Fatigue and Cachexia in the Oncologic Population: Clinical Significance

Barbara A. Murphy, MD
Director, Pain and Symptom Management Program
Why are fatigue and cachexia clinically meaningful to patients?

• Not confined to patients who have terminal disease
  – May be associated with chemotherapy and radiation
• Seldom occur in isolation
  – Usually a component of a symptom complex
• Associated with adverse outcomes
  – Decreased survival
  – Decreased in physical functioning
    • Impact social roles and social identity
  – Decreased treatment tolerance
    • Impact on drug dosing
• May persist long term in survivors
  – Scientific question: effect on long overall survival?
  – Patient question: Why aren’t I getting better and will I be normal?
Inflammatory Disease States:

• Universal underlying biologic responses to disease
• Mediators:
  – Host biologic mechanisms meant to deal with stress and aid in repair
  – Chronic or exuberant host response results in damage
• Stereotypical Manifestations of Acute/Chronic Disease:
  – Fatigue and weakness
  – Anorexia
  – Cachexia and deconditioning
  – Anemia
  – Neurocognitive changes
  – Mood disorders
Wasting Syndromes in Cancer:

- Secondary to cancer
  - Previously untreated patients with advanced disease
  - Treatment refractory patients – advanced disease
- Associated with acute and late effects of therapy
  - Radiation based therapy
  - Chemotherapy
## Change in Body Composition:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>1-month post</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>87.0±15.32</td>
<td>77±10.63</td>
<td>0.000</td>
</tr>
<tr>
<td>BMI</td>
<td>28.7±3.61</td>
<td>25.3±2.47</td>
<td>0.000</td>
</tr>
<tr>
<td>% Fat</td>
<td>32.7±6.67</td>
<td>34.0±5.75</td>
<td>0.802</td>
</tr>
<tr>
<td>Fat mass kg</td>
<td>28.0±5.34</td>
<td>24.5±4.48</td>
<td>0.003</td>
</tr>
<tr>
<td>Lean mass kg</td>
<td>52.3±11.3</td>
<td>46.6±96.534</td>
<td>0.005</td>
</tr>
<tr>
<td>REE (kcal/d)</td>
<td>1666.7±238.33</td>
<td>1645.9±210.0</td>
<td>0.736</td>
</tr>
<tr>
<td>REE/FFM (kcal/kg)</td>
<td>30.6±3.22</td>
<td>34.9±6.60</td>
<td>0.019</td>
</tr>
<tr>
<td>Energy Intake</td>
<td>2454±938</td>
<td>2108±780</td>
<td>0.200</td>
</tr>
<tr>
<td>EI/REE (%)</td>
<td>1.45±0.55</td>
<td>1.22±0.42</td>
<td>0.165</td>
</tr>
<tr>
<td>Cal to Nitrogen Ratio</td>
<td>158.0±24.22</td>
<td>154.3±30.4</td>
<td>.630</td>
</tr>
<tr>
<td>RQ (VCO2/VO2)</td>
<td>0.74±0.11</td>
<td>0.77±0.12</td>
<td>0.457</td>
</tr>
</tbody>
</table>

Silver, Head and Neck 2007
Results: Muscle Wasting and Decrease in Physical Function

- 66-80% body mass loss was lean body mass
  - Average LBM loss: 6.8 kg (p<0.0001)
  - Decrease in LBM associated with
    - Decrease in ADL (r = -.58, p=0.02)
    - Increase time for performance testing (r = -.71, p=0.004)
- Increase in pro-inflammatory cytokines (IL-6 and IL-1B)
  - @ with decrease in ADL (p=0.02) and IADL (p=0.04)
- Decrease in anti-inflammatory cytokines (IL-10)
  - @ with decrease in physical activity (p=0.015)
- Oxidative stress
  - Serum F2 isoprostane levels increased p=.007
  - @ with loss of fat and fat-free mass p=.04
Marked Changes in Body Composition Following Neoadjuvant Chemotherapy for Esophagogastric Cancer

