HIGHLIGHTS FROM THE 3RD INTERNATIONAL CONFERENCE ON CANCER NUTRITION THERAPY

Complex Patients and Early Interventions for Patients Undergoing Cancer Therapy

Abbott Nutrition Health Institute®
Science. Illuminated.

SEOR
Sociedad Española de Oncología Radioterápica

Abbott
A Promise for Life

The 3rd International Conference on Cancer Nutrition Therapy was held in Madrid, Spain, May 9-10, 2012, in association with the Spanish Society for Radiotherapy Oncology (SEOR) at the Ateneo de Madrid, a private cultural society established in 1835 to advance science, literature, and art within Spain. The focus of the conference was on complex patients and early intervention for patients undergoing cancer therapy. Included in the program were sessions on basic science of cancer cachexia, translational science with a focus on sarcopenic obesity, importance of nutritional assessment, early nutritional support during chemo and radiotherapy, and clinical evidence from around the world. Additionally, Abbott Nutrition partnered with SEOR to support investigators and their research with an abstract submission and award program.

For the 3rd year, the conference was chaired by **Kenneth C.H. Fearon, M.D., FRCS (GLAS), FRCS (ED), FRCS (ENG), Professor of Surgical Oncology, University of Edinburgh, Scotland. Maria Isabel Correia, M.D., Ph.D., Professor of Surgery, Federal University of Minas Gerais, Belo Horizonte, Brazil**, served as Co-chair and **Josep M. Argiles, Ph.D., Professor, Cancer Research Group, Universitat de Barcelona, Spain**, served as Honorary Chair. The program included 17 speakers from 12 countries with experience in surgical, radiation, and medical oncology, gastroenterology, basic science research, cardiology, palliative medicine, pathology, and nutrition. One hundred forty-eight health care professionals including oncologists, surgeons, internists, palliative care specialists, hematologists, basic scientists, dietitians and a nurse from 21 countries attended this year's conference.

Representing the SEOR, **Jorge Contreras Martinez, M.D., Ph.D., Associate Professor, Faculty of Medicine, University of Malaga, Spain**, opened the conference by discussing how cancer is the 2nd leading cause of death worldwide with 1/3 of these deaths related to nutrition. The prevalence of weight loss in people with cancer ranges from 31%-87% and is associated with negative clinical outcomes.[1]

The Conference Chair, Professor Fearon, stated in his opening remarks that we are here to think about cancer nutrition therapy and share knowledge. He encouraged everyone to ask questions so that they would come away with a greater understanding of cancer nutrition therapy. In addition, he stated how all cancer patients are not the same: some are obese, sarcopenic, diabetic, or anorexic. He challenged all to think of the complexity of their patients. Patients now are also undergoing cycles of complex treatment. Muscle is the key organ to support; however, adipose tissue is also important.

Basic Science: Fat-muscle physiology in cancer cachexia

Gerald Höfler, M.D., Medical University of Graz, Austria, presented information on fat metabolism in cancer cachexia. Increased lipolysis is seen in cancer cachexia, with patients losing both adipose tissue and skeletal muscle mass. Cancer cachexia differs from anorexia in that it cannot be reversed nutritionally. In comparing body mass between normal and cachectic patients, body fat was markedly reduced in the cachectic patients.[2] Factors released by the tumor (TNF-α, proteolysis inducing factor, IL-6) cause an increase in lipolysis, proteolysis, and resting energy expenditure.[3,4]

Dr. Höfler discussed an animal study where white adipose tissue (WAT) disappeared when tumor was injected into the mice.[5] Muscle and weight decreased resulting in cachexia in 2-3 weeks. When the gene of the first enzyme of the lipolysis pathway (adipose triacylglyceride lipase-ATGL) was knocked out, the mice did not develop cachexia. Muscle mass was lost due to proteasome activity; however, if proteasome activity is stopped, muscle is maintained.

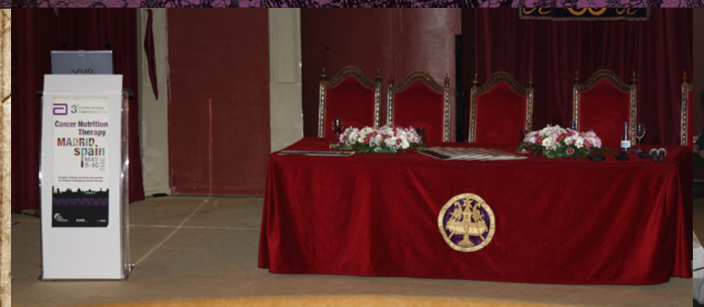
Patients with cancer have higher lipolysis activity in adipose tissue. A negative correlation exists between body mass index (BMI) and WAT activity. Pharmacological inhibition of ATGL may help prevent cachexia.

Phil Atherton, BSc, MSc, Ph.D., University of Nottingham Medical School, Derby, UK, discussed muscle protein physiology in both normal and cachetic individuals. In healthy, weight-bearing individuals, muscle equilibrium is maintained due to a balance between muscle protein synthesis and breakdown, which fluctuates over the course of a day. Muscle protein turnover can be measured by incorporating tracer amino acid isotopes into protein and then measuring the isotope in the blood. Essential amino acids cause an increase in post-prandial muscle protein synthesis that is not dependent on insulin.[6,7] The decrease in postprandial muscle protein breakdown is mediated by insulin.[6] Dr. Atherton went on to describe the concept of anabolic resistance as a regulator of atrophy/cachexia. Anabolic resistance in muscle wasting has been observed in the elderly and immobile as well as cancer patients.[8-10]

Dr. Atherton presented unpublished data on his work in protein metabolism in patients with colorectal cancer. Muscle protein metabolism was evaluated in these patients before and 6 weeks after surgery using an isotope labeled mixed amino acid feed infused during the fasted and fed state. Lean leg muscle mass loss was increased 6 weeks after surgery. Additionally, he observed anabolic resistance to muscle protein synthesis and an increase in muscle protein breakdown in these patients before and after resection surgery in postabsorptive and postprandial conditions. Dr Atherton observed an inverse relationship between percent of lean leg muscle loss (postoperative muscle atrophy) and postprandial muscle protein synthesis, suggesting that maintaining an anabolic response to feeding is a key component of muscle maintenance (limiting postoperative muscle atrophy).

