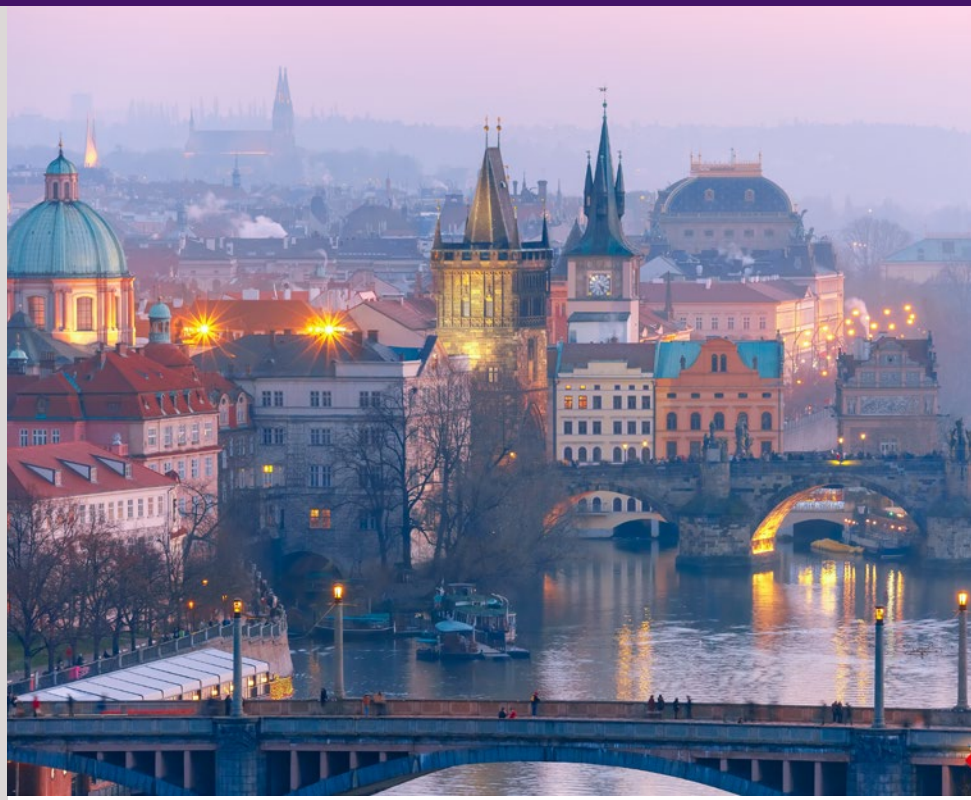
Cancer Cachexia & Omega-3 Fatty Acids Conference

CONFERENCE HIGHLIGHTS



The **Cancer Cachexia & Omega-3 Fatty Acids Conference** was held in Prague, Czech Republic, on May 26, 2016, supported by the Adriatic Club of Clinical Nutrition and Abbott Nutrition. The meeting was chaired by **Professor P. Tesinsky** (CZ) from the Czech Society for Clinical Nutrition and Intensive Metabolic Care, and **Professor Z. Krznarić** (CRO) from the Adriatic Club of Clinical Nutrition. The focus of the conference was to optimize multimodal cancer treatment by defining the best nutritional and metabolic supportive care for the management of patients with cancer. Participants in the conference included oncologists and dietitians from Croatia, Czech Republic, Slovakia, and Slovenia.

Goals for Patients with Cancer

Professor P. Tesinsky (CZ) opened the conference by discussing hospital malnutrition. The cause of hospital malnutrition is often due to both inadequate nutrient intake and disease-related cachexia. Based on observational studies, poor nutritional status is associated with increased adverse events, impaired quality of life, and higher mortality. Professor Tesinsky also identified several goals for cancer patients:

- Stabilise weight
- Maintain/gain fat free mass
- Improve energy and protein intake
- Reduce treatment toxicity
- Less delay in treatment/less dose adaptations
- Reduce postoperative complications
- Improve overall and recurrence-free survival
- Improve quality of life and performance status

CANCER CACHEXIA: THERAPEUTIC APPROACH

An Early, Parallel Supportive Care Pathway to Prevent Cachexia

Professor M. Muscaritoli (IT) began his presentation by discussing the most recent definition of cancer cachexia, which was published in 2011 by Fearon and colleagues.

