Parenteral Nutrition Support for Patients with Pancreatic Cancer – Improvement of the Nutritional Status and the Therapeutic Outcome

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Abstract. *Background: Malnutrition is a frequent and serious problem of patients with pancreatic cancer (i.e. due to exocrine pancreatic insufficiency, postoperative syndromes, anorexia, chemotherapy, and/or tumor progression). In many cases it has negative effects on the quality of life or on the tumor therapy. We investigated if malnutrition can be resolved or corrected by adequate home parenteral nutrition (PN) of pancreatic cancer (PaCa) patients, in cases where dietary advice and oral nutrition supplementation failed to correct the deficiencies. The energy supply via PN was analyzed in patients with PaCa, with focus on the single components in compounded PN. Patients and Methods: We examined a group of six women and eleven men with assured PaCa disease at different tumor stages (mean age: 64 years). Indications for PN were a reduction of body weight of >5 % in three months and/or a long-term reduced nutritional status, reduced results of the bio-electrical impedance analysis (BIA), malassimilation and/or clinical symptoms like severe diarrhoea/vomitus, preventing adequate oral nutrition for weeks. The PN, administered via port-catheter, was initiated while the patients were undergoing chemotherapy. The course of treatment was assessed based on body weight, BIA (Data-Input Nutriguard-M), on laboratory parameters and on personal evaluation of the patients' quality of life. Retrospectively, the patients were subdivided into two groups (Gr): Gr1 (n=10) had a survival period of more than 5, up to more than 37 months, after the start of PN and Gr2 (n=7) had a survival between 1-4 months after start of PN. The calculations of the energy supply were based on the patients' body weight (per kg). Fluid volume, relation of macronutrients and addition of fish oil to PN are described in detail. Results: Gr1: Eight of ten patients already showed an increase of body weight with the initial PN, two patients after dose adaption. This positive impact was also observable on the cellular level by means of BIA results (phase angle, body cell mass (BCM), extracellular mass (ECM), cell content and ECM/BCM Index). Two patients, who were receiving PN for over two or three periods, showed reproducibility of the results; while when PN was interrupted all BIA parameters degraded and they ameliorated with the restart of PN. Gr2: In these patients PN was started in the late stage of the tumor disease in order to allow for a – from the retrospective point of view – last, but ineffective chemotherapy. The data indicated that the weight loss could be retarded, even if the effects on body weight and BIA parameters were found to be less pronounced compared to Gr1. The mean energy supply of both groups, however, was similar: 8,823 kcal (Gr1) per week compared to 9,572 kcal (Gr2) per week. The majority of patients claimed to be quicker and more powerful under PN and to some extent the appetite was enhanced. Conclusion: A timely onset of PN with sufficient calories leads to an improved nutritional status of patients with PaCa disease. PN enhances the quality of life, the administration of tumor therapy without interruption and therefore may lead to a better success of the entire therapy. For late-stage tumor patients (Gr2) the quality of life can, at least, be improved. The success of PN is significantly dependent upon the patients' compliance, which could be achieved through intensive consulting and support of all patients and their relatives.*

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Pancreatic carcinoma (PaCa) is an extremely aggressive malignant tumor characterized by early metastasis and profound cachexia. The five-year survival rate is still less than 5 % (1). Besides the rapid tumor progression, patients suffer from absence of appetite, feeling of satiety, abdominal pain, nausea, emesis and diarrhea, which cause involuntary weight loss to the point of anorexia, tissue wasting and malnutrition (2, 3). In combination these symptoms are named "cancer

anorexia-cachexia syndrome" which is considered as a predictor of mortality and poor therapeutic response. Muscle wasting and functional impairment appear as a result of protein degradation and of reduced protein synthesis. It finally affects the performance status and the quality of life and may lead to an interruption of the tumor therapy (4, 5).

To assess the nutritional status, BIA measurements are accepted as an objective method. The phase angle and the ECM/BCM Index (ratio of extra cellular mass to body cell mass) are suitable parameters to evaluate the nutritional status, taking into account potential disturbing factors, as retention of fluids (edema, ascites) (6).

In the case of threatening malnutrition in pancreatic patients, nutrition advice generally starts with an adequate oral intake of pancreatic enzymes to compensate for the exocrine pancreatic insufficiency. As a second step, energy enrichment of normal diet with high caloric sip feed are included in the nutrition recommendations. In cases of further insufficient oral nutrition with weight loss and worsening BIA parameters, intravenous nutrition can be indicated. Parenteral nutrition (PN) in ambulatory patients needs a port catheter system, cooperation of dieticians, physicians and oncologists as well as some equipment at the patient's residence. As a consequence, PN is generally involved in the care for these patients in late or too late stages of the disease, if at all.

The current study, therefore, addresses the value of supportive PN during chemotherapy in ameliorating the nutritional status of patients with pancreatic cancer. To assess the impact of the nutritional support, changes in body weight, different BIA parameters as well as personal interviews are used.

