. Enteral nutrition in the post-operative period could also reduce infective complications. The evidence for immune-enhanced feed in patients undergoing pancreaticoduodenectomy for pancreatic cancer is supported by the available clinical data. Nutritional support during the post-operative period on a cyclical basis is preferred because it is associated with low incidence of gastric stasis. Postoperative total parenteral nutrition is indicated only to those patients who are unable to be fed orally or enterally. Thus nutritional deficiency is a relatively widespread and constant finding

suggesting that we must optimise the nutritional status both before and after surgery.

Keywords Chronic pancreatitis · Nutritional status · Nutritional support · Pancreatic cancer · Pancreatectomy

Introduction

Pancreatic adenocarcinoma — a highly aggressive gastrointestinal malignancy — is characterised by marked cachexia, and early metastasis [1]. Most of patients with gastrointestinal malignancies including pancreatic cancer, suffer from a variety of symptoms from the digestive tract such as vomiting, abdominal pain, anorexia and malabsorption, symptoms that substantially contribute to an impairment both in the performance status and the quality of life [2]. All the above-mentioned symptoms, corresponding to the term “cancer-cachexia syndrome” are predictors of bad prognosis and poor response to treatment [3]. Most of patients with advanced pancreatic carcinoma are suffering from cancer cachexia [4].

Malnutrition is considered to be a major risk factor of poor outcome after surgical resection and of increased toxicity after chemo- and radiotherapy. However, malnutrition and significant weight loss are two, often underestimated, symptoms in pancreatic cancer patients [5]. On the contrary, it seems that, by improving nutritional status, we could improve quality of life and increase tolerance to chemotherapy.

The important questions that we must answer are: What is the nutritional status of patient diagnosed with pancreatic cancer either before or after diagnosis? Must we provide enteral and/or parenteral nutritional support in pancreatic cancer patient before or after major surgical operation to cope with nutritional needs and prevent cancer-related cachexia?

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This review aims to provide some answers to the above-mentioned questions based on the results of the current literature.

Influence of Pancreatic Cancer on Patients' Nutritional Status

Cachexia and reduction in food intake due to anorexia represent the most important pathophysiological consequences of pancreatic cancer.

Cachexia

As it was mentioned before, cachexia is a major clinical consequence of pancreatic carcinoma. It has been estimated that at the time of operation, 40 % of patients have cachexia manifested by low levels of protein, albumin, haemoglobin and abnormal nutritional parameters. The resection and survival rates are reduced in patients either undergoing tumor resection or palliatively treated. It must be stressed that cachexia does not depend on the tumor size [6].

Patients with pancreatic cancer and cachexia exhibit reduced fat tissue amounts. In a relevant study, it was found that rapid weight loss represents an indication of very aggressive neoplasm. If the loss of weight is greater than 10 % then the resection rate is significantly reduced [7]. Reduction in food intake together with a 10 % weight loss, are considered to be significant bad prognostic parameters.

The mechanisms of weight loss are quite different in cancer cachexia and starvation. In the first case weight loss is due to equal loss of muscle mass and adipose tissue, whereas in starvation, weight loss is mainly attributed to the loss of fat and only a small amount to the body muscle mass [8].

Total body fat and potassium, but not protein, are reduced in pancreatic cancer patients who are candidates for surgery compared with healthy controls. Patients with larger tumours and involved margins present greater losses of body fat and lean tissue, thus greater reductions in nutritional status. Fat mass at presentation had a predictive effect on survival, although only a small percentage of patients presented with severe cachexia. Therefore, when a patient presents significant weight loss, this could be considered as a sign compatible with a more advanced stage of cancer.

Anorexia

Anorexia, meaning the loss of desire to eat or loss of appetite, is an important symptom causing weight loss in cancer cachexia, unrelated to the effect of chemotherapy. In patients with cancer-induced anorexia, no beneficial effect is obtained even with food supplementation, and discontinuation of

chemotherapeutic drug intake fails to counteract the wasting process. Thus, cancer-induced anorexia is an independent and irreversible process [9].

Imbalance between orexigenic signals (those that increase appetite, as neuropeptide Y) and anorexigenic signals (those that decrease appetite, as pro-opiomelanocortin) may play a role in anorexia. Ghrelin is a growth hormone-releasing peptide which has been found to be an appetite stimulant. Significantly lower levels in the plasma ghrelin of patients with pancreatic cancer versus controls have been demonstrated, a reduction that might be due to the severity and progression of the underlying malignant disorder [10].