Omega-3 fatty acids have been shown to have a positive effect on muscle protein anabolic response.[11] Dr. Atherton presented results of his study on the effect of omega-3 fatty acids on muscle protein synthesis in older adults.[12] After 8 weeks of supplementation, muscle protein synthesis was greater in omega-3 fatty acid supplemented patients versus the corn oil control group during the hyperaminoacidaemic-hyperinsulinaemic clamp period compared to basal. Dr. Atherton posed the question on whether the benefit of omega-3 fatty acids is due to anti-inflammatory or anabolic effects. To evaluate the potential non-anti-inflammatory anabolic effect of long-chain omega-3 fatty acids, he conducted a study in young, glucose tolerant, non-inflamed individuals. Similar to what was observed in his study of older individuals; he noted an increase in muscle protein synthesis (anabolic effect) of omega-3 fatty acids in the younger adults.[13] He summarized by saying additional studies are needed to evaluate the effect of omega-3 fatty acids on muscle metabolism in human cancer.

MADRID Spain MAY 9-10 2012



Translational Science: Obesity and cachexia together: how to manage friend or foe?

Dr. Vickie Baracos, University of Alberta, Canada, discussed the effects of sarcopenia and obesity on function and survival in patients with cancer. Cancer patients are now more likely to be overweight or obese and sarcopenic rather than being clinically underweight. Data on BMI (in kg/m^2) in 441 patients in Northern Alberta, Canada, with non-small cell lung cancer IIIB/IV, revealed that 60% of the patients had a BMI around 25.[14] Cachexia is defined as a complex metabolic syndrome due to underlying illness characterized by the loss of muscle with or without the loss of fat.[15] Therefore, measuring both muscle and fat can help in assessing for cancer cachexia. One method to do this is to look at computed tomography (CT) images of skeletal muscle at defined vertebral landmarks: e.g., the 3rd lumbar vertebra and the 4th thoracic vertebra.

Sarcopenia has been associated with increased risk for mortality with lower muscle mass associated with increased mortality risk.[16] Body mass index does not reveal signs of muscle wasting. Abdominal CT images of patients with the same BMI can show one with sarcopenia and one without. Sarcopenia has also been shown to be a prognostic indicator in other disease conditions, for example, patients with cirrhosis.[17]

In patients with metastatic breast cancer who were receiving capecitabine,[18] sarcopenia was found to be a factor in dose-limiting toxicity and treatment interruptions (dose reductions or delays). A BMI < 25 and sarcopenia was associated with dose-limiting toxicities in patients with renal cell carcinoma.[19]

In patients with hepatocellular carcinoma treated with sorafenib, dose limiting toxicity was observed in about 80% of sarcopenic patients with over 40% of the sarcopenic patients experiencing grade 3/4 diarrhea.[20]

Muscle wasting can occur due to a number of factors, such as cancer, aging, malnutrition, co-morbid conditions, inactivity, and medications (for example, high doses of corticosteroids). Dr. Baracos discussed the following muscle building treatments to reverse muscle wasting:

- physiology (anabolic assistance through the use of testosterone, resistance training, insulin) and nutrition (nutrients essential for muscle building-protein, amino acids, omega-3 fatty acids, creatine, vitamin D)
- drugs (anabolic steroids)

Gianni Biolo, M.D., Ph.D. University of Trieste, Italy, presented data on how to treat the obese patient with cachexia. He described a vicious cycle of sarcopenic obesity that is characterized by a systemic inflammatory response, insulin resistance, anabolic resistance to amino acids and protein, muscle atrophy, positive energy balance, increased fat deposition, and decreased physical activity. In a study he conducted he found that positive energy balance compared to near neutral energy balance resulted in muscle atrophy and an increase in fat mass during 5 weeks of bed rest.[21]

Anabolic resistance to amino acids can develop as a result of inactivity, aging, cancer, and acute and chronic diseases with systemic inflammation. To overcome anabolic resistance, protein requirement is increased. In addition, resistance exercise has been shown to enhance the anabolic efficiency of amino acids and protein.

In a randomized, controlled trial in non-dialyzed patients with chronic kidney disease, changes in muscle strength were significantly greater after 12 weeks in the resistance exercise training group ($P = 0.001$) compared to the control group.[22, 23]

Timing of protein supplementation has been found to be important for muscle protein synthesis. Muscle hypertrophy was greater in elderly individuals consuming protein immediately after resistance training compared to those who consumed protein 2 hours post exercise.[24]

In a prospective, observational study of 2987 women diagnosed with stage I, II, or III breast cancer, physical activity in the form of walking about 3 to 5 hours per week was shown to reduce risk of death from the disease.[25]

Dr. Biolo also discussed functional nutrients including a study of fish oil supplementation in elderly women participating in strength training.[26] Muscle strength and functional capacity improved after 90 days in the women who received 2 g fish oil/day compared to the control group.

In summary, treatment of obese patients with cachexia should include exercise, energy balance, protein intake, and functional nutrients.

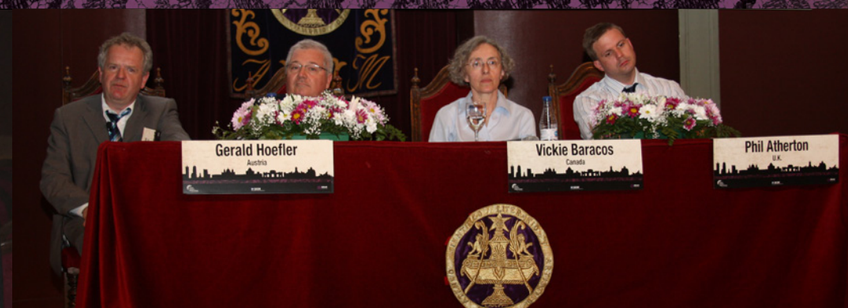
Selected Clinical Evidence From Around the World

Hiromitsu Takeyama, M.D., Ph.D., Nagoya City University Graduate School of Medical Sciences, Japan, presented results of his study on EPA and pancreatic cancer. The objective was to evaluate the effect of omega-6 fatty acid arachidonic acid (AA) and omega-3 fatty acid eicosapentaenoic acid (EPA) on growth of pancreatic cancer *in vitro* and *in vivo*.

