CANCER ANOREXIA

Živa Mrevlje
Universitiy Medical Center
Ljubljana

Slides by: Alessandro Laviano
Department of Clinical Medicine
University La Sapienza, Rome, Italy
alessandro.laviano@uniroma1.it
Learning Objectives

• Understand the clinical relevance of cancer anorexia
• Understand the pros and cons of the available tools for the diagnosis of cancer anorexia
• Understand the pathogenic mechanisms of cancer anorexia
• Understand the role of the central nervous system in controlling host metabolism during tumor growth
• Discuss possible therapeutic options
Impact of definition on the prevalence of the disease

Table 1: Characteristics of cancer patients identified as having cachexia based on the different definitions and compared with cancer patients without cachexia.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cancer patients with cachexia ICD-9 code (799.4) n = 205</th>
<th>Cancer patients with cachexia ICD-9 codes (cachexia, anorexia, abnormal weight loss, or feeding difficulties) n = 467</th>
<th>Cancer patients with prescription for megestrol acetate, oxandrolone, somatropin or dronabinol n = 546</th>
<th>Cancer patients with weight loss ≥5% n = 1257</th>
<th>Cancer patients with cachexia by any definition n = 1975</th>
<th>Cancer patients without cachexia† n = 6,566</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean</td>
<td>65.6*</td>
<td>66.9**</td>
<td>64.4*</td>
<td>66.3**</td>
<td>65.8**</td>
<td>63.0</td>
</tr>
<tr>
<td>Gender, men, %</td>
<td>34.1</td>
<td>37.0</td>
<td>46.7**</td>
<td>49.7**</td>
<td>46.9**</td>
<td>38.4</td>
</tr>
</tbody>
</table>

n = 8541 cancer patients

Fox KM et al. J Oncol 2009
Definition of cancer anorexia

“Anorexia is the loss of appetite or lack of desire to eat”

(Harrison’s Principles of Internal Medicine, XVII edition)

Pathologically persistent satiety
CLINICAL RELEVANCE OF CANCER ANOREXIA
Van Cutsem E & Arends J. Eur J Oncol Nurs 2005
Symptoms at presentation of lung and GI cancer

Number of symptoms - reduced food intake

Cancer: disease and nutrition are key determinants of patients’ quality of life

QoL function scores are determined:

- cancer location (30%)
- nutritional intake (20%)
- weight loss (30%)
- chemotherapy (10%)
- surgery (6%)
- disease duration (3%)
- stage of disease (1%)
### Factors associated with increased risk of death in cancer patients

<table>
<thead>
<tr>
<th>Survival after referral (n=549)</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status (per 1 point increase)</td>
<td>1.4</td>
<td>1.3-1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (M/W)</td>
<td>1.3</td>
<td>1.1-1.6</td>
<td>0.012</td>
</tr>
<tr>
<td>Dysphagia (Yes/No)</td>
<td>1.3</td>
<td>1.0-1.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Early satiety (Yes/No)</td>
<td>1.3</td>
<td>1.1-1.5</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Impact of anorexia on mortality

Have you lost weight unintentionally within the last 3 months?

How well have you eaten during the last week?

Palliative Nutritional Intervention in Addition to Cyclooxygenase and Erythropoietin Treatment for Patients with Malignant Disease: Effects on Survival, Metabolism, and Function

A Randomized Prospective Study

Lundholm K et al. Cancer 2004; N=309
# Impact of anorexia on mortality

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Group A</th>
<th>Group WL</th>
<th>Group N</th>
<th>Group CACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.</td>
<td>484 (100%)</td>
<td>163 (34%)</td>
<td>46 (10%)</td>
<td>125 (26%)</td>
<td>150 (30%)</td>
</tr>
</tbody>
</table>

Lasheen W & Walsh D. Support Care Cancer 2010; 10:265-272

cancer anorexia-cachexia syndrome (CACS)
AVAILABLE TOOLS FOR DIAGNOSIS OF CANCER ANOREXIA
Diagnostic tools

- Visual analogue scale (VAS)
- Questionnaires
  - National Central Cancer Treatment Group (NCCTG) anorexia questionnaire
  - Functional Assessment of Anorexia Cax Therapy (FAACT) questionnaire
Questionnaire

- Meat aversion
- Changes of taste/smell
- Nausea/vomiting
- Early satiety
Table 1
Symptom-based assessment of anorexia (adapted from AC/S-12 of FAACT questionnaire).