Other factors also seemed to contribute to the appearance of anorexia. Gastrointestinal cancer patients have decreased taste and smell of food, which may be attributed to the tumor itself or to depression. In addition, the release of chemicals by the tumor may induce anorexia. Various cytokines such as macrophage inhibitory cytokine-1, interferon- γ , TNF- α and IL-1, released in the hypothalamus have been implicated in anorexia [11]. TNF- α levels are detectable in the serum of pancreatic cancer patients, particularly in those with advanced disease. In general, serum TNF- α levels are inversely associated with haematocrit, haemoglobin, BMI, and serum albumin thus with poor nutritional status [12]. Other cytokines including transforming growth factor β , IL-1, and IL-6 also mediate anorexia [13, 14].

On the other hand, early satiety, that is a feeling of fullness after the consumption of even a small amount of food, has also been reported in gastrointestinal cancer patients. It is considered either as a direct effect of the tumor in the gastrointestinal tract, which obstructs the passage of food, or the altered mucosa, thus leading to malabsorption.

Treatment of anorexia includes appetite stimulants, drugs against cachetic signaling molecules, and mediators, which help prevent and treat wasting [15]. Counteracting weight loss and anorexia are possible with central and peripheral appetite stimulants and nutritional supplements such as ω -3 fatty acids and essential aminoacids. Central appetite stimulant-like megestrol acetate acts on the hypothalamus. Ghrelin has also been shown to increase the appetite. Resting energy expenditure is controlled by the reduction in acute phase response proteins by anti-inflammatory drugs such as ibuprofen. Protein wasting is inhibited by agents such as EPA fatty acid and anti-TNF- α factors including infliximab. A combination approach is required for the treatment of cachexia [16].

Pathophysiological Consequences after Pancreatic Surgery for Cancer and Chronic Pancreatitis

The type and severity of pathophysiological consequences following the various surgical procedures in patients with

pancreatic disease differ significantly and depend on the type of operation.

Pancreaticoduodenectomy with Extended Lymphadenectomy

This type of operation (the procedure of choice for pancreatic head carcinoma) involves removal of head of the pancreas, duodenum and distal common bile duct. However it accompanied in some percentage by at least two important complications namely gastric stasis and pancreatic fistula. Pancreatoduodenectomy results in loss of gastric pacemaker due to removal of the interstitial cells of Cajal. This, together with the physiologic consequences of pancreatic resection and biliary and pancreatic diversion, could result in post-operative gastric stasis [17].

On the other hand enteral nutrition delays gastric emptying in patients who underwent Whipple's resection for cancer of the pancreas. In a relevant study, among 62 operated-on patients, 30 received enteral and 32 non-enteral nutrition. Significantly greater proportion of delayed gastric emptying was observed in the first compared with the second group (57 % vs 16 %) although they had longer hospital stay and longer duration of nasogastric tube compared with the non-enteral nutrition group [18].

The circumferential dissection of the nerve plexus around superior mesenteric artery during pancreaticoduodenectomy with extended lymphadenectomy results in severe diarrhea, malnutrition, and impairment in the postoperative quality of life. This is a consequence of the loss of the small bowel extrinsic nerve which regulates its motility via loss of the tonic inhibitory effects of sympathetic nerves on gastrointestinal function [19]. The other factor predisposing to diarrhoea is related to the altered homeostatic balance of intestinal ion transport, a physiological abnormality that favors secretion [20, 21]. In most cases diarrhoea could be so severe that patients develop severe malnutrition in the postoperative days despite the short survival time.

Generally, pancreatic resection results in significant alterations in the digestive physiology because of the absence of pancreatic contribution to food digestion and balance of many nutrients [22]. The total pancreatectomy and intestinal denervation can cause severe physiologic abnormalities, manifested by acutely disordered intestinal function, and diabetes mellitus because of the lack of the two major glucoregulatory hormones, namely insulin and glucagon. Given the antral resection and malabsorption, it is expected that the pancreatectomized patient will be at risk for osteopenia development manifested by decreased with time radial bone mineral content after surgery [23].

