Resection and palliation of pancreatic and periampullary carcinoma
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CHAPTER 12

The effect of a protein and energy, n-3 fatty acid enriched oral supplement
on loss of weight and lean tissue in cancer cachexia:

A randomised double blind trial

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Submitted
Abstract

Background: Conventional nutritional support has limited impact on cachexia. N-3 polyunsaturated fatty acids, especially eicosapentaenoic acid (EPA), may possess anti-cachectic properties. This trial compared a protein and energy dense supplement enriched with n-3 fatty acids and antioxidants (experimental:E) with an isocaloric, isonitrogenous control supplement (C) for their effects on weight, lean body mass (LBM), dietary intake, and quality of life in cachectic patients with advanced pancreatic cancer.

Methods: Patients were asked to consume two cans/day of the E or C supplement (480 mls, 620 kcal, 32 g protein ± 2.2g EPA) for eight weeks in a multicentre, randomised, double-blind trial.

Results: Two hundred patients (95 E; 105 C) were randomised. At baseline patients were losing weight at -3.3 kg/month. Over the eight week study period, patients in both groups stopped losing weight (Δ weight E:-0.26 kg/month versus C:-0.38 kg/month; NS) and lean body mass (Δ LBM E:0.27 kg/month versus C: 0.12 kg/month; NS) to an equal degree (change from baseline E and C; p<0.001). Disease burden appeared greater in the E group and there was non-compliance in both groups. Correlation analyses were undertaken to examine the relationships between changes in nutritional intake and study endpoints. E patients demonstrated significant correlations between their total intake of protein (meals plus supplement) and both weight gain (r=0.52, p<0.001) and increase in LBM (r=0.46, p=0.004). Such correlations were not observed in C patients. Increased plasma EPA levels in the E group were associated with weight and LBM gain (r=0.50, p<0.001; r=0.51, p=0.001), maximal effect was at 1.5-2 cans/day. Weight gain was associated with improved quality of life.

Conclusions: The use of a protein and energy dense oral supplement can attenuate weight loss in cancer cachexia. When enriched with n-3 fatty acids and antioxidants and taken in sufficient quantity, net gain of weight and lean tissue can be achieved.
Cancer cachexia

Introduction
The complex syndrome of cancer cachexia is a major contributor to the morbidity and mortality of patients with advanced malignancy.\textsuperscript{1,2} Causative factors include metabolic alterations which result in hypermetabolism, anorexia leading to reduced food intake, and severe weight loss. Previous studies using conventional nutritional support have suggested there is a partial block to the accretion of lean tissue in cancer patients.\textsuperscript{3} Moreover, oral supplementation trials have failed to show weight gain compared with controls.\textsuperscript{4,5} Such data would tend to confirm the view that although food intake needs to be increased in the cachectic cancer patient gain in lean tissue mass is difficult unless the underlying metabolic abnormalities are downregulated.. The mediators responsible for these changes are thought to be both tumour- and host-derived and include pro-inflammatory cytokines, the neuro-endocrine system and certain tumour-specific factors such as proteolysis inducing factor (PIF).\textsuperscript{6}

Eicosapentaenoic acid (EPA, an n-3 fatty acid) has been shown to have anti-tumour and anti-cachectic effects in the murine MAC-16 colon adenocarcinoma model.\textsuperscript{7} The administration of n-3 fatty acid capsules or high purity EPA capsules has been associated with weight stabilisation in weight-losing patients with advanced pancreatic cancer.\textsuperscript{8,9} However, to improve functional ability and hence quality of life, patients need to regain the lean tissue lost in the cachectic process. Additional protein and energy are required for lean tissue synthesis; hence the rationale for incorporating EPA as part of a high protein, high energy oral supplement. Furthermore, including specific antioxidants may enhance the effect by protecting the unsaturated n-3 fatty acids.\textsuperscript{10} In an open label trial, consumption of two cans per day of such an oral supplement resulted in a median weight gain of 1 kg at 3 weeks and 2 kg at 7 weeks in weight-losing patients with pancreatic cancer. Approximately 95\% of the weight gain was lean body mass (LBM).\textsuperscript{11}

The aim of the present study was to compare the effect of the same n-3 fatty acid and antioxidant enriched supplement (experimental:E) with an isocaloric, isonitrogenous supplement (control:C) on the weight, body composition, dietary intake, and quality of life of weight-losing pancreatic cancer patients. The hypothesis was that n-3 fatty acids would modulate metabolic abnormalities and thus promote anabolism in patients with cachexia. The addition of protein and energy would provide the elements necessary for net gain of weight and lean tissue.

