Advanced Enteral Nutrition Program For Dietitians

Week 4

Nutrition in Cancer: Are We Making Progress?

Presented on December 2, 2015
Sponsor Disclosure: Financial support for this presentation was provided by Nestlé HealthCare Nutrition, Inc. The views expressed herein are those of the presenter and do not necessarily represent Nestlé’s views. The material herein is accurate as of the date it was presented, and is for educational purposes only and is not intended as a substitute for medical advice. Reproduction or distribution of these materials is prohibited.

© 2015 Nestlé. All rights reserved.
Nutrition in Cancer Therapy: Are We Making Progress?

Robert Martindale MD, PhD
Professor of Surgery
Chief, General Surgery Service
Oregon Health and Science University
Portland Oregon
USA
Objectives

- Identify the stage of cachexia the patient is in
- Explain how nutrition support can influence the quality of life
- Describe the relationship between inflammation, cancer, and nutrition and how it can influence outcome
Impact Malnutrition on the Cancer Patient

- 68% of Americans diagnosed with Ca live > 5 years
- 80% Cancer patients suffer weight loss and malnutrition during course of illness

**Malnutrition leads to;**
- Worse overall outcome
- Longer hospitalization
- Increased cost of care
- Decreased QOL and performance
- Lower tolerance to cancer therapies
- Increased postoperative wound complications
- Decreased survival

**Cancer therapies with effects on nutritional status**
- Radiation
- Surgery
- Chemotherapy
- Immunotherapy
- Complementary and alternative medicine

Fearon K NEJM 2011
Gupta D Ann Nutr Met 2011
Where does nutrition fit into cancer care?

What are the goals?

Objectives will depend on goal!

Expected benefits of nutrition therapy in cancer treatment:
- Improved tolerance
- Better therapeutic response
- Improved QOL
- Improved survival

Palliative

Goal of Nutrition: Achievement best QoL
- Symptom control
- Patient tailored

Curative

Goal of nutrition:
- Support patient through cancer therapy
- Eradication
- Intensive
- Promotes malnutrition
Key determinants of in QoL after Ca diagnosis

- Cancer location (30%)
- Weight loss (30%)
- Nutritional intake (20%)
- Chemotherapy (10%)
- Surgery (6%)
- Disease duration (3%)
- Stage of disease (1%)

Ravasco P et al Supp Care Ca 2004
Body composition

Increasing importance

In cancer therapy:

1) Tolerance to therapy
2) Calculating chemo doses
3) Predicting outcome in cancer therapy
   medical
   surgical

Several screening tools are validated

- MUST = Malnutrition Universal Screening Tool
- NRS 2002
- NUTRIC score - in ICU

Gibson DJ et al European J Clin Nutr 2015
The Hidden Cachexia

3 patients with esophageal cancer: all with similar amount of LBM

BMI 17  BMI 28  BMI 35

Sarcopenic obesity predicts a very poor prognosis

Sarcopenia is a predictor of survival independent of age, sex, functional status

Prado CMM, Baracos VE et al Lancet 2008
Sarcopenia vs Cachexia:

**Key pathophysiological features:**

**Sarcopenia**
- Weight loss not compulsory
- Can be age-related without any other chronic disease
- Reduced muscle mass and functional impairment (reduced strength)
- Inflammation: Low-grade

**Cachexia**
- Weight loss compulsory
- Muscle loss and function not compulsory for diagnosis in the present definition
- Chronic disease compulsory
- Inflammation: Middle to high grade

Definition sarcopenia: absolute muscle mass < 2 SD below normal healthy individual
Metabolic Derangements Result in Cancer Cachexia

- Multi-factorial syndrome;
  - with reduced food intake
  - abnormal metabolism
    - Muscle, adipose, CNS, immune tissue
- Associated with *systemic inflammation*

- “Cachexia” results in reduction in:
  - Treatment tolerance
  - Response to therapy
  - Quality of life
  - Duration of survival

**Question:**
Can appropriate and focused nutrition intervention alter this syndrome of progressive loss of skeletal muscle/adipose and functional impairment?

