

# 1<sup>st</sup> Abbott International Conference for Cancer Nutrition Therapy

## Proceedings Booklet



# The 1st Abbott International Conference for Cancer Nutrition Therapy

April 12-14, 2010

The 1st Abbott International Conference for Cancer Nutrition Therapy was held April 12-14, 2010, in Istanbul, Turkey. Kenneth C. H. Fearon, MD, FRCS (GLAS), FRCS (ED), FRCS (ENG), Professor of Surgical Oncology, University of Edinburgh, Scotland, served as Chairman of the Conference. Anne Coble Voss, PhD, RD, Research Scientist with Abbott Nutrition, Columbus, OH, USA, served as moderator. The day-and-a-half conference included 12 speakers from 10 countries with experience in surgical oncology, radiation oncology, medical oncology, gastroenterology, and nutrition.

## **Highlights:**

- Conference Objectives
- Defining Cancer Cachexia
- The Role of Nutrition Therapy in Cancer
- Clinical Practice from Around the World-Patient Centered Outcomes
- Bridging the Gap From Clinical Research to Practice-Clinical Practice Guidelines
- Investigator Research
- Where do we go from here? – The future of cancer cachexia study design

## **Conference Objectives and Program**

The objective of the Conference was to bring together professionals from multi-disciplinary fields involving nutrition and cancer in order to share knowledge (best practices) and promote discussion on how to bridge the gap between science and clinical practice. The conference included talks on the problem of cancer cachexia, the role of nutrition therapy in cancer, clinical practice from around the world as it relates to patient centered outcomes, the role of practice guidelines in bridging the gap from clinical research to practice, clinical study results, case studies, and a panel discussion on the future of cachexia study design.

# Defining Cancer Cachexia

## Definition and Classification of Cancer Cachexia

*Kenneth C. H. Fearon, MD, FRCS (GLAS), FRCS (ED), RFCS (ENG)*

*Professor*

*Department of Surgical Oncology, University of Edinburgh, Scotland*

The purpose of this presentation was to introduce the development of the definition and classification of cancer cachexia. Cancer cachexia is a severe wasting syndrome commonly seen in patients with cancer. Observed as early as 300 BC, Hippocrates described this condition as “the shoulders, clavicles, chest and thighs melt away.” Patients demonstrating these conditions were close to death.

To date, more than 4500 articles on cancer cachexia are found in Pubmed. However, there is no agreed definition of cancer cachexia. Most studies simply use a cutoff of percentage weight loss to define cachexia. Recently, a generic definition defines cachexia as weight loss of at least 5% in 12 months or less plus 3 of 5 conditions including decreased muscle strength, fatigue, anorexia, low fat-free mass index, and abnormal biochemistry (increased inflammatory markers, anemia and/or low serum albumin)<sup>1</sup>. However, this cachexia definition is used in patients with any disease condition; it is not specific for patients with cancer given the fact that anorexia and fatigue may not exist in cancer cachectic patients<sup>2</sup>.

An evidence-based mathematical model was developed and validated in patients with advanced pancreatic cancer<sup>3</sup>. The definition was based on three indices: weight loss  $\geq$  10%,  $<1500$  kcals/day, and C-reactive protein  $> 10$  mg/L<sup>3</sup>. Pancreatic cancer patients who exhibited these symptoms demonstrated significantly deteriorated functional status and prognosis. However, generalization of this model to all cancer patients requires further validation.

Recently, an international consensus was developed by a group of physicians and scientists supported by the European Union (EU) using the Delphi process, which defines cancer cachexia as “*a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism.*” Preservation/restoration of muscle mass and function are addressed during treatment of cancer cachexia.

Based on the definition, diagnosis of cancer cachexia includes involuntary weight loss >5% over last 6 months (in absence of simple starvation), or weight loss >2% with BMI <20, or weight loss >2% with an appendicular skeletal muscle index consistent with sarcopenia (males <7.26 kg/m<sup>2</sup>; females <5.45 kg/m<sup>2</sup>). With fluid retention, a large tumor mass or overweight/obesity, a direct measure of muscularity is particularly recommended. It is noted that high BMI (overweight and obese) is prevalent in patients with cancer, who are in fact sarcopenic<sup>4</sup>. In patients with pancreatic cancer, age and the presence of sarcopenia and overweight/obesity are independent prognostic factors<sup>4</sup>. The interaction of high fat mass and sarcopenia may be a result of insulin resistance and requires attention when providing nutrition support for these patients.

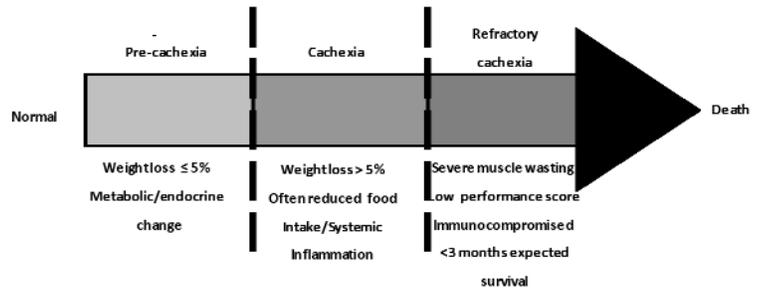


Figure 0: Phases of cancer cachexia

Cancer cachexia can be described as progressing along a continuum of 3 phases (Figure 0) of increasing severity before resulting in death. The first phase is precachexia where weight loss may be ≤ 5% and some metabolic and endocrine changes may be occurring. The second phase is cachexia with weight loss > 5% often with reduced food intake and systemic inflammation. The third phase is refractory cachexia where there is severe muscle wasting, low performance scores, immune compromise, and expected survival of < 3 months. The severity of cachexia can be classified according to the depletion of protein and energy stores (cumulative deficit from the past or low starting point, as defined by current BMI <20) compounded by the degree of ongoing loss (current negative energy and protein balance as defined by % weight loss: 5%, 10%, 15% or more).

|                     | Past  | Present  | Future   |
|---------------------|---|--|--|
| <b>S</b> TORES      | Stable Weight <input type="checkbox"/>  | Weight <input type="checkbox"/><br>Weight Loss <input type="checkbox"/><br>Duration WL <input type="checkbox"/><br>BMI <input type="checkbox"/><br>Active Weight Loss Y / N  | <ul style="list-style-type: none"> <li>For Prevention (Pre-cachexia) Y / N <input type="checkbox"/></li> <li>For Repletion (BMI &lt; 20 Weight Loss &gt; 10%) Y / N <input type="checkbox"/></li> </ul>  |
| <b>I</b> NTAKE      |   | Loss of Appetite Y / N<br>Early Satiety Y / N<br>Loss of Intake <input type="checkbox"/><br>Secondary anorexia :<br><ul style="list-style-type: none"> <li>Pain Y / N</li> <li>Depression Y / N</li> <li>Constipation Y / N</li> <li>Obstruction Y / N</li> </ul>  | Requires <input type="checkbox"/> Intake<br><ul style="list-style-type: none"> <li>Target Intake <input type="checkbox"/></li> </ul> Treat primary anorexia <input type="checkbox"/><br>Treat secondary anorexia <input type="checkbox"/>  |
| <b>P</b> ERFORMANCE |   | Performance Score (0-4) <input type="checkbox"/>   | Activity :<br><ul style="list-style-type: none"> <li>ADL's Y / N</li> <li>Ever else Y / N</li> </ul>   |
| <b>P</b> OTENTIAL   | Cancer Type<br>Cancer Stage (I -IV)<br>Goals of Therapy:<br><ul style="list-style-type: none"> <li>Cure Y / N</li> <li>Control Y / N</li> <li>Palliation Y / N</li> </ul> Expectations:<br>_appetite Y / N<br>_Intake Y / N<br>_Weight Y / N<br>_Activity Y / N | Bloods:<br><ul style="list-style-type: none"> <li>C-reactive Protein <input type="checkbox"/></li> <li>Albumin <input type="checkbox"/></li> <li>Haemoglobin <input type="checkbox"/></li> </ul> Therapy:<br><ul style="list-style-type: none"> <li>Chemotherapy Y / N</li> <li>Radiotherapy Y / N</li> <li>Opiates Y / N</li> </ul> | Likely Course of Cancer (3m) :<br><ul style="list-style-type: none"> <li>Progress Y / N</li> <li>Stable Y / N</li> <li>Regress Y / N</li> </ul> Survival expectation :<br><ul style="list-style-type: none"> <li>&lt;3m Y / N</li> <li>3-6m Y / N</li> <li>&gt;6m Y / N</li> </ul> |

Figure 1: Cachexia Assessment (SIPP) tool developed by EPCRC

Assessment of nutritional status is recommended for all cancer patients. Four domains are to be considered, which can be guided using Cachexia Assessment (SIPP) tool developed by European Palliative Care Research Collaborative (EPCRC) (Figure 1).