Patients and Methods

Patients
Patients with unresectable pancreatic cancer were selected specifically for this study as these patients usually experience severe weight loss. Patients were included if they had lost more than 5\% of their pre-illness stable weight over the previous six months, had a Karnofsky performance score of 60 or more, and had a life expectancy greater than two months. Patients were excluded if they had undergone surgery, endoscopic stenting, radiotherapy or chemotherapy during the previous four weeks; had other active medical conditions (major gastrointestinal disease, chronic renal failure, uncontrolled diabetes, and human immunodeficiency virus); a body mass index (BMI) greater than 30 kg/m\textsuperscript{2}; or received medication which could profoundly modulate
metabolism or weight, in particular, the use of fish oil or n-3 fatty acid preparations exceeding 200 mg/day EPA or one capsule of fish oil/day within the previous 90 days. At the time of enrollment no patients had gross ascites or oedema, jaundice, pyrexia, severe anaemia, clinical or radiological evidence of infection and none were taking steroids at doses above that for physiological replacement. Pancreatic enzyme supplements were administered if patients had or developed clinical evidence of steatorrhoea. The ethics committees for human research of the participating centres approved the protocol, and written informed consent was obtained from all patients. Procedures followed were in accordance with the International Committee for Harmonization, Good Clinical Practices and the Helsinki Declaration.

Study Design
The study design was an international, multicentre, randomised, double-blind trial and was conducted between January 27, 1999 and January 1, 2001. Stratification was applied for the twelve participating centres and histological confirmation of pancreatic cancer. Patients were randomised at enrolment in permutation blocks using a sequential series of numbered, sealed envelopes containing computer-generated assignments. A copy of the randomization sequence was kept in a locked cabinet apart from the study personnel. Randomization envelopes were opened by a third party who shipped the product directly to the patients’ homes. The patients, investigators and study personnel were blinded to the treatment group allocation. Study products were packaged identically and not easily distinguishable from each other. A sample size of 68 patients was calculated to detect a difference in body weight of 1.6 kg (i.e. an effect size of 0.8) between groups with a significance level of 0.05 and a power of 0.9. Statistical power was based on changes in weight from the pilot study data. Sample size was inflated to 80 patients due to anticipating smaller effect size in other measures (i.e. quality of life). Therefore, 200 patients were required to be enrolled in the study to obtain a minimum of 80 patients, based on an anticipated 60% attrition rate.

Patients were asked to consume two cans per day of either a specially designed n-3 fatty acid and antioxidant enriched oral supplement (E) or the identical supplement without n-3 fatty acids and enhanced antioxidants (C) for an eight week period. Compliance was evaluated after the blind was broken using the supplement consumption records kept daily by patients and measurement of plasma phospholipid EPA levels.

Both oral supplements were provided by Ross Products Division, Abbott Laboratories, Columbus, Ohio, USA and were ready-to-use, energy dense, high protein, low-fat formulations intended to act as a supplement to the patient’s usual diet. Each 237 mL can provided 310 kcal.

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Cancer cachexia

16 g protein, 6 g fat, with or without 1.1 g of the n-3 fatty acid, eicosapentaenoic acid (EPA), and enriched antioxidants as described by Barber et al. Patients were assessed for weight, body composition, dietary intake and quality of life at baseline, four and eight weeks.

**Weight and body composition**
At the initial assessment, height, pre-illness stable weight and duration of weight loss were self-reported. Patients were weighed without shoes and wearing light clothing on spring balance scales (Tanita Solar Powered Scale Model 1618, Tanita, Uxbridge, Middlesex, UK). The same scales were used for consecutive visits.