The appearance of diabetes mellitus represents an important consequence in totally pancreatectomized patients. Pancreatic diabetes has unique clinical and metabolic features

such as diabetic instability and glycemic fluctuations, including postprandial hyperglycemia and delayed decreases in blood glucose levels. The blood glucose profiles in these patients have similarities with what is seen in type I diabetes mellitus [24]. As it was mentioned before, these patients could develop hypoglycaemia manifested with brain dysfunction, coma, and (rarely) death [25]. Therefore, it is extremely important for the patients to adopt rigorous home glucose monitoring with administration of multiple, small (smaller than patients with type I diabetes) daily doses of insulin as required [26]. In completely pancreatectomized patients insulin resistance is comparable to that seen in patients with type I diabetes [27]. In these patients, basal glucagon replacement induced a further significant reduction in tissue insulin responsiveness [28].

The role of glucagon in the maintenance of glucose concentrations is well established. Many studies have clearly demonstrated that glucagon is absent or markedly reduced in totally pancreatectomized patients [29]. Pancreatectomized patients have an exaggerated hyperglycemic response to glucagon administration suggesting that chronic glucagon deficiency enhances sensitivity to exogenous glucagon. Therefore, that impaired regulation of hepatic glucose production could be a probable cause of the frequent hypoglycemia seen in these patients.

The development of lipid accumulation in the liver (fatty liver) represents an uncommon but worrisome finding in totally pancreatectomized patients, a phenomenon that has also been described in experimentally pancreatectomized animals [30]. It has been suggested that uncontrolled diabetes, weight loss, and malabsorption could be the main contributing factors. However, the severity of hepatic steatosis, even in patients with satisfactory blood glucose levels, suggests the co-existence of additional pathogenic mechanisms.

Distal Pancreatectomy

In patients who underwent distal pancreatectomy no severe diarrhea usually occurs because more than half of the plexus of the celiac and superior mesenteric artery and bilateral ganglions are preserved. In distal pancreatectomy, complete preservation of the duodenum and intestinal continuity can be achieved resulting in much better digestive and absorptive function compared to pancreaticoduodenectomy, so patients can maintain satisfactory exocrine function of the remnant pancreas [31].

On the other hand, neuropeptidergic control of small intestinal transit by peptide YY released from the distal intestine is activated by ingestion of the nutrients in the distal small intestine and colon, thus slowing intestinal transit time and helping digestion and absorption of nutrients [32]. Since secretion of peptide YY is stimulated by cholecystikinin, patients who have undergone distal

pancreatectomy, the mechanism of the small bowel transit by peptide YY might be maintained even after surgery [33].

Because patients undergoing distal pancreatectomy scarcely suffer from intractable diarrhea, maintaining desirable nutritional status after surgery makes them able to receive adjuvant chemotherapy. In a recent study, the nutritional status, bowel movements, and tolerance to adjuvant chemotherapy were investigated in 40 patients with pancreatic carcinoma who underwent distal pancreatectomy with en-bloc celiac axis and circumferential plexus of the superior mesenteric artery removal. After a median 39-month follow-up, 38 % of patients needed no anti-diarrheal agents. The remaining patients effectively controlled diarrhoea with conservative measures. Laboratory nutritional parameters were lower 1 month postoperatively and returned to normal between 3 and 12 months [34].

Middle Pancreatectomy

Middle pancreatectomy is a surgical technique that, by sparing active pancreatic parenchyma, reduces the risk of pancreatic insufficiency. In a study aiming to evaluate the results of this operation it was shown that, compared to left-side and right-side pancreatectomies, this operation had significantly shorter operation time although with higher fistula formation. None of the patients developed diabetes mellitus postoperatively. Patients presented better postoperative nutritional status compared to controls [35].

Gastrin Effects on Pancreatoduodenectomized Patients

It is well known that gastrin is a hormone with major trophic impact on gastrointestinal tract mucosa including pancreas, both in humans and animals. However in humans pancreatoduodenectomy results in further atrophy of the pancreatic remnant instead of regeneration. In a randomized prospective study, 37 patients submitted to pylorus-preserving pancreatoduodenectomy were treated with either proton pump inhibitor (lansoprazole 30 mg/d) or placebo. The volume of pancreatic remnant was estimated with the use of spiral computed tomography. Serum gastrin and pancreatic endocrine and exocrine function were estimated preoperatively and 3 months postoperatively. The results showed that the volume of pancreatic remnant was almost unaffected (reduction in size of 10 %) compared to severe atrophy in the placebo group. The results concerning exocrine and endocrine pancreatic function were significantly better in the lansoprazole group [36]. Therefore, hypergastrinemia produced by administration of proton pump inhibitors could be useful in either prevention or confronting of pancreatic insufficiency following resection or injury. However, more data are needed concerning this interesting topic.