1. Anorexia/reduced food intake
2. Catabolic drivers (e.g., severity of inflammation)
3. Muscle mass and strength (this can be evaluated based on CT scan image as a part of clinical examination)
4. Impact of cachexia (such as impact on functional status and Karnofsky score)

It was suggested that treatment of cancer-associated weight loss should start with treatment of secondary anorexia and dietary/exercise counseling. Oral nutritional supplement and artificial nutrition and drugs may be considered as needed.

# Molecular Targeting Immunonutrition: a New Light on Cancer Patients

Chikao Miki, MD, PhD

Clinical Professor of Surgery

Department of Gastrointestinal and Pediatric Surgery, Mie University Hospital, Japan

Targets for anti-cancer treatment involve two factors: tumor-related factors and host-related factors. Frequently, treatments, such as chemotherapy, radiation or surgery, are associated with disturbance of host physiological homeostasis and increase of the host's co-morbidity. Unfortunately, no specific treatments are currently available to normalize host-tumor interaction, which is characterized by immune-suppression and systemic deterioration of nutritional status, i.e., cancer cachexia. Immunonutrition may be a novel means in tumor treatment.

During cachexia, the body undergoes systemic inflammation, associated with weakness and loss of weight, fat and muscle mass. Large amounts of cytokines, such as tumor necrosis factor- $\alpha$ , (TNF- $\alpha$ ), interleukin-1 (IL-1), and IL-6, are constantly released by immune cells and tumor cells, causing systemic derangements. The systemic imbalance worsens treatment-related adverse reactions and decreases response to tumor treatment. Severity of cachexia is a TNM-staging independent prognostic factor.

Existing literature suggests that systemic inflammation, reflected by C-reactive protein (CRP), plays an important role in cancer prognosis. A clinical trial was conducted in 300 patients with colorectal cancer in Japan by Dr. Miki. It was noted that body weight loss was significantly higher and creatinine height index was lower in patients whose albumin was lower than 3.5 g/dL and CRP level was higher than 0.5 mg/dL, indicating the existence of high protein degradation in those patients. In addition, significant numbers of patients were found to have pre-cachexia and cachexia even in early stages (I and II) of the disease. The prognosis was poorer in patients with high CRP levels compared to nutritionally depleted patients without systemic inflammation. In comparing preoperative CRP in survivors to non-survivors for the four stages, non-survivors with stage I and II disease had similar mean CRP levels as non-survivors with stage III and IV disease (Figure 1). These data suggest that CRP may independently predict survival in patients with stage I and II disease.

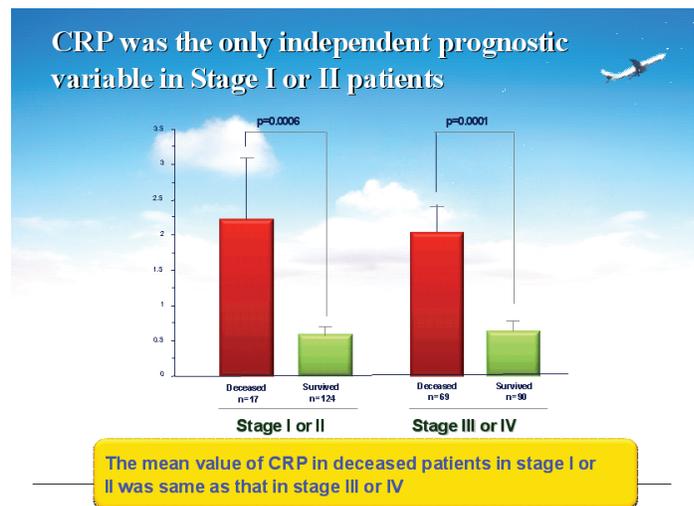


Figure 1: CRP levels in deceased and survived patients

Professor Miki further introduced molecular background of cancer cachexia. Tumor cells are known to release proinflammatory cytokines (IL-1, IL-6, vascular endothelial growth factor [VEGF]) into the portal circulation, resulting in systemic metabolic derangements, demonstrated by increased synthesis of acute response protein, such as CRP, and decreased synthesis of albumin. Significantly increased cytokines in the circulation also cause proteolysis of muscle protein and glucose depletion, leading to negative energy balance and muscle wasting in cachectic patients. This mechanism may be a possible explanation of cachexia in patients with cancer.

Tumors grow by inducing immune tolerance of the host leading to immunosuppression. Tumor cells may interact with neutrophils, which release IL-6. Tumor cells themselves also release IL-6 and induce growth factor (VEGF) release. The cytokine storm exists and inflammatory response may get worse even after tumor resection.

Resistance to cancer therapy is common in patients with cancer cachexia, which may also be due to the presence of inflammation. IL-6 is known to counteract the anti-tumor effects of 5-FU by inhibiting p53-mediated apoptosis. Anti-tumor effect of CRP-11 is also suppressed by IL-6 by down-regulating the expression of TOP1. Therefore, the target for molecular immunonutrition in cancer patients may focus on regulating IL-1 and IL-6 cascade both in tumor cells and neutrophils.

Toll-like receptors (TLRs) are involved in tumor survival and chemo-resistance via increased cytokine production<sup>5</sup>. Cancer cells and neutrophils express TLR4. Resolvins E1 and D2 are endogenous lipid mediators derived from EPA/DHA. They may, via TLR pathways, normalize IL-1-IL-6 cascade in both neutrophils and tumor cells<sup>6, 7</sup>; thus attenuating host-resistance to anti-tumor therapy and improving the therapeutic effects of molecular targeting therapy and radiation therapy in cachectic patients.

In summary, systemic inflammation is predominant in cachectic cancer patients. Therapies targeting systemic inflammation may be useful to attenuate nutritional depletion and counteract tumor resistance to anti-cancer therapy.

# The Role of Nutrition Therapy in Cancer

## Effect of Nutrition Interventions in Cancer Patients

*Maria Isabel Correia, MD, PhD*

*Professor of Surgery*

*Medical School, Federal University of Minas Gerais, Brazil*

Professor Correia reviewed the important role nutrition intervention plays in cancer patients and provided recommendations on nutritional counseling and nutrition support. Cancer is a leading cause of death in the United States and around the world. Weight loss is a frequent symptom in patients with cancer with more than half of those patients demonstrating moderate to severe malnutrition over time. It has been reported that pre-treatment weight loss is associated with survival time; patients who stopped losing weight have better survival rates<sup>8</sup>. Malnutrition and hypoalbuminemia were associated with chemotherapy-related toxicity<sup>9</sup>.

Although nutrition awareness is low among medical practitioners, appropriate nutritional support is highly required in cancer patients and their family members. Based on an online survey conducted in young cancer patients, 60% of respondents expressed a desire or need for nutritional information, particularly information about diet and nutrition counseling. Nutritional supplements are used in a large number of patients.

To help improve malnutrition and reverse weight loss frequently seen in patients with cancer, nutrition screening and assessment are highly recommended. Nutritional risks can be screened by Patient Generated Subjective Global Assessment (PG - SGA), Malnutrition Screening Tool (MST), Nutritional Risk Screening (NRS 2002), University of Nottingham Hospital tool, and Malnutrition Universal Screening Tool (MUST, BAPEN). Tools to diagnose malnutrition include SGA, anthropometry, Bioelectrical Impedance Analysis (BIA), biochemical markers, Tomography, and functional tests. More than one test may be used as needed. For example, weight should be measured and monitored in cancer patients from the time of diagnosis including a history of recent unplanned weight loss. In addition, dietary assessment should be combined when screening and assessing for nutritional risk.

In terms of nutritional intervention for patients with cancer, it should start with nutritional counseling for improvement of dietary intake; oral supplementation, enteral nutrition and parenteral nutrition are recommended as needed. More than 80% of nutritional requirements can be reached by oral diet alone. While modulating oral diet, individual preferences and eating habits should be considered although they may not always be the best choice. Comparing conventional oral supplementation in a variety of patients receiving radiation therapy, it was found that nutritional counseling including oral supplements was the most effective way to improve energy and protein consumption.

In conclusion, weight loss/malnutrition is a significant problem in patients with cancer. An increase in nutrition awareness is needed in medical professionals. Nutrition screening, assessment and dietary assessment should be conducted before providing nutritional intervention. Nutrition counseling is an effective method to reach nutritional requirements in patients with cancer. In addition to nutritional intervention, physical therapy and exercise may need to be encouraged in cancer patients to improve muscle mass and function.

## The Mechanism of Action of EPA

Stephen Wan Leung, MD

President of Taiwan Society of Therapeutic Radiology and Oncology

Yuan's General Hospital, Taiwan

Eicosapentaenoic acid (EPA) is an omega 3, long-chain polyunsaturated, 20-carbon fatty acid.

Fish oil is a source of EPA. The human body has a limited ability to synthesize EPA from shorter chain omega 3 fatty acids.

The effects of EPA in humans (alone or with other omega-3 sources) have been extensively studied.

Its ability to decrease inflammation and have beneficial effects on mental status, wound healing, and metabolism are well recognized. EPA may have an effect on blood clotting.

Cachexia is associated with many co-morbidities and mortality in patients with cancer. It is manifested by decreased body weight, muscle wasting, resistance to therapy, and increased weakness, infections and other complications. Quality of life is significantly compromised in cancer cachectic patients.