In a COX-2 positive human pancreatic cells BxPC-3, AA stimulated growth while EPA decreased growth.[27] When prostaglandin E_2 and E_3 (PGE_2 and PGE_3) were exposed to the cell line, PGE_2 stimulated BxPC-3 growth, whereas PGE_3 decreased cell growth. However, COX-2 inhibitor was shown to reverse the AA mediated increase in cancer cell growth. In contrast, EPA appears to affect both COX-2 dependent and COX-2 independent mechanisms in decreasing cell growth.

In an *in vivo* mouse study, tumor volume was lower in the animals fed fish oil compared to those fed corn oil. There was also a difference in PGE_2 and PGE_3 levels, with PGE_3 not detected in the corn oil fed group. Apoptotic cells were increased in the fish oil group, correlating with decreased tumor growth. Dr. Takeyama concluded by stating that omega-3 fatty acids may be beneficial as monotherapy or in combination with standard chemotherapeutic agents in patients with pancreatic cancer.

Joan Trabal, RD, MS, Barcelona, Spain, presented results of his study on the potential usefulness of EPA-enriched nutritional supplement on chemotherapy tolerability in cancer patients without overt malnutrition.[28] Patients who receive chemotherapy can experience weight loss which can lead to the development of toxicities and lower doses of chemotherapy, which in turn can lead to poor outcomes. Nutrition, however, can improve tolerance to chemotherapy. Is there scientific evidence and which intervention is the best? The omega-3 fatty acid eicosapentaenoic acid (EPA) has been show to suppress proteolysis and lipolysis[29] and attenuate weight loss.[30] Patients with stage IV disseminated colorectal cancer receiving 1st line chemotherapy treatment (FOLFOX, capecitabine) with a Subjective Global Assessment (SGA) score of malnourished were enrolled. The intervention in this 3-month prospective, randomized, controlled, open-label study included 2 packs/day of an oral nutritional supplement enriched with EPA and protein, dietary counseling, and handouts, while the control group received only dietary counseling and handouts. The primary outcome was chemotherapy tolerability. Patients completing the study included 6 in the supplement group and 7 in the control group. After 12 weeks, weight gain was observed in the supplement group (69.58 kg to 74.52 kg) with a slight decrease in the control group (72.62 kg to 71.45 kg), ($P = 0.045$). No differences were seen in biochemical parameters between groups at baseline and 3 months. No differences were seen in energy and protein intakes before and after chemotherapy, although the supplement group had slightly higher protein intake. Results of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QoL) revealed higher scores for role function and social function, fatigue, and improvement in appetite in the supplement group compared to the control group. No differences in SGA or food related chemotherapy side effects were observed between the groups. There were 0 interruptions/delays in chemotherapy in the supplement group compared to 4 in the control group. These results suggest that intervention with an EPA-enriched nutritional supplement and dietary counseling can have a positive effect on chemotherapy tolerability in patients with advanced colorectal cancer.



Investigator Award Presentations

To support investigators and their research, the conference included an abstract submission and poster presentation. Seventeen abstracts were submitted and included research in basic and translational science and clinical nutrition practice. As a sponsor of this session, the Spanish Society for Radiotherapy Oncology (SEOR) selected three abstracts for oral presentations. Summaries of these three presentations are highlighted below.

Jenny Turcott, Mexico City, Mexico, presented results of her study on the effect of chemotherapy with paclitaxel and cisplatin on development of dysgeusia in patients with advanced non-small cell lung cancer (NSCLC).

Dysgeusia (change in taste) is a common toxicity that can manifest as a:

- Distortion in taste
- Lack of taste (ageusia)
- Decreased sensitivity of perception (hypogeusia)
- Increased sensitivity to some or all flavors (hypergeusia)

The objective of her study was to evaluate changes in perception and recognition thresholds of bitter, sweet, and umami tastes and their relationship with diet consumption in patients with advanced NSCLC. Seventy patients naïve to treatment were enrolled in this cohort study. Perception and recognition thresholds of bitter, sweet, and umami tastes were measured at baseline and after 2 cycles of chemotherapy (approximately 6 weeks). Tastes were presented in high concentrations to assess hypogeusia and low concentrations to assess hypergeusia. A Spanish-based food frequency questionnaire was used to collect dietary intake.

Umami-*a fifth basic taste described as savory with a pleasant "brothy" or "meaty" taste usually imparted by glutamate and ribonucleotides, which occur naturally in foods such as meat, fish, vegetables, and dairy products. Umami produces a long lasting, mouthwatering and coating sensation over the tongue. (http://en.wikipedia.org/wiki/Umami)*

Fifty-seven patients were included in the results. At baseline, 59.6% of patients were well nourished as assessed by SGA. The most frequent adverse events as measured by the Common Terminology Criteria for Adverse Events included anorexia (38.6%), lymphopenia (31.6%), dysgeusia (29.8%), and nausea (28.1%). Taste disorders reported by the patients included bitter taste, no taste, unpleasant taste, and different taste. Trends were found in bitter perception threshold ($P = 0.051$) and in umami recognition threshold ($P = 0.060$). Patients who experienced high sweet perception threshold consumed less calories, proteins, and micronutrients than those with low sweet perception threshold. The presence and type of dysgeusia should be evaluated in patients as this can affect nutrient intake and nutritional status.

Chikao Miki, M.D., Ph.D., Japan, conducted a study to assess the effect of age-related changes in metabolic response to cancer and surgery on body protein breakdown and cytokine profile in patients with gastrointestinal (GI) cancer. Seventy patients who underwent surgery for GI cancer were enrolled: 25 with gastric cancer and 45 with colorectal cancer. Creatinine height index (CHI) and daily excretion of urinary 3-methylhistidine (3-MH) were used to measure whole-body protein catabolism. Data were analyzed based on age group: younger patient group (n=35, mean age 58 years), elderly patient group (n=35, mean age 76 years). The elderly patients had a statistically higher rate of infection than the younger group ($P = 0.0168$). Protein breakdown ratio was found to be significantly associated with septic complications in the elderly group ($P = 0.0340$). Additionally, a positive correlation was observed between protein breakdown ratio and hospital length of stay in the elderly patients.