Pylorus-preserving Total Pancreatectomy

It has long been shown that compared to total pancreatectomy, pylorus-preserving pancreatectomy in patients with pancreatic cancer has better results regarding nutritional recovery [37]. Moreover, pylorus-preserving pancreatoduodenectomy and pylorus resecting pancreatoduodenectomy do not significantly differ in terms of nutritional status and quality of life while the latter significantly reduces the appearance of gastric emptying compared with pylorus-preserving pancreatoduodenectomy [38].

Surgical Treatment of Chronic Pancreatitis

Concerning pancreatic surgical resection for chronic pancreatitis it seems that duodenum preserving pancreatic head resection offers better results compared with pancreatoduodenectomy in many parameters including quality of life, pain relief and nutritional status [39]. The presence of malnutrition is associated with a higher rate of postoperative complications. An increase in operative morbidity might be related to decreased protein synthesis and impaired immunocompetence. It has been claimed that low serum albumin levels increase operative morbidity as it was reflected by a higher rate of infectious complications as well as increased intensive care unit stay [40].

Operative Complications Related to Nutritional Status

Nutritional status also seems to influence the rate of postoperative complications. In a relevant study it was found that preoperative low prognostic nutrition index and low preoperative serum levels of albumin were associated with poor survival and higher rate of postoperative complications, respectively. Low prognostic nutrition index and low BMI were associated with the appearance of pancreatic fistula [41].

Nutritional Support in Patients Undergoing Pancreatectomy for Cancer

Nutritional intervention, either parenteral or enteral, in pancreatic cancer patients aims mainly to prevent or attenuate cachexia. During the last two decades, a number of clinical studies tried to answer the question whether perioperative nutritional support could be beneficial in patients with pancreatic carcinoma who are candidates for total pancreatectomy using parenteral or enteral nutrition. The results of these studies are subsequently analysed.

Parenteral Nutrition

According to ESPEN nutritional guidelines, candidates for parenteral nutrition are patients who are not able to be fed

orally or enterally for various reasons [42]. Bearing in mind the fact that preoperative nutrition is an important prognostic index for postoperative survival and response to chemotherapy, accurate assessment of the nutritional status and immediate nutritional support are important elements of our strategy. However, routine use of parenteral nutrition should generally be discouraged [42].

A positive impact of additional parenteral nutrition has been detected. A phase II study examined the impact of additional parenteral nutrition in 32 outpatients with advanced pancreatic cancer and progressive cachexia using bio-electrical impedance analysis method, for 18 weeks. A significant benefit was noticed in 84 % of patients, while 43.7 % of patients were improved or remained stable [43].

It has been long ago suggested that routine postoperative parenteral nutrition after major pancreatic surgery is not recommended. In a relevant study patients were randomized to either receive (starting from the first postoperative day or not) adjuvant parenteral nutrition. The results showed no benefit, while the rate of complications was higher in the group of parenteral nutrition [44].

A recent study showed that short-term perioperative administration of recombinant growth hormone, octreotide and insuline plus hypocaloric parenteral nutrition could overcome the postoperative stress response [45]. The therapeutic regime resulted in significant increase in protein synthesis and immune function and decreased rate of postoperative infectious complications.

In cachectic patients a high fat-to-glucose ratio in the intravenous feeding may be adopted because of their ability to maintain a high capacity to metabolize fats.

Home parenteral nutrition can also be applied in some patients. This results in improvements in parameters such as quality of life, and body composition, while it prolongs survival. Home parenteral nutrition is indicated in pancreatic cancer patients who are unable to consume food and consequently are at significant risk of death from starvation prior to tumor spread [46].