CANCER CACHEXIA RE-DEFINED

"A multifactorial syndrome charactertised 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 characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism."[1]

Weight loss is prevalent in patients with cancer and can occur anytime during three distinct phases of the disease: before or at diagnosis, during the course of the disease, or after medical/radiation/surgical treatment. The frequency and severity of weight loss is high in patients with gastric and pancreatic cancer: around 70%-80% of patients with 20%-40% of these patients experiencing >10% weight loss.[3]

Both percent weight loss and body mass index (BMI) have been shown to independently predict survival. **Patients with a low BMI and high % weight loss had the shortest survival, 4.3 months, compared to weight-stable patients with a BMI ≥ 25 kg/m², who survived 20.9 months, (*P* < .001).**[4]

Professor Muscaritoli discussed how cachexia is a preventable comorbidity of cancer when a novel strategy using the **T.A.R.G.E.T.** approach, which he and colleagues developed, is applied. Active interventions and or research in the areas of **T**eaching, **A**wareness, **R**ecognition, **G**enetics, **E**arly Exercise, and **T**reatment should be implemented.[5]

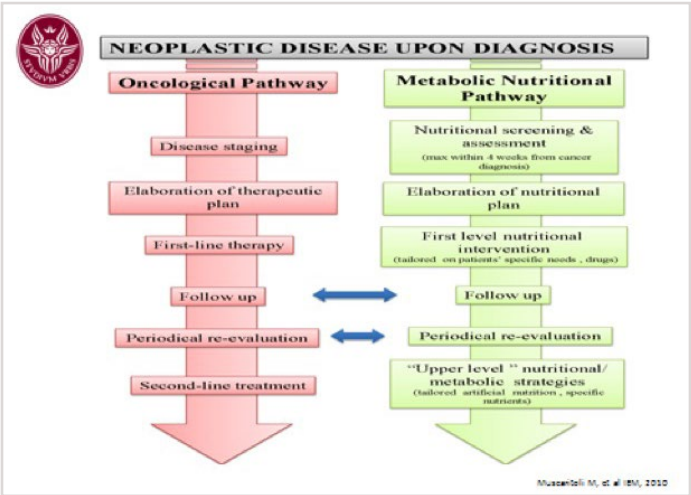
Previously, cachexia was thought of as an end-stage disease where supportive and palliative care was provided. Current thinking is to identify patients in the precachexia stage in order to provide early, active, multi-modal intervention to prevent or delay cachexia.

Along with the definition of cancer cachexia published in 2011, three stages of cancer cachexia have been defined: precachexia, cachexia, and refractory cachexia.[1]

The pathogenesis of cancer-related weight loss is multi-factorial. The tumor itself initiates an **inflammatory response** that can cause anorexia and **altered macro-nutrient metabolism** leading to reduced food intake and loss of weight and lean body mass. Tumors can also increase the production of pro-cachetic factors that increase proteolysis and lipolysis leading to loss of weight and lean body mass.[6]

Body composition (specifically muscle mass) has been shown to be an independent predictor of chemotherapy toxicity.[7,8] Toxicity can lead to dose reductions, treatment delays, or discontinuation of therapy.

A negative effect of cancer cachexia is weight and muscle mass loss, which can reduce tolerance to treatment, impair physical function and quality of life, and shorten survival.