Acute Inflammation to Scar:

Fleckenstein K. Semin Radiat Oncol. 2007;17: 89-98
Late Metabolic Effects:

Acute Tissue Damage
Due to Cancer or Therapy

Tissue Repair
Return to Normal
Metabolic State

Ongoing Tissue Damage
And/Or
Failure to Return to
Normal Metabolic State

Question: Can tissue damage result in a self-perpetuating process that results in worsening metabolic late effects over time?
Sickness Behavior and Symptom Complexes

Mood
- Depression
- Anxiety
- Irritability
- Aggression

Cognition
- Memory loss
- Inattention
- Decreased alertness
- Disorientation

Neurovegetative
- Fatigue
- Slowed behavior
- Decreased appetite

Somatic
- Pain
- GI distress
**General Symptom Survey**

- I have unexplained fatigue
- Fatigue limits my day to day activity
- I have problems falling asleep
- I have problems staying asleep
- I have episodes of unexplained sweating
- There are times when I am cold and others around me are not
- There are times when I am hot and others around me are not
- I have trouble with my memory or processing my thoughts
- I have joint pain or muscle aches other than in my neck and shoulders
- I feel sad or depressed
- I feel anxious
Adverse Outcomes:

- Survival
- Dose alterations
- Toxicity
- Physical Function
- Psychological Distress
- Mood Disorders
- Body Image
- Social Function
- Quality of Life
Impact of Sarcopenia:

• Decrease in Quality of Life
  – Capuano, Supportive Care Cancer (2010) 18:433-437

• Increase in nosocomial infection

• Increased hospitalization

• Decreased Activities of Daily Living
Predicting Survival as an Outcome:

• Survival correlates with weight loss and decreased performance status
  – Clearly defining this parameters is a challenge
• Liver produces acute-phase proteins in response to tissue damage or tumor
  – Up regulated by interleukin-6 and TNF-α
  – C-Reactive Protein (CRP)
• Decline in albumin is noted concurrent with increase in CRP
• Glasgow Prognostic Score:
  – 0: no metabolic abnormalities
  – 1: CRP < 10mg/l OR albumin <35 g/l
  – 2: CRP < 10mg/l AND albumin <35 g/l
• GPS prognostic for outcome in numerous cancers

GPS: Impact on Survival in Metastatic Breast Cancer Patients

GPS Scores:
0 – top line
1 – dotted line in center
2 – solid line on bottom

GPS Score: Predicts Survival in Pre-Op Esophageal Cancer

Kobayashi et al, Surgery
(2008) 144: 729-35
Prado et al: Sarcopenic Obesity Associated with Decrease Survival

Patients:
• N=2115
• Lung or GI
• 250 met criteria for obesity

Methods:
• CT scan analysis with slicomatic

Results:
• 38/250 met criteria for sarcopenia
• Sarcopenia associated with decrease functional status (p=.009)

Cancer Cachexia: Atrophy of Lean Muscle Mass

Normal

Cachexia
Computed Tomography Images: Two Cancer Patients

Sarcopenic patient with low lean body mass: BMI 23.5 kg/m²

Patient with normal lean body mass: BMI 24.5 kg/m²

Tsai S Nutr Clin Pract 2012;27:593-598
A) Absolute force-frequency relationship
B) Maximal tetanic force
C) Specific force–frequency relationship
D) Maximum specific force
E) Time to peak twitch tension
F) One half twitch relaxation time
G) Anti-laminin antibody
H) Cross sectional area of muscle fiber type
I) Percentage of each EDL muscle fiber type in control and C-26 mice.