Patients and Methods

The patient population consisted of six women and eleven men with assured PaCa diseases at different tumor stages (age 48-77 years, mean age 64 years, median age 66 years; mean body mass index (BMI) 22.1 kg/m^2 ±3.3 SD). A dietician assessed the baseline nutritional status in all patients, using the Subjective Global Assessment (SGA) by Detsky *et al*. (7). The median loss of body weight at first consultation was 17.5%. Indications for PN were a reduction of body weight of more than 5% during the three preceding months and/or a long-term reduced nutritional condition, pathological results of the BIA measurements as well as malabsorption and maldigestion, despite pancreatic enzyme substitution and/or high caloric supplementation (energy enrichment to normal diet, high caloric sip feed) and frequently dietary counseling. This conforms to the ESPEN guidelines for PN (8). PN was initiated while the patients were undergoing chemotherapy. It was administered *via* a port-catheter as an overnight home treatment. Changes in nutritional status were assessed by body weight, BIA parameters (Data-Input Nutriguard-M), laboratory parameters (electrolytes, serum albumin, triglycerides, blood glucose, creatinin, liver enzymes) and personal evaluation of the patients' quality of life. BIA measurements were recommended every four weeks, body weight controls every week or every two weeks. Depending on the clinical situation and the progression of the diseases the patients received PN for one or more periods.

Retrospectively, according to the overall survival, the patients were subdivided into two groups (Gr): Gr1 (n=10) with a survival period of more than 5, up to more than 37 months (five patients are still alive) and Gr2 (n=7) with a survival period of 1-4 months after the start of PN. PN was stopped at time of convalescence.

All patients received PN compounding (instead of industrial produced 'all-in-one' bags), based on the patient's body weight, age and the individual needs. The calculations of the energy supply were based on body weight (per kg). Both groups received nearly the same caloric intake *via* PN (med 24 kcal/ kg). Lipids were 34% (Gr1) and 33% (Gr2) of the total energy *via* PN. Vitamins, electrolytes and trace elements were added to PN as recommended by the ESPEN guidelines (8), if indicated ω-3-fatty acids, were added too (in 13 of 17 patients). In Gr1 PN was administered between 4 and 7 days per week (med 5.7 days). In Gr2, four patients got PN daily, two patients six days and one patient five days a week. Daily total PN was indicated if patients were not able to eat orally (less than 500 kcal/day). In general, however, every patient was told to eat orally more or less small amounts every day in addition to PN in order to sustain the gastrointestinal function. Oral supply was not considered in the calculations of this study. According to the DGEM guidelines for PN (9), the oral energy demand was calculated with the formula: 20-25 kcal/kg body weight × activity factor (1.1-1.5). The amount of kcal depended on the age of the patient (20-30 years: 25 kcal/kg body weight; 30-70 years: 22.5 kcal/kg body weight; >70 years: 20 kcal/ kg body weight).

Results

We investigated 17 ambulatory patients with severe pancreatic carcinomas in our unit for internal medicine, in Hamburg/Germany. All of them were willing to receive PN, in most cases additionally to their more or less reduced oral food intake. Nutritional status was assessed by regulatory control of body weight, BIA measurements and personal interviews.

All patients in Gr1 showed an increase of body weight, eight out of ten patients already with the initially calculated PN regimen, two patients after increase of the intravenous caloric support *via* PN (Figures 1a and 2). The positive impact was also observable at the cellular level, by means of BIA parameters (phase angle, body cell mass (BCM), extra cellular mass (ECM), cell content and ECM/BCM Index).

Gr2 included seven patients in which, from a retrospective point of view, the tumor therapy was not able to significantly stop or delay tumor progression. These patients died from tumor disease within 1 to 4 months (median 2 months) after the beginning of the PN. For these patients, Figure 1b and 1d show only marginal changes in body weight and phase angle, if at all, after start of PN (2-4 months before death). Probably, the progressive tumor disease superimposed or covered the potential positive effects of PN as seen on the Gr1 patients. However, PN in these patients replaced the need to eat. Clinical symptoms such as vomiting, nausea, stenoses and problems with fluid intake could be reduced and the patients' quality of life clearly improved.