Enteral Nutrition

Enteral nutrition in malnourished cancer patient has been shown to reduce complications, hospital stay, and toxicity of chemotherapy while increasing energy intake and nutritional status. Patients submitted to pancreatoduodenectomy use less frequently total parenteral nutrition and have lower rate of complications if they are submitted to early postoperative tube feeding [47]. In these patients immunonutrition probably improves the surgical outcome.

Some other parameters also could influence the outcome of postoperative nutritional support. These include the composition of the enteral formula and the route of

administration. In a relevant clinical study in patients who had undergone pancreatoduodenectomy for pancreatic carcinoma, it was shown that immunonutrition with an enteral formula enriched with arginine and omega-3- fatty acids resulted in significantly lower rate of postoperative complications and length in hospital stay compared to standard enteral formula and total parenteral nutrition [48]. These results were confirmed in another study [49] thus supporting the assumption that early postoperative enteral feeding and immunonutrition could safely replace parenteral nutrition in these patients.

The role of immunonutrition was further investigated in another trial which showed that administration of an immunoenriched formula or an immunoenriched formula plus arginine for 5 days preoperatively and also 7 days postoperatively produced better results regarding hospital staying, serum endotoxin levels and infectious complications compared with patients who received the immunonutrition feeding only postoperatively [49]. Recent reports reinforce the potential benefit of early oral nutrition [50]. The results of a recent clinical trial showed a significantly shorter median postoperative hospital stay in the immunomodulated enteral diet compared to the standard oligopeptide diet in malnourished upper gastrointestinal cancer patients. Moreover, fewer infectious complications were observed in the immunomodulated enteral diet group compared to the standard oligopeptide diet group. Significant differences were also observed in overall morbidity and mortality [51].

However, not all data agree with the results of the above-mentioned studies. In a double-blind trial, 183 well-nourished patients who had undergone surgery for pancreatic and gastric carcinoma received postoperatively enteral nutrition with either immunostimulating diet or standard oligopeptic diet. The results showed that median postoperative hospital stay was similar in standard oligopeptic diet and immunostimulating diet groups. No difference was noticed concerning complication rate [52].

An interesting study revealed that supplementation with glutamine enhanced the efficacy of chemo-radiation treatment, improving the outcome, and reducing toxicity while perioperative supplementation with arginine increases long-term survival [53].

It seems that medium chain triglyceride and protein enriched enteral nutrition can improve the protein and prealbumin plasma levels and reduce the length of hospital day compared with an isocaloric protein enriched enteral nutrition [54].

Another study showed that administration of omega-3- fatty acids improves the outcome in many biochemical clinical and functional parameters [55]. Nevertheless, the underlying mechanisms of action of ω -3 polyunsaturated fatty acids, and glutamine, remain to be elucidated [56].

An eicosapentaenoic acid-enriched oral diet could restore cachexia in patients with advanced cancer [57]. The same

group of investigators also showed that administration of fish-oil results in improvement of nutritional status and metabolic response in patients with pancreatic carcinoma [58].

It is well established that oxidative stress due to ischemia/reperfusion injury enhances systemic inflammation. In a very recently published study, perioperative oral nutritional supplementation increased plasma levels of vitamin C and total endogenous antioxidant capacity after surgery however without reducing oxidative stress and inflammatory indices in patients undergoing pancreatectomy for pancreatic cancer [59].

Parenteral Versus Enteral Nutrition

Some studies have also tried to answer the question whether enteral nutrition is preferable to total parenteral nutrition in patients with pancreatic cancer. In a study aiming to determine the effects of total parenteral and enteral nutrition on biochemical and clinical outcomes in patients who had undergone pancreatoduodenectomy for pancreatic carcinoma, it was found that enteral nutrition was better in terms of a number of clinical and biochemical parameters [60].

In another prospective, randomized, clinical trial, 257 patients with esophageal, gastric and pancreatic cancer received either postoperative total parenteral nutrition or early enteral nutrition. The nutritional goal (25 kcal/kg/day) was reached in 79.3 % patients in the enteral group compared to 97.7 % in the total parenteral group. Disturbances in the serum electrolyte levels were significantly lower in the enteral compared to parenteral group, although the overall complication rate was similar. Enteral nutrition was four-fold less expensive than total parenteral nutrition [61].