Body composition was assessed using a Xitron Hydra multiple frequency bioelectrical impedance analyser (Xitron Technologies, San Diego, California, USA) as previously described. Resistance was measured at 5 KHz and 200 KHz. Total body water (TBW) was derived using equations validated in surgical patients. Lean body mass was calculated from TBW assuming that lean tissue contains 73% water. Pre-illness lean body mass was estimated from pre-illness body weight using predictive equations based on height and weight for TBW.

**Dietary intake**
Three-day diet diaries completed prior to assessments at baseline (week 0), and weeks four and eight were used to assess the patients' dietary intake. Diet diaries have been shown to reflect usual dietary intake. One weekend day and two week days were used to account for potential day-of-the-week effects on dietary intake. A diettian instructed patients on how to record food and beverage intake. Mean total energy and macronutrient intakes were calculated using country-specific computerised dietary analysis packages. Patients also were asked to record the number of cans of supplement, or parts thereof, consumed each day. Total dietary intake was calculated by adding oral supplement consumption to spontaneous food intake.

**Plasma fatty acid analysis**
Analysis of EPA in patients' plasma phospholipids before study commencement and at four and eight weeks was performed by gas chromatography as previously described. A plasma EPA level of 1.6% is approximately the 90th percentile in free-living unsupplemented pancreatic cancer patients, and this was used as the upper limit of the normal range.

**Quality of Life Assessment**
Quality of life was measured at baseline, four and eight weeks using two self-administered questionnaires, EuroQol EQ-5D, a generic quality of life measure that provides a single index score (EQ-5D index) and the respondent's assessment of their overall health state (EQ-5D vs). and EORTC QLQ-C30, a multidimensional cancer specific measure that includes a global health status and quality of life scale, function and symptom scales. The physical function and global
health status components alone were used in the statistical analysis. Karnofsky Performance Score was also documented.

Statistical analysis
The primary analysis was conducted on an intention-to-treat (ITT) basis, therefore available data from all patients entered into the study were used. Study groups were assessed for comparability at study entry. For continuous variables, changes were calculated at week four minus baseline and week eight minus baseline. Continuous variables were analysed using a two sample t-test or Wilcoxon Rank Sum test as appropriate. Categorical variables were analysed using a Chi-square Test or Fishers Exact Test as appropriate. Post-hoc within group analyses were conducted to examine the changes from week four to baseline and week eight to baseline using the paired t test or Wilcoxon Signed Rank test as appropriate. Correlation product moment analyses were performed, within group, on a subset of the data variables. The relationship of supplement consumption, plasma EPA and dietary intake with the study endpoints was assessed separately for the experimental and control groups using the Pearson correlation coefficient. The Wilcoxon Signed Rank test was used to examine whether there was a relationship between the amount of experimental product consumed and specific outcomes. Patient survival was estimated from the date of study enrolment by the Kaplan-Meier method. All results were considered to be statistically significant if the p value was less than 0.05.

Results
Two hundred weight-losing patients (95E and 105C) with unresectable pancreatic cancer were enrolled and randomised in the study. Patient characteristics at enrolment and baseline are shown in Table 1. The two groups were comparable on all variables. However, there was a trend towards a greater proportion of stage IV disease patients in the experimental group (52%) than in the control group (41%). In addition, mean time elapsed between diagnosis and study entry in these stage IV patients was 250 (SEM ± 54) days in the experimental group, which tended to be longer than the C group, 153 (SEM ± 29) days; p=NS. At baseline, patients had been losing approximately -3.3 kg/month (2.2 kg of which was estimated to be lean body mass) and had lost 17% of their pre-illness stable weight. Approximately one-third of patients in each group (32% E, 28% C) were using pancreatic enzyme supplements for the treatment of steatorrhoea/malabsorption at the start of the study. Patients were well matched for Karnofsky Performance Score and quality of life characteristics (Table 1). In general the values reflect a debilitated older group of patients with significant impairment of physical function and global health status. Fifteen patients withdrew between enrolment and baseline. Thus, 185 patients (88E and 97C) were assessed at baseline. Thereafter, 148 patients were assessed at four weeks (70E and 78C) and 110 at eight weeks (50E and 60C) (Figure 1). The reasons for sample attrition between enrolment and the end of the eight week study period are also shown in Figure 1. Both the experimental and control oral supplements were well tolerated. There were no significant differences in the number of patients who experienced adverse events or serious adverse events
between the experimental and control groups. None of the serious adverse events were considered to be due to the oral supplements, rather the investigators concluded that they were due to disease progression.

