Weight Loss in Lung Cancer: Fighting a Losing Battle?

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No Conflicts to Disclose
1) Describe the difference between catabolic weight loss and simple starvation.

2) List interventions used to manage primary & secondary cachexia in lung cancer patients.

3) Identify the most common nutrition-impact symptoms in lung cancer and nutritional strategies to manage these symptoms.
Schattner, J Clin Gastroenterol, 2003

- 80% of patients with advanced cancer → weight loss & malnutrition (cachexia).
- Most common in lung & upper GI malignancies.
- Malnutrition is considered to be main contributing factor in 20% of all cancer deaths.
Consequences of Weight Loss

Severe Weight Loss

↓ muscle mass (sarcopenia)
↓ energy -- ↑ fatigue
↓ immune function
↓ tissue healing
↓ treatment tolerance
↑ hospitalization
↓ QoL & self-esteem
↓ survival
• Weight loss is an independent predictor of both prognosis & survival in cachectic cancer patients.

• Total weight loss & rate of loss are directly related to survival.

• As little as 5% loss may worsen survival (DeWys, 1980).

• ~30% loss of pre-diagnosis weight → high risk of death due to generalized weakness, immobility & loss of respiratory function.
## Classification of Weight Loss

**NCIC Coding**

<table>
<thead>
<tr>
<th>Weight Loss</th>
<th>Other Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>&lt; 5.0%</td>
</tr>
<tr>
<td>Grade 1</td>
<td>5.0 to 9.9%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>10.0 to 19.9%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>&gt; 20.0%</td>
</tr>
</tbody>
</table>
## Classification of Weight Loss

**Blackburn, JPEN, 1977**

<table>
<thead>
<tr>
<th>Time</th>
<th>Significant Wt Loss (%)</th>
<th>Severe Wt Loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td>1-2</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>1 month</td>
<td>5</td>
<td>&gt; 5</td>
</tr>
<tr>
<td>3 months</td>
<td>7.5</td>
<td>&gt; 7.5</td>
</tr>
<tr>
<td>6 months</td>
<td>10</td>
<td>&gt; 10</td>
</tr>
</tbody>
</table>

\[
\% \text{ Wt Loss} = \frac{\text{wt change (previous wt-current wt)}}{\text{previous wt}} \times 100
\]
Catabolic Weight Loss (cancer cachexia) ≠ Simple Starvation (dieting, famine)
Simple Starvation

- Metabolic adaptation → altered substrate choice.
- Preferential fat loss → ↑ fat metabolism in liver to supply energy (~75% of weight loss is adipose).
- Ketone bodies from fat breakdown → important energy source for the brain.
- Slowed muscle loss → conservation of lean body mass (LBM).
- Resting energy expenditure (REE) is lowered in starving individuals which matches their reduced energy intake.
Catabolic Weight Loss vs Simple Starvation

**Catabolic Weight Loss**

- Both lean body mass & fat are reduced → ↑ in proteolysis & lipolysis.
- Preferential loss of skeletal muscle over adipose tissue.
- Visceral muscle protein (i.e. internal organs) is spared.
- Inappropriate elevation in REE even though energy intake is reduced (anorexia).
Catabolic Weight Loss vs Simple Starvation

**Catabolic Weight Loss**

- ↑ production of acute-phase proteins (C-reactive protein, fibrinogen).
- ↑ in pro-inflammatory cytokines (secreted from tumor or host) which initiate systemic inflammatory response.
- Cytokines (TNF-α, IL-6, IL-1β) play an important role in causing muscle wasting.
### Table 1: Cancer cachexia differs from starvation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cachexia</th>
<th>Starvation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting energy expenditure</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Loss of skeletal muscle</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Loss of fat</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Loss of visceral muscle</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Acute-phase response</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Proinflammatory cytokines</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Toxohormones</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Increased liver metabolism</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Liver size</td>
<td>++</td>
<td>--</td>
</tr>
</tbody>
</table>

+ increased
- reduced

*Couch et al, Head & Neck, 2007*
Baracos, Am J Clin Nutr, 2010

- Prospective cohort study of 441 patients with non-small cell lung cancer.
- Assess body composition using routine CT imaging of a vertebral lumbar landmark (L3).
- Skeletal muscle & adipose tissue in this region correspond to whole-body tissue quantities and have been validated in patients with cancer.
- Sarcopenia → severe muscle wasting (>2 SDs below that of typically healthy adults).
Table 1: Anthropometric & demographic characteristics of patients with NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Men (n=229)</th>
<th>Women (n=212)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI (kg/m(^2))</strong></td>
<td>25.2 ± 4.1</td>
<td>24.6 ± 5.9</td>
</tr>
<tr>
<td><strong>&lt;18.5 (%) → underweight</strong></td>
<td>2.6</td>
<td>12.3</td>
</tr>
<tr>
<td><strong>18.5 – 24.9 (%) → healthy</strong></td>
<td>46.7</td>
<td>43.4</td>
</tr>
<tr>
<td><strong>25 – 29.9 (%) → overweight</strong></td>
<td>35.8</td>
<td>28.8</td>
</tr>
<tr>
<td><strong>≥ 30 (%) → obese</strong></td>
<td>14.9</td>
<td>15.6</td>
</tr>
<tr>
<td><strong>Weight loss in 6 months (%)</strong></td>
<td>-6.39 ± 7.76</td>
<td>-5.58 ± 8.06</td>
</tr>
<tr>
<td><strong>Sarcopenic (%)</strong></td>
<td>61.1</td>
<td>31.3</td>
</tr>
<tr>
<td><strong>Vital status (% deceased)</strong></td>
<td>83.8</td>
<td>78.7</td>
</tr>
<tr>
<td><strong>Median time to death (d)</strong></td>
<td>244</td>
<td>320</td>
</tr>
</tbody>
</table>

