

Special topic by C. Dervenis

Nutritional aspects in the management of pancreatic cancer

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Nutritional and metabolic considerations represent a major challenge in the management of patients with pancreatic cancer. This concerns both the clinical presentation of these patients with frequent occurrence of cachexia and its consequences on the quantity and quality of remaining life for this category of patients. Furthermore, nutritional aspects influence the peri- and postoperative course of pancreatic cancer patients subjected to surgery with radical intent. The majority of patients, however, are not candidates for radical surgery but will merely be in need of various supportive regimens including nutrition which, as will be indicated below, also may affect the quality of life of the in general short expected survival time in patients with pancreatic cancer.

DIETARY RISK FACTORS FOR PANCREATIC CANCER

Diet as a factor for the development of pancreatic adenocarcinoma has been widely discussed. So has obesity and fat, especially in the form of animal fat content of the diet, been suggested as a risk factor.¹ A direct correlation between the intake of both total and animal fat and mortality from pancreatic cancer has been described,² while other authors have not been able to demonstrate any association between the risk for developing pancreatic cancer and the total fat intake.³ Vegetable intake has been reported to decrease the risk of death in pancreatic cancer.^{2,4,5} A correlation with calories derived from animal sources of food with mortality from pancreatic cancer has also been reported.² In sharp contradiction to what is known for patients with chronic pancreatitis, a relation with the use of alcoholic beverages and

the development of pancreatic cancer has not been reported.⁶

PANCREATIC CANCER AND CACHEXIA

A majority of patients with pancreatic cancer will be cachectic at the time of death and are frequently so already at the time of diagnosis.⁷ There seems to be a relationship between the nutritional status and the quality of life and the cachectic state is associated with fatigue and declining quality of life and has been attributed responsible for up to 25 % of deaths in patients with pancreatic cancer.⁸ The progressive weight loss seen in patients with advanced pancreatic cancer seems to accelerate close to the time of death, correlated with reduction in patients' functional capacity.⁹ There are also reasons to believe that pancreatic cancer and cachexia is associated with increased inflammatory activity caused by elevated levels of proinflammatory cytokines which aggravates the patients' condition, but also renders a potential for future targetted treatment with nutrition and immunomodulation, as will be mentioned below. The syndrome of cachexia include weakness, weight loss and progressive impairment of vital functions. Pallor, severe skeletal muscle wasting and loss of subcutaneous fat stores are also seen. The severity of cachexia does not seem directly to relate to the size of the pancreatic tumor (Table 1).

The cachexia is depending both on the presence of anorexia and malnutrition, frequently present at the time of diagnosis. Anorexia depends on less food intake and changed eating behavior with more pronounced intake

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Table 1. Cachexia

- Weakness, weight loss, progressive impairment of vital functions
- Pallor, severe skeletal muscle wasting, loss of subcutaneous fat stores
- Severity of cachexia not directly related to size of tumor

of carbohydrates. The causes of anorexia seem to depend on a variety of factors including cytokine release (TNF α , interleukin-1), intermediate metabolites like lactate, ketones and oligonucleotides as well as islet amyloid polypeptide (IAPP). IAPP seems to be an important satiety factor regulating appetite and interfering with glucose metabolism and with the potential of causing reduction in food intake and thereby reduction in body weight.¹⁰ A variety of causes of anorexia exist, many which can be dealt with and managed as part of the palliation of pancreatic cancer patients. Contributory factors to anorexia thus include pain, depression, anxiety, steatorrhea and constipation. Furthermore, debility and side effects of treatments like chemotherapy, radiotherapy and the use of opiates, are additive factors. Tumor obstruction of the gastrointestinal tract (usually the descending part of the duodenum) is probably a less frequent course of anorexia than previously was thought and palliative gastroenteroanastomosis are to be advocated only in selected cases.¹¹

Malnutrition results from changes in the digestive tract ending up in atrophy of the intestinal mucosa, a feeling of fullness, delayed emptying and impaired digestion of nutrients. Malnutrition in general relates to increased postoperative morbidity and mortality and an increase in infectious complications, prolonged rehabilitation, influence on organ function and impaired wound healing, immune response and skeletal muscle function. Furthermore, the nutritional status affects the overall quality of life as has been mentioned above (Table 2). A number of factors contribute to the state of malnutrition seen in pancreatic cancer. These factors include malabsorption, pain, drug, therapy, anxiety and anorexia. The results may be decreased protein synthesis, increased protein catabolism and increased energy expenditure, together with insulin resistance. The changes seen in relation to malnutrition include both somatic and psychosomatic changes. Somatic alterations include muscle weakness, a decrease in visceral proteins and an impaired immune response. As mentioned, wound healing may be

Table 2. Malnutrition

➤ Correlation with postoperative morbidity and mortality
➤ Infectious complications
➤ Prolonged rehabilitation
➤ Influence on organ function
➤ Impaired wound healing, immune response and skeletal muscle function
➤ Nutritional status affects quality of life

impaired and multiple organ dysfunction may result. The adaptive ability may also be decreased. Psychosomatic changes include tiredness, apathy, depression, irritability and concentration problems as well as decrease in self discipline.