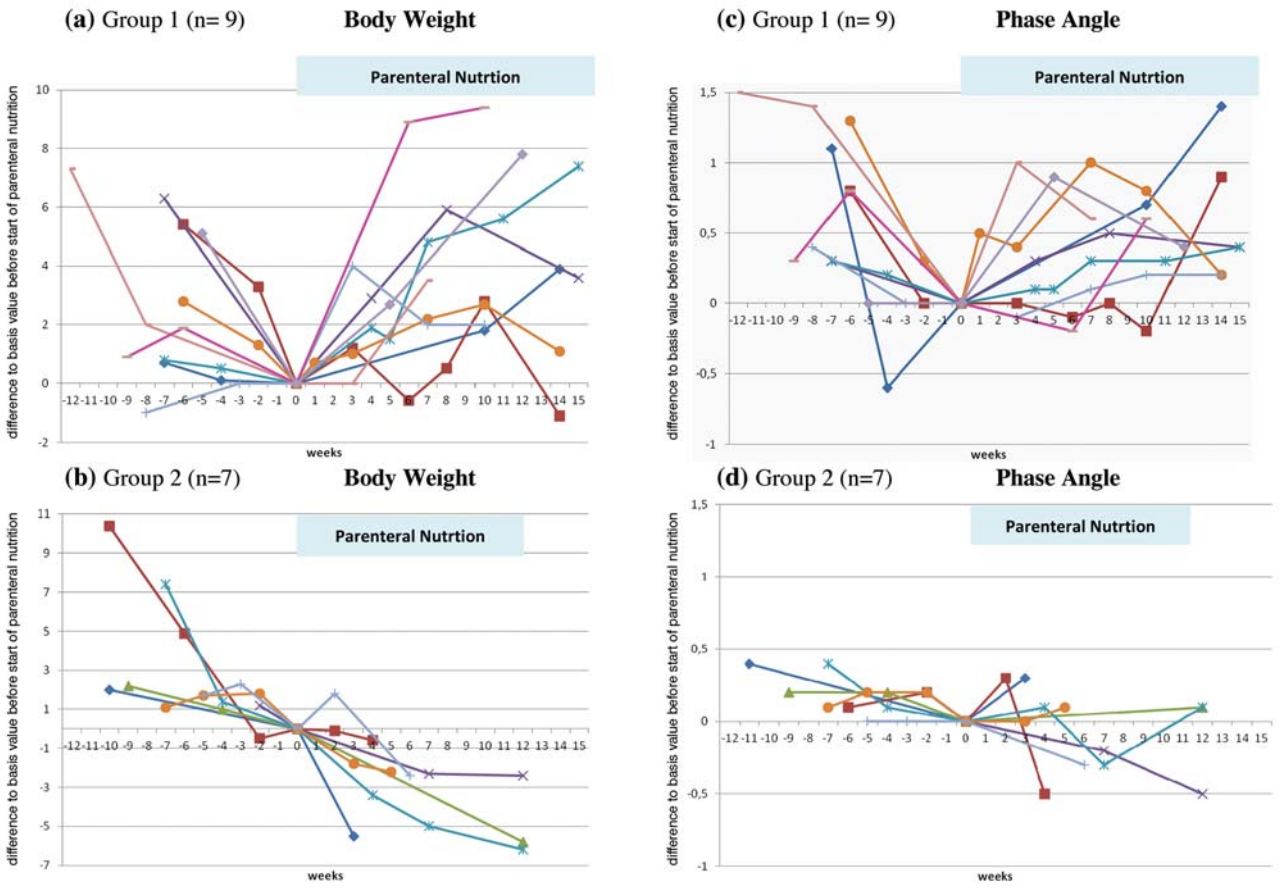


Figure 1. *Difference in the course of body weight and of phase angle before and after the start of PN in 16 patients with PaCa. (a), (c) Gr1- patients with longer survival time. (b), (d): Gr2 - patients with shorter survival time. The decrease of body weight and of phase angle is reversed and an increase in both parameters is obtained in nearly every patient of Gr1 (a, c) whereas the body weight and the phase angle stagnate and decline after a few weeks in most patients of Gr2 (b, d).*