Concerning cyclic versus continuous enteral feeding after pylorus-preserving pancreatoduodenectomy, the available data support the assumption according to which, cyclic enteral nutrition is associated with shorter length of administration and hospital staying and faster return to normal diet. In a prospective randomised trial, the authors compared continuous post-operative enteral nutrition delivered via a needle catheter jejunostomy in 30 patients undergoing pancreaticoduodenectomy to cyclical post-operative enteral nutrition, while in 27 patients post-operative feed was delivered for 18 h with a 6 h non-feeding window. The results showed no difference in the number of days of nasogastric intubation, although the mean number of days to resumption in normal diet was significantly shorter in patients receiving cyclical enteral nutrition than in the continuous group. Cholecystokinin levels were lower in patients receiving cyclical nutritional support. Moreover, in cyclical patients, fasting plasma cholecystokinin levels increased significantly after starting the enteral nutrition, while in continuous patients, cholecystokinin levels did not change during testing [62]. Therefore, this type of

nutritional support could be considered as a feeding regimen of choice in patients who had undergone pancreatoduodenectomy. However, the trial evaluating cyclical enteral feeding in comparison to continuous feeding was small and it remains to be seen whether these results can be reproduced.

In conclusion, as the enteral route of nutritional support might be as good as the parenteral nutrition should be the method of choice in pancreatic cancer patients. Other reasons for using enteral nutrition include the fact that local intestinal stimulation prevents mucosal atrophy and bacterial translocation [63].

Palliative Treatment after Major Pancreatic Surgery

Total pancreatectomy results in postoperatively altered endocrine function of the pancreas including insulin and glucagon secretion. It is well established that the concomitant administration of insulin and glucagon and the maintenance of blood insulin/glucagon ratio at a level similar to the physiological value are extremely important in order to improve the energy and nutritional metabolism following total pancreatectomy [64].

Exocrine insufficiency of the pancreas is an important consequence of pancreatic cancer and after total pancreatectomy, the treatment of which is based on oral administration of pancreatic enzymes. The enzymes must be administered in the form of enteric-coated microspheres thus preserving lipase inactivation and gastric emptying of pancreatic enzymes in parallel with food, although some situations including bacterial overgrowth may reduce fat digestion and absorption [65]. Pancreatic enzyme replacement therapy (at least 20,000Ulipase/major meal), routine calcium and vitamin supplementation, and adherence to a regimen of multiple calorie-dense meals per day could prevent nutritional deficiencies and loss of weight. Thus nutritional and pharmacological support could improve pancreatic cancer patients at least temporarily although without any favourable influence on course of the disease or patients' Karnofsky performance status [66]. We must not forget that these patients also require vitamin D and selenium supplementation [67]. Finally a review of 3 studies noticed that the efficacy of pancreatic enzyme supplementation depends on adequate meal-time enzyme replacement treatment [68].

As it was mentioned earlier, proinflammatory cytokines play a significant role in cancer cachexia, and consequently drugs that could inhibit these cytokines would have beneficial effect in these patients. Thalidomide, an anti-TNF- α drug could be beneficial in patients with cancer cachexia. The available data indicate that thalidomide can attenuate loss of weight and

Table 1 Clinical trials on the use of perioperative enteral or parenteral nutritional support in patients undergoing pancreatic surgery for pancreatic malignancy