Causes of cancer cachexia include systemic inflammation, cytokine production, loss of appetite, altered metabolism, disturbance of hormonal balance, and increased proteolysis<sup>10, 11</sup>. Conventional nutrition interventions often have limited success because they do not address the underlying cachexia and the accompanying metabolic alterations that occur. For example, nutrition counseling may increase caloric intake; however, no significant weight gain is observed<sup>12</sup>. Appetite stimulants (Megestrol acetate [Megace®]) also have limited benefit in enhancing weight gain in cancer patients due to weight gain being mainly water or adipose tissue and the side effect profile of the drug, including hyperglycemia, thrombophlebitis, pituitary-adrenal suppression, impotence, deep vein thrombosis. The cost of drug is generally high.

**Food Sources of EPA**

- ◆ Can an individual consume more fish in their diet and see the same benefits as usual commercial products?
  - + No
  - + Serving sizes of fish that provide 2 g of EPA

|                       |
|-----------------------|
| Bluefin tuna, 0.93 kg |
| Shrimp, 0.93 kg       |

The deep sea fish can supply us EPA, from our daily diet intake evaluation, it only contains average 0.25g EPA. If we need 2 g/day, we have to eat almost 1 kg Bluefin tuna or 1 kg shrimp daily

Figure 1: Food sources of EPA

Supplementation of EPA appears to be beneficial in patients with cancer. Many studies have shown that EPA decreases proinflammatory cytokine production, down-regulates inflammatory response and proteolysis-inducing factor (PIF). Barber *et al*<sup>3</sup> showed that protein and energy-dense fish oil containing supplement significantly increased body weight and lean body mass in patients with cancer. Further, Wigmore *et al*<sup>4, 15</sup> found 2 g EPA per day is the optimal dose to have an effect on weight stabilization in patients with pancreatic cancer.

Although EPA can be consumed from food sources such as fish and seafood, an individual may have to consume about 1 kg Bluefin tuna or 1 kg shrimp per day to get 2 g EPA (Figure 1). Most fish oil supplements one can buy at stores contain 1000-1200 mg concentrated fish oil, with about 300-360 mg EPA per softgel. One would have to take 6-7 softgels per day to get 2 g EPA. In patients whose oral consumption is limited, an oral nutritional formula, such as ProSure, may be considered. Based on practice in Taiwan, ProSure may be mixed with different flavors (strawberry, pineapple jelly, etc.) in order to improve compliance. Importantly, in the United States, dietary supplement quality such as fish oil capsules is not regulated with the same rigor as drugs. As such, quality can vary with dietary supplements. The fish oil used in ProSure must meet Abbott Nutrition product quality specifications including meeting the absolute amount of EPA and low level of contaminants.

## EPA Alone or in Combination Therapy for Cancer-Induced Weight Loss

Anne Coble Voss, PhD, RD

Associate Research Fellow

Abbott Nutrition Global Nutrition Research & Development, Columbus, OH, USA

Following presentations on mechanisms of cancer cachexia and effects of conventional nutrition support and EPA supplementation, evidence to use EPA alone or in combination therapy to treat cancer induced weight loss was discussed in this presentation.

First, studies to determine optimal EPA doses were reviewed. Studies were conducted in pancreatic cancer patients because (1) these patients demonstrate weight loss and muscle wasting in a short period of time; (2) pancreatic cancer is a severe condition, results obtained in these patients may be generalized to other cancer patients exhibiting a similar weight loss pattern and cytokine profile. Based on existing *in vivo* and *in vitro* data, the first study supplemented 2 g EPA to 18 pancreatic cancer patients with a median weight loss of 2.9 kg per month prior to study entry<sup>14</sup>. Patients consumed 16 – 18 fish oil capsules (~ 2.2 g EPA) for a median length of 3 months gaining 0.3 kg per month after supplementation ( $p < 0.002$ ) without changes in total body water (Figure 1). CRP level decreased and plasma phospholipid EPA level increased at 1 month<sup>14</sup>. Similar findings were reported by Gogos *et al.*<sup>16</sup>, who also observed improved survival rate. In a later study, 6 g EPA was supplemented to pancreatic cancer patients for 12 weeks<sup>15</sup>. Weight stabilization was reported in these patients; however, increasing the dose of EPA from 2 to 6 g per day did not improve clinical outcomes<sup>15</sup>. Therefore, it appears that 2 g EPA per day is the optimal dose to attenuate cancer cachexia.

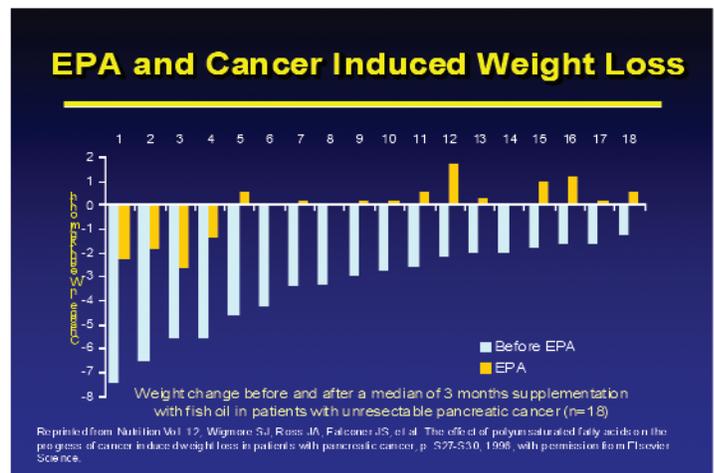


Figure 1: EPA supplementation and weight changes.

Secondly, effects of supplementation of EPA alone or with other therapies were discussed. In a double-blind, placebo controlled study by Bruera *et al.*<sup>17</sup>, 91 patients with advanced cancer of various tumor types who experienced >5% pre-illness weight loss were randomized to receive fish oil capsules for a goal of 3 g EPA/day (18 capsules) or olive oil control capsules for 2 weeks. Due to tolerance issues, patients were only able to take an average of 10 capsules/day (1.8 g EPA). Weight was stabilized in the fish oil group (0.3 kg) while the olive oil group lost weight (-0.89 kg). The authors concluded that in order to promote weight gain, EPA must be combined with additional calories and protein<sup>17</sup>.

In a similar study of EPA given as a single agent, Fearon *et al.*<sup>18</sup> conducted a double-blind, randomized, placebo-controlled study in 518 patients with cancer cachexia who received either 2 g or 4 g of EPA/day for 8 weeks and observed no statistically significant improvement in survival, weight or other nutrition variables. They concluded that EPA as a single agent without calorie and protein supplementation may not be enough to stop cancer induced weight loss.

In connection with earlier discussion, it was addressed that most fish oil products contain both EPA and DHA. The proportions of EPA and DHA depend on the manufacture process. It was also noted that although EPA may be synthesized from  $\alpha$ -linolenic acid (ALA), the conversion rate is low (10%) and occurs slowly over time. Thus, supplementation of EPA may not be substituted by ALA.

| Study  | Design   | Results   |
|--|--|---|
| Wigmore et al: <i>Nutrition</i> 1996;12:27.    | Pancreatic cancer, 2.2 g EPA,12 weeks; 2.9 kg/mo wt loss prior to supplementation          | Weight stabilization                                    |
| Gogos et al: <i>Cancer</i> 1998;82:395.        | Mixed tumor types, 3.1 g EPA+200 mg Vit E or placebo; 14% wt loss prior to supplementation | Weight stabilization, improved performance and survival |
| Wigmore et al: <i>Nutr Cancer</i> 2000;36:177. | Pancreatic cancer, 6 g EPA/day, 12 weeks; 2.0 kg/mo wt loss prior to supplementation       | Weight stabilization                                    |
| Bruera et al: <i>J Clin Oncol</i> 2003;21:129. | Mixed tumor types, 1.8 g EPA/day or placebo, 2 weeks; >5% wt loss prior to supplementation | Weight stabilization                                    |

Table 1: Summary of EPA alone clinical trials

In conclusion, 2 g EPA per day is the optimal dose in patients with cancer. EPA supplementation should be combined with adequate/balanced provision of macro- and micronutrients and minerals to help improve lean body mass and body function.

# Clinical Practice from Around the World – Patient Centered Outcomes

## Appetite and Food Intake

*Diclehan Kilic, MD*

*Associate Professor*

*Gazi University Hospital, Department of Radiology Oncology, Turkey*

Anorexia is defined as the loss of the desire to eat (appetite loss) resulting in reduced food intake. At the time of cancer diagnosis as many as 50% of patients experience anorexia, and in terminal patients, up to 60%-64% experience anorexia. However, it is often neglected in clinical practice and its etiology is multifactorial. Dietary intake is controlled by the hypothalamus under normal conditions. During pathological conditions, anorexia occurs as a result of peripheral signal defects, signal transduction errors, neuropeptides and cytokine production. Serotonin and 5-hydroxytryptamine (5-HT) mediate the anorexic effects of cytokines on the hypothalamus.