Maria Isabel Correia, M.D., Ph.D., Federal University of Minas Gerais, Brazil, gave the oral presentation for her student, **Sílvia Fernandes Maurício**, (who was not in attendance). Ms Maurício looked at the relationship between nutrition assessment using SGA and Glasgow Prognostic Score (GPS) in patients with GI cancer. Glasgow Prognostic Score is an inflammation-based prognostic score. Gastrointestinal cancer patients who had not received chemotherapy were enrolled. Morbidity was evaluated based on the National Cancer Institute Common Toxicity Criteria. Weight loss of >10% was found in 49.9% of the patients. Over 54% of the patients were severely malnourished based on SGA. When GPS was aligned with SGA, 100% of the patients with a GPS score of 2 were in the SGA C category (severely malnourished). Patients in SGA C category and with a GPS score of 1 or 2 had more complications. These results suggest that as the prevalence of malnutrition increases, so does morbidity. In her conclusion, Ms Maurício stated that in outpatient oncology clinics GPS should be used as a screening and predictive tool.

Posters

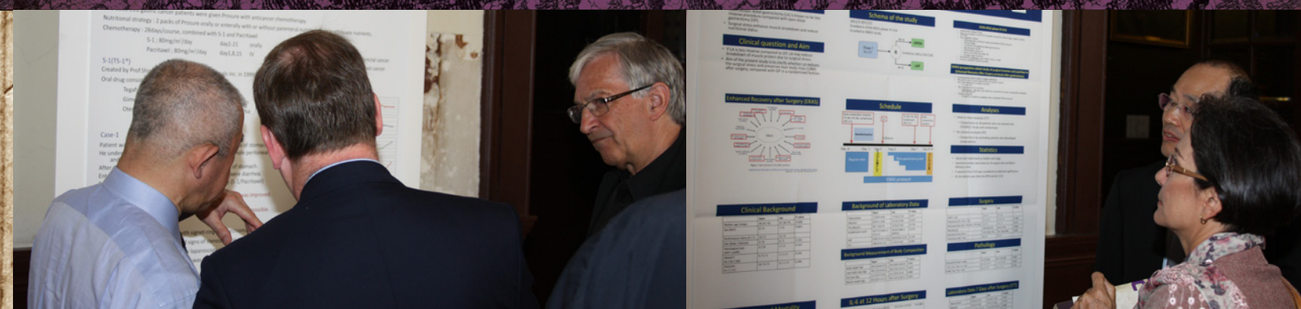
Four of the submitted abstracts included studies conducted with an oral nutritional supplement enriched with EPA and protein. Findings from these studies are summarized below.

1. **Dr. Hiroshi Imamura from Japan** evaluated the effect of an oral nutritional supplement enriched with EPA and protein in patients with gastric cancer with a C-reactive protein (CRP) level > 0.5 mg/dL and an albumin level < 3.5 g/dL who were receiving primary chemotherapy. Nine of the 14 patients showed an improvement in CRP and 8 had an improvement in albumin.

2. **Dr. Masaaki Taniguchi from Japan** highlighted data on two patients with gastric cancer receiving chemotherapy who consumed an oral nutritional supplement enriched with EPA and protein. The first patient was a 60-year-old man who underwent surgery for gastric cancer. After surgery he developed stenosis of his stomach which affected his ability to eat or drink. Enteral feeding through a jejunostomy was given but failed due to severe diarrhea. Parenteral nutrition (PN) and chemotherapy were initiated. After 2 weeks of chemotherapy, the stenosis improved so that the patient could begin to take liquids. He was advised to consume 2 packs of an oral nutritional supplement enriched with EPA and protein each day. The second patient was a 56-year-old woman who also developed stenosis. Parenteral nutrition and chemotherapy were also initiated. Because she was able to take liquids, but not food, she was also given 2 packs of an oral nutritional supplement enriched with EPA and protein and 2 packs of an energy-dense, standard nutrition formula. Drinking an oral nutritional supplement enriched with EPA and protein helped both patients to gradually consume food and wean off PN. Weight and albumin levels were maintained. With the help of chemotherapy, these 2 patients were able to consume an oral nutritional supplement enriched with EPA and protein, which enabled them to continue receiving treatment.

3. **Dr. Yoshihiro Tanaka from Japan** retrospectively evaluated the effect of an oral nutritional supplement enriched with EPA and protein on body weight loss and duration of chemotherapy in patients with recurrent stage IV esophageal cancer. Six patients were included in the standard diet and supplement group (Group A) and six were in the standard diet without supplement group (Group B). Patients in Group A experienced a positive change in weight (+0.25 ± 3.43 kg) while those in Group B had a negative change (-8.15 ± 3.83 kg; $P = 0.004$). Although not significant, there was a trend toward more months of receiving chemotherapy in Group A (mean duration 11 vs 8.6; $P = 0.314$).

4. **Dr. Tibor Csóka from Slovakia** evaluated the effect of an oral nutritional supplement enriched with EPA and protein on weight, inflammatory blood parameters, compliance, and quality of life in weight-losing patients receiving treatment for various types of solid tumors. Patients were enrolled if they had > 5% pre-illness weight loss during the previous 6 months. Anticancer treatment included chemotherapy, radiotherapy, surgery, or no or other treatment. Patients were to consume 2 containers of an oral nutritional supplement enriched with EPA and protein each day for 4 months. Data was collected monthly. Weight stabilized during the study. Inflammatory markers decreased. C-reactive protein decreased significantly ($P = 0.01$) and albumin showed an increase ($P < 0.01$). Intake of > 1.5 containers/day was noted in 77%, 75%, and 69% of the patients after month 2, 3, and 4, respectively. The main reason for discontinuing the supplement was loss of appetite or nausea.



Early Nutritional Support During Chemotherapy and Radiotherapy

Jann Arends, M.D., Tumor Biology Center at Freiburg University, Germany, described the use of multimodal management of nutritional problems during oncological therapy. Many patients have lost weight before a cancer diagnosis,[1] with weight loss continuing after diagnosis.[31] Patients with pancreatic cancer without cachexia survive significantly longer than those with cachexia ($P < 0.001$).[32] Practically, the approach to treatment should be simple: curative treatment, palliative oncological treatment, and/or supportive care. A vicious cycle exists in cancer patients between reduced oral intake, decreased physical activity, and inflammation. All 3 of these factors have an effect on body weight and muscle mass. Therefore, treatment should be multimodal that includes, in addition to anti-cancer therapy, nutrition to increase energy and protein intake, muscle training, and anti-inflammatory drugs. Use of non-steroidal anti-inflammatory drugs has been shown to prolong survival in weight losing cancer patients ($P < 0.03$).[33]