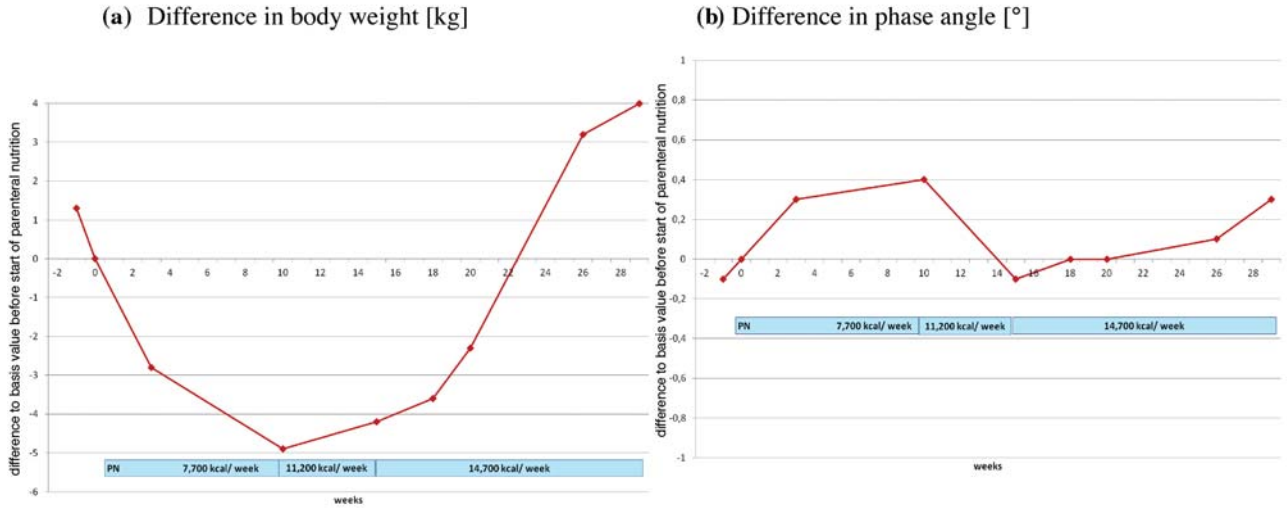


Figure 2. *Difference in the course of body weight and of phase angle before and after the start of PN using the example of one patient (of Gr1). After initial weight loss the patient could clearly increase its body weight under continuation of PN and dose-adjustment. The phase angle could be stabilized. The variations of the phase angle of this patient were between –0.1° and +0.4° after the start of PN (last measured phase angle 4.0°).*

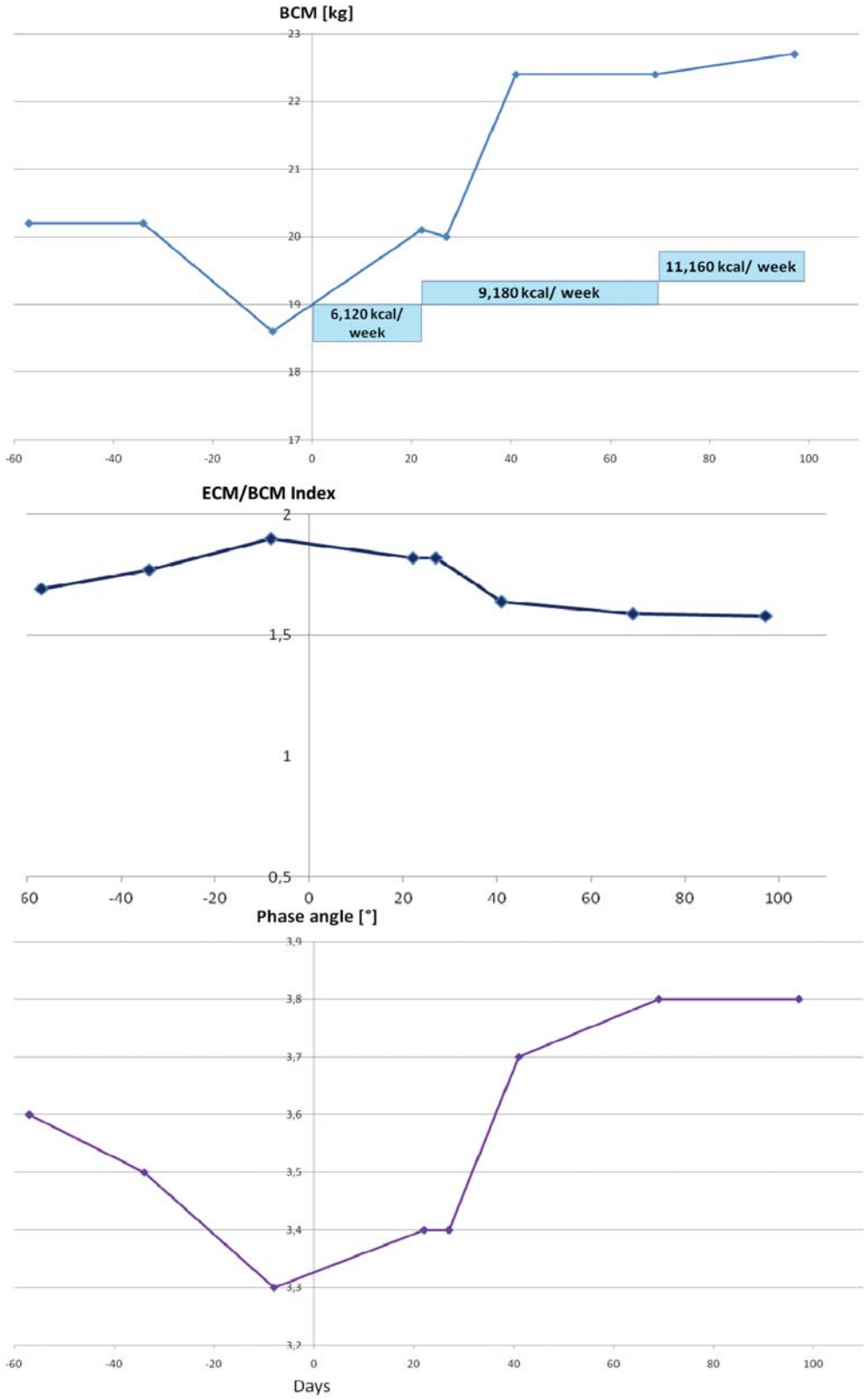


Figure 3. *Changes in BIA parameters using the example of one patient (of Gr1): With an increase in body weight, body cell mass, ECM/BCM Index and phase angle, as well as the cell content (not shown) ameliorated under PN. Calculated energy demand: 11,395 kcal/week (1,632 kcal/day).*