There are many ways to assess nutritional status and dietary intake. The Subjective Global Assessment (SGA) is the gold standard. The Malnutrition Screening Tool (MST) has been used in some studies. However, defining and diagnosing anorexia is difficult. A useful tool used in epidemiological and prospective studies is the Visual Analogue Scale (VAS), which is quite unreliable for small changes. Other reliable assessment tools include the North Central Cancer Treatment Group (NCCTG) Anorexia/Cachexia questionnaire and the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire.

The clinical impact of anorexia includes reduced oral intake of calories, and the development of malnutrition and cachexia, which can lead to increased morbidity and mortality. In patients receiving radiation, appetite loss and gastrointestinal symptoms are major contributors to deteriorated nutritional status<sup>19</sup>. Oral nutrition supplementation significantly attenuates the incidence and/or severity of mucositis and dysphagia<sup>19</sup>. In addition, quality of life (QoL) is negatively impacted by anorexia and reduced food intake<sup>19</sup>. Therefore, treating anorexia and improving food intake is important in clinical care for patients with cancer. An effective therapeutic strategy should include nutritional counseling<sup>20</sup> and pharmacological approaches that target cytokine reduction. EPA is a pharmacological agent to attenuate proinflammatory cytokines and tumor-derived catabolic factors.

In conclusion, cancer anorexia is a frequent presenting symptom and is associated with increased morbidity and mortality, early recognition and management is essential. Although an effective approach to treat anorexia is lacking, individualized nutritional counseling combined with pharmacological therapy may be useful to improve patient-centered outcomes.

# Weight or LBM - What's Most Important in Cancer Patients

Cesar A. Rodriguez, MD

Medical Oncologist & Associate Professor

Department of Medical Oncology, University Clinic Hospital of Salamanca, Spain

Widely recognized, cancer cachexia is associated with anorexia, decreased food intake, loss of fat and lean body mass, and muscle atrophy. Compared to starvation, tumors induce increased resting energy expenditure (REE), protein degradation, proteolysis and the acute phase response. In a study conducted by Rodriguez's group, nutritional status of 100 hospitalized patients with cancer was assessed<sup>21</sup>. Weight loss of 0-5% was experienced by 34% of these patients and 26% experienced weight loss of 5%-10%. Protein depletion was observed in 70% of patients and moderate-to-several malnutrition was noticed in 66% patients. Protein depletion and malnutrition occurred in early stages of the disease. These data suggest that weight loss frequently does not reflect the true nutritional status in patients with cancer and may not be the appropriate target for nutritional intervention in the early stages of the disease.

In planning nutritional and metabolic support for patients with cancer cachexia, the goal should be not only to restore body composition, but also to improve function and quality of life<sup>3</sup>. Studies have shown that attenuated weight loss using appetite stimulants did not improve QoL<sup>22-24</sup>, which may be due to the lack of improvement in lean body mass (LBM)<sup>25</sup>. Thus, it was commented that "weight, as endpoint,

can't be the main goal of nutritional treatment and isolated primary objective in clinical trials. Final purpose of the treatment must be QoL, performance status, and if possible, survival."

A number of studies have demonstrated that an increase in LBM is positively correlated with improvements in QoL scores<sup>13, 26, 27</sup>, performance status<sup>13</sup>, and physical activity level<sup>25, 28</sup>. However, LBM is typically not measured in clinical practice. In a systematic review by

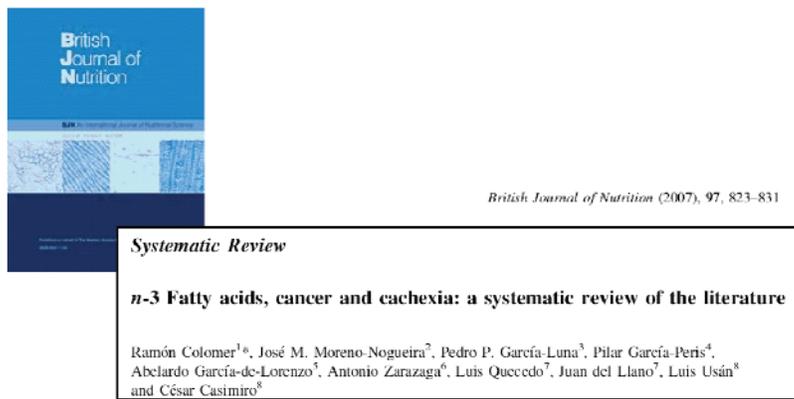
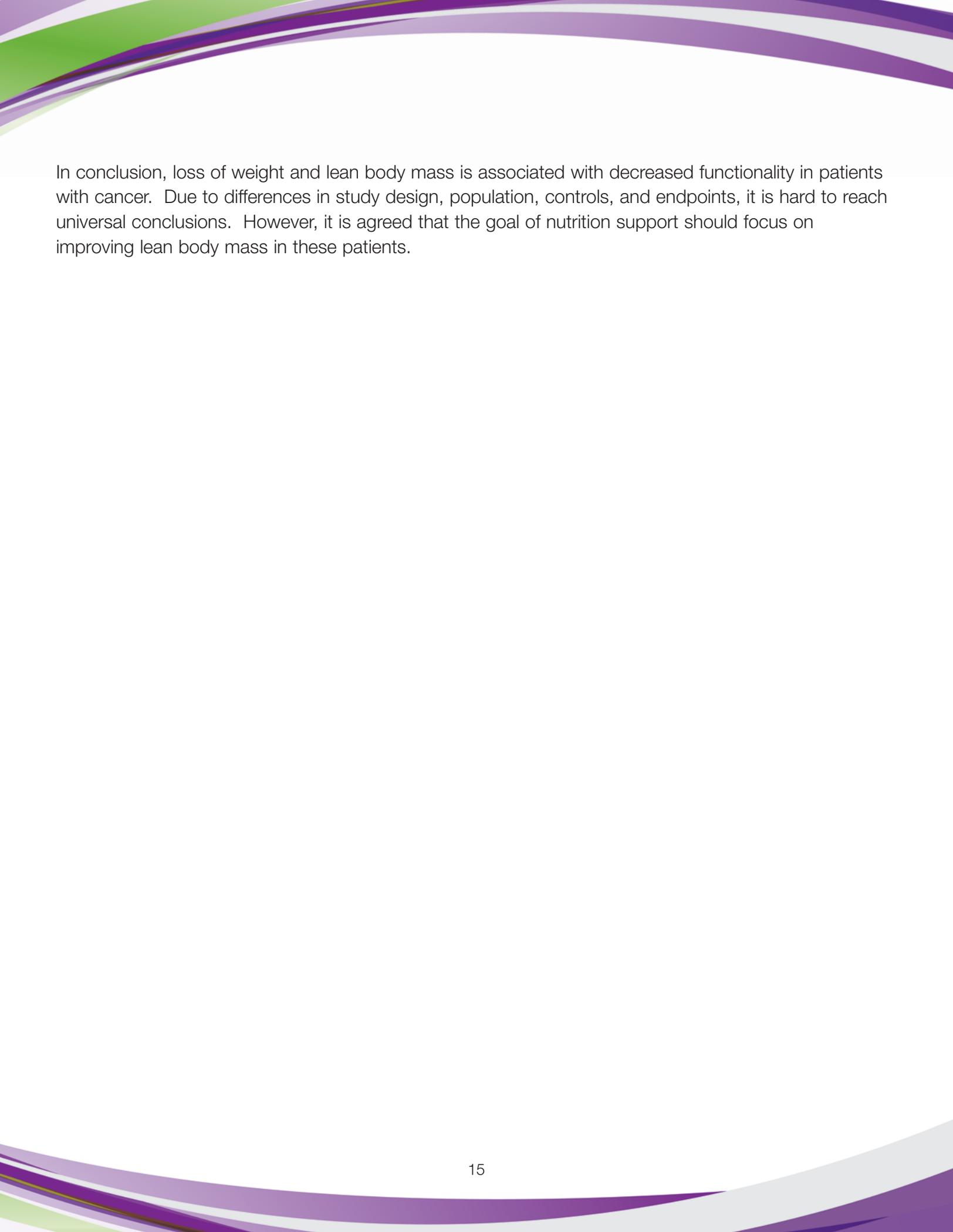


Figure 1: A systemic review on omega-3 fatty acid supplementation in cancer cachectic patients

Colomer *et al.*<sup>27</sup> (Figure 1), they recommend that omega-3 fatty acids in a dose of 1.5-2.0 g EPA per day be provided for at least 8 weeks to patients with advanced cancer and weight loss. EPA may be supplemented alone or with DHA in a 2:1 ratio. The review also recommends that anthropometric measures (weight, body mass index [BMI]), bioimpedance analysis (BIA) to assess LBM, functional parameters and QoL scales be used to assess efficacy and effectiveness of omega-3 fatty acid supplementation<sup>27</sup>.



In conclusion, loss of weight and lean body mass is associated with decreased functionality in patients with cancer. Due to differences in study design, population, controls, and endpoints, it is hard to reach universal conclusions. However, it is agreed that the goal of nutrition support should focus on improving lean body mass in these patients.