The **parallel pathway** approach involving novel nutritional and metabolic interventions can help prevent/correct malnutrition and prevent or delay the onset of cancer cachexia.[9] Early identification of malnutrition and cachexia is key to implementing timely intervention to improve treatment and patient outcomes.[10] Early intervention, as part of multimodal therapy, includes nutrition support with oral nutritional supplements (ONS).[11]

Eicosapentaenoic Acid (EPA) Helps Reduce Cancer-Related Inflammation

Eicosapentaenoic acid (EPA), an omega-3 fatty acid, is a component of cell membranes that is metabolized to cytokines that are less proinflammatory, thereby playing a role in attenuating inflammation. Additionally, omega-3 fatty acids have been shown to promote muscle protein synthesis in older adults.[12]

In a study in patients with non-small cell lung cancer receiving chemotherapy, fish oil supplements (2.2 g EPA/day) have been shown to stabilize weight and skeletal muscle mass compared to standard care.[13] Fish oil supplements (2.25 g EPA + DHA/day) have also been shown to **increase chemotherapy response rate** (complete or partial) in patients with advanced non-small cell lung cancer compared to standard of care (60.0% vs 25.8%, *P* =.008).[14]

Studies have also been conducted with ONS enriched with EPA. In a randomized, controlled trial in patients with lung cancer undergoing chemo-radiotherapy, a significant increase in physical activity level was observed at weeks 3 and 5 in the EPA group compared to the standard ONS control group without EPA.[15]

In another randomised controlled trial in patients with advanced non-small cell lung cancer, an ONS enriched with EPA improved lean body mass and protein and energy intake compared to an isocaloric standard diet. Fatigue and neuropathy also decreased in the EPA ONS group.[16] A systematic review published in 2015 provides support for the use of omega-3 fatty acid supplements in patients undergoing chemotherapy and/or radiotherapy in maintaining or improving weight, modifying body composition, and improving quality of life.[17]

New ESPEN Oncology Guidelines: The Role of Omega-3 Fatty Acids (EPA)

Professor Krznarić (CRO) discussed both Croatian guidelines for the use of EPA and megestrol acetate in cancer cachexia syndrome and the new unpublished ESPEN guidelines including the oncology recommendations. The Croatian guideline states that an oral nutritional supplement that is polymeric, high protein, high energy with EPA (2.2 g/day) should be the first choice for nutritional support.[18]

A few of the proposed ESPEN guidelines reviewed include:

- screening, assessment
- energy requirements (25-30 kcal/kg/day)
- efficacy of nutritional intervention
- protein requirements (1-1.5 g/day)
- use of omega-3 fatty acids (2.0 g/day) to improve appetite and body weight
- enhanced recovery after surgery

How Can We Improve Our Practice?

Professors F. Novak, P. Benes, and M. Tomiska (CZ) moderated this section of the conference that focused on country cancer nutrition practices presented by national speakers.

Czech Working Group for Nutritional Care in Oncology

Dr. V. Manasek (CZ) presented information on the Czech Working Group for Nutritional Care in Oncology, a part of the Czech Oncology Society. The Working Group was established in 2010 to define standards of nutritional care in oncology and improve nutritional status of oncology patients in the Czech Republic. The Working Group created an Oncology Nutritional Screening Protocol. A screening project was initiated in 2011 and 2012. National data were obtained from 10,000 oncology patients. **In the outpatient setting, 71.4% of cancer patients were found to be at risk of malnutrition.** Interestingly, the average BMI was 26.8. Screening can help identify patients who are malnourished and require intervention.

A **health economics oncology project** was conducted evaluating the effect of pre- and postoperative nutritional support on complications in 107 patients with colorectal cancer. A high protein ONS was consumed at least 10 days before surgery and two weeks after. Risk of wound dehiscence, anastomosis dehiscence, infection, and re-hospitalization were lower in the ONS group compared to the control group.

Individualized Nutritional Care with ONS

Dr. P. Holeckova (CZ) presented results of a study that evaluated the effect of individualized vs standard nutritional care on nutrition status in 82 patients undergoing oncology treatment. Individualized nutritional intervention included dietary counseling and ONS to provide 1 g/kg protein and 30 kcal/kg vs standard nutritional care for 60 days with 90 day follow-up. BMI was stable at week 12 in the intervention group but decreased in the standard group. Weight was maintained at week 12 in the intervention group but decreased in the standard of care group. Average hand grip strength was stable at week 12 in the intervention group but decreased in the control group. A significant correlation was noted between protein intake and muscle strength. The intervention group also had significantly fewer infectious complications (8%) than the standard group (24%). These findings suggest that individual nutrition care together with ONS can help prevent loss of weight and muscle strength and help decrease infectious complications.