In a study by Ravasco and colleagues,[34] patients with colorectal cancer who were starting radiotherapy (n = 111) were randomized to receive dietary counseling, protein supplements, or usual care. Patients in the dietary counseling group had the greatest increase in caloric intake at the end of radiotherapy and 3 months after than the other 2 groups. Data in 152 patients with colorectal cancer demonstrated a greater survival advantage in patients who received 500 kcal/day from parenteral nutrition.[35]

Elisabeth Isenring, Ph.D., AdvAPD, Queensland University of Technology, Australia, discussed the use of conventional nutrition therapy during radiotherapy and chemotherapy. Patients can experience side effects from the tumor or from cancer treatment. Side effects of cancer treatment have many recognized nutritional symptoms (e.g., nausea, vomiting, diarrhea, dysphagia, loss of appetite). A number of evidence-based guidelines are available that provide guidance on nutritional care in head and neck cancer patients, patients with cancer cachexia, patients receiving radiotherapy and chemotherapy, and patients requiring enteral or parenteral nutrition support. Recommendations are graded based on level of evidence, with randomized, controlled trials being the gold standard for highest level of evidence. Dr Isenring is the chair of the committee that is updating evidence-based practice guidelines for the nutritional management of radiotherapy. The goal of the update is to include chemotherapy and combine the guidelines with the evidence-based practice guidelines for the nutritional management of adult patients with head and neck cancer in order to create one set of oncology guidelines. Clinical questions that were evaluated included appropriate access to care, nutrition intervention, and nutrition monitoring and evaluation. A literature search found 5 randomized, controlled trials in chemotherapy. This suggests that the data is not as strong for nutrition intervention in chemotherapy and more studies are needed to establish a recommendation.

Vera C Mazurak, Ph.D., University of Alberta, Canada, discussed fish oil supplementation during chemotherapy. Earlier studies have demonstrated that fish oil supplementation may attenuate muscle and weight loss,[30, 36] improve physical function,[37] and quality of life.[38]

Lung cancer is the leading cause of death worldwide.[39] Over 75% of lung cancer diagnoses are made at an advanced stage. Malnutrition is common in these patients, particularly muscle and adipose tissue wasting.[40]

Dr. Mazurak conducted an open-label study in patients with NSCLC receiving 1st line chemotherapy to assess the effect of fish oil supplementation on weight loss, skeletal muscle, tumor response, and side effects[41, 42]. Body composition was measured using diagnostic CT images. People in the fish oil group were able to maintain weight and muscle while losing intermuscular adipose tissue. Fish oil was found to improve response rate (60% in fish oil vs. 26% in standard of care, $P = 0.008$) and clinical benefit to chemotherapy (80% in fish oil vs. 42% in standard of care, $P = 0.02$). Patients in the fish oil group received more chemotherapy. No difference in toxicity was found between the groups. Although not statistically significant possibly due to the small sample size, there was a trend towards improved one-year survival in the fish oil group. Dr. Mazurak concluded by recommending that interventions should be implemented before patients become cachexic. Providing a choice of supplement format (capsules or liquid) may increase compliance, which was 95% in her study.

Karla Sanchez Lara, MSc, Ph.D., Médica Sur University Hospital, Mexico City, Mexico, presented results of her study on the effect of an oral nutritional supplement (ONS) with EPA on nutritional and inflammatory parameters, response and toxicity to chemotherapy, quality of life, and survival in treatment-naïve patients with advanced NSCLC.

Patients who were newly diagnosed with NSCLC and were eligible to receive 1st line palliative chemotherapy were enrolled. Individual energy needs were assessed at 30 kcals/kg. The control group received diets based on set calorie levels (1400-2200 kcal). The experimental group received similar calorie diets in addition to 590 kcals provided by an ONS with EPA. Patients in the experimental group (n=46) maintained their weight between baseline and the end of the 2nd chemotherapy cycle, whereas patients in the control group (n=46) lost weight. Additionally, significant changes in inflammatory markers (CRP, TNF-α) between baseline and the end of the 2nd chemotherapy cycle were found in the experimental group but not the control group. Dietary intake revealed that the ONS did not replace food intake. Significant changes between baseline and the end of the 2nd chemotherapy cycle between the groups were noted for global health status, fatigue, nausea and vomiting, appetite loss, and neuropathy (health related quality of life domains measured by EORTC QLQ C-30). [43] Progression free survival was also significantly higher in the ONS-EPA supplement group ($P = 0.05$).

Jorge Contreras Martinez, M.D., Ph.D., University of Malaga, Spain, gave a presentation on nutrition intervention during radiotherapy. The goal of radiotherapy (RT) is to provide the maximum dose to kill the cancer cells while producing minimum toxicities. A number of nutritional problems can develop as a result of radiotherapy including anorexia, difficulty swallowing, altered sense of smell, taste changes, mucositis, xerostomia, weight loss, nausea, vomiting, constipation, and diarrhea. These nutritional problems can cause a decrease in tolerance and effect of radiotherapy and reduce quality of life. Dr. Contreras described a number of objectives of nutritional intervention during radiotherapy:

- To prevent and treat malnutrition
- To reduce the toxicity of radiotherapy
- To improve the effect of the treatment
- To improve QoL

Dr. Contreras discussed a prospective non-randomized comparative study of prophylactic gastrostomy (PEG) versus no PEG in 50 patients with stage III and IV head and neck cancer receiving radiotherapy. Weight loss was less in the PEG group at 4 weeks and 8 weeks. Quality of life was higher at week 1 in patients with PEG compared to those without PEG, and remained higher at both week 4 and 8 in the patients with PEG. He concluded by stating: “We can obtain better results in terms of local control and survival with RT by doing a nutritional intervention.”

Nutrition-Related Assessment and Outcomes during Cancer Treatment

Marie Fallon, M.D., University of Edinburgh, Scotland, discussed how to screen patients for entry into clinical trials. Patients may be experiencing symptoms other than the index symptom(s) being measured in the trial. These confounding symptoms should be stable before patients enter a trial to avoid compromising the trial results. In screening patients for study eligibility, one needs to consider prognosis, physical symptoms, psychological symptoms, family or caregiver support, and family anxieties.

A typical clinical scenario is uncontrolled pain, which can lead to poor appetite and weight loss. Analgesia for pain can also cause nutritional problems, e.g., constipation, nausea, and vomiting. Depression is also common in cancer patients, which if not treated, can contribute to significant weight loss.