# Supplemental Drinks Containing Omega-3 Fatty Acids Improve Nutritional Status in Lung Cancer

P.A.M. van Leeuwen, MD, PhD

Professor of Surgery

VU Medisch Centrum, Amsterdam, The Netherlands.

Prevalence of malnutrition and cachexia in lung cancer patients is 30%-50% at diagnosis, which further deteriorates after subsequent surgical and chemo-radiation therapy. In this and the next presentation, Professor Paul van Leeuwen and Ms. van der Meij presented results of a clinical study in 40 patients with stage III non-small cell lung cancer receiving chemo-radiation therapy (Figure 1).

This study was a randomized, double-blinded, placebo-controlled clinical trial. Intervention group received a protein and energy-dense supplemental drink containing omega-3 fatty acids (ProSure) 2 containers per day, which provided 2.02 g EPA and 0.92 g DHA. Controls received an isocaloric, control supplemental drink at 2 cans per day. Measurements were done every week for 5 weeks. Professor van Leeuwen reported results on body weight and fat free mass.

The baseline characteristics were similar between the intervention group and controls in age, stage of disease, Karnofsky performance score (KPS), weight loss in 6 month, and malnutrition proportion, except intervention group had more male subjects. At week 5, plasma phospholipid EPA proportion was significantly increased in the intervention group ( $p < 0.05$ ) whereas no changes in the control group. In addition, loss of body weight and fat-free mass was significantly attenuated in patients receiving ProSure. Lower IL-6 production was observed in the intervention group. Serum IL-6, CRP, sTNF-p55, albumin and HLA-DR expression on monocytes were similar between the two groups. In the intervention patients with plasma phospholipid EPA increase  $\geq 1.5\%$ , at week 5, plasma phospholipid EPA was significantly, inversely correlated with IL-6 ( $r=-0.8$ ,  $p=0.041$ ) and CRP ( $r=-0.8$ ,  $p=0.048$ ).

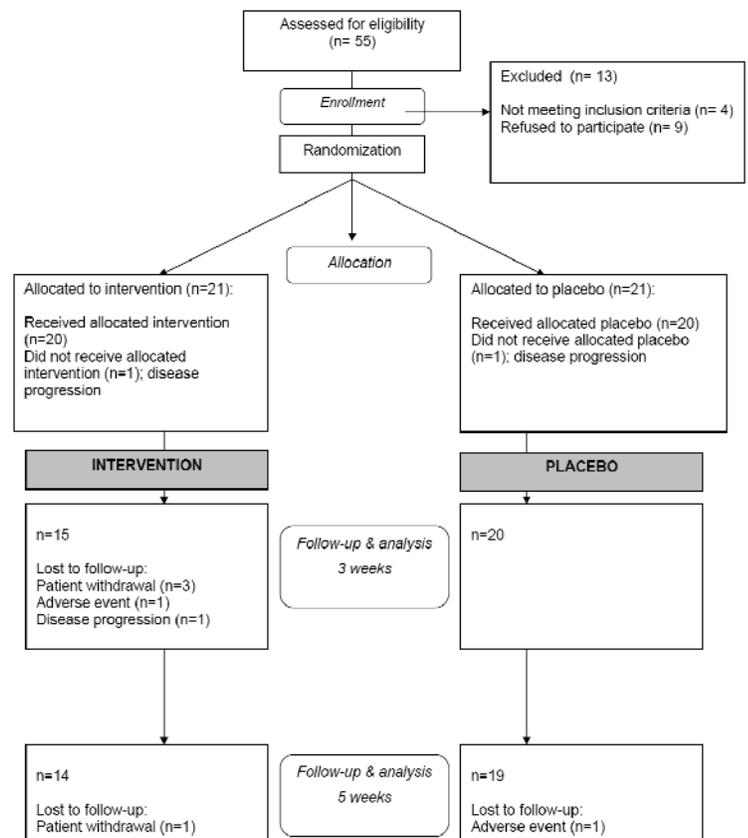


Figure 1: Subject enrollment

Taking these results together, the authors concluded that supplementation of ProSure has beneficial effects on body weight and fat-free mass in patients with stage III non-small cell lung cancer receiving chemo-radiation therapy.

# Physical Activity and Quality of Life in Lung Cancer: Effects of Omega-3 Fatty Acids

Barbara van der Meij, MS  
 Research Dietician  
 VU University Medical Center, The Netherlands

Following Dr. van Leeuwen’s presentation, results of omega-3 fatty acid supplementation on physical activity and QoL in lung cancer patients were presented.

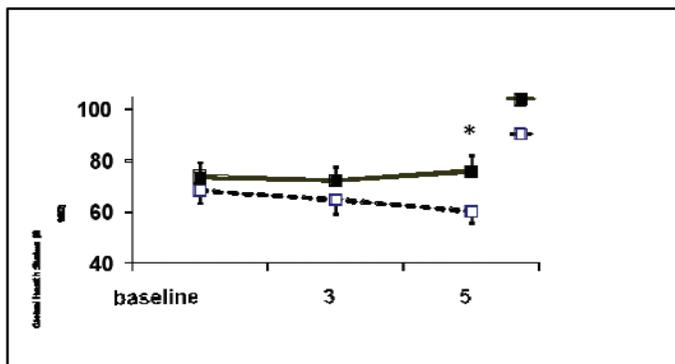
Physical activity is compromised in patients with cancer. To assess physical activity, the current gold standard is using doubly labeled water plus indirect calorimetry. However, this is expensive and requires expertise to perform. Other methods include bicarbonate-urea methods, physical activity meters (PAM) and some questionnaires. In this study, physical activity was measured by PAM accelerometer (Figure 1) and expressed daily movements in PAM score. Patients were instructed to wear PAM for 7 consecutive days.



Figure 1: Demonstration of a physical activity meter

At weeks 3 and 5, PAM score was significantly higher in the intervention group compared to controls. Karnofsky performance score in patients receiving ProSure was 5.3 units higher at week 3 ( $p = 0.04$ ) and 7.2 units higher at week 5 ( $p = 0.10$ ). Quality of life was improved at weeks, measured by European

Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, a cancer specific, validated, quality of life instrument. Changes in Global Health Status are shown in Figure 1. In patients whose plasma EPA level was  $\geq 1.6\%$ , weight change (%) was positively associated with PAM score.



mean  $\pm$  SEM, \*  $p < 0.05$ , compared to control group

Figure 1: Changes of Global Health Status

improved at weeks, measured by European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, a cancer specific, validated, quality of life instrument. Changes in Global Health Status are shown in Figure 1. In patients whose plasma EPA level was  $\geq 1.6\%$ , weight change (%) was positively associated with PAM score.

It was concluded supplementation of enteral nutrition enriched in omega-3 fatty acids is useful to improve nutritional status, physical activity and quality of life. During the discussion, it was commented that an individual’s genetic profile and underlying disease condition may lead to different response to nutrition therapy. Personalized therapy will be the future direction of nutritional intervention.

# Bridging the Gap from Clinical Research to Practice- Clinical Practice Guidelines

## Croatian Guidelines

*Zeljko Krznaric, MD*

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Incidence and prevalence of cancer are rising in Croatia. The Croatian Guidelines for Use of Eicosapentaenoic Acid and Megestrol Acetate in Cancer Cachexia Syndrome (Figure 1) were published in 2007. The goal of the guidelines is to standardize therapeutic procedures for nutritional support of cancer patients in relation to:

- preventing and treating undernutrition,
- enhancing anti-tumor treatment effects,
- reducing adverse effects of anti-tumor therapies,
- improving quality of life.

The process and method used to develop these guidelines were described in this presentation.

The guidelines were developed by an interdisciplinary group of experts from the Croatian Medical Association, Croatian Society of Enteral and Parenteral Nutrition, Croatian Society of Oncology, Croatian Society of Medical Oncology, and experts from leading Croatian hospitals. The basis of the guidelines include general Croatian medical practice, world-wide medical literature and relevant publications, and evidence-based medicine. Given the fact that weight loss/malnutrition interferes with medical and surgical treatment of cancer, these guidelines particularly focus on reorganization and treatment of precachexia and early cachexia in patients with cancer. Patient-tailored treatment was recommended.

After extensive research and discussion, eicosapentaenoic acid (EPA) and megestrol acetate were chosen to be used to promote weight gain and stimulate appetite, respectively, in this publication.