Fearon K NEJM 2011, Fearon Lancet Oncology 2011
Current trends in Cachexia: Multimodality therapy

• Cachexia vs simple starvation
  – Well over 150 clinical trials with limited to no benefit to nutrition alone in reversing cachexia
    • *Cachexia cannot be reversed by nutrient repletion*
  – Recognition that cachexia can be divided into pre-cachexia --- cachexia --- refractory cachexia

• New targets/therapy and management options for management of cachexia
  – distinct molecular targets
    • Skeletal muscle androgen receptor, myostatin, ghrelin, IL-6 and IL1α

*Baracos V J Clinical Oncology 2013*
Success will require a multifaceted approach.

Uniformly unsuccessful

Not well studied, early work promising

Current major focus
THE SECRET KILLER

The surprising link between inflammation and heart attacks, cancer, Alzheimer's and other diseases.

What you can do to fight it.
Diseases where Inflammation is thought to be part or all of the etiology of the disease!

- Diabetes
- Obesity
- Metabolic syndrome
- Heart disease  
  - atherosclerosis
- Neuropsychiatric  
  - Depression  
  - Anorexia nervosa  
  - Alzheimer’s  
  - Parkinsons
- Hepatic diseases  
  - NASH  
  - cirrhosis
- Infectious disease  
  - General, TB, Malaria
- Asthma
- Allergy

- Inflammatory Bowel Disease
- Autoimmune diseases
- Peptic ulcer disease
- HIV / AIDS
- Cancer  
  - Metabolic effects (cachexia)  
  - metastasis
- Critical Care / Surgery  
  - Trauma  
  - Pancreatitis  
  - Transplantation  
  - Sepsis  
  - ARDS / ALI
- Hypoxia
- Aging
- etc etc etc
Cancer association with inflammation

- Estimated that 20% of cancer deaths worldwide are related to chronic infection and/or inflammation
  - gastrointestinal and lung cancers accounting for the substantial portion of the total burden
    - Examples: H.pylori, scar carcinoma, UC, etc
    - Human neutrophils can induce malignant transformation which suggests that phagocytic cells are carcinogenic

- Inflammation can promote all stages of tumorigenesis
Inflammation can promote all stages of tumorigenesis

- DNA damage
- Insensitivity to growth inhibitors
- Tissue invasion and metastasis
- Sustained angiogenesis
- Evasion of apoptosis
- Limitless replicative potential
- Self-sufficiency in growth signals
- Inflammatory microenvironment

H. pylori infection

H. pylori infects at least half of the world’s population. The prevalence among middle-aged adults is over 80% in many developing countries, as compared with 20% to 50% in industrialized countries.

WHO classifies H. pylori as class one carcinogen

Suerbaum & Michetti NEJM 2002; 347:1175

Morowitz MJ Ann Surg 2011; 253:1094-1101
Nutrients / compounds with anti-inflammatory activity

- Vitamin C
- Vitamin E
- Zinc
- Selenium
- Probiotics
- Omega-3 FA (EPA/DHA)
- Carnitine
- Curry paste
- Resveratrol
- Glutamine
- Arginine
- Taurine
- Cysteine
- Willow Bark
- Leucine
- Threonine
- Glutathione
- Creatine
- Caffeine
- Glucosamine
- Echinacea
- Garlic
- Boswellia
- Tumeric
- Saffron
- Shark cartilage
- Ginger
- Licorice
- Chamomile
- Capsaicin
Omega-3 in Cancer: Animal models

• Tumor effects:
  – Decrease tumor cell proliferation
  – Enhance tumor cell apoptosis
  – Promote cell differentiation
  – Limit tumor angiogenesis
  – Modulate tumor-extracellular matrix interaction