Professor Fallon presented a case study of a 72-year-old man with advanced NSCLC who was evaluated for participation in a cachexia study. He was experiencing pain due to a right Pancoast tumor that had not been relieved by palliative radiotherapy, weight loss of 15%, poor appetite, and inability to sleep due to the pain. After 2 weeks of pain medication (duloxetine) his pain, appetite, sleep, and mobility improved.

Professor Fallon summarized by saying that timing is important. All symptom studies should include standard best supportive background care; otherwise what one thinks they are measuring in a trial may be different from what they are actually measuring.

Vickie Baracos, Ph.D., discussed what clinicians need to assess. There are now published definitions and classifications for cancer cachexia[44] and adult starvation and disease-related malnutrition.[45] She described the consensus process used by the international expert panel to achieve the statements used to define and classify cancer cachexia.[44] Statements were scored from 1 (disagree) to 10 (agree). Consensus was achieved when there was a mean score greater than 7, with no score less than 5.

Four domains of the conceptual framework include:

1. depletion of reserves
2. limitation of food intake
3. catabolic drivers
4. impact and outcomes

The first two domains define malnutrition and the first three define cachexia. Cachexia is disease-associated malnutrition. Examples of conditions associated with each domain include:

- weight loss, muscle wasting, sarcopenia
- nutrition related symptoms-nausea, dysphagia, anorexia
- inflammation, tumor burden, insulin resistance
- quality of life, physical function, survival, treatment outcomes

Domains of the conceptual framework are found in nutrition assessment tools, for example the Patient-Generated Subjective Global Assessment (PGSGA) and Mini-Nutritional Assessment (MNA). She cautioned, however, that because the criteria and scoring systems of the different assessment tools vary, malnutrition may not be uniformly diagnosed. Dr. Baracos looked at the question of whether these concepts are applied in nutritional assessment in research and practice. In a review of the literature from 2006-2011, 209 studies on nutrition in head and neck cancer patients were reviewed. Twelve studies defined and assessed malnutrition based on 5-7 criteria, while 96 studies used 2-4 criteria. Surprisingly, 101 studies used only one criterion to define malnutrition (10% weight loss or BMI <18.5, low albumin, presence of dysphagia). Dr. Baracos feels we need more consensus processes to define nutrition screening and assessment plans. She listed the following online resources to help monitor patients:

- BMI calculator http://www.nhlbisupport.com/bmi/
- Weight loss calculator http://www.fitwatch.com/qkcalc/calculate-weight-loss-percentage.html
- 24-hour food intake calculator: National Cancer Institute Automated Self-administered 24-hour recall http://riskfactor.cancer.gov/tools/instruments/asa24/

Dr. Baracos concluded by discussing the use of CT or magnetic resonance imaging (MRI) images as a way for clinicians to monitor nutritional status based on:

- skeletal muscle wasting
- altered distribution of body fat
- accumulation of visceral adipose tissue
- pathological accumulation of lipids in tissues (i.e., hepatosteatosis, myosteatosis)

These images are readily available for most cancer patients and provide a way to monitor changes over time.

Stephan von Haehling, M.D., Ph.D., Charité Medical School, Berlin, Germany, gave a presentation on cancer therapy, cardiac function and cachexia. Similar clinical signs and symptoms are found in patients with heart failure and advanced cancer including easy fatigue, dyspnea, > 10% weight loss, and edema.[46] Dr. von Haehling described a study that looked at the effect of chemotherapy on the heart. In a study of 3941 patients, 88 developed doxorubicin-induced congestive heart failure.[47] Anthracyclin is known to cause cardiotoxicity that can become chronic. In a study by Cardinale et al[48] in 703 patients with advanced malignant tumours undergoing high-dose chemotherapy (HDC), the highest level of troponin I was associated with the greatest risk of left ventricular ejection fraction (LVEF) reduction.

Does the tumor itself hurt the heart? Angiotensin II levels were found to be high in cachexic heart failure and cachexic cancer patients (Anker & Coats. Pub No WO00/21509, 2000. Patent No is US 7,417,038 B1, patent date August 26, 2008). Dr. von Haehling found atrial natriuretic peptide to be elevated in patients with pancreatic cancer compared to healthy controls.[49] He also found a decrease in exercise capacity (measured by VCO_2 max) in patients with NSCLC. (Paland & von Haehling. In preparation.)

In a cachexia prevention study in rats, heart weight was found to decrease after tumor inoculation, (Tschirner, von Haehling & Springer. Submitted.) which may be due to a decrease in left ventricular mass.

In conclusion, Dr. von Haehling stated that cardiovascular interventions may help to improve the QoL of patients with cancer and potentially also their survival.

Eduardo Ferriolli, M.D., Ph.D., University of São Paulo, Brazil, discussed physical activity as a patient-focused end point. A number of intervention endpoints can be evaluated, for example, changes in body composition, decrease in inflammation, increase in function or performance status, decrease in pain. Is physical activity one of them?

Disease stage, inflammation, treatment, pain, fatigue, cachexia can all decrease physical activity. If treatment is successful, it can counteract decreases in physical activity.

Physical activity can be measured using accelerometers and pedometers. However, the accelerometers do not discriminate activity and pedometers do not discriminate time. Newer generations of equipment can now discriminate both activities and time.

Dr. Ferriolli conducted a study[50] to look at how daily physical activity is affected by disease state and treatment and the correlation between physical activity, QoL, and performance status. He enrolled 162 patients that included those who had undergone curative surgery and some who were receiving palliative chemotherapy and radiotherapy. Performance status was evaluated based on World Health Organization/Eastern Cooperative Oncology Group (WHO/ECOG) and Karnofsky Performance Status scores. Quality of life was measured using the EORTC QLQ-C30. Physical activity was measured by the ActivPAL™ system. Results show similar activity levels between the healthy controls and early diagnosed cancer patients; however, patients with advanced cancer spent more time sitting/lying. Patients receiving palliative and adjuvant chemotherapy spent more time sitting/lying than the healthy controls. In addition, surgery for upper GI cancer also affected the time spent sitting/lying 1 week after surgery and up to 3 months after with a decrease in time noted 6 months after surgery to a level similar to pre-surgery. Patients with an ECOG score of 2 were found to spend >20 hours sitting/lying.