Czech Guidelines for Nutritional Care of Patients with Colorectal Cancer

Dr. P. Benes (CZ) discussed Czech guidelines for nutritional care of patients with colorectal cancer. Colorectal cancer is the 3rd most common type of cancer in the Czech Republic. The guidelines were developed to help identify patients at nutritional risk and to identify when during the course of treatment nutritional intervention should be provided. All patients must be nutritionally assessed using a formalized tool and educated on the importance of nutrition. For surgical oncology patients who are identified as mild/moderate nutrition risk, an ONS with EPA is prescribed for 7-10 days preoperatively along with 40 g protein/day for pre-cachexia. For patients undergoing other treatment and who are identified as being at mild/moderate nutrition risk, written educational material is provided and supplemental ONS are recommended based on need (i.e., ONS that are high protein or contain omega-3 fatty acids). Guidelines also address special situations such as mucositis/enteritis, radiation enteritis, and symptomatic care. The Czech guidelines are expected to be published in *Clinical Oncology* by year end.

Cancer Cachexia Management in Slovenia

Professor N. Rotovnik Kozjek (SLO) discussed cancer cachexia management in Slovenia. In 2006 Slovenia developed a consensus statement that includes a **recommendation for 2 g/day of omega-3 fatty acids.** Prof Kozjek was an author on an article about the Slovenian multidisciplinary agreement statement on the definition, staging, clinical classification and multimodal approach to the treatment of cachexia in cancer patients.[19] In 2016 at the Institute of Oncology in Ljubljana, **a clinical pathway for nutritional support** was implemented for the early diagnosis and treatment of nutritional and cachexia risk. She stressed the fact that there is an urgent need for research. Areas of focus include integrating the diagnosis of pre-cachexia and cachexia into clinical practice, biomarkers for the early diagnosis of cancer cachexia, and multimodal cachexia treatment.

Prof Kozjek reviewed results of a study in patients with head and neck cancer undergoing chemo-radiotherapy, which showed that **phase angle was a useful predictor for cachexia development.** Mean phase angle was higher in well-nourished compared to malnourished patients. Mean phase angle was also lower in cachectic vs. well-nourished patients.[20]

Nutrition Support in Palliative Care

Dr. A. Skripekova (SK) shared her perspective on palliative care, an approach to improving quality of life of patients with a life-threatening illness, such as patients with advanced cancer requesting nutritional support. She described five principles that are important when treating cancer cachexia:

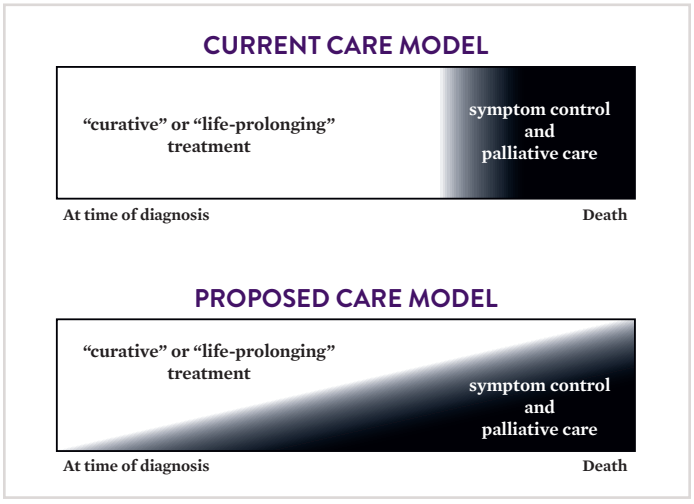
1. Is there anabolic potential?
2. Is the GI tract functional?
3. What is the phenotype of cachexia?
4. Treat the underlying disease
5. Establish nutritional therapy goals with the patient

Work by Prado and colleagues found that there is anabolic potential to gain or maintain muscle mass about 90 days before death.[21]

Is there any clinical evidence to support providing nutrition intervention to advanced cancer patients similar to the approach described by Prof Skripekova? A randomized, controlled trial in non-small cell lung cancer patients found better quality of life and improved survival (11.6 vs 8.9 mo) in the intervention group that consulted with a palliative care specialist on a regular basis compared to the control group.[22]

Cancer Cachexia Treatment

Professor S. Pleština (CRO) described a proposed model for cancer cachexia treatment where symptom control and palliative care are started at diagnosis in parallel to curative and life-prolonging therapy.