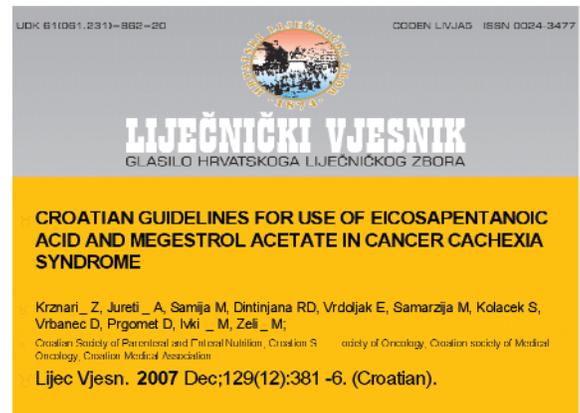


Figure 1: Croatian guidelines

Key points of the guidelines include:

- AD.1. Malnutrition as a part of cancer anorexia and cachexia syndrome is a common problem in the treatment of oncological patients.
- AD.2. Diagnosing malnutrition is done with simple clinical indices and basic anthropometric parameters.
- AD.3. Clinical nutrition is an important component of supportive treatment of oncological patients in various stages of disease. Cancer cachexia syndrome can appear in the earliest stages of disease.
- AD.4. Depending on the stage of cancer cachexia, the nutritional approach is as follows:
  - a) first step: nutritional counseling or dietetic advice;
  - b) second step: oral nutrition supplement (ONS), where enteral nutritional formulas with increased administration of EPA have an important role.
- AD.5. Enteral nutrition per os as a nutritional supplement (high-protein, high-energy, polymeric formula with increased intake of EPA, 2.2 g/day) is first choice in use of nutritional support.
- AD.6. Megestrol acetate is effective in treatment of patients with anorexia-cachexia syndrome (400-800 mg/day) and is a first choice in pharmacotherapy.
- AD.7. Combination of megestrol acetate and enteral nutrition with increased intake of EPA for a minimum of 8 weeks is a desirable therapeutic approach.

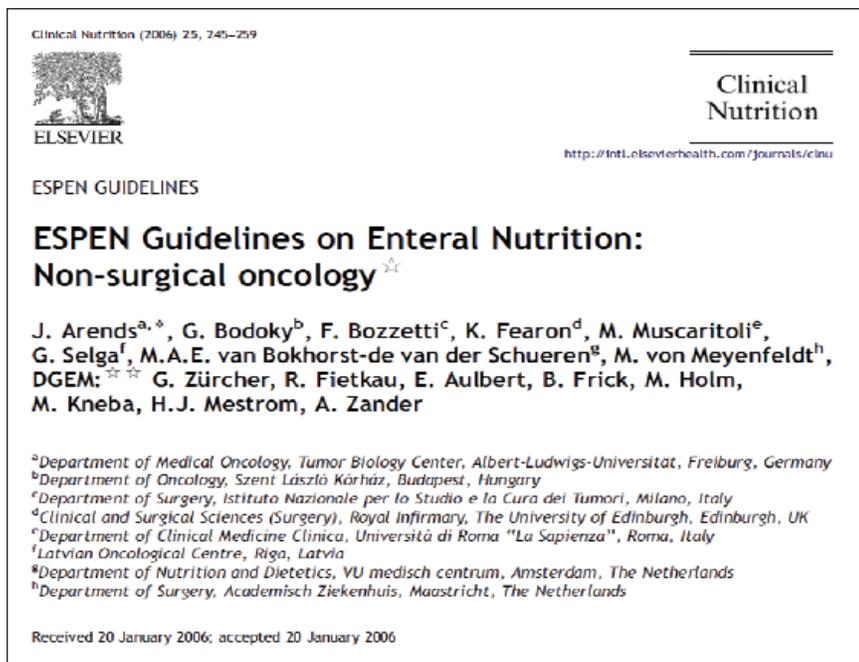
In these guidelines, it is recommended that nutrition support should begin when it may facilitate oncological treatment, may improve the quality of life, or may prevent patients from death from starvation. Professor Krznarić reported that two years after the guidelines were published there has been an increase in the number of patients with cancer cachexia treated with an EPA-containing protein and energy dense supplement. Results of a survey conducted in March 2010 revealed that 78% of Croatian oncologists have changed their attitude regarding cancer cachexia (Juretić, unpublished data). Professor Krznarić stated that the guidelines will be revised and improved in 2010-2011.

# ESPEN Guidelines

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This presentation discussed the 2006 ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology<sup>29</sup>. Similar to the Croatian guidelines, the ESPEN guidelines describe specific goals of enteral nutrition support in cancer patients including “preventing and treating undernutrition, enhancing anti-tumor treatment effects, reducing adverse effects of anti-tumor therapies, and improving quality of life.”

Figure 1: ESPEN Guidelines on enteral nutrition in non-surgical oncology

Topics discussed in this presentation were:

- timing to start enteral nutrition (EN)
- Effectiveness of EN on nutritional status in cancer patients
- Effectiveness of omega-3 fatty acid supplementation
- Indications for EN during radiotherapy or combined radio-chemotherapy
- Indications for routine EN during chemotherapy, autologous or allogeneic hematopoietic stem cell transplantations (HSCT), and in incurable cancer patients

The Guidelines state that available data showed no effects of EN on tumor growth. It is recommended that patients at risk of malnutrition should be referred to a nutrition specialist for assessment and/or treatment.

The ESPEN guideline 2.5 states that randomized clinical trial evidence is contradictory/controversial regarding the beneficial effects of supplemental omega-3 fatty acids on improving nutritional status/physical function in patients with cancer. This guideline is given a grade C. Evidence to support this statement includes studies that provide fish oil capsules or EPA in an oral nutritional supplement (ONS). Additional information is stated regarding the EPA/ONS suggesting that patient compliance with the supplement is a critical factor in its efficacy. An unpleasant aftertaste of the EPA/ONS may be the limiting factor in compliance. An improvement in the palatability of the EPA/ONS may improve compliance and treatment effectiveness. Results of additional trials are needed.

It was concluded that ESPEN 2006 EN Guidelines is an indispensable tool to help clinicians to provide nutrition therapy. Given the ongoing advances in cachexia definition and staging and research data on EPA/ONS-EN, supplementation clinical practice guidelines for cancer nutrition therapy should be made available soon. For example, physical exercise to preserve lean body mass, prevent cachexia and improve quality of life should be integrated into the guidelines.

## Omega-3 Fatty Acids in Cancer: Update on the Clinical Evidence

*Barbara van der Meij, MS*

*Research Dietician*

*VU University Medical Center, The Netherlands*

This presentation addressed the question, “Where do we stand regarding the quality of the evidence for the use of omega-3 fatty acids in cancer?” Current ASPEN guidelines<sup>30</sup> state that in cancer treatment and hematopoietic stem cell transplantation, “Omega-3 fatty acid supplementation may help stabilize weight in cancer patients on oral diets experiencing progressive, unintentional weight loss.” This statement is Grade B and is based on 16 studies from 1995 to 2005 (Level I evidence: n=3, II: n=5, III: n=1, IV: n=0, V: n=7). There are no data on omega-3 fatty acid supplementation parenterally<sup>31</sup>.

Since 2005, there are many publications suggesting beneficial effects of omega-3 fatty acid supplementation in patients with cancer. Update of omega-3 fatty acid guidelines is needed. Therefore, a systematic review was conducted by the presenter and collaborators regarding effects of omega-3 fatty acids on clinical outcomes and its incorporation and washout. Included in the systematic review were randomized, controlled trials of fish oil capsules or enteral or parenteral supplements that included outcome parameters of nutritional status, quality of life, morbidity, mortality, and length of stay and measurement of omega-3 fatty acid in plasma and blood. The literature search found eight studies of oral nutritional supplements in non-surgical oncology patients; four of which were not included in the ESPEN or recently published A.S.P.E.N. guidelines<sup>30</sup>. Recommendations for non-surgical oncology patients based on the eight studies suggest that beneficial effects of oral supplementation of 2 g/day EPA can be seen in body weight, survival, and physical performance. Oral supplementation of omega-3 fatty acids is recommended for cancer patients who are at high risk of cachexia. This recommendation was given a grade B.

Recommendations for surgical oncology patients based on four studies suggest that perioperative supplementation with a tube feeding or ONS containing omega-3 fatty acids might reduce postoperative infectious complications and loss of fat-free mass. Perioperative parenteral supplementation of omega-3 fatty acid might shorten length of hospital stay (Grade C) and has no effects on complications or survival. Ms. van der Meij suggested that more studies are needed in cancer surgery.

Six publications using enteral supplementation and two using parenteral supplementation were found regarding omega-3 fatty acid incorporation and washout. It is suggested that with oral/enteral omega-3 fatty acid supplementation, increased EPA levels in plasma, peripheral blood mononuclear cells, and erythrocytes occur in 1-2 weeks. Parenteral EPA supplementation increases plasma or thrombocyte EPA levels in 5-7 days. Washout may take 4-7 days after cessation of supplementation.

Taking all the evidence together, it is recommended that supplementation of omega-3 fatty acids for at least two weeks is the minimal length of time to reach and maintain optimal incorporation into phospholipid membranes. Optimal dose of EPA is 2 g per day. A meta-analysis will be conducted to further examine the effects of omega-3 fatty acids in patients with cancer.

## Investigator Research

### Nutritional Support Including EPA in the Prevention of Chemoradiotherapy Induced Acute Gastrointestinal Complications: A Prospective, Controlled, Clinical Evaluation - A Pilot Study

Diclehan Kilic, MD

Associate Professor

Gazi University Hospital, Department of Radiology Oncology, Turkey

Pelvic radiation is associated with toxic responses such as diarrhea, cramping, tenesmus, bleeding, etc. EPA has been shown to decrease systemic inflammation and attenuate treatment-associated adverse effects. Therefore, a pilot study was conducted by Dr. Kilic to examine the effects of an EPA-containing ONS (ProSure) on chemo-radiation-associated GI toxicity and quality of life in rectal cancer patients receiving pelvic radiation therapy.