Baracos et al, Am J Clin Nutr, 2010
Baracos, Am J Clin Nutr, 2010

• 25% of patients presented with weight loss > 10% in the 6 months preceding referral.

• 50% of patients were overweight or obese at referral despite previous weight loss.

• Sarcopenia is not unique to underweight and is an important nutritional risk factor, prognostic factor and potential predictor of cancer treatment toxicity.

• Estimated lean body mass was not strongly related to BSA.
Etiology of Malnutrition & Weight Loss

- **Multi-factorial in all cancer patients;**
  - primary cachexia → altered metabolism & systemic inflammatory response
  - secondary cachexia → reduced nutritional intake often associated with nutrition-impact symptoms (NIS)

- **In patients with secondary cachexia, it is expected that weight will stabilize or increase once these issues are resolved and intake improves.**
Improving Nutritional Intake

• **Step 1 – Aggressive Symptom Management**

• Identify potentially correctable causes of poor intake:
  
  - dysgeusia
  - nausea
  - pain/odynophagia
  - constipation
  - xerostomia
  - dysphagia
  - diarrhea
  - reflux
  - psychological factors
  - social factors
  - concurrent medical illness
Improving Nutritional Intake

• **Step 2 – Nutritional Therapy**

• Maximize nutritional-density → “make every sip & bite count”.

• Negotiate an individualized care plan:
  
  ✓ emphasis on energy-dense foods/liquids (goal → 30 kcal per kg)
  
  ✓ inclusion of high-protein foods, liquids &/or supplements at all meals & snacks (goal → 1.3 to 1.5 grams per kg)
  
  ✓ 180 lb (80 kg) → 2400 kcal; 104–120 grams protein
Increasing Energy Density

3 servings/day
1.0 kcal/mL
720 kcal
30 grams protein

3 servings/day
1.5 kcal/mL
1080 kcal
42 grams protein

3 servings/day
2.0 kcal/mL
1440 kcal
60 grams protein
Treatment of Secondary Cachexia

**Improving Nutritional Intake**

- **Step 2** – *Nutritional Therapy*
  
  - Negotiate an individualized care plan;
    
    - small, frequent meals/snacks (for nausea & early satiety) – “mechanical eating”
    
    - frequent mouth-rinsing before & after meals (for taste changes)
    
    - soft or liquid diets may be needed (for esophagitis & taste changes)
Treatment of Primary Cachexia

Countering Altered Metabolism/Inflammation

- **anti-cachexia agents**
- **glucocorticosteroids (e.g. dexamethasone)**
  - ✓ short term increase in appetite & food intake
  - ✓ do not increase body weight
  - ✓ anti-emetic benefits
  - ✓ side effects may be significant with prolonged use (4-6 weeks)
  - ✓ osteoporosis, proximal muscle weakness, immunosuppression, delirium, may induce skeletal muscle atrophy
Treatment of Primary Cachexia

Countering Altered Metabolism/Inflammation

- **megestrol acetate (e.g. Megace®)**
  - orexigenic agent (appetite stimulant)
  - synthetic hormone that can interfere with hormonal signaling
  - no documented effect on LBM or change in performance status
  - weight gain $\rightarrow$ ↑ body fluid & adipose
Treatment of Primary Cachexia

Countering Altered Metabolism/Inflammation

- megestrol acetate (e.g. Megace®)

  ✓ may cause acute hypercalcemia in patients with bone metastasis
  ✓ has been associated with hyperglycemia
  ✓ doses of 160-320 mg/day given during & after treatment have resulted in weight gain and decreased cytokine levels
Treatment of Primary Cachexia

Countering Altered Metabolism/Inflammation

- **eicosapentanoic acid (EPA)**
  - essential omega-3 fatty acid found in marine products
  - modulate levels of pro-inflammatory cytokines, acute-phase proteins & tumor toxohormones
  - shown to increase LBM in pancreatic cancer patients (added to a nutritional supplement)
  - recent placebo-controlled RCTs have not shown benefit (compliance issues)
Key Messages

• **Pathophysiology of cancer cachexia is very different from simple starvation.**

• **Accurate & timely diagnosis of catabolic weight loss is essential.**

• **Prompt intervention can greatly impact patient’s QoL & overall prognosis.**
• Nutritional therapy alone is often insufficient in addressing catabolic weight loss.

• Anti-cachexia agents may also be required → more research is needed to identify effective agents.

• Future research → focus on body composition.

• Multidisciplinary approach is crucial.