• Therapeutic effects:
  – Enhances tumor toxicity to antineoplastic drugs
    • Antracyclines, cisplatin, alkylating agents, vincristine, 5-FU
  – Offers protection to non-tumor tissues
    • Cyclophosphamide, arabinosylcytosine, doxorubincin, CPT-11
  – Multiple mechanisms and tissues showing benefit
    • Gut weight, histopathology, epithelial apoptosis, inflammatory mediators
  – PGE3 alteration of Akt phosphorylation

Laviano, A Curr Opin Nutr Metabolic Care 2013
Baracos V J Clin Onc 2013
Yang P et al Mol Carcinogen 2014
Fish oils: Overall Recommendations

• **2007 Cochrane Reviews:**
  • Insufficient evidence for or against with most tumor types compared to placebo:
    – 5 trials (N=587) met inclusion criteria
    – 3 trials compared different doses of EPA to 2 outcomes: nutritional status and adverse events
    – No evidence that EPA supplement + appetite stimulant better than supplements w/o EPA
    – Insufficient data to determine optimal dose

  Baughan et al. Cochrane Database Syst Rev. 2007

Why: Heterogeneity of tumor biology, type, location, stage
Increasing the therapeutic index
Fish oil effect on body composition in NSCLC patients receiving first line chemotherapy

- Positive linear relation between change in plasma phospholipid, EPA and change in muscle mass

\[ R^2 = 0.55; P = 0.01 \]

Murphy et al., Cancer 2011 a

NSCLC = non small cell Lung Ca
EPA effects on the tumor

- EPA effect on tumor growth has been well documented in many experimental models after first intervention by Karmali and coworker

Karmali et al., J. Natl Cancer Inst. 1984

<table>
<thead>
<tr>
<th>Diet, µL/day</th>
<th>Body wt (g)</th>
<th>Tumor wt [g (P)]</th>
<th>Tumor wt [cm³ (P)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>150 ± 2.5</td>
<td>3.87 ± 0.50</td>
<td>4.10 ± 0.55</td>
</tr>
<tr>
<td>laxEPA, 100</td>
<td>146 ± 2.7</td>
<td>2.65 ± 0.33 (0.05)</td>
<td>2.46 ± 0.32</td>
</tr>
<tr>
<td>laxEPA, 200</td>
<td>148 ± 2.3</td>
<td>2.97 ± 0.27</td>
<td>2.59 ± 0.27</td>
</tr>
<tr>
<td>laxEPA, 400</td>
<td>149 ± 2.0</td>
<td>2.80 ± 0.29 (0.08)</td>
<td>2.24 ± 0.25</td>
</tr>
</tbody>
</table>

EPA effect on tumor growth has been well documented in many experimental models after first intervention by Karmali and coworker.
Fish oil and chemotherapy response rate

- Nutritional intervention with fish oil in first line platinum-based chemotherapy in patients with Advanced Non-Small Cell Lung Cancer

Table 3. Chemotherapy Outcomes and Survival in the Standard of Care and Fish Oil Groups

<table>
<thead>
<tr>
<th></th>
<th>Standard of Care(^a)</th>
<th>Fish Oil(^b)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate, no. (%)</td>
<td>8 (25.8)</td>
<td>9 (60.0)</td>
<td>.008</td>
</tr>
<tr>
<td>Clinical benefit, no. (%)</td>
<td>13 (41.9)</td>
<td>12 (80.0)</td>
<td>.02</td>
</tr>
<tr>
<td>Complete response, no. (%)</td>
<td>1 (3.2)</td>
<td>1 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Partial response, no. (%)</td>
<td>7 (22.6)</td>
<td>9 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Stable disease, no. (%)</td>
<td>5 (16.1)</td>
<td>2 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease, no. (%)</td>
<td>18 (58.1)</td>
<td>3 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Number of chemotherapy cycles received</td>
<td>3.0 ± 1.4</td>
<td>3.9 ± 0.9</td>
<td>.02</td>
</tr>
<tr>
<td>Time on chemotherapy, d</td>
<td>60.3 ± 31.1</td>
<td>78.9 ± 23.5</td>
<td>.05</td>
</tr>
<tr>
<td>1-Year survival (%)</td>
<td>38.7</td>
<td>60.0</td>
<td>.15</td>
</tr>
</tbody>
</table>

Mean ± standard deviation, two-sample t-test and \(\chi^2\)-test.

