The evidence for nutritional support in multimodal therapy for cancer cachexia

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Outline

- What is cancer cachexia?
- The two pathways to wasting
- Energy balance in cancer cachexia
- Body composition in cancer cachexia
- Interventions
- Conclusions
Malnutrition in cancer patients

- Associated with adverse outcomes
- Involves loss of muscle and fat
- Reflects a catabolic metabolism
  - Host response to tumour presence
  - Tumour factors
Cancer cachexia - not easily defined!

- Weight loss
- Anorexia
- Early satiety
- Fatigue
- Decreased muscle strength
- ...

...
“Cancer cachexia is defined as a multifactorial syndrome characterised 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.”

Fearon et al Lancet Oncol 2011; 12: 489–95
Stages of cancer cachexia

Fearon et al Lancet Oncol 2011; 12: 489–95
Development of malnutrition: The two pathways

- Anorexia → Low intake
- Disease → Tissue wasting
- Catabolism
Development of malnutrition: The two pathways

- Anorexia → Low intake
- Disease
- Inflammation
- Catabolism
- Tissue wasting
Development of malnutrition: The two pathways

- **Anorexia** → **Low intake**
  - **Tissue wasting**
  - **Catabolism**
  - **Inflammation**
  - **Disease**
The pathways to weight loss

- Low intake
- Disease
  - Catabolism
- Weight loss
How do the pathways differ?

Low intake = Negative energy balance

Cancer cachexia with systemic inflammation

Fat stores depleted more than muscle

Muscle breakdown and fat depletion
Metabolic changes in weight loss

Pathway
- Resting energy metabolism
- Protein loss
- Protein-sparing effect of nutrition

Low intake
- Resting energy metabolism
- Protein loss
- Protein-sparing effect of nutrition

Catabolism
- Resting energy metabolism
- Protein loss
- Protein-sparing effect of nutrition
Acute phase metabolic response

- Elevation of resting energy expenditure
- Export of amino acids from muscle to liver
- Increase in gluconeogenesis
- Expansion of extracellular fluid
- Shift toward production of positive acute phase reactants
Energy balance

Intake
- Protein
- Fat
- CHO

Expenditure
- AEE
- TEF
- REE
Negative energy balance in cancer

Intake
- Protein
- Fat
- CHO

Decreased intake

Expenditure
- AEE
- TEF
- REE

Decreased activity

Increased REE
Diet, REE and weight loss in cancer

- Low dietary intake, but not lower in hypermetabolic or weight-losing patients
- Uncoupling of food intake to energy expenditure in cancer promotes weight loss
- Elevated REE important factor
- Early dietary intervention might be better than late artificial nutrition

Bosaeus et al IJC 2001;93:380
Diet, REE and weight loss in cancer

Conclusions

- Weight loss, reflecting negative energy balance, decreases survival in advanced cancer
- Increased REE and low energy intake both contribute to negative balance
- Therapy based on intervention towards both mechanisms might improve survival
The pathways to weight loss

- Low intake
- Disease
  - Catabolism
  - Weight loss
Cancer cachexia: Loss of muscle and fat

Fuel for energy deficit:
\[ \uparrow \text{Lipolysis} \]

Fuel for hepatic protein & glucose synthesis

\[ \downarrow \text{Protein synthesis} \]
\[ \uparrow \text{Protein breakdown} \]

Preservation of viscera
Nutritional support in inflammation: Limited effect – low intake pathway only

Fat stores repleted

but

Muscle breakdown continues driven by systemic inflammation

Skeletal muscle atrophy

Preservation of viscera
Clinical guidelines

A.S.P.E.N. Clinical Guidelines: Nutrition Support Therapy During Adult Anticancer Treatment and in Hematopoietic Cell Transplantation

ESPEN GUIDELINES

ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology

ESPEN Guidelines on Parenteral Nutrition: Non-surgical oncology

F. Bozzetti a, J. Arends b, K. Lundholm c, A. Micklewright d, G. Zurcher e, M. Muscaritoli f

DAA Evidence based practice guidelines for the nutritional management of cancer cachexia

ADA Oncology Evidence-based Nutrition Practice Guideline
Nutrition support

Oral nutrition

- Dietary counseling
  - Choice of food
  - Meal pattern
- Oral nutritional supplements (ONS)
- Food modification
  - Texture, fortification
  - ... and more

Artificial nutrition

- Tube feeding
- Parenteral nutrition

What is optimal nutrition support?
Oral nutritional support in cancer patients

- Meta-analysis 13 RCT, 1414 pts
- Improvements in weight and energy intake, and QoL
- Considerable heterogeneity, when removed no significant effects
- No effect on mortality

Baldwin et al J Natl Cancer Inst 2012
Meta-analysis: Body weight


Energy intake: mean difference
432 kcal/day, P=0.001, $I^2=97\%$ (Baldwin 2012)
381 kcal/day (Elia 2006)
Meta-analysis: Global QoL