Forty-patients were enrolled; 20 patients received the EPA-ONS supplementation (ProSure) at 2 tetra packs per day and 20 received standard care. The primary endpoint of toxicity score was measured by diarrhea scale and LENT-SOMA scale. Quality of life (QoL) was measured at the beginning and end of chemoradiotherapy using EORTC QLQ-C30 and CR38. Chemoradiotherapy was administered similarly to both groups.

Ten percent of the patients in the EPA-ONS group reported a grade 3 toxicity score for diarrhea, and none for grade 4, compared to 35% and 10%, respectively in the control group. The weekly LENT-SOMA grade results showed that EPA-ONS patients had less GI toxicity since week 3. Although all patients were well-nourished at study entry, there were 7 (35%) control patients developed malnutrition (SGA score  $\mu$  or C) at the end of study. Only one subject in the EPA-ONS group had SGA score B. The baseline quality of life scores were similar between the two groups. The quality of life scores remained stable in the EPA-ONS group; however, the control group, experienced a decrease in the quality of life and an increase in symptoms with treatment.

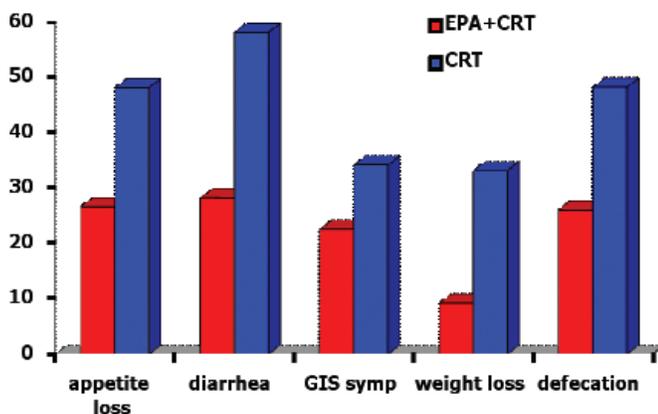


Figure 1: At the end of treatment, EPA-ONS group showed less QoL reductions

EPA-containing ONS helps to preserve QoL and it appears that chemoradiotherapy-related acute GI toxicity may be attenuated by EPA-containing ONS. Future randomized clinical trials are warranted.

# The Benefit of Eicosapentaenoic Acid in Nasopharyngeal Cancer Patients Receiving Concurrent Chemoradiotherapy in Outpatient Clinic – an Open Label Prospective Randomized Trial

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Professor of Medicine

Department of Radiation Oncology, Chang Gung Memorial Hospital, Taiwan

Nasopharyngeal cancer (NPC) is a common disease in Southeast Asia, south China, Hong Kong and Taiwan. Radiotherapy is the primary treatment for this disease. A number of prospective, randomized clinical trials suggest concomitant chemo-radiotherapy can improve tumor control and overall survival. However, a large proportion (35%-75%) of patients experience grade 3-4 mucositis and grade 3-4 neutropenia. Many patients have to terminate the treatment prematurely due to treatment-associated complications.

EPA is known to reduce inflammation by producing less proinflammatory cytokines and EPA may play a role in reducing chemo-radiotherapy toxicities. This presentation reported results of an open label, prospective, randomized trial which examined the effects of supplementation of an EPA-containing ONS (ProSure) in NPC patients receiving chemoradiotherapy. One hundred sixteen patients were randomized to receive either the EPA supplement group or an isotonic, low-residue formula. Each group was to consume two servings of supplementation formula per day for three months. Nutritional consultation was provided. Subjects were followed weekly.

|                           | OR           | 95% C.I.    |               | P value      |
|---------------------------|--------------|-------------|---------------|--------------|
|                           |              | Lower       | Upper         |              |
| <b>Age (mean/SD)</b>      | <b>1.05</b>  | <b>1.01</b> | <b>1.10</b>   | <b>0.023</b> |
| <b>Supplement feeding</b> |              |             |               |              |
| <b>ISO</b>                | <b>1.00</b>  | -           | -             | -            |
| <b>EPA</b>                | <b>0.21</b>  | <b>0.06</b> | <b>0.69</b>   | <b>0.010</b> |
| <b>Diabetes</b>           |              |             |               |              |
| <b>no</b>                 | <b>1.00</b>  | -           | -             | -            |
| <b>yes</b>                | <b>15.48</b> | <b>2.37</b> | <b>101.05</b> | <b>0.004</b> |

Table 2: Multivariate analysis of infection admission

Compliance was noted to be low with only 37.8% of patients completing 12 weeks of supplement intake. Mucositis was high in both groups with 54% in the EPA group and 67% in the control group ( $p = 0.071$ ). Ten percent of the patients in the EPA group were admitted to the hospital for infection compared to 28% in the control group ( $p = 0.014$ ). There were no differences in nutritional intake, body weight change, radiation and chemotherapy regimen between the study group and controls. In

multivariate analysis, age, EPA supplementation and diabetes were predictors of hospital admission for infection. EPA-ONS supplementation was associated with less likelihood to develop infections requiring hospital admission (OR=0.21,  $p = 0.01$ , Table 2).

Therefore, it was concluded that NPC patients in this study do not accept well the EPA formula due to its flavor. EPA supplement did not improve the energy intake, body surface and body weight change compared to the control supplement. However, patients with EPA supplement had less chance of hospital admission for infection and a trend for less severe mucositis. In the discussion, Dr. Tung-Chieh Chang was asked if there was any relationship between infection and EPA supplementation. What the compliance rate was for the patients in the EPA group who were admitted to the hospital for infection? These may be important factors to interpret the results. It was also suggested that measuring plasma EPA levels can be a useful indicator of compliance in future studies. Additional studies are required to examine the mechanism of EPA supplement that decreases the risk of infection.

## When to start nutritional support? In pre-cachexia or cachexia?

Maurizio Muscaritoli, MD

Associate Professor of Medicine

Department of Clinical Medicine, University La Sapienza, Rome, Italy

Lack of nutrition awareness is prevalent in oncologists worldwide. Results of a questionnaire answered by 357 oncologists revealed that 69% feel a barrier to including nutrition intervention in oncological patient care is the lack of guidelines<sup>32</sup>. In this presentation, Dr. Muscaritoli provided insight into the question of when to start nutritional intervention – when the patient is in the pre-cachexia stage or cachexia stage.

Many studies have shown that pretreatment weight loss is a prognostic factor in patients with cancer<sup>33</sup>. For example, lung cancer patients with weight loss have worse clinical outcomes, such as intolerance to chemo/radiation treatment and high mortality rate, compared to those without weight loss<sup>34</sup>. It is important to keep in mind that not all malnourished patients are cachectic, but invariably all cachectic patients are malnourished<sup>35</sup>. Pre-cachexia and cachexia are part of a multifactorial syndrome that requires multimodal treatment. The most clinically relevant feature of cancer cachexia is muscle loss, which is associated with many negative clinical outcomes. It was noted that proteolytic activities exist in cancer patients regardless of the presence of weight loss<sup>36</sup>. Thus, a new philosophical approach to treat cancer patients should employ a parallel pathway involving a multidisciplinary, multimodal approach (Figure 1).

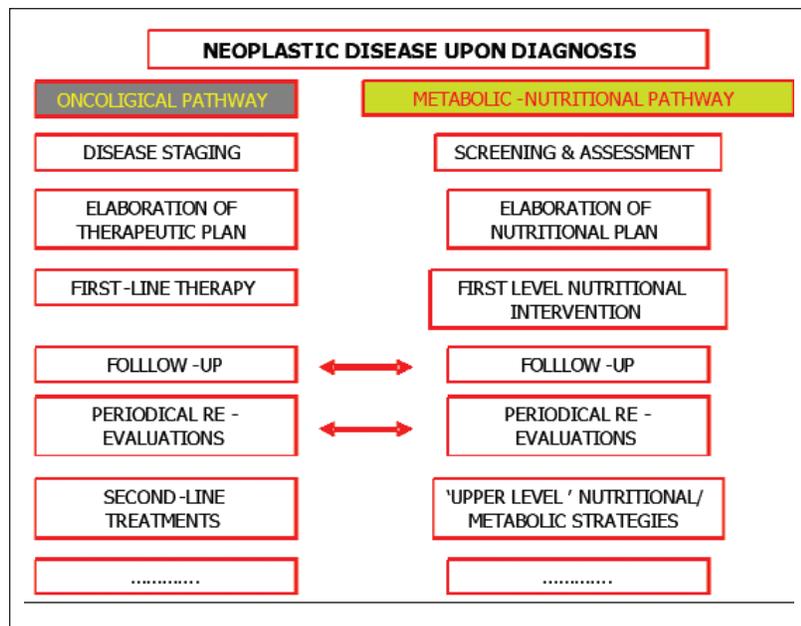


Figure 1: Parallel pathway of nutrition support for cancer patients

The “Parallel Pathway” model suggests clinical care for cancer patients is a collaborative work involving physician, dietitian, nurse, psychologist, etc. Components of this model include :

- Medical history
- Nutrition history
- General examination
- Anthropometric measurements (body weight [BW], body mass index [BMI], % body weight loss [%BWL])
- Screening/assessment of anorexia (visual analogue scale [VAS], questionnaire)
- QoL
- Hand-grip dynamometry (HGD)
- Body composition (optional)
- Estimation of nutritional needs
- Elaboration of nutritional plan
- Planning of metabolic-nutritional follow-up

Based upon available evidence, it was suggested that nutritional issues in cancer patients should be taken into account as soon as cancer is diagnosed. Nutritional and metabolic surveillance and intervention should become part of the standard of care for patients with cancer, and run parallel to the patient’s cancer treatment. Cost-effectiveness of this multimodal, multidisciplinary approach warrants prospective evaluation.