\(^a\) \(n = 31\).

\(^b\) \(n = 15\).

**Fish oil intervention in per protocol population result in increased chemotherapy efficacy without affecting the toxicity profile and may contribute to increased survival**

*Murphy et al., Cancer 2011 b*
Improved outcome of FEC 75 chemotherapy in metastatic breast cancer

- Open-label single arm study on response rate and safety:
  - 1.8 gr DHA was devoid of adverse side effects and can improve the outcome of chemotherapy when highly incorporated.
  - High incorporators (n=12) displayed significantly high response rate and overall survival than low incorporators (n=13).

*Bougnoux et al., Br J Cancer 2009*
Effect of EPA in palliative cancer patients

- 60 patients with solid tumors
  - 50% malnourished (MN),
  - 50% well nourished (WN)

- Fish oil: >40 days until death

- Results:
  - Immune function in MN receiving EPA ↑
  - Performance status in MN patients on EPA ↑
  - Survival was significantly longer for MN+WN patients receiving EPA (P<0.025)

Gogos et al., Cancer 1998
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

BS van der Meij, JAE Langius, MD Spreeuwenberg, SM Slootmaker, MA Paul, EF Smit and PAM van Leeuwen

**Figure 1.** Physical activity (daily PAM score) over time for the I and C groups. Values are mean ± s.d., baseline: n = 12 (I), n = 16 (C); week 3: n = 13 (I) and n = 17 (C); week 5: n = 8 (I), n = 13 (C). *P < 0.05, difference between the I and C group (analysed by generalised estimating equations, with baseline value and sex as covariate).
Summary: Proposed influence of EPA in Cancer

- **Proteolysis**
  - Reduced muscle apoptosis and necrosis
  - Down regulation of ubiquitin proteosome pathway
  - Decreased production of pro-inflammatory cytokines

- **Protein synthesis**
  - Improved insulin sensitivity
  - Increased protein and caloric intake

- **Indirect effects**
  - Reduced side effects from chemotherapy
  - Enhanced response to chemotherapy
Importance of Vitamin D in Cancer

- Gut – $\uparrow$ Ca$^{++}$ absorption
  Bone - Ca$^{++}$ mobilization
- Reduces mortality
- Immune modulator
  Affects T and B cells, immunoglobulin, and cytokines
  ↓ Risk of asthma, colds, URIs
  Affects TLR-4 to bind Tuberculosis
- Pancreas receptors, deficiency $\uparrow$ risk diabetes
- Inhibits cancer growth
  Sun exposure delays onset colon, prostate, breast cancer
- Reduces skin proliferation - Used to treat psoriasis
- Muscle function – Deficiency causes aches, pain, ↓ strength, falls
- Pregnancy - Defic $\uparrow$ risk pre-eclampsia, need for C-Section
- Deficiency $\uparrow$ risk of MS, RA, Osteoarthritis, HTN ?
  - In aging 25OH < 25nmol/L is deficient
  - Deficiency reported in > 70 % of elderly living in the community
Diagnosing and Treating Vit D Deficiency

- **Diagnosis** (based on 25-OH Vit D levels)
  - Deficient < 10 ng/ml, insufficient 11-20 ng/ml
  - Optimal 30-60 ng/ml (>30 ng/ml to ↓ PTH)

- **Dosing Vit D**
  - Rx of major deficiency  50,000 IU/week x 8 wks
  - Supplementation 0-50 yrs (200 IU/d), 50-70 yrs (400 IU/d), >70 yrs (600 IU/d), but 800-1000 IU/d may be better?