Prof Pleština also discussed the Croatian guidelines for the use of EPA and megestrol acetate in cancer cachexia syndrome that recommend an EPA-containing, high energy, high protein, formula as the first choice for nutritional support.

A survey of oncology healthcare professionals to assess awareness and implementation of the Croatian guidelines revealed that more than 80% use enteral nutrition formulas enriched with EPA.[2]

EPA ONS CLINICAL EVIDENCE

Dr. R. Hegazi (US) provided an overview of EPA ONS clinical evidence. Malnutrition and weight loss are common in cancer patients with up to 85% of patients with certain cancers developing weight loss and malnutrition during treatment.[23] In addition to weight loss, loss of lean body mass is associated with reduced functional status and reduced tolerance to treatment.[24-26] Society guidelines in the US and Europe support the use of omega-3 fatty acids (EPA) as a nutrition intervention to help gain or stabilize weight in cancer patients. EPA helps down regulate the inflammatory response[27-30] and has been shown to down-regulate the level and activity of proteolysis-inducing factor.[29,31]

ProSure: ONS enriched with EPA

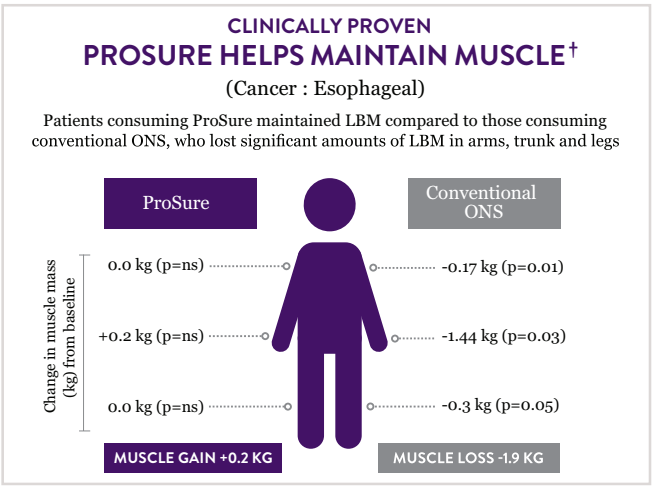
ProSure® is an oral nutritional supplement containing 1.1 g EPA per serving specifically designed for people at risk for or experiencing cancer-induced weight loss. To date, there are 21 ProSure studies and 27 publications with **2,002** patients with pancreatic, lung, head and neck, gastric, colorectal, and esophageal cancers, and in pediatric patients with leukemia and solid tumors.

In a 12-week prospective, randomized, open-label trial patients with colorectal cancer were randomized to two servings per day of ProSure or dietary counseling. After 12 weeks, patients in the ProSure group gained 4.94 kg weight compared to the control group who lost 1.17 kg, P =0.045.[32] Although the sample size was small, none of the five patients in the ProSure group experienced interruptions or stopping of the chemotherapy compared to 67% (4 of 6) in the control group.

Seven studies (n=805) compared ProSure to control ONS in patients with pancreatic, head and neck, lung, and esophageal cancer. Statistically significant clinical outcomes from these studies included:

- Gain in weight and lean body mass
- Improved quality of life
- Improved physical activity

In a randomized, double-blind, controlled trial 53 patients undergoing esophagectomy were randomized to receive two servings per day of either ProSure or an isocaloric, standard nutritional formula for 5 days before and 21 days after surgery. Patients fed ProSure had no significant loss in lean body mass throughout the study, while patients fed standard enteral nutrition without EPA lost significant amounts of muscle from the arm (0.2 kg; P =0.01), trunk (1.4 kg; P =0.03), and leg (0.3 kg; P =0.05): a total loss of 1.9 kg lean body mass.