**Table 1.** Enrolment and baseline characteristics of 200 weight-losing patients with unresectable pancreatic cancer

<table>
<thead>
<tr>
<th>Enrolment characteristics</th>
<th>Experimental [n=95]</th>
<th>Control [n=105]</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M : F)</td>
<td>54 : 41</td>
<td>56 : 49</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 (1)</td>
<td>68 (1)</td>
<td>NS</td>
</tr>
<tr>
<td>Histological proof of diagnosis</td>
<td>55 (58%)</td>
<td>61 (58%)</td>
<td>NS</td>
</tr>
<tr>
<td>Stage of Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>31 (33%)</td>
<td>40 (39%)</td>
<td>NS</td>
</tr>
<tr>
<td>III</td>
<td>14 (15%)</td>
<td>21 (20%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>49 (52%)</td>
<td>42 (41%)</td>
<td></td>
</tr>
<tr>
<td>Usual weight (kg)</td>
<td>72.7 (1.2)</td>
<td>74.7 (1.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Pancreatic enzyme supplementation</td>
<td>30 (32%)</td>
<td>29 (28%)</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline characteristics (0 weeks)</td>
<td>Experimental</td>
<td>Control</td>
<td>p Value</td>
</tr>
<tr>
<td>Weight at baseline (kg)</td>
<td>60.3 (1.1) [n=88]</td>
<td>61.4 (1.2) [n=97]</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of weight loss (weeks)</td>
<td>26.0 (2.1)</td>
<td>25.3 (2.0) [n=96]</td>
<td>NS</td>
</tr>
<tr>
<td>Rate of weight loss (kg/4 weeks)</td>
<td>2.9 (0.2)</td>
<td>3.2 (0.3) [n=96]</td>
<td>NS</td>
</tr>
<tr>
<td>% weight loss from usual weight</td>
<td>17.9 (0.9)</td>
<td>17.1 (0.8) [n=97]</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>21.8 (0.4) [n=88]</td>
<td>22.0 (0.4) [n=97]</td>
<td>NS</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>43.3 (0.9) [n=80]</td>
<td>43.4 (0.9) [n=91]</td>
<td>NS</td>
</tr>
<tr>
<td>Karnofsky Performance Score</td>
<td>74.9 (1.2)</td>
<td>73.9 (1.0) [n=98]</td>
<td>NS</td>
</tr>
<tr>
<td>EQ-5D index</td>
<td>0.62 (0.03) [n=86]</td>
<td>0.62 (0.03) [n=91]</td>
<td>NS</td>
</tr>
<tr>
<td>EQ-5D v5s</td>
<td>52.3 (2.2) [n=87]</td>
<td>57.2 (1.9) [n=96]</td>
<td>NS</td>
</tr>
<tr>
<td>EORTC QLQ-C30 Global Health Status</td>
<td>48.8 (2.2) [n=86]</td>
<td>53.1 (2.2) [n=95]</td>
<td>NS</td>
</tr>
<tr>
<td>EORTC QLQ-C30 Physical Function</td>
<td>64.1 (2.2) [n=87]</td>
<td>67.7 (2.3) [n=96]</td>
<td>NS</td>
</tr>
<tr>
<td>Meal intake (kcal/d)</td>
<td>1504 (54) [n=84]</td>
<td>1613 (51) [n=95]</td>
<td>NS</td>
</tr>
<tr>
<td>Meal intake (g prot/d)</td>
<td>60 (2) [n=84]</td>
<td>63 (2) [n=95]</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean (SEM) or n [%].
Oral supplement consumption and dietary intake are shown in Table 2. On average, patients in both groups consumed less than the recommended dose (1.5-2.0 cans/day). There was no significant difference between the groups for change in total dietary intake over the eight-week period. However, there was a significant increase in total (meals plus supplement) dietary intake from baseline for those patients in the experimental group completing eight weeks (224 kcal/day; p=0.001; and 15 g protein/day; p<0.001). In contrast, protein intake increased significantly but there was only a trend towards an increase in energy intake for those patients completing eight weeks in the control group, (6 g protein/day; p=0.036 and 68 kcal/day; p=0.098).