PANCREATIC CANCER AND GLUCOSE METABOLISM

Pancreatic cancer has been reported associated with an impaired glucose tolerance in most patients or even overt diabetes mellitus,¹² while diabetes has not been reported as a risk factor per se.¹³ Interestingly, glucose tolerance and insulin sensitivity was reported to be improved in diabetic patients undergoing tumor resection (subtotal pancreatectomy), implying the existence of a diabetogenic factor produced by the pancreatic adenocarcinoma.¹⁴

NUTRITIONAL ASSESSMENT IN PANCREATIC CANCER

A gross sense of the nutritional status and requirements can be achieved by non-invasive means like patient's history with information concerning muscle wasting, specific nutrient deficiencies and weakness. Weight loss exceeding 15% signals an increased risk of complications. At physical examination, loss of body weight, patient's appearance and skin folds together with functional impairment and estimation of protein stores by inspection and palpation (muscles) should render further information. Indicators of immunocompetence include proteins like albumin and transferrin, immune function by total lymphocyte count and CRP. Methods for nutritional assessment are summarized in Table 3.

NUTRITIONAL SUPPORT

The aim of perioperative nutritional support should

Table 3. Methods for nutritional

Anthropometry	Body weight
	Skinfold thickness
	Arm muscle circumference
Energy intake	Calorie and protein intake
Energy output	Resting energy expenditure
Skeletal muscle function	Hand grip strength
Respiratory function	Tidal volume and vital capacity
Proteins	Albumin
	Transferrin

be to maintain or improve the nutritional state and thereby reduce postoperative complications and/or mortality. Nutritional management has by many been considered as useless rendering no positive effect on neither the tumor nor the prognosis in pancreatic cancer. There are, however, data speaking in favor of providing pancreatic cancer patients with sufficient calory intake, improving quality of life and even potentially prolonging survival.¹⁵ There are reports where no demonstrable effect of adjuvant parenteral nutrition following major pancreatic resection for malignancy could be shown, but instead an increased complication rate (infections) following total parenteral nutrition was seen.¹⁶ Others have, however, shown that perioperative nutritional support is effective in reducing postoperative complications following bilio-pancreatic malignancies¹⁷ and that supportive nutritional efforts may decrease complications, shorten hospital stay, reduce costs and improve the patient's sense of wellbeing.¹⁸

Factors to consider influencing the effect of postoperative nutrition include preexisting, preoperative malnutrition, the magnitude of the surgical trauma and if the patients are challenged by postoperative complications and additional treatments like chemotherapy.

One should consider the choice of energy substrate and the requirements of the individual patients. The resting energy expenditure is usually in the range of 1400-1800 kcal/24 hr.¹⁹ Overfeeding is merely to be linked with an increased rate of complications. Less known is if specific substrates and key nutrients will provide any benefits for the pancreatic cancer patient, e.g. in the way that has been implied by substances like glutamine and arginine in critical illness. To consider is also the type of nutritional composition, the route of administration and if the addition of novel immunonutrients may provide any benefits.

The type of operative procedure performed in patients undergoing radical resection for pancreatic cancer may influence on postoperative nutritional outcome. It seems that pylorus-preserving pancreatoduodenectomy improves nutritional recovery as compared to standard Whipple procedures, which partly could be explained by the fact that the pylorus-preserving procedure leaves the secretory function and capacity of the upper part of the gastrointestinal tract almost unchanged.²⁰⁻²² The route of administration of postoperative nutritional support has been discussed. So have no clinical benefits been observed in patients fed enterally as compared with parenteral feeding and neither did enteral nutrition obviously modulate gut barrier function during the postop-

erative course.²³ Furthermore, early enteral feeding with an immune-enhancing formula including arginine, RNA and omega-3 fatty acids was not by Hesslin et al²⁴ found to be of any benefit and was not recommended to be used in a routine fashion. There are, however, others reporting that early enteral feeding in the postoperative course is of beneficial value and that the regimen is well tolerated. Patients receiving an enriched solution enterally with arginine, RNA and omega-3 fatty acids recovered their nutritional and immunological status quicker as compared to controls receiving either standard enteral or total parenteral nutrition²⁵ and the enriched formula seems to be most beneficial in malnourished and transfused patients reducing both severity of infection and length of stay as compared with the parenteral group.²⁶ It also seems that cyclic (18 hrs/day) enteral feeding after pylorus-preserving pancreatoduodenectomy shortens the period of enteral nutrition, results in a faster return to a normal diet and shortens hospital stay as compared to continuous enteral nutrition. Continuously high CCK levels were suggested to be a potential cause of the prolonged time until a normal diet was tolerated in patients on continuous enteral nutrition.²⁷

Polyunsaturated fatty acids derived from fish oil rich in eicosapentaenoic acid (EPA) and omega-3 fatty acids seems to alter membrane biology and insulin sensitivity as well as they modify both prostaglandin and cytotoxin production.²⁸ Thereby these substances may modulate the acute phase response and proinflammatory cytokine production. Fish oil enriched oral nutritional supplements with EPA have been tried in advanced pancreatic cancer and were found to result in a stabilization of acute phase protein synthesis²⁹ as well as stabilized weight loss and improved performance status and appetite.³⁰ It thus seems that EPA-enriched supplements may reverse cachexia in advanced pancreatic cancer and improve quality of life.

CONCLUSION

Malnutrition and cachexia are frequent already at diagnosis of pancreatic cancer. The cachectic state is associated with fatigue and the nutritional state influences both the postoperative course and also the quality of life in general. There is now evidence supporting that the early identification of patients with malnutrition, for the insertion of nutritional supplements, may render benefits both for cases subjected to radical surgery and patients with pure palliative management. Nutritional demands depend on pre-existing malnutrition, additive surgical trauma and potential complications. In many pa-

tients enteral nutrition seems feasible and then may render benefits e.g. in the postoperative course. As pancreatic cancer and cachexia seem to be associated with an increase in the acute phase response, there may be a role for specific supplements to the nutritional formula that modify the immune response, e.g. as has been implied by the addition of fish oils in advanced pancreatic cancer.

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