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention Mean</th>
<th>SD</th>
<th>Total</th>
<th>No intervention Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean difference</th>
<th>Mean difference</th>
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<tbody>
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<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
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<tr>
<td>Baldwin et al. 2008a (17)</td>
<td>2.06</td>
<td>22.7</td>
<td>54</td>
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<td>20</td>
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<td>4.91 [-5.92–15.74]</td>
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<td>Baldwin et al. 2008b (17)</td>
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<td>3.51 [-7.48–14.50]</td>
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<tr>
<td>Baldwin et al. 2008c (17)</td>
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<td>21.9</td>
<td>46</td>
<td>-2.85</td>
<td>20.5</td>
<td>21</td>
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<td>2.22 [-8.59–13.03]</td>
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<td>Isenring et al. 2004 (27)</td>
<td>5</td>
<td>20</td>
<td>25</td>
<td>-12.6</td>
<td>22.7</td>
<td>29</td>
<td>10.3%</td>
<td>17.60 [6.21–28.99]</td>
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<td>Persson et al. 2002 (18)</td>
<td>15.2</td>
<td>25.5</td>
<td>50</td>
<td>13.8</td>
<td>24.6</td>
<td>50</td>
<td>10.7%</td>
<td>1.40 [-8.42–11.22]</td>
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<td>Ravasco et al. 2005a (19)</td>
<td>32</td>
<td>6</td>
<td>25</td>
<td>-19</td>
<td>4</td>
<td>13</td>
<td>11.9%</td>
<td>51.00 [47.80–54.20]</td>
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<td>Ravasco et al. 2005b (19)</td>
<td>20</td>
<td>4</td>
<td>25</td>
<td>-19</td>
<td>4</td>
<td>12</td>
<td>11.9%</td>
<td>39.00 [36.25–41.75]</td>
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<td>Ravasco et al. 2005c (20)</td>
<td>35</td>
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<td>37</td>
<td>-18</td>
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<td>53.00 [49.86–56.14]</td>
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<td>37</td>
<td>-18</td>
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<td>18</td>
<td>12.0%</td>
<td>33.00 [30.75–35.25]</td>
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<td>Subtotal (95%CI)</td>
<td>358</td>
<td></td>
<td></td>
<td>202</td>
<td>100.0%</td>
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<td>24.02 [14.33–33.72]</td>
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Heterogeneity: $\tau^2 = 203.42$; $\chi^2 = 349.77$, df = 8 ($P < .00001$); $I^2 = 98$
Test for overall effect: $Z = 4.86$ ($P < .00001$)

EORTC

Conclusion: Oral nutritional interventions are effective at increasing nutritional intake and improving some aspects of QOL in patients with cancer who are malnourished or are at nutritional risk but do not appear to improve mortality.

Baldwin et al J Natl Cancer Inst 2012
Evaluation of nutrition support – inherent problems

- Compliance
- Variable impact of the catabolic pathway, between subjects and over time
- Various anti-tumor and anti-catabolic strategies, with limited knowledge of metabolic effects
Artificial nutrition in cancer

- **Chemotherapy (25 studies):**
  - Body weight preserved but probably not body cell mass
  - No difference survival

- **Radiation therapy (11 studies):**
  - No difference survival or complications

- **Palliative care**
  - No controlled studies identified

- **Insufficient data for clinical guidelines**
RCT (n=309) in pts with solid tumors, mainly G-I in origin

All received anti-inflammatory treatment (NSAID) + anemia prevention

Intervention: Individualized nutrition support (Dietary counseling + ONS + supplemental PN)

Lundholm et al Cancer 2004;100:1967-77
Nutritional intervention

- All patients (n=309):
  - Anti-inflammatory treatment (NSAID)
  - Anemic patients: EPO

- Nutrition support group (n=139):
  1/ Dietary counseling + oral nutritional supplements
  2/ Home parenteral nutrition (about 50%, mean duration 46 days)

Lundholm et al Cancer 2004;100:1967-77
Effects on function (maximum exercise capacity)

Lundholm et al Cancer 2004;100:1967-77
Effects on survival

Lundholm et al Cancer 2004;100:1967-77
Supplemental parenteral nutrition (PN) in cancer

- 152 pts on palliative chemo/radiotherapy
- Oral nutrition support to all, randomized to long-term PN (30% of requirements) or not
- PN improved 48 week survival, body composition and quality of life

Shang et al JPEN 2006;30:222-30
Supplemental parenteral nutrition (PN) in cancer

- 82 pts on palliative chemotherapy
- Oral nutrition support to all, randomized to long-term PN (30% of requirements) or not
- PN slowed weight loss, stabilized body composition, and improved QoL and survival

Hasenberg et al Colorectal disease 2010
Conclusions

Limited evidence supports that, in patients with wasting due to malignant disease:

1/ Nutrition is a limiting factor influencing survival

2/ Nutrition support can improve energy metabolism and function, when given together with anti-inflammatory treatment.
Perspectives

- What is optimal anti-catabolic therapy?
- What is optimal nutrition support?
- Which patients will respond well?
Treatment strategies

- Adequate nutrition – adjusted to the condition
- Metabolic control
- The future – improved means to modify inflammatory metabolic alterations?

How optimize nutrient metabolism by modifying the inflammatory response?
Summary (1)

- The evidence base for effects of nutrition support on outcome is still limited.
- Many inherent problems in evaluating the role of nutrition support in relation to other factors, especially catabolism and nutrition impact symptoms at different stages of the cachexia journey.
The evidence is stronger for nutrition support to increase intake and decrease weight loss.

The effect of increased intake on outcome will likely depend on the impact of the catabolic pathway.

The conceptual case for multimodal intervention is thus quite strong.
Thanks for your attention!
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