† Reference: Ryan AM, et al. *Ann Surg.* 2009;249(3):355-363.

MENAC Pilot Study Results are Positive

The **MENAC** trial is an ongoing, randomised, open-label trial of a **m**ultimodal intervention (**e**xercise, **n**utrition, and **a**nti-inflammatory medication) vs standard of care in patients with cachexia. A multicentre, randomised phase II study was conducted in 46 patients with advanced lung cancer or pancreatic cancer expected to start palliative chemotherapy. Patients in the multimodal intervention (exercise, anti-inflammatories, energy dense oral nutritional supplements with EPA [Two Prosure servings providing 2.0 g/day EPA] combined with dietary advice) experienced a 0.91% positive change in weight from baseline to 6 weeks compared to -2.12% weight loss in the standard care group, $P < 0.001$.[33] A phase III trial to enroll 240 patients is currently under way in 15 research centers in Europe and Canada. The duration of the trial is 12 weeks (to complete two chemotherapy cycles). Outcomes include:

- Weight, lean body mass
- Tolerance to anti-cancer therapy (dose reductions, delays in treatment, number of cycles administered, breaks in treatment, toxicity)
- Physical function/performance
- Quality of life
- Dietary intake

Delicious ProSure Smoothies Can Help Improve Patient Compliance

During the conference participants had the opportunity to taste three different ProSure smoothies: Choco Orange, Bananarama, and Almond Coffee. Flavor variety and a great tasting product are important for maintaining compliance. Access recipes through your Abbott Nutrition representative.

Professor Muscaritoli sampling a ProSure Cocktail

REFERENCES

1. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. May 2011;12(5):489-495.
2. Krznaric Z, Juretic A, Kunovic A, Kekez D, Vranesic Bender D. A survey of the implementation of Croatian guidelines for use of eicosapentaaenoic acid and megestrol acetate in cancer cachexia syndrome. *Support Care Cancer*. 2011;19 (Suppl 2):S258.
3. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med*. Oct 1980;69(4):491-497.
4. Martin L, Senesse P, Gioulbasanis I, et al. Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol*. Jan 1 2015;33(1):90-99.
5. Muscaritoli M, Molfino A, Lucia S, Rossi Fanelli F. Cachexia: a preventable comorbidity of cancer. A T.A.R.G.E.T. approach. *Crit Rev Oncol Hematol*. May 2015;94(2):251-259.
6. Muscaritoli M, Bossola M, Aversa Z, Bellantone R, Rossi Fanelli F. Prevention and treatment of cancer cachexia: new insights into an old problem. *Eur J Cancer*. Jan 2006;42(1):31-41.
7. Prado CM, Baracos VE, McCargar LJ, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clin Cancer Res*. Jun 1 2007;13(11):3264-3268.
8. Muscaritoli M, Molfino A, Rossi Fanelli F. Muscle depletion and the prediction of chemotherapy toxicity. *Intern Emerg Med*. Aug 2013;8(5):373-375.
9. Muscaritoli M, Molfino A, Gioia G, Laviano A, Rossi Fanelli F. The "parallel pathway": a novel nutritional and metabolic approach to cancer patients. *Intern Emerg Med*. Apr 2011;6(2):105-112.
10. Aapro M, Arends J, Bozzetti F, et al. Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force. *Ann Oncol*. Aug 2014;25(8):1492-1499.
11. Fearon KC. Cancer cachexia: developing multimodal therapy for a multidimensional problem. *Eur J Cancer*. May 2008;44(8):1124-1132.