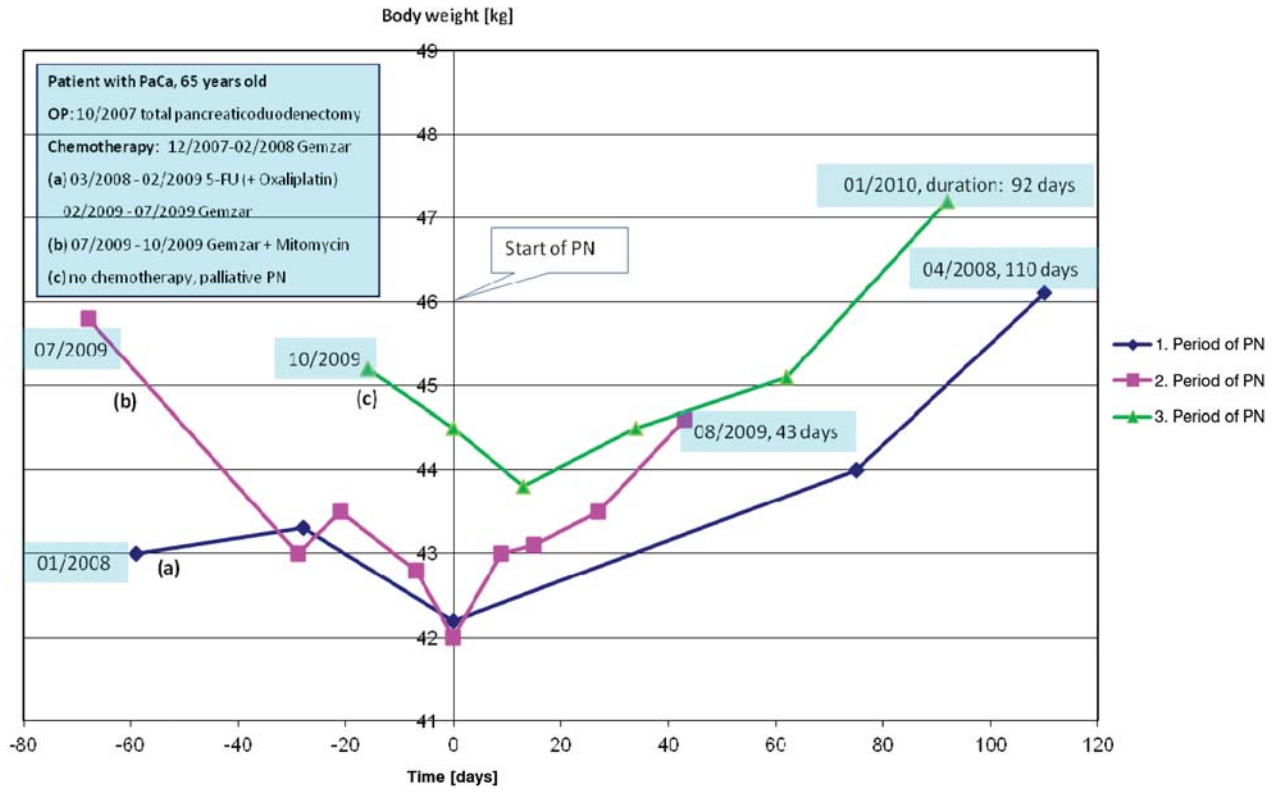


Figure 4. *Reproducibility of increase in body weight under PN using the example of one patient of Gr1. During the tumor therapy, the patient received PN over three periods (see graphs): (a) 1/2008-4/2008: PN in order to start palliative chemotherapy with Gemzar/5-FU. (b) 7/2009-8/2009: PN in order to continue palliative chemotherapy with Gemzar + Mitomycin. (c) 10/2009-1/2010: PN to satisfy the nutritional needs of the patient (oral intake <500 kcal/day). The survival time after the start of PN was three years.*