Author/year Reference	Design	Arms	Number of cases	Results	Conclusion
Liu et al. 2011 [45]	RCT	EN group vs TPN group	60	Significant difference on the 14th postoperative day in terms of urinary levels of nitrogen, TP, TF, retinol binding protein, ALT, AST, ALP, γ GT, bilirubin, BUN, Cr, and glucose. Incidence of delayed gastric emptying in the EN and TPN groups: 0 % and 20 %, respectively.	EN is better than TPN for patients with pancreatic cancer who have undergone pancreatoduodenectomy
Barlow et al. 2011 [50]	P R C T	EN vs Nil by mouth — IV fluid	121 pts including 29 pancreatic cancers	Operative morbidity: Less common after EEN (32.8 %) than control management (50.9 %, $p=0.044$), due to fewer wound infections, chest infections, and anastomotic leaks. Median length of hospital stay : 16 days after EEN vs 19 days after control management ($p=0.023$)	EEN is associated with shortened length of hospital stay and improved clinical outcomes. Potential benefit of early oral nutrition in principle and as championed within enhanced recovery after surgery programmes.
Klek et al. 2011 [51]	Prospective double-blind trial	Preoperative 2 weeks of parenteral feeding Impact of enteral immunonutrition in postoperative period vs standard oligopeptide diet	305 patients with gastric or pancreatic cancer	Median postoperative hospital stay: 17.1 days in SEN and 13.1 days in IMEN group ($p=0.006$). Infectious complications: in 60 patients (39.2 %) in SEN and 43 (28.3 %) in IMEN group ($p=0.04$). Differences were observed in overall morbidity (47.1 vs 33.5 %, $p=0.01$) and mortality (5.9 vs 1.3 %, $p=0.03$).	Postoperative immunomodulating enteral nutrition should be the treatment of choice in malnourished surgical cancer patients.
Pelzer et al. 2010 [43]	Clinical trial	Median treatment duration: 18 weeks.	32 patients	Improvement in 27 pts (84 %) in at least one parameter. 14 pts (43.7 %) improved or stabilised in all three parameters Median ECM/BCM index: 1.7 at start of APN and improved down to 1.5 during therapy. Median BMI increased from 19.7 to 20.5 Median phase angle improved by 10 % from 3.6 to 3.9.	Positive impact of APN on the assessed parameters. At least a temporary benefit or stabilisation of the nutritional status in the majority of patients.
Klek et al. 2008 [52]	Randomised Clinical Trial	Postoperative enteral nutrition with immunostimulating diet (IMEN) vs Standard oligopeptic diet (SEN).	183 pts with pancreatic or gastric cancer	Median postoperative hospital stay: 12.4 days in SEN and 12.9 days in IMEN group (NS). Complications: 23.1 % in SEN and 25.2 % in IMEN group (NS). Surgical complications: 4.4 % patients in SEN and 4.4 % in IMEN group (NS)	No benefit of IMEN over SEN in patients after major gastrointestinal surgery for malignancy.

Table 1 (continued)

Author/year	Reference	Design	Arms	Number of cases	Results	Conclusion
Baradi et al. 2004 [47]		Retrospective clinical study	Groups: Early postoperative tube feeding (96 patients) vs. Patients with no planned feeding (82 patients).	180 patients undergoing Whipple operation	<p>Jejunal feeding: Bridled nasojejunal tube (56 %)</p> <p>Gastrojejunal tube (44 %). Of pts Vomiting and use of TPN were less in the jejunal feeding group as well as rates of readmission, early and late complications, and infections. Tube-related complications occurred in 6 of 98 patients, all of which were associated with gastrojejunal tubes.</p> <p>Nutritional goal was reached in 79.3 % of pts in the EEN group and in 97.7 % of pts in the TPN group ($p < .001$).</p> <p>No significant difference was found in nutritional, immunologic, and inflammatory variables between the two groups. Similar overall complication rate.</p> <p>No difference for either infectious or noninfectious complications, length of hospital stay, and mortality. EEN was less expensive vs TPN.</p>	Early post-operative tube feeding after pancreaticoduodenectomy is associated with less use of TPN and lowers rates of re-admission and complications. A bridled nasojejunal feeding tube is a safe and reliable method of short-term enteral feeding.
Braga et al. 2001 [61]		PRCT	EN vs TPN	257 GI cancer pts (110 with pancreatic cancer)	<p>Delayed gastric emptying occurred significantly more in patients with EN vs patients with no-enteral nutrition. EN group had a nasogastric tube for a significantly longer period and longer hospital stay vs patients in the no-enteral nutrition group.</p> <p>No differences in the frequency of other postoperative complications</p>	EEN represents a rational alternative to TPN in patients who undergo upper GI surgery for cancer, who require postoperative artificial nutrition.
Martignoni et al. 2000 [18]		Observational study	2 arms: EN vs Nil	62	<p>Delayed gastric emptying occurred significantly more in patients with EN vs patients with no-enteral nutrition. EN group had a nasogastric tube for a significantly longer period and longer hospital stay vs patients in the no-enteral nutrition group.</p> <p>No differences in the frequency of other postoperative complications</p>	Enteral nutrition is associated with delayed gastric emptying without reduction in other complications.
Gianotti et al. 2000 [49]		RCT	3 arms: EN I-EN TPN	212 patients [68 – 73 – 71]	<p>Full nutritional goal was achieved in: 87 % of EN vs 95 % in TPN group.</p> <p>Immunonutrition group: significantly better recovery of the immunometabolic parameters on postoperative day 8 vs the two other groups.</p> <p>Rate of postoperative complications: Lower in the immunonutrition group (33.8 %) vs EN (43.8 %) or TPN group (58.8 %).</p> <p>Mean length of hospital stay: Shorter in the I-EN group vs EN and TPN groups (15.1 vs. 17.0 vs. 18.8 days).</p>	Early post-operative enteral feeding can replace parenteral nutrition in patients undergoing pancreaticoduodenectomy. Compared to TPN, immune-enhanced enteral nutrition ameliorates the immunometabolic response and improves outcome.