In conclusion, Dr. Ferriolli stated that measuring physical activity is relatively inexpensive and can provide an objective and meaningful estimate of patient function as well as a surrogate for quality of life.

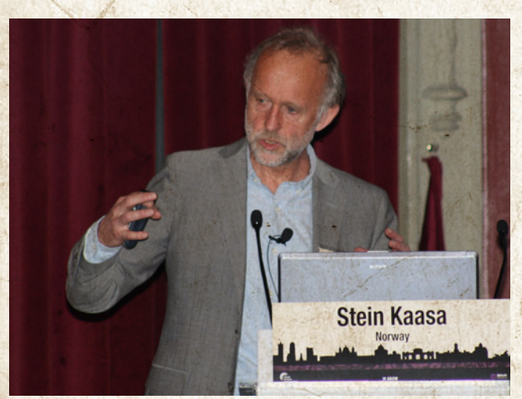
Future of Multimodal Therapy and Cancer Cachexia

Stein Kaasa, M.D., Ph.D., Norwegian University of Science and Technology, Trondheim, Norway, discussed the future of multimodal therapy by describing the MENAC (Multimodal Exercise/Nutrition/Anti-inflammatory treatment for Cachexia) Trial. This trial is being run by the European Palliative Care Research Centre. Currently there is no consensus on how to treat patients with cachexia. So where does one start? With weight loss, inflammation, anorexia, reduced physical function? Or should we look at clinical biomarkers?

Nutrition alone is not enough. A multimodal treatment approach is necessary to deal with the complex pathophysiology. In the MENAC trial, treatment will include a combination of:

- Oral nutritional supplements containing EPA (2 cartons/day for 6 weeks) and nutrition information and dietary advice
- Home-based self-assisted physical exercise program that includes daily walking and resistance exercises performed 3 times/week
- Anti-inflammatory treatment with celecoxib

Patients in the control group will receive standard cancer care treatment.



Currently, a phase II feasibility study is being conducted with 40 patients. A phase III randomised multicentre study will follow completion of the feasibility study. The primary objective of the feasibility study is to evaluate compliance with study intervention and study procedures and to assess for any contamination in the control group with interventions in the treatment group. Patients will be enrolled who have advanced NSCLC (stage III-IV) or non-operable pancreatic cancer and are scheduled to begin chemo- or chemo radiotherapy. Three centers are currently participating in the feasibility study; Dr. Kaasa invited others to join.

In his closing remarks Professor Fearon commented that "Nutritional support is not a hobby, but a professional activity." Nutrition is a core component of supportive oncology. Nutritional support should be provided at a high level to reduce complications and achieve full support.

References

1. DeWys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Am J Med. 1980;69:491-497.
2. Fearon K. The mechanisms and treatment of weight loss in cancer. *Proc Nutr Soc*. 1992;51:251-265.
3. Tisdale M. Cachexia in cancer patients. *Nature Rev Cancer*. 2002;2:862-871.
4. Tisdale MJ. Cancer cachexia. *Curr Opin Gastroenterol*. Mar 2010;26(2):146-151.
5. Das SK, Eder S, Schauer S, et al. Adipose triglyceride lipase contributes to cancer-associated cachexia. *Science*. Jul 8 2011;333(6039):233-238.
6. Greenhaff PL, Karagounis LG, Peirce N, et al. Disassociation between the effects of amino acids and insulin on signaling, ubiquitin ligases, and protein turnover in human muscle. *Am J Physiol Endocrinol Metab*. Sep 2008;295(3):E595-604.
7. Atherton PJ, Etheridge T, Watt PW, et al. Muscle full effect after oral protein: time-dependent concordance and discordance between human muscle protein synthesis and mTORC1 signaling. *Am J Clin Nutr*. Nov 2010;92(5):1080-1088.
8. Cuthbertson D, Smith K, Babraj J, et al. Anabolic signaling deficits underlie amino acid resistance of wasting, aging muscle. *FASEB* J. Mar 2005;19(3):422-424.
9. Glover EI, Phillips SM, Oates BR, et al. Immobilization induces anabolic resistance in human myofibrillar protein synthesis with low and high dose amino acid infusion. *J Physiol*. Dec 15 2008;586(Pt 24):6049-6061.
10. Deutz NE, Safar A, Schutzler S, et al. Muscle protein synthesis in cancer patients can be stimulated with a specially formulated medical food. *Clin Nutr*. Dec 2011;30(6):759-768.
11. Gingras AA, White PJ, Chouinard PY, et al. Long-chain omega-3 fatty acids regulate bovine whole-body protein metabolism by promoting muscle insulin signalling to the Akt-mTOR-S6K1 pathway and insulin sensitivity. *J Physiol*. Feb 15 2007;579(Pt 1):269-284.
12. Smith GI, Atherton P, Reeds DN, et al. Dietary omega-3 fatty acid supplementation increases the rate of muscle protein synthesis in older adults: a randomized controlled trial. *Am J Clin Nutr*. Feb 2011;93(2):402-412.
13. Smith GI, Atherton P, Reeds DN, et al. Omega-3 polyunsaturated fatty acids augment the muscle protein anabolic response to hyperinsulinaemia-hyperaminoacidaemia in healthy young and middle-aged men and women. *Clin Sci (Lond)*. Sep 2011;121(6):267-278.
14. Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. *Am J Clin Nutr*. Apr 2010;91(4):1133S-1137S.
15. Evans WJ, Morley JE, Argiles J, et al. Cachexia: a new definition. *Clin Nutr*. Dec 2008;27(6):793-799.
16. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol*. Jul 2008;9(7):629-635.
17. Montano-Loza AJ, Meza-Junco J, Prado CM, et al. Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol*. Feb 2012;10(2):166-173, 173 e161.

References continued

18. Prado CM, Baracos VE, McCargar LJ, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res*. Apr 15 2009;15(8):2920-2926.

19. Antoun S, Baracos VE, Birdsell L, Escudier B, Sawyer MB. Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. *Ann Oncol*. Aug 2010;21(8):1594-1598.

20. Blanchet B, Billemont B, Cramard J, et al. Validation of an HPLC-UV method for sorafenib determination in human plasma and application to cancer patients in routine clinical practice. *J Pharm Biomed Anal*. May 1 2009;49(4):1109-1114.