## Where do we go from here? The future of cancer cachexia study design

In the last session of the conference, a panel discussion with all the speakers was conducted to brainstorm on what they would like to see for the next cancer cachexia study design. Major topics for discussion are listed below.

- Patient groups  
Esophageal cancer, Stage II or III NSCLC, and liver cancer
- Duration of intervention  
From pretreatment until the end of surgical, chemo/radiation therapy
- Control product  
Isocaloric oral supplementation
- Primary outcomes  
Infections, length of hospital stay, body weight, lean body mass (measured using DEXA), chemotherapy toxicities, appetite, dietary intake, QoL, plasma phospholipid EPA levels at 4-6 weeks after EPA supplementation, organ functions
- Secondary outcomes  
Oral intake, tolerance to chemotherapy, amount of chemotherapy received, functional 6-minute walk, physical activity level, disease-free survival, overall survival, cost effectiveness, muscle mass and strength

In addition, it was suggested that future studies may target on appropriate product profile, e.g., one carton or two, flavors/consistency, and effects of other nutrients such as leucine/hydroxymethylbutyrate (HMB). There was also a discussion on doing multi-center international studies versus the need to do more pilot studies.

## References:

1. Evans WJ, Morley JE, Argiles J, et al. Cachexia: a new definition. *Clin Nutr.* 2008;27(6):793-799.
2. Bozzetti F. A critical reappraisal of the definition of cancer cachexia and proposal for a staging system. *Nutritional Therapy & Metabolism.* 2008;26(3):109-117.
3. Fearon KC, Voss AC, Hustead DS. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. *Am J Clin Nutr.* 2006;83(6):1345-1350.
4. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res.* 15 2009;15(22):6973-6979.
5. Szajnik M, Szczepanski MJ, Czystowska M, et al. TLR4 signaling induced by lipopolysaccharide or paclitaxel regulates tumor survival and chemoresistance in ovarian cancer. *Oncogene.* 2009;28(49):4353-4363.
6. Schwab JM, Chiang N, Arita M, Serhan CN. Resolvin E1 and protectin D1 activate inflammation-resolution programmes. *Nature.* 2007;447(7146):869-874.
7. Spite M, Norling LV, Summers L, et al. Resolvin D2 is a potent regulator of leukocytes and controls microbial sepsis. *Nature.* 2009;461(7268):1287-1291.
8. Andreyev HJ, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer.* 1998;34(4):503-509.
9. Arrieta O, Michel Ortega RM, Villanueva-Rodriguez G, et al. Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: a prospective study. *BMC Cancer.* 2010;10:50.
10. Argiles JM, Lopez-Soriano FJ. Host metabolism: a target in clinical oncology? *Med Hypotheses.* 1998;51(5):411-415.
11. Cabal-Manzano R, Bhargava P, Torres-Duarte A, Marshall J, Wainer IW. Proteolysis-inducing factor is expressed in tumours of patients with gastrointestinal cancers and correlates with weight loss. *Br J Cancer.* 2001;84(12):1599-1601.
12. Ovesen L, Allingstrup L, Hannibal J, Mortensen EL, Hansen OP. Effect of dietary counseling on food intake, body weight, response rate, survival, and quality of life in cancer patients undergoing chemotherapy: a prospective, randomized study. *J Clin Oncol.* 1993;11(10):2043-2049.
13. Barber MD, Ross JA, Voss AC, Tisdale MJ, Fearon KC. The effect of an oral nutritional supplement enriched with fish oil on weight-loss in patients with pancreatic cancer. *Br J Cancer.* 1999;81(1):80-86.
14. Wigmore SJ, Ross JA, Falconer JS, et al. The effect of polyunsaturated fatty acids on the progress of cachexia in patients with pancreatic cancer. *Nutrition.* 1996;12(1 Suppl):S27-30.
15. Wigmore SJ, Barber MD, Ross JA, Tisdale MJ, Fearon KC. Effect of oral eicosapentaenoic acid on weight loss in patients with pancreatic cancer. *Nutr Cancer.* 2000;36(2):177-184.

16. Gogos CA, Ginopoulos P, Salsa B, Apostolidou E, Zoumbos NC, Kalfarentzos F. Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy: a randomized control trial. *Cancer*. 1998;82(2):395-402.
17. Bruera E, Strasser F, Palmer JL, et al. Effect of fish oil on appetite and other symptoms in patients with advanced cancer and anorexia/cachexia: a double-blind, placebo-controlled study. *J Clin Oncol*. 2003;21(1):129-134.
18. Fearon KC, Barber MD, Moses AG, et al. Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. *J Clin Oncol*. 2006;24(21):3401-3407.
19. Ünsal D, Aksu A, Akmansu M, Pak Y. The influence of early nutritional intervention on treatment related complications: A prospective clinical trial in head-neck cancer patients undergoing radiotherapy. *ESPEN* Lisbon 2004.
20. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Dietary counseling improves patient outcomes: a prospective, randomized, controlled trial in colorectal cancer patients undergoing radiotherapy. *J Clin Oncol*. 2005;23(7):1431-1438.
21. Reguero V, Sanchez M, Rodriguez CA. *Proc SEOM CC*. 2008.
22. Simons JP, Aaronson NK, Vansteenkiste JF, et al. Effects of medroxyprogesterone acetate on appetite, weight, and quality of life in advanced-stage non-hormone-sensitive cancer: a placebo-controlled multicenter study. *J Clin Oncol*. 1996;14(4):1077-1084.
23. Jatoi A, Rowland K, Loprinzi CL, et al. An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: a North Central Cancer Treatment Group and National Cancer Institute of Canada collaborative effort. *J Clin Oncol*. 2004;22(12):2469-2476.
24. Lesniak W, Bala M, Jaeschke R, Krzakowski M. Effects of megestrol acetate in patients with cancer anorexia-cachexia syndrome--a systematic review and meta-analysis. *Pol Arch Med Wewn*. 2008;118(11):636-644.
25. Mantovani G, Maccio A, Madeddu C, et al. Randomized phase III clinical trial of five different arms of treatment in 332 patients with cancer cachexia. *Oncologist*. 2010;15(2):200-211.
26. Fearon KC, Von Meyenfeldt MF, Moses AG, et al. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. *Gut*. 2003;52(10):1479-1486.
27. Colomer R, Moreno-Nogueira JM, Garcia-Luna PP, et al. N-3 fatty acids, cancer and cachexia: a systematic review of the literature. *Br J Nutr*. 2007;97(5):823-831.
28. Moses AW, Slater C, Preston T, Barber MD, Fearon KC. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. *Br J Cancer*. 2004;90(5):996-1002.
29. Arends J, Bodoky G, Bozzetti F, et al. ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology. *Clin Nutr*. 2006;25(2):245-259.
30. August DA, Huhmann MB. A.S.P.E.N. clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. *JPEN J Parenter Enteral Nutr*. 2009;33(5):472-500.

31. Bozzetti F, Arends J, Lundholm K, Micklewright A, Zurcher G, Muscaritoli M. ESPEN Guidelines on Parenteral Nutrition: non-surgical oncology. *Clin Nutr.* 2009;28(4):445-454.
32. Spiro A, Baldwin C, Patterson A, Thomas J, Andreyev HJ. The views and practice of oncologists towards nutritional support in patients receiving chemotherapy. *Br J Cancer.* 2006;95(4):431-434.
33. Jeremic B, Milicic B, Dagovic A, Aleksandrovic J, Nikolic N. Pretreatment clinical prognostic factors in patients with stage IV non-small cell lung cancer (NSCLC) treated with chemotherapy. *J Cancer Res Clin Oncol.* 2003;129(2):114-122.
34. Ross PJ, Ashley S, Norton A, et al. Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers? *Br J Cancer.* 2004;90(10):1905-1911.
35. Muscaritoli M, Anker SD, Argiles J, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics." *Clin Nutr.* 2010;29(2):154-159.
36. Bossola M, Muscaritoli M, Costelli P, et al. Increased muscle proteasome activity correlates with disease severity in gastric cancer patients. *Ann Surg.* 2003;237(3):384-389.