- **Criticism**
  - Effect size greater in *observational studies* vs PRCTs
  - Confounding factors (obesity, exercise, milk intake, chronic dz)
  - measurement of DBP in various states

- **Institute of Medicine statement**
  - Benefits beyond bone health may not be reliable
  - Healthy adults should take 600 IU/d to optimize bone health

Antioxidant Supplements in Cancer?

- Observations?
  - Antioxidant levels lower in patients w/cancer
  - 45-80% of patients reportedly use antioxidant supplements during anti-neoplastic treatments

- Bottom Line: No major consistent data to support additional antioxidants in Ca
It is all about “Risk vs. Benefit”
Can nutrition therapy be harmful in cancer?

- Excess calories
  - Hyperglycemia
  - Fatty liver

- Refeeding syndrome

- “Excessively” aggressive enteral feeding
  - Feeding in hemodynamic instability
  - Aspiration
  - Feeding the compromised gut --- bacterial or toxin translocation

- Access complications
  - PEG, J tube, Nasojejunal feeding
  - PN line infections, pneumothorax

- Giving nutrition during chemotherapy will nullify effects of chemo
  - Most chemo agents are potent oxidizing agents

- Nutrition stimulating cancer growth?
- Nutrition support at end of life cost effectiveness?
Summary: When To Use PN Nutrition during radiation and chemotherapy

• **PN practice to avoided**
  • unrestricted use of parenteral nutrition
  • When at risk for refeeding syndrome
    – (macro/micronutrients)

• **In well selected patients**:
  • high nutritional risk
  • Use an individualized patient specific plan
  • oral + nocturnal enteral nutrition (tube, G-tubes, NOT PN)

• Therapy should be adapted and evaluated on individual bases
Does Nutrition Stimulate Cancer Growth?

- Difficult to get definitive answer!
  - Ethical issues in study design
  - Complexity of tumor growth characteristics in-vivo
  - Heterogeneity of tumors between cell type and even tumors of same class

- Methods used in attempt to answer question:
  - Tumor size
    - Result from increased growth
    - Results from apoptosis
  - Relative number of tumor cells
  - # cells in the S phase
    - DNA synthesis or replication
  - Ploidy
    - DNA content
  - Thymidine uptake
  - Tumor protein synthesis
  - Measure cell cycle kinetics
    - Followed by label with bromodeoxyuridine
Does PN stimulate tumor growth?

- **16 studies in humans**
  - 3 studies received PN for only 24h
  - 2 studies lack control groups
    - 5-7 days
    - One of these showed growth
  - 7 studies had controls (total 154 pts)
    - Duration of study 7 to 18 days
    - Multiple methods to measure growth rates
    - 4 studies nutrition had no influence on tumor growth
    - 3 studies nutrition had cellular proliferation influence

- **Summary PN stimulating tumor growth**
  - Impossible to definitive answer!
  - Some early work with leucine uptake shows increase in AA uptake into tumor when infused preop
  - Bottom: this should not prevent the use of PN in well selected patients

Bossola NCP 2011
Does EN stimulate tumor growth?

• 3 small human trials
  • Edstrom (1)
    – 6-8 days support (n=13) H and N Ca
    – Methods: Flow cytometry
    – Conclusion: increased aneuploid cells / no change in ODC
  • Dionigi (2)
    – H and N Ca Unknown duration of therapy
    – No changes
  • Baron (3)
    – 8 days EN support (n=6) H and N Ca
    – NO control
    – No change

• Bottom line:
  – EN support appears to have NO stimulatory activity

ODC = Ornithine decarboxylase

1) Edstrom S Eur J Ca Clin Oncol 1989
2) Dionigi P Clin Nutr 1991
3) Baron PL Arch Surg 1986
Toxicity in Chemotherapy — When Less Is More

Alessandro Laviano, M.D., and Filippo Rossi Fanelli, M.D.