21. Biolo G, Agostini F, Simunic B, et al. Positive energy balance is associated with accelerated muscle atrophy and increased erythrocyte glutathione turnover during 5 wk of bed rest. *Am J Clin Nutr*. Oct 2008;88(4):950-958.

22. Castaneda C, Gordon PL, Uhlin KL, et al. Resistance training to counteract the catabolism of a low-protein diet in patients with chronic renal insufficiency. A randomized, controlled trial. *Ann Intern Med*. Dec 4 2001;135(11):965-976.

23. Castaneda C, Gordon PL, Parker RC, Uhlin KL, Roubenoff R, Levey AS. Resistance training to reduce the malnutrition-inflammation complex syndrome of chronic kidney disease. *Am J Kidney Dis*. Apr 2004;43(4):607-616.

24. Esmarck B, Andersen JL, Olsen S, Richter EA, Mizuno M, Kjaer M. Timing of postexercise protein intake is important for muscle hypertrophy with resistance training in elderly humans. *J Physiol*. Aug 15 2001;535(Pt 1):301-311.

25. Holmes M.D., Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA*. May 25 2005;293(20):2479-2486.

26. Rodacki CL, Rodacki AL, Pereira G, et al. Fish-oil supplementation enhances the effects of strength training in elderly women. *Am J Clin Nutr*. Feb 2012;95(2):428-436.

27. Funahashi H, Satake M, Hasan S, et al. Opposing effects of n-6 and n-3 polyunsaturated fatty acids on pancreatic cancer growth. *Pancreas*. May 2008;36(4):353-362.

28. Trabal J, Leyes P, Forga M, Maurel J. Potential usefulness of an EPA-enriched nutritional supplement on chemotherapy tolerability in cancer patients without overt malnutrition. *Nutr Hosp*. Oct 2010;25(5):736-740.

29. Tisdale MJ. Inhibition of lipolysis and muscle protein degradation by EPA in cancer cachexia. *Nutrition*. 1996;12:31s-33s.

30. Wigmore SJ, Barber M.D., 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.

31. Wigmore SJ, Plester CE, Richardson RA, et al. Changes in nutritional status associated with unresectable pancreatic *cancer. Br J Cancer. 1997;75:106-109.*

32. Bachmann J, Ketterer K, Marsch C, et al. Pancreatic cancer related cachexia: influence on metabolism and correlation to weight loss and pulmonary function. *BMC Cancer*. 2009;9:255.

33. Lundholm KG, Gelin J, Hyltander A, et al. Anti-inflammatory treatment may prolong survival in undernourished patients with metastatic solid tumors. *Cancer Res*. 1994;54:5602-5606.

34. Ravasco P, Monteiro-Grillo I, Vidal P, Camilo M. Dietary counseling improves patient outcomes: a prospective, randomized controlled trial in colorectal cancer patients undergoing radiotherapy. *J Clin Oncol*. 2005;23:1431-1438.

35. Shang E, Weiss C, Post S, Kaehler G. The influence of early supplementation of parenteral nutrition on quality of life and body composition in patients with advanced cancer. *JPEN J Parenter Enteral Nutr*. May-Jun 2006;30(3):222-230.

36. Barber M, Ross J, Voss A, et al. The effect of an oral nutritional supplement enriched with fish oil on weight-loss in patients with pancreatic cancer. *Brit J Can*. 1999;81:80-86.

37. Moses A, Slater C, Preston T, Barber M, Fearon K. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by energy and protein dense oral supplement enriched with n-3 fatty acids. *Br J Can*. 2004;90:996-1002.

38. Bauer JD, Capra S. Nutrition intervention improves outcomes in patients with cancer cachexia receiving chemotherapy--a pilot study. *Support Care Cancer*. Apr 2005;13(4):270-274.

39. World Health Organization *Cancer* 2012; Fact sheet N°297. Available at: http://www.who.int/mediacentre/factsheets/fs297/en/.

40. Murphy RA, Mourtzakis M, Chu QS, Reiman T, Mazurak VC. Skeletal muscle depletion is associated with reduced plasma (n-3) fatty acids in non-small cell lung cancer patients. *J Nutr*. Sep 2010;140(9):1602-1606.

41. Murphy RA, Mourtzakis M, Chu QS, Baracos VE, Reiman T, Mazurak VC. Supplementation with fish oil increases first-line chemotherapy efficacy in patients with advanced nonsmall cell lung cancer. *Cancer*. Feb 15 2011.

42. Murphy RA, Mourtzakis M, Chu QS, Baracos VE, Reiman T, Mazurak VC. Nutritional intervention with fish oil provides a benefit over standard of care for weight and skeletal muscle mass in patients with nonsmall cell lung cancer receiving chemotherapy. *Cancer*. Apr 15 2011;117(8):1775-1782.

43. Sanchez-Lara K, Turcott J, Juarez E, et al. Randomized trial effect of an oral nutritional supplement with eicosapentaenoic acid on nutritional and inflammatory parameters, response and toxicity to chemotherapy, quality of life, and survival in treatment-naive patients with advanced non-small lung cancer. *J Clin Oncol*. 2012;30:suppl; abstr e19594.

44. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. Feb 4 2011.

45. Jensen GL, Mirtallo J, Compher C, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. *JPEN J Parenter Enteral Nutr*. Mar-Apr 2010;34(2):156-159.

46. Walsh D, Donnelly S, Rybicki L. The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. *Support Care Cancer*. May 2000;8(3):175-179.

47. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med*. Nov 1979;91(5):710-717.

48. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation*. Jun 8 2004;109(22):2749-2754.

49. von Haehling S, Jankowska EA, Morgenthaler NG, et al. Comparison of midregional pro-atrial natriuretic peptide with N-terminal pro-B-type natriuretic peptide in predicting survival in patients with chronic heart failure. *J Am Coll Cardiol*. 2007;50(20):1973-1980.

50. Ferriolli E, Skipworth RJE, Hendry P, et al. Physical activity monitoring: a responsive and meaningful patient-centered outcome for surgery, chemotherapy, or radiotherapy? *J Pain Symptom Manage*. 2012;43(6):1025-1035.

The conference is funded by Abbott. The conference program was developed by an independent scientific committee chaired by Professor Kenneth C H Fearon and the content of the presentations was developed by the individual speakers with no input from Abbott.

Abbott Nutrition Health Institute®
Science. Illuminated.

SEOR
Sociedad Española de Oncología Radioterápica

Abbott
A Promise for Life