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. 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.
14. 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*. Aug 15 2011;117(16):3774-3780.
15. van der Meij BS, Langius JA, Spreeuwenberg MD, et al. Oral nutritional supplements containing n-3 polyunsaturated fatty acids affect quality of life and functional status in lung cancer patients during multimodality treatment: an RCT. *Eur J Clin Nutr*. Mar 2012;66(3):399-404.
16. Sanchez-Lara K, Turcott JG, Juarez-Hernandez E, et al. Effects of an oral nutritional supplement containing eicosapentaenoic acid on nutritional and clinical outcomes in patients with advanced non-small cell lung cancer: randomised trial. *Clin Nutr*. Dec 2014;33(6):1017-1023.
17. de Aguiar Pastore Silva J, Emilia de Souza Fabre M, Waitzberg DL. Omega-3 supplements for patients in chemotherapy and/or radiotherapy: A systematic review. *Clin Nutr*. Jun 2015;34(3):359-366.
18. Krznaric Z, Juretic A, Anzulovic D. Review of Croatian guidelines for use of eicosapentaenoic acid and megestrol acetate in cancer cachexia syndrome. *Nutritional Therapy & Metabolism*. 2009;27:1-8.
19. Rotovnik Kozjek N, Mrevlje Ž, Koroušič Seljak B. Kaheksija pri bolnikih z rakom. *Zdrav Vestn*. 2013;82:133-141.
20. Stegel P, Kozjek NR, Brumen BA, Strojan P. Bioelectrical impedance phase angle as indicator and predictor of cachexia in head and neck cancer patients treated with (chemo) radiotherapy. *Eur J Clin Nutr*. May 2016;70(5):602-606.
21. Prado CM, Sawyer MB, Ghosh S, et al. Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential? *Am J Clin Nutr*. Oct 2013;98(4):1012-1019.
22. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. Aug 19 2010;363(8):733-742.
23. Laviano A, Meguid MM. Nutritional issues in cancer management. *Nutrition*. 1996;12(5):358-371.
24. Silver HJ, Dietrich MS, Murphy BA. Changes in body mass, energy balance, physical function, and inflammatory state in patients with locally advanced head and neck cancer treated with concurrent chemoradiation after low-dose induction chemotherapy. *Head Neck*. Oct 2007;29(10):893-900.
25. Kadar L, Albertsson M, Areberg J, Landberg T, Mattsson S. The prognostic value of body protein in patients with lung cancer. *Ann N Y Acad Sci*. May 2000;904:584-591.
26. 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*. Mar 1998;34(4):503-509.
27. 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*. Jan 1996;12(1 Suppl):S27-30.
28. Wigmore SJ, Fearon KC, Maingay JP, Ross JA. Down-regulation of the acute-phase response in patients with pancreatic cancer cachexia receiving oral eicosapentaenoic acid is mediated via suppression of interleukin-6. *Clin Sci (Lond)*. Feb 1997;92(2):215-221.
29. Barber MD, Fearon KC, Tisdale MJ, McMillan DC, Ross JA. Effect of a fish oil-enriched nutritional supplement on metabolic mediators in patients with pancreatic cancer cachexia. *Nutr Cancer*. 2001;40:118-124.
30. Jho D, Babcock TA, Helton WS, Espat NJ. Omega-3 fatty acids: implications for the treatment of tumor-associated inflammation. *Am Surg*. Jan 2003;69(1):32-36.
31. Lorite MJ, Cariuk P, Tisdale MJ. Induction of muscle protein degradation by a tumour factor. *Br J Cancer*. 1997;76(8):1035-1040.
32. 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.
33. Kaasa S, Solheim T, Laird BJA., et al. A randomised, openlabel trial of a Multimodal Intervention (Exercise, Nutrition and Antiinflammatory Medication) plus standard care versus standard care alone to prevent/attenuate cachexia in advanced cancer patients undergoing chemotherapy. *J Clin Oncol*. 2015;33(suppl; abstr 9628).

Adriatic Club of Clinical Nutrition (ACCN)
The ACCN is an informal club founded in Zagreb, Croatia, in 2004 that includes members from countries surrounding the Adriatic Sea and other countries in the Mediterranean region.

The purpose of the ACCN is to encourage rapid dissemination of nutrition knowledge and its application in the field of clinical nutrition and metabolism in the Adriatic Region.

If you are interested in ACCN initiatives, please contact Prof. Z. Krznarić at **zeljko.krznaric1@zg.t-com.hr**.