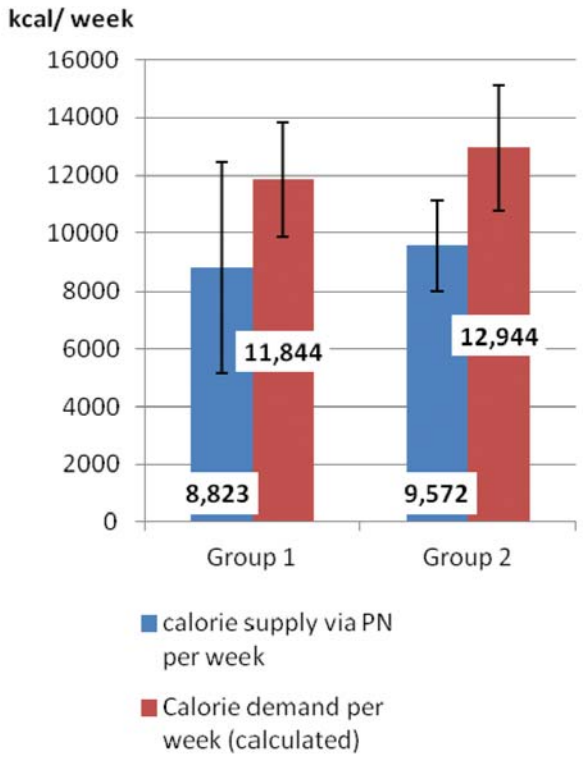
After the first week of PN the patients of Gr1 and Gr2 were asked if they would like to continue PN and if they felt better. All patients (Gr1 and 2) wanted to continue PN, the majority claimed to be quicker and more powerful under PN (15 of 17 patients), and to some extent the appetite was enhanced. The compliance of our patients was guaranteed because of detailed information before the start of PN and continuous assistance during PN for the patients and their relatives. The nutritionist and the nursing service, who were responsible for the home care, communicated with our patients at least once a week.

In Figure 2 one patient of Gr1 is solely shown because of the completely different course of body weight after the start of PN: Only a high-dose adjustment of PN could stop the weight loss and finally led to an increase of body weight. The phase angle of this patient varied during the PN periods and was stabilized at a level of 4.0°.

Figure 3 illustrates in a single patient the positive, dose dependent effects of PN on the BIA parameters BCM, ECM/BCM-Index and phase angle, as a typical example.

Two patients, who were getting PN over two or three months, showed reproducibility of the results: while interruption of PN made the body weight as well as all BIA parameters to degrade and ameliorated with the restart of PN. This is shown in Figure 4 for the body weight in one patient (after adjuvant Gemcitabine therapy after total duodenopancreatectomy (10/2007)). Over a period of two years this patient got three palliative chemotherapeutic regimens (5-FU/FA + Oxaliplatin/ Gemcitabine mono/ Gemcitabine + Mitomycin) and three periods of PN. The 1st period of PN (a) was necessary in order to strengthen the patient for tumor therapy. The 2nd period of PN (b) was initiated in order to resume chemotherapy before the patients' general condition worsened. The 3rd period of PN (c) was started some weeks after the end of the 2nd period of PN without concomitant chemotherapy because of new aggravation of gastrointestinal symptoms, preventing the patient from oral intake of nutrition (less than 500 kcal per day) on the one hand, and on the other hand, as the patient refused further chemotherapy. The survival time after diagnosis of PaCa disease (time of total duodenopancreatectomy) was 39 months; survival time after the 1st period of PN was 35 months.

Concerning the compounding of PN, the mean energy supply of both groups was similar: Gr1 received 8,823 kcal



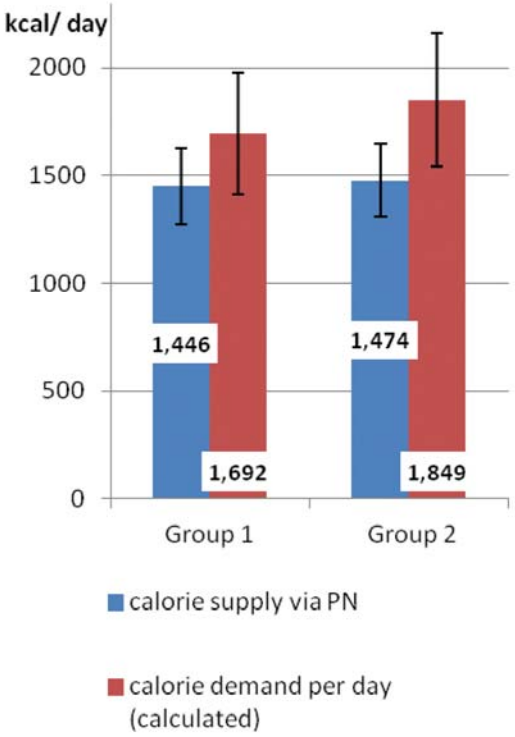


Figure 5. *Mean energy supply in Groups 1 and 2 per day (below) and per week (above) via parenteral nutrition. The calculated mean energy demand for each group is also shown. There is no significant difference (Mean±SD).*