Based on plasma phospholipid EPA levels, there was evidence of deviation from protocol in both the control and experimental groups. There were patients in both groups with high levels of EPA at baseline (14%), suggesting possible undisclosed prior supplementation with n-3 fatty acids. In addition, 18% of control patients had high EPA levels at weeks four and/or eight. Conversely, 26% of experimental patients had reported at least some intake of the experimental supplement and yet had little or no elevation of EPA (i.e. ≤1.6%) in the plasma at either weeks four or eight.
Table 2. Change in oral nutritional supplement intake, meal intake and total dietary intake for the experimental and control groups over the 8 week study period

<table>
<thead>
<tr>
<th></th>
<th>Experimental</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppl. intake (cans/d)</td>
<td>1.44 (0.1) [n=44]</td>
<td>1.43 (0.06) [n=56]*</td>
</tr>
<tr>
<td>Suppl. intake (kcal/d)</td>
<td>448 (23) [n=44]</td>
<td>444 (19) [n=56]*</td>
</tr>
<tr>
<td>Suppl. intake (g pro/d)</td>
<td>23 (1.2) [n=44]</td>
<td>23 (1.0) [n=56]*</td>
</tr>
<tr>
<td>Meal intake (kcal/d)</td>
<td>-241 (65) [n=45] *</td>
<td>-376 (65) [n=56]* *</td>
</tr>
<tr>
<td>Meal intake (g pro/d)</td>
<td>-9 (3.2) [n=45] *</td>
<td>-17 (3.2) [n=56]* *</td>
</tr>
<tr>
<td>Total intake (kcal/d)</td>
<td>224 (68) [n=44] *</td>
<td>68 (64) [n=56]* *</td>
</tr>
<tr>
<td>Total intake (g pro/d)</td>
<td>15 (3.5) [n=44] *</td>
<td>6 (3.3) [n=56]* *</td>
</tr>
</tbody>
</table>

* Experimental vs. Control p=NS
Change from baseline to 8 weeks \* p<0.05, \* p<0.001, \* p=NS
Values are mean (SEM). pro = protein; d = day; suppl = supplement

Observed changes in weight and LBM after four and eight weeks of oral supplementation are shown in Figures 2 and 3. Over the eight week study period, weight (Δ weight E: -0.25 kg/month versus C: -0.37 kg/month) and LBM (Δ LBM E: 0.27 kg/month versus C: 0.12 kg/month) were stable and not significantly different between the groups. When compared with the rates of loss at baseline there was a significant attenuation of weight and LBM loss in both study groups at 4 and 8 weeks (p<0.001 for all within group comparisons). There were no significant differences in prestudy rates of loss of weight and LBM between patients who did or did not complete the 8-week study period. With respect to other indices over the trial period, there were no significant differences between groups in performance scores or any of the quality of life measures.

Correlation analyses were undertaken to assess the relationship between study variables and outcomes over the eight week study period. There was a significant, positive correlation in the experimental group between daily total protein intake (food plus supplement) per day and increases in both body weight (r=0.52, p<0.001) (Figure 4A) and LBM (r=0.46, p=0.004) (Figure 4C). In contrast, there were no such correlations in the control group (Figures 4B and 4D). Maximal gain in weight and LBM was observed with an intake of 1.5-2 cans per day (Figure 5) in the experimental group. There was a significant, positive correlation between week eight plasma EPA and increases in weight (r=0.50; p<0.001) and LBM (r=0.51, p=0.001) (Figure 6) in the experimental group.