Roberts et al, Biochemical and Biological Research Communications (2013), 435:488-492
## Body Composition and Physiological Function: Patients With and Without Sarcopenia

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sarcopenia (n = 83)</th>
<th>Without Sarcopenia (n = 81)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>43.4</td>
<td>7.7</td>
<td>47.4</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>12.6</td>
<td>5.5</td>
<td>16.3</td>
</tr>
<tr>
<td>Skeletal muscle (kg)</td>
<td>20.8</td>
<td>4.7</td>
<td>23.4</td>
</tr>
<tr>
<td>Skeletal muscle index, (kg/m²)</td>
<td>7.4</td>
<td>1.1</td>
<td>8.5</td>
</tr>
<tr>
<td>Right hand grip</td>
<td>26.7</td>
<td>8.0</td>
<td>30.4</td>
</tr>
<tr>
<td>Left hand grip</td>
<td>25.0</td>
<td>7.5</td>
<td>28.3</td>
</tr>
<tr>
<td>Right knee ext</td>
<td>29.2</td>
<td>8.8</td>
<td>32.7</td>
</tr>
<tr>
<td>Left knee ext</td>
<td>27.7</td>
<td>10.3</td>
<td>31.9</td>
</tr>
<tr>
<td>6MWT</td>
<td>483.4</td>
<td>94.9</td>
<td>494.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>78.8</td>
<td>45.5</td>
<td>64.3</td>
</tr>
</tbody>
</table>
Sarcopenia and Drug Dosing:

- BSA commonly used for dosing chemotherapy agents
- For any given BSA, lean tissue mass may vary considerably
- Lower lean tissue mass may result in decreased tissue for drug distribution thus lower capacity for drug metabolism and/or clearance
Fluorouracil Dose as Moderated by Fat Free Mass

Treatment Related Toxicity and Lean Muscle Mass

Four studies relating treatment toxicity and depletion of skeletal muscle/lean body mass

Agents:
- Fluoropyrimidines
- Anthracyclines
- Tyrosine kinase inhibitors

DOI: 10.1097/MCO.0b013e32834558d5
Influence of GPS on Pre-dose Plasma Concentration of Oxycodone

<table>
<thead>
<tr>
<th>Oxycodone/noroxycodone</th>
<th>GPS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Oxycodone $C_{12}$ (ng/mL per mg/kg)</td>
<td>60.9 (41.0–70.0)</td>
</tr>
<tr>
<td>Noroxycodone $C_{12}$ (ng/mL per mg/kg)</td>
<td>74.4 (57.5–117.0)</td>
</tr>
<tr>
<td>Noroxycodone $C_{12}$/Oxycodone $C_{12}$</td>
<td>1.33 (1.08–2.29)</td>
</tr>
</tbody>
</table>

*P<0.05 and **P<0.01
Body Image

Disfigurement          Dysfunction

Patient Characteristics  Social Factors  Environmental Factors

Reintegration

Diagnosis     Treatment     Post-treatment

Quality of Life

Social Outcomes

Psychological Outcomes
Weight Loss and Body Image in Advanced Cancer

<table>
<thead>
<tr>
<th></th>
<th>No Substantial Weight Loss N=33</th>
<th>Substantial Weight Loss N=48</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIS Score</td>
<td>9.3</td>
<td>12.6</td>
<td>0.021</td>
</tr>
<tr>
<td>Age</td>
<td>49</td>
<td>57</td>
<td>0.018</td>
</tr>
<tr>
<td>HADS-A</td>
<td>7</td>
<td>7</td>
<td>0.916</td>
</tr>
<tr>
<td>HADs-D</td>
<td>4</td>
<td>8</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Why are fatigue and cachexia clinically meaningful to patients?