Table 1 (continued)

Author/year Reference	Design	Arms	Number of cases	Results	Conclusion
Di Carlo et al. 1999 [46]	Clinical study	pancreatectomy for pancreatic head cancer Standard enteral formula vs Immunonutrition vs TPN	100	Full nutritional goal (25 kcal/kg) was achieved in 84 % of SEN vs 96 % in the TPN group (NS). Rate of postoperative complications 33 % in IEN group vs 40 % in the SEN and 59 % in the TPN group Sepsis score: Lower in the IEN vs SEN and TPN groups ($p<0.05$). Length of hospital stay: Shorter in the IEN vs SEN and TPN groups ($p<0.05$).	In patients undergoing PD the established nutritional goal can be obtained by enteral feeding. Immunonutrition seems to improve outcome.
Brennan et al. 1994 [44]	PRT	Patients with major pancreatic resection. Randomization on postoperative day one to either receive or not receive adjuvant TPN. 2 arms: TPN vs Nil	117	No benefit was demonstrated by the use of adjuvant TPN. Complications: significantly greater in the group receiving TPN. Complications tended to be those associated with infection.	Routine applications of postoperative TPN to patients undergoing major pancreatic resection for malignancy cannot be recommended.

EN enteral nutrition*EN* Immune enteral nutrition/*TPN* total parenteral nutrition*RCT* Randomized Clinical Trial

NS Not significant

lean body mass in patients with advanced pancreatic cancer [69]. Finally, administration of albumin does not improve the clinical outcome if it is given early in the postoperative period after gastrointestinal surgery [70].

A summary on the results of the main clinical studies related to perioperative nutritional supplementation in patients undergoing pancreaticoduodenectomy is given in Table 1.

Conclusions

Cachexia and reduction in food intake due to anorexia represent the most important pathophysiological consequences of pancreatic cancer. Malnutrition and significant weight loss are two often underestimated symptoms in pancreatic cancer patients. All pathophysiological consequences result from pancreatectomy, the type and severity of which differ significantly and depend on the type of operation. Pancreatic resection results in significant alterations in the digestive physiology because of the absence of pancreatic contribution to food digestion and balance of many nutrients. Delayed gastric emptying and development of diabetes represent the most important consequences in totally pancreatectomized patients. Development of fatty liver represents an uncommon but worrisome finding in totally pancreatectomized patients. Nutritional intervention, either parenteral or enteral, in pancreatic cancer patients must be given in order to prevent or attenuate cachexia. Administration of oral nutritional supplements could reduce mortality, postoperative complications including infectious ones, and hospital stay. Enteral nutrition reduces gastrointestinal toxicity derived from chemotherapy, increases appetite and improves nutritional status. Oral nutrition is always preferable to parenteral nutrition. Placement of nasojejunal tube could avoid the risks of surgical jejunostomy. The evidence for immune-enhanced feed in patients operated-on for pancreatic carcinoma is supported from most of the available clinical data. Cyclic postoperative enteral nutrition represents the preferable method of nutrient administration because it is accompanied by low incidence of postoperative gastric stasis. Postoperative routine total parenteral nutrition in every patient is not recommended. Finally, the efficacy of pancreatic enzyme supplementation in those patients with pancreatic insufficiency depends on adequate meal-time enzyme replacement treatment. In order to synthesize this evidence into practical suggestions, it could be said that nutritional deficiency is relatively widespread as it consists a constant preoperative finding. As a result, it is of great importance that the nutritional status prior to and after surgery is optimised.

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