Although there were no significant differences between the two groups, the experimental supplement intake correlated positively with weight (r=0.50, p<0.001), LBM (r=0.33, p=0.036), quality of life as measured by EQ-5D index (r=0.37, p=0.01), while the quantity of control supplement showed no such correlations (r=0.16, p=0.23; r=-0.09, p=0.50; r=0.04, p=0.77). In addition, weight gain in the experimental supplement group correlated significantly with EQ-
Figure 2. Effect of protein and calorie dense oral supplements ± n-3 fatty acids and antioxidants on weight change in patients with pancreatic cancer cachexia.

Figure 3. Effect of protein and calorie dense oral supplements ± n-3 fatty acids and antioxidants on change in lean body mass in patients with pancreatic cancer cachexia.

5D_{index} (r=0.46, p=0.001), EQ-5D_{vas} (r=0.38, p=0.01), and the physical functioning domain of EORTC QLQ-C-30 (r=0.33, p=0.022). There were no such statistically significant correlations observed within the control group.

The median duration of survival from study enrolment for all patients was 130 days and there was no significant difference between the treatment groups (E: 142 days, C: 128 days).
Discussion
When compared with rates of weight loss at baseline the present study has shown that protein and energy dense oral supplements can attenuate weight loss in cancer cachexia. Furthermore, based on correlation analyses the study has demonstrated that when such oral supplements are enriched with n-3 fatty acids and antioxidants and are taken in sufficient quantity, net gain of weight and lean tissue can be achieved.

Figure 4. Effect of a protein and calorie dense oral supplement with (Δ) or without (▲) n-3 fatty acids and antioxidants on weight (A and B) and lean body mass (C and D) of patients with pancreatic cancer cachexia after 8 weeks of supplementation.

A

\[ n=45, \ r=0.52, \ p=0.001 \]

B

\[ n=55, \ r=0.24, \ p=0.08 \]
Patients at baseline (n=185) had lost on average 17% of their pre-illness weight and were actively losing weight at a rate of approximately -3.3 kg/month. Patients completing the 8 week study (n=110) had become relatively weight stable thereby demonstrating a marked attenuation of rate of weight loss whether or not their supplement contained enhanced levels of EPA and antioxidants (see Figure 2). It could be argued that the most cachectic patients had either died or withdrawn by week 8 thus leaving the patients who were more weight stable. However, the baseline rate of weight loss was similar in patients who did or did not reach week 8 thereby suggesting that this was not the case.
Baseline intakes of energy (1500-1600 kcal/day) and protein (60-65 g/day) were insufficient to allow patients to maintain body weight. This may reflect the increased basal requirements of cachectic cancer patients. During the study, patients in both groups on average consumed 1.3-1.4 cans of oral supplement per day (equivalent to 420 kcal and 21g/day). Although, spontaneous meal intake was reduced, it was not completely replaced by the supplement and the net gain in total energy and protein intake was sufficient to allow the patients to achieve overall weight stability (Figure 2). Interestingly, there was a trend for patients receiving the experimental supplement to have less suppression of meal intake and a greater overall energy and protein intake. This might have contributed to the correlations between experimental supplement intake and greater weight, lean body mass and quality of life, whereas there were no such correlations in the control group.
Patients had been stratified for centre and histological proof of diagnosis, but not for stage of disease. Baseline characteristics revealed that there tended to be more stage IV patients randomised to the experimental group. The time from diagnosis to study entry also tended to be longer in those with stage IV disease in the experimental group compared with the control group. Therefore there may have been greater disease burden in the experimental group. This could have influenced the results observed on group comparison since the patients with more advanced disease might have been less able to take in normal food, and consume and respond to the intervention. In addition, the combined effect of some patients in both groups failing to declare n-3 fatty acid supplement use at baseline and some patients in the control group supplementing themselves with an alternative source of n-3 fatty acids during the trial may have further dampened any treatment differences that could be observed between groups. A post hoc series of correlation analyses based on the ITT population was therefore undertaken to investigate the relationship between documented supplement and dietary intake, plasma EPA and study endpoints. These analyses demonstrated a significant, positive correlation between body weight and LBM and total protein intake (from food plus supplement) in the group receiving the experimental product (Figures 4A and 4C). There was, however, no such relationship in the control group (Figures 4B and 4D). Such findings are in agreement with previous observations suggesting that during conventional nutritional support there is a partial block to the accretion of lean tissue in cachectic cancer patients. The data also suggests that this partial block may be overcome by the addition of n-3 fatty acids and antioxidants. In those randomised to the experimental group, there was a significant, positive correlation between week eight plasma EPA and an increase in weight. Moreover, plasma EPA levels correlated strongly with changes in LBM (Figure 6) thereby suggesting a dose-response relationship between EPA and the accretion of lean tissue. These findings are consistent with the administration of EPA leading to the preservation of lean tissue in the MAC-16 murine model of cachexia. They are also consistent with the ability of EPA to down-regulate the increased expression of the key regulatory components of the ubiquitin-proteasome proteolytic pathway, considered to be the major mechanism of protein loss in cachexia. EPA attenuates protein degradation induced by a tumour factor (proteolysis-inducing factor) a known mediator of cachexia, previously isolated from the urine of weight-losing pancreatic cancer patients. EPA may also have acted via downregulation of the production of catabolic pro-inflammatory cytokines. In the present study weight gain and net accretion of lean tissue were observed in the experimental group in those patients taking approximately 1.5-2 cans of the n-3 fatty acid enriched supplement (Figure 5) thereby reproducing the results of the pilot study where median can consumption was 1.9 cans/day. However average supplement intake in the present study was lower (1.3-1.4 cans/day) than the pilot study. At this level of supplementation there was no advantage for the supplement enriched with n-3 fatty acids and antioxidants although an attenuation of weight loss was observed (Figure 2). This observation suggests that it is vital to achieve good compliance if the potential benefits of the specialised supplement are to be realised.
One explanation for the difference in compliance between the pilot study and the present randomised controlled trial would be different levels of patient motivation for supplement consumption based on the patient’s perception of potential benefit in the context of a single arm study versus a randomised trial. Further studies focused on methods of optimising compliance (e.g., information sheets) both within and outwith the context of randomised studies would be useful. Moreover, although compliance could be checked for the experimental supplement using plasma EPA levels, it would be useful for further studies to have a tracer (e.g., deuterated water) in both the control and experimental oral supplements.