• Not confined to patients who have terminal disease
• Usually a component of a symptom complex
• Associated with adverse outcomes
• May affect survivors
Systemic Effects of Chemoradiation: Fatigue

- Definition: excessive tiredness involving the entire body which is disproportionate to exertion and does not resolve with rest
- Most common complaint of patients undergoing cancer therapy
- Reported in 40 to 100% of patients undergoing radiation therapy
Hickock: Frequency, Severity and Clinical Course of Fatigue

• 372 patients undergoing radiation therapy
• Methods: Symptom Inventory at baseline and weekly for 4 weeks after
• Results:
  – 58% of patients had some degree of fatigue at baseline
  – At week 4, this increased to 78%
  – Of the patients without fatigue at baseline, 70% developed fatigue
  – Fatigue was high at baseline in head and neck cancer patients (64%)
  – At week 4, 93% of head and neck cancer patients reported fatigue
Schubert Review: Fatigue and Inflammatory Markers

• Methods:
  – 18 studies (1037 participants)

• Results:
  – Fatigue correlated with overall inflammatory markers (p<0.0001), IL-6 (p=0.004), Il-1ra(p=0.005) and neopterin (p=0.001)
  – Fatigue did not correlate with TNF or IL-1b

Brain, Behavior and Immunity, 2007, 413-427
Starvation vs Cancer Cachexia

**Starvation**
- Decrease in calories
- Decrease in REE to spare calories
- Increased hepatic production of ketones from fatty acids
- Increased peripheral use of fatty acids
- Sparing of muscle

**Pro-inflammatory Cachexia**
- Decrease in calories
- Increased REE
  - Futile cycling
- Increased lipolyisis
- Increase muscle breakdown with loss of lean muscle mass
Neurocognitive Functioning in Adults with Upper Aerodigestive System Cancers

• PI: Stewart M. Bond, PhD, RN, AOCN (Funding: Hartford Foundation)

• Goal:
  To determine the extent of neurocognitive impairment in adults with newly diagnosed cancers of the upper aerodigestive system prior to, during, and at the completion of outpatient cancer treatment

• Specific Aims:
  1) To estimate the prevalence of baseline neurocognitive impairment prior to initiation of outpatient treatment
  2) To estimate the incidence of neurocognitive impairment during outpatient cancer treatment
  3) To describe how neurocognitive functioning changes over time during treatment
  4) To identify predictors of neurocognitive functioning (including biological correlates)
Concept of Energy Balance

Weight Maintenance

Energy in

EI = Energy Intake

Energy out

PAEE = Physical Activity Energy Expenditure
REE = Resting Energy Expenditure

EI = Energy Intake
PAEE = Physical Activity Energy Expenditure
REE = Resting Energy Expenditure
Starvation vs Cancer Cachexia

**Starvation:**
- Decrease in calories
- Decrease in REE to spare calories
- Increased hepatic production of ketones from fatty acids
- Increased peripheral use of fatty acids
- Sparing of muscle

**Cancer Cachexia:**
- Decrease in calories
- Increased REE
  - Futile cycling
- Increased lipolysis
- Increase muscle breakdown with loss of lean muscle mass
## Inflammatory Mediators:

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Post-Treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRP</strong></td>
<td>5.04</td>
<td>10.32</td>
<td>.09</td>
</tr>
<tr>
<td><strong>IL-6</strong></td>
<td>5.7</td>
<td>14.1</td>
<td>.08</td>
</tr>
</tbody>
</table>
# Change in Physical Performance and Function

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>1 month post treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Physical Activity Score</td>
<td>5.33±4.58</td>
<td>1.64±1.75</td>
<td>0.003</td>
</tr>
<tr>
<td>Physical Performance Test</td>
<td>14.6±1.59</td>
<td>12.50±4.16</td>
<td>0.140</td>
</tr>
<tr>
<td>ADL Score</td>
<td>0.00±0.00</td>
<td>2.36±3.34</td>
<td>0.020</td>
</tr>
<tr>
<td>IADL Score</td>
<td>3.21±2.12</td>
<td>6.07±2.76</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Inflammation and Oxidative Stress

• Increase in pro-inflammatory cytokines (IL-6 and IL-1B) @ with decrease in ADL (p=0.02) and IADL (p=0.04)

• Oxidative stress
  – Serum F2 isoprostane levels increased p=.007
  – @ with loss of fat and fat-free mass p=.04