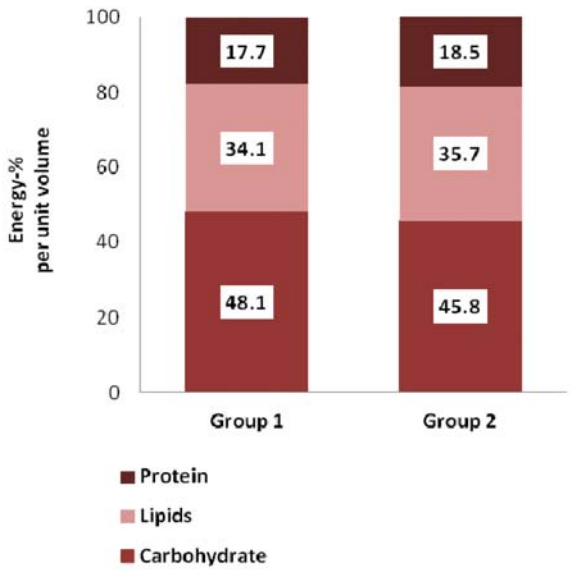


Figure 6. *Energy supply – mean content of macronutrients in one 'compounding bag' of parenteral nutrition (mean±SD).*

per week (1,446 kcal per day), whereas Gr2 received 9,572 kcal per week (1,474 kcal per day) (Figure 5). Per week and per kg body weight, the fluid volume of Gr1's PN was smaller and contained significantly less amino acids and fat. Unlike the weekly energy intake, the daily intake showed no significant difference in the supply of macronutrients. There was also no difference in the relation of macronutrients between the two groups (Figure 6).

In both groups the energy supply *via* PN was less than the mean calculated energy demand (Gr1: -246 kcal, Gr2: -375 kcal), due to the fact that PN was supportive to food intake. Eight out of ten patients in Gr1 and five out of seven in Gr2 also got additive lipid emulsions containing fish oil (ω-3-fatty acids, Omegaven®). In case of treatment with anticoagulants, fish oil was not added to the lipid emulsion at the same time in order to avoid the blood-thinning effect of ω-3-fatty acids. The mean content of ω-3-fatty acids amounted to 3.8 g of the total amount of lipids (±1.5 g) in Gr1 and to 2.3 g (±1.8 g) in Gr2 (no significant difference). This corresponds to 7.2 % (Gr1) or 6.2 % (Gr2) ω-3-fatty acids of the total lipids. Both groups received similar amounts of electrolytes, vitamins (FrekaVit® fat- and water-soluble) and trace elements (Tracitrans Plus®) *via* PN.

Side effects of PN were observed in two patients. One patient had transient minor nausea, and one was dyspneic. However, nausea, also due to chemotherapy, or dyspnoea due to the progress of a concomitant lung disease, had to be discussed. At no time did severe side effects or complications appeared during the PN periods.

Discussion

Pancreatic cancer is known to be associated, in a rather high percentage, with exocrine pancreatic insufficiency, abdominal pains, meteorism, nausea, fatigue, early satiety, taste abnormalities, stenoses and motility disturbances of the upper gastrointestinal tract. These symptoms result for nearly every patient in the so called "cancer anorexia-cachexia syndrome", appearing with decrease of body weight and changes in the body composition accompanied with protein degradation and reduced protein synthesis. This phenomenon is considered as an independent predictor of mortality and of poor therapeutic response (4, 5). The changes in the body composition can be assessed with the BIA method, allowing for the measurement of different parameters like BCM, ECM/BCM Index and the phase angle, a parameter which has some predictive value (6).

However, until today there are only few reports dealing with the therapy of the anorexia-cachexia syndrome in pancreatic cancer, and especially with the question on the potential value of PN. Bauer *et al*. (10) and Shang *et al*. (11) positively demonstrated that in patients with advanced carcinoma the quality of life can be ameliorated by supportive PN. Preoperative PN reduces major complications and mortality in patients with carcinoma of the stomach and of the esophagus (12): in the control group 17 out of 55 patients had major complications, compared to 8 out of 58 in the PN group. The operative mortality rate was 11 out of 55 patients in the control group and 4 out of 48 in the PN group. A study of Mueller *et al*. (13) described ten days preoperative, total PN in patients with different tumor sites. Three groups were formed: group one as a control group, group two receiving PN calories from glucose and amino acids, and group three receiving 50% of the non-protein calories from lipids, and 50% from glucose. Group two showed positive effects, especially in patients with gastric or esophageal cancer. Operative mortality was 4.5%, and in the control group it was 19%. Group three, however, showed again a higher complication and mortality rate, which-according to the authors-might be explained by the high content of lipids in the PN (50 % of non-protein energy). The study of Mueller *et al*. therefore suggests that not only the total energy, but also the composition of PN may play a major role for the benefit of the patient. In accordance with these findings, the ESPEN guidelines (8) emphasize that higher than usual percentage of lipids (≥50% of non-protein energy) may be beneficial only for cancer patients with frank cachexia needing prolonged PN (Grade C).