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat a bit</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have a good appetite</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>The amount I eat is sufficient to meet my needs</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am worried about my weight</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Most food tastes unpleasant to me</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>I am concerned about how thin I look</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>My interest in food drops as soon as I try to eat</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>I have difficulty eating rich or “heavy” foods</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>My family or friends are pressuring me to eat</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>I have been vomiting</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>When I eat, I seem to get fully quickly</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>I have pain in my stomach area</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>My general health is improving</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
## Questionnaire vs. Anorexia Score

<table>
<thead>
<tr>
<th></th>
<th>N.</th>
<th>M:F</th>
<th>Age (years)</th>
<th>Anorexia score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexic (questionnaire)</td>
<td>28</td>
<td>19:9</td>
<td>70.9±15.2</td>
<td>30.4±7.1*</td>
</tr>
<tr>
<td>Non anorexic (questionnaire)</td>
<td>22</td>
<td>20:8</td>
<td>64.7±17.8</td>
<td>36.1±4.2*</td>
</tr>
</tbody>
</table>

*p<0.01

Arezzo A et al. (unpublished observations)
PATHOGENESIS OF CANCER ANOREXIA
Peripheral acute and chronic challenges (i.e., trauma, cancer, cardiac failure, etc.) trigger a number of biochemical changes in different organs and tissues, leading to clinically relevant clinical signs, heavily influencing patients' morbidity, mortality,...


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Cytokines
Eicosanoids
Energy signals
Hormones
Neurotransmitters
Nitric oxide
Peptides

Anorexia

Malnutrition and cachexia
Increased morbidity and mortality
Decreased quality of life
ROLE OF THE CENTRAL NERVOUS SYSTEM IN CONTROLLING HOST METABOLISM DURING TUMOR GROWTH
Regulation of food intake

Woods SC. Cell Metab 9:489-98, 2009
### Role of peripheral signals

<table>
<thead>
<tr>
<th></th>
<th>Short-term signals</th>
<th>Intermediate-term signals</th>
<th>Long-term signals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>stimulation</strong></td>
<td>ghrelin</td>
<td></td>
<td>E signals</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>inhibition</strong></td>
<td>CKK</td>
<td>PYY</td>
<td>leptin</td>
</tr>
<tr>
<td></td>
<td>Afferent pthws - distension</td>
<td>Plasma concentration of substrates</td>
<td>Insulin E signals</td>
</tr>
</tbody>
</table>
Peripheral signals

- Leptin
- Ghrelin
Energy signals

Ratio oxidation vs. Synthesis Fatty Acids in HT neuron cells
Key: in diff btwn anabolism and catabolism

FA OXIDATION

Malonyl-CoA

FA SYNTHESIS

INCREASED FOOD INTAKE

DECREASED FOOD INTAKE
Nevropeptidi
Pathogenesis of cancer anorexia

Different peripheral challenges (i.e., tumors, renal failure, pulmonary disease, etc.) are sensed by the vagus nerve, possibly by local interaction with proinflammatory cytokines.

Pathogenesis of cancer anorexia

**Peripheral tissue**

**Challenge** → ↑ Inflammatory cytokines

**vagus nerve**

↓ food intake

**Brainstem**

↑ ACh, NA, 5HT innervation

**Hypothalamus**

↑ MCoA ← ↓ FA oxidation

↓ CPT1c

↑ POMC → CK

↓ NPY

5HT

↑ APP

↑ UCPs

**sympathetic outflow**

↑ energy expenditure

↑ catabolism


Molfino A et al. Nat Rev Cancer 2009
CPT mRNA in the hypothalamus of Tumor Bearing rats

Carnitine administration reduces cytokine levels, improves food intake, and ameliorates body composition in tumor-bearing rats.

Seelaender M, Laviano A, et al. (Cancer Invest 2011)
Pathogenesis of cancer anorexia

Peripheral tissue

Challenge $\rightarrow$ ↑ Inflammatory cytokines

vagus nerve

Brainstem

$\uparrow$ ACh, NA, 5HT innervation

Hypothalamus

$\uparrow$ MCoA $\leftarrow$ $\downarrow$ FA oxidation

$\downarrow$ CPT1c

$\uparrow$ POMC $\rightarrow$ CK

$\downarrow$ NPY

5HT

$\downarrow$ APP

$\uparrow$ UCPs

↑ catabolism

↑ energy expenditure

↓ food intake


$Molfino$ A et al. Nat Rev Cancer 2009
Sympathovagal balance and cancer anorexia

P-185: Heart rate variability (HRV) correlates with anorexia and energy expenditure in cancer patients: a pilot clinical study

M. Martuscelli, A. Laviano, L. Tubani, L. Preziosa, Y. Tari and F. Rossi-Fanelli


Rationale: The hypothalamus is involved in the control of food intake and energy expenditure via the autonomous nervous system. In cancer patients, anorexia and cachexia frequently occur, which can be related to deranged sympathovagal balance. HRV is a reliable index of the autonomous nervous system activity. Thus, in cancer patients a relationship may exist between HRV and anorexia and energy expenditure.

Method: Anorexia and body cell mass (BCM) were measured in 4 lung cancer patients, using a visual analogue scale (VAS; +100, hunger; -100, satiety) and bioimpedance analysis, respectively. Resting energy expenditure (REE) was calculated based on BCM. HRV was measured using Holter EKG recordings via a computerized software, and the time domain of pNN50 was obtained. Pearson's correlation test was used.