A Mice Fed Ad Libitum

- Normal cells
- Cancer cells
- Chemotherapy
- Destruction of normal cells
- Shrinkage of tumor volume
- Objective response
- Side effects, toxicity

B Mice Subjected to Short-Term Fasting

- Normal cells
- Cancer cells
- Short-term fasting
- Differential stress resistance leads to activation of protective response
- Oncogenes prevent differential stress resistance
- Chemotherapy
- Decrease in side effects and toxicity
- Increase in objective response
- Additional shrinkage of tumor volume

Patients will follow physicians nutrition recommendations

**Head & Neck 2005; 27: 659-668**

**IMPACT OF NUTRITION ON OUTCOME: A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL IN PATIENTS WITH HEAD AND NECK CANCER UNDERGOING RADIOThERAPY**

Paula Ravasco, MD, Isabel Monteiro-Grillo, MD, PhD, Pedro Marques Vidal, MD, PhD, Maria Ermelinda Camilo, MD, PhD

1 Unidade de Nutrição e Metabolismo, Instituto de Medicina Molecular Faculdade de Medicina da Universidade de Lisboa, Avenida Prof. Egas Moniz, 1649-028 Lisboa, Portugal. E-mail: p.ravasco@fm.ul.pt
2 Radiotherapy Department of the Santa Maria University Hospital, Lisbon, Portugal

**Journal of Clinical Oncology**

Dietary Counseling Improves Patient Outcomes: A Prospective, Randomized, Controlled Trial in Colorectal Cancer Patients Undergoing Radiotherapy

**Individualized nutrition intervention is of major benefit to colorectal cancer patients: the long-term follow-up of a randomized controlled trial of nutritional therapy**

Paula Ravasco, Isabel Monteiro-Grillo, and Maria Camilo

Am J Nutr 2012
Exercise in pre and post-op Ca surgical management

- Exercise with appropriate AA and nutrition shown to be anabolic in multiple models
  - Burn (Wolfe 1990’s)
  - Cancer (Biolo 2010)
  - Post-op (Baracos 2013)

- Exercise: multiple mechanisms of benefit
  - Increases nutritive blood flow to muscle (decreases precapillary shunting)
  - Anti-inflammatory – via gene expression
  - Lowers insulin resistance
  - Increase nutrient uptake in multiple tissue beds
  - Animal models- reduced inflammation, decreased wasting, longer survival
Anaerobic exercise reduces tumor growth, cancer cachexia and increases macrophage and lymphocyte response in Walker 256 tumor-bearing rats

Figure 3: Tumor weight comparison between sedentary and trained tumor-bearing groups. The graph shows that the tumor weight is significantly lower in the trained group compared to the sedentary group.*
Conclusions: Nutrition issues in Ca care
Take Home Messages!

• Cachexia is insidious and develops much earlier in cancer patients than previously recognized
• Early identification and early treatment of nutritional deficits are mandatory to show any clinically relevant benefits
  • Surgical oncology – preop prehabilitation
• Nutrition in Ca therapy should be individualized for optimal outcome
  • Nutrition --- targeted multimodel therapy --- exercise
  • Counseling by MD makes a difference
• Nutrition alone does not work!
Article Discussion

Case Presentations
Q and A Session
Week 5

Topic
Underfeeding in the ICU: Good or Bad?

Objectives:
• Identify flaws in the literature claiming that underfeeding is better than full feeding
• Describe the significance of studies which show underfeeding has similar outcomes to full feeding
• Explain how nutritional risk impacts the decision to underfeed the ICU patient
Homework

• Answer questions
  – Fax responses by Friday to 866-546-3005
    Attn: Yvette Gaughan
• Prepare case presentation
  – Example from your facility
  – Pertinent to next week’s topic
  – Four assigned participants to present
    (~5 minutes each)
• Prepare article review
  Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM,
  Tammin HM, Jones G, Mehta S, McIntyre L, Solaiman O,
  Sakkiha MH, Sadat M, Afesh L, PermiT Trial Group.
  Underfeeding or Standard Enteral Feeding in Critically Ill
  – Four assigned participants to present
    (~5 minutes each)
Thank you !

Nutrition-related resources and tools are available from Nestlé Nutrition Institute:
www.nestlenutrition-institute.org