A recent publication reports on the effects of PN on the BIA parameters, the BMI, BCM/ECM Index and on the phase angle in PaCa patients (14). An improvement of the three BIA parameters was found in 28% of the patients, and improvement of at least one BIA parameter in 84%. However, overall normalization of the BIA parameters was not achieved by PN. 47% of the 32 patients had a temporarily improved phase angle, 41 % showed stabilization and 13% a decrease in spite of PN. The patients were treated with PN until they or their physicians did not see any further benefit from it. The behavior of these parameters during the pre-PN period, as well as the behavior of the body weight were not described. Moreover, the study does not address the issue concerning the time point of first PN application within the course of the tumor disease, the potential effects of dose adjustment or the issue concerning the reproducibility of the effects of PN.

Regarding the study of overall survival, we retrospectively subdivided our patients into two groups: Gr1 with a survival between more than 5 up to more than 37 months (5 patients are still alive) and Gr2 with a survival between 1 to 4 months after the start of PN. The short survival of Gr2 could be explained by the fact that the chemotherapy at that time could not stop the rapid progress of the disease in the patients of this group. Six out of these 7 patients of Gr2 got 2nd-line chemotherapies at the beginning of PN, and one patient of Gr2 only got a 1st-line therapy. This patient died from not treatable, protracted local complications of the tumor disease and not from progressive tumor disease. Consequently, PN was started in the patients of Gr2 during a period of progressive worsening, with at least irreversible tumor disease until the death of the patients. Therefore, in Gr2 stabilization of the body weight or stabilization of other parameters of the nutritional status (with retarded deterioration) might also be interpreted as a positive effect of PN. The positive acceptance of PN by the patients was also generated by these amelioration of *e.g*. vomiting, nausea, stenoses, and of problems with fluid intake. Besides, PN replaced the need to eat.

In contrary to Gr2, in Gr1 PN reversed pre- and/or long-lasting postoperative malnutrition and improved clinical benefit in order to start or continue adjuvant treatment in time or to continue active chemotherapies in advanced tumor stages. In all patients of Gr1 additional PN resulted in an increase of body weight and in an amelioration of the patient's nutritional status and of its quality of life, with the consequence that the chemotherapy could be performed as originally planned and in the case of clinical indication also, subsequent 2nd- and 3rd-line strategies, following the concept of Klapdor *et al*. (15, 16). The results suggest that the longer the patients can keep their nutritional and performance status, they stay stronger for the tumor therapy (15, 16). Especially in the case of two patients with several PN periods, the positive impact of PN could be demonstrated: the improvement of phase angle, BCM and ECM/BCM index as well as the body weight could be reproduced in every PN period.

In addition to the flexible continuation of PN, our data emphasize the necessity to start early with PN supplementation, before the patient is already cachectic. To yield improvement

of nutritional parameters, adaptation of initially planned PN seems to be necessary in some patients, as shown in Figure 3.

Moreover, the composition of PN might play a role, as *e.g.* the amount of lipids within the PN or the addition of special lipids, like ω-3 fatty acids. Most industrial produced 'all-in-one' bags of PN do not contain ω-3 fatty acids. Our patient-individual PN compounding contained low content of ω-3 fatty acids, between 2 and 7 g fish oil, corresponding to 3.9-12% of the total lipids. Fish oil is supposed to ameliorate the immune and the hyper-inflammatory response in severely ill patients (17) and to lessen stress-induced immune-suppression (18). Furthermore, 'all-in-one' bags generally have a slightly higher content of glucose and less amino acids than what our patients receive *via* PN. Today, based on our experience, our 'compounding' for our PaCa patients and their common diabetes problems often contains less glucose (about 40-42 energy-%, corresponding to 50% of non-protein calories), compared to 48 energy -% of glucose in al-in-one bags.

With our relatively small patient population we are not able to draw further conclusions about the composition of PN, *e.g.* a better compatibility for the patient with more or less glucose or lipids, for the positive effects of ω-3 fatty acids or other nutrients that support the immune response. Those detailed aspects shall be investigated in a future study enrolling more patients. At the time of the study, our "compounding" resulted for both groups in a benefit for the patients. With sufficient supply of calories *via* PN, we were able to maintain the general condition of our PaCa patients, suffering inoperable carcinoma and poor prognosis. Especially in patients of the Gr1, we were able to treat the patients by effective chemotherapy as initially planned. That was possibly a decisive factor for the rather long term survival of most of these patients.

Conclusion

The present study demonstrated that PN as a nutritional support has a positive impact on the nutritional status and on the quality of life of patients with PaCa. PN is capable of improving the nutritional parameters and the patients' general condition and, therefore, enables the administration of tumor therapy without interruption and in many cases a success of the entire therapy. For patients with aggressive tumor diseases it is highly recommendable to start PN with sufficient calories early, before the patients are expected to die from starvation prior to tumor progression. For late-stage tumor patients (Gr2), the quality of life can at least be improved. The success of PN is significantly dependent up-on several factors, such as the patients' compliance, the intensive consulting and support of all patients and their relatives by a professional and committed nutritionist, and pon the constructive cooperation between the patient, the nutritionist, the supervising physician and the home care organization.

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