Results: VAS significantly correlates with pNN50 (r=0.994; p < 0.01); negative correlations exist between pNN50 and BCM and REE (r=-0.967, p < 0.05; r=-0.966, p < 0.05; respectively).

Conclusions: Data obtained support the hypothalamic involvement in anorexia and cachexia. If confirmed by larger studies, HRV may also represent a useful, non-invasive tool to detect and predict the development of nutritional complications in cancer patients.
Sympathovagal balance and BMI
inverse correlation BMI to PSY activity (low to high)

Figure 1  Correlation between BMI and HF in the patients studied.

Autonomic dysfunction and survival in cancer patients

Fig. 2. Kaplan-Meier curve for survival in patients with and without autonomic dysfunction (AD). AD is present if Ewing score is $>2$. 

Autonomic dysfunction and survival in (HCC) cancer patients

Fig. 1. Plots of TP (ln TP) and HF (ln HF power) against TTD in patients with terminal hepatocellular carcinoma.

Chiang J-K et al. J Pain Symptom Manage 2010; 39:673-9
HRV and length of survival of (terminal) cancer patients

Fig. 1. Kaplan-Meier survival curves (n=68). (A) Karnofsky performance status scale (P<0.001). (B) Anorexia (P=0.015). (C) Dyspnea (P=0.037). (D) Mean heart rate (dichotomized by 100 bpm). (E) SDNN (dichotomized by quartile 3, 21.3 msec).

*KPS variable was grouped according to the reference level of palliative prognostic score.

HRV and length of survival of cancer patients

Table 4. Multivariate analysis using Cox’s proportional hazard model to identify factors associated with survival duration (N=54)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Parameter estimate</th>
<th>Standard error</th>
<th>Hazard ratio</th>
<th>95% Hazard ratio confidence limits</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnofsky scale</td>
<td>-0.99854</td>
<td>0.35907</td>
<td>0.368</td>
<td>0.182</td>
<td>0.745</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0.87627</td>
<td>0.34194</td>
<td>2.402</td>
<td>1.229</td>
<td>4.695</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0.95624</td>
<td>0.40461</td>
<td>2.602</td>
<td>1.177</td>
<td>5.75</td>
</tr>
<tr>
<td>SDNN</td>
<td>-2.77822</td>
<td>1.21511</td>
<td>0.062</td>
<td>0.006</td>
<td>0.673</td>
</tr>
<tr>
<td>Inter</td>
<td>0.01042</td>
<td>0.00488</td>
<td>1.01</td>
<td>1.001</td>
<td>1.02</td>
</tr>
</tbody>
</table>

SDNN, standard deviations of normal-to-normal R-R intervals; Inter, SDNN×total cholesterol.

Cancer anorexia – (possible) therapeutic targets

Normal conditions
Hypothalamus
Anorexigenic signals
Prophagic signals

Cancer
Peripheral signals
Arcuate nucleus
Ghrelin
↑POMC/CART
↓NPY/AgRP
↑Serotonin
↑Cytokines

Tumor
Immune system

BCAA
Anti-MC4R
MA
N3 FA
eradication

Cancer anorexia – therapeutic options

- Nutritional support, counselling
- Pharmacological Rx.
  - Prophagic agents – megestrol acetate
  - Cannabinoids (dronabinol)
  - Steroids
  - Ghrelin?
  - BCAA
  - Omega 3 FA - EPA
Nutritional counselling

– Small, frequent meals
– E dense meals
– Feeding in company, pleasant environment
– Foods low in fat (gastric emptying)
– Avoiding extremes (T, spices, textures..)
Prophagic Rx’s

<table>
<thead>
<tr>
<th></th>
<th>Megestrol acetat</th>
<th>dexametazon</th>
<th>fluoksimesteron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite increase</td>
<td>73%</td>
<td>61%</td>
<td>60%</td>
</tr>
</tbody>
</table>

CAVE!!

1. SAEs and SEs: thrombosis, sexual dysfunction, vaginal bleed

2. Wt increase mainly secondary to water retention and fat accumulation

Cannabinoids: less prophagic
Supplementation - pharmaconutrition

- BCAAs
- Omega 3 FA - EPA
Effect of nutritional intervention in anorexia-cachexia

Effect of nutritional intervention on PS.  
BJC 2004
Nutritional intervention – E and protein intake

P. Ravasco in: Support Cancer Ther 2004; the best results observed in the nutritional counselling group.
ActRIIB antagonism reverses cancer cachexia

Zhou X et al. Cell 2010; 142:531-543
Key Messages

• Cancer anorexia is clinically relevant since it is an independent negative prognostic factor and contributes to worsening of quality of life.

• The presence of cancer anorexia should be qualitatively and quantitatively assessed.
Key Messages

- Tumor-induced neuro-inflammation largely contributes to the pathogenesis of cancer anorexia
- Cancer-associated anorexia and tissue wasting may share common pathogenic pathways involving brain areas controlling energy homeostasis