Clearly the aim of nutritional and metabolic support in cancer cachexia is not only to restore normal body composition but also to improve function and quality of life. Previous studies using the appetite stimulant medroxyprogesterone acetate have demonstrated a significant attenuation of weight loss in cachectic cancer patients. However, this did not translate into an improved quality of life (as assessed by the EORTC QLQ C-30). One explanation was that the main tissue preserved was fat rather than lean body mass. In the present study the lean body mass of patients who took the experimental supplement at the recommended dose (1.5–2 cans/day) increased (Figure 5) and intake of the experimental supplement was correlated positively with improved LBM and EQ-5D\textsubscript{index}. Moreover, weight gain in the experimental group was significantly associated with higher scores in the physical function domain of the EORTC QLQ-C30, EQ-5D\textsubscript{index} and EQ-5D\textsubscript{vas}. These significant correlations were not observed in the control group. It cannot be determined whether the relationship between improved nutritional status and better quality of life is a cause and effect relationship. Nonetheless, these findings are some of the first to link improved nutritional status (lean body mass) with quality of life in patients with advanced cancer.

Previous studies both in vitro and in vivo have suggested that n-3 fatty acids may have potential as anti-neoplastic therapy. Tumour response was not evaluated in the present study. However, there was no difference in the survival duration between control and experimental arms. The median survival of all patients from the time of enrolment was 130 days which is similar to that reported in recent randomised trials of chemotherapy or novel anti-neoplastic agents. These studies, however, did not contain a best supportive care arm. The results of the present study imply that a reassessment of this policy is required.

In summary, patients with cancer cachexia are treatable. Provision of an energy and protein dense oral supplement can stabilise weight loss. The previous pilot study and the present randomised controlled trial also suggest that if taken in sufficient quantity, addition of n-3 fatty acids and antioxidants may lead to an increase in not only body weight but also lean body mass and to some domains of quality of life assessment measures. Further studies are required to optimise compliance and explore fully the potential for such intervention to influence patients’ physical function, quality of life and overall health status.
References


