Nutritional & Metabolic Support of the Cancer Patient
An update, with a focus on oral feeding

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The Learning curve: why?

Prevalence and prognosis
Severe weight loss is present in 28% of patients at diagnosis and in 85% of patients at palliative care.

- Weight loss: 28% at diagnosis, 85% at palliative care
- Anorexia: 58% at diagnosis, 81% at palliative care
- Satiety: 20% at diagnosis, 69% at palliative care
- Ileus: 7% at diagnosis, 59% at palliative care
- Taste alterations: 13% at diagnosis, 16% at palliative care
- Smell alterations: 6% at diagnosis, 10% at palliative care

Prevalence of cachexia in cancer

CLCC 2005 (n=1928 pts)
NUTRICANCER 2006 (n=2068 pts)
CLCC 2008 (n=1545 pts)
Cancer

- Host/Tumor interactions
  - Pro-cachectic tumor factors

- Anti-cancer treatments


- Anorexia
  - Physical activity
  - Psychologic disorders

- Mechanical obstacles
  - Intake impairment
    - Gut absorption disorders

- Negative energy balance
  - Metabolic disturbances
    - Metabolism of:
      - Carbohydrates
      - Lipids
      - Proteins

- Intake impairment
  - Physical activity
  - Psychologic disorders

- Cachexia

- Mechanical obstacles
Cachexia = « poor condition »

Accelerated loss
of the skeletal muscle
in a context of chronic inflammatory response

Kotler DP Ann Intern Med 2000; 133: 622-34
NF-κB activation
The French Multicenter Study (2008)

- Mortality at 30 days: 6.73%
- Comparison between alive and dead pts at D30

WL > 10%: 36.8% vs 18.9% (p<0.05)
BMI ≤ 18.5: 21.8% vs 8.1% (p<0.05)
The Learning curve: for whom?

Nutritional assessment

Prevalence and prognosis
Many tools ...

<table>
<thead>
<tr>
<th></th>
<th>No malnutrition</th>
<th>Mild to moderate malnutrition</th>
<th>Severe malnutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6 months WL</strong></td>
<td>&lt; 10%</td>
<td>10-15%</td>
<td>≥ 15%</td>
</tr>
<tr>
<td><strong>1 month WL</strong></td>
<td>&lt; 5%</td>
<td>5-10%</td>
<td>≥ 10%</td>
</tr>
<tr>
<td><strong>BMI:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70 years old</td>
<td>&gt; 18.5</td>
<td>≤ 18.5</td>
<td>≥ 18.5</td>
</tr>
<tr>
<td>&gt; 70 ans old</td>
<td>&gt; 20</td>
<td>≤ 20</td>
<td>≥ 20</td>
</tr>
<tr>
<td><strong>Brachial perimeter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 26 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SGA</strong></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td><strong>Serum albumin</strong></td>
<td>≥ 30 g/L</td>
<td>20-30 g/L</td>
<td>&lt; 20 g/L</td>
</tr>
<tr>
<td><strong>Thansthyretin</strong></td>
<td>≥ 110 mg/dL</td>
<td>50-110 mg/dL</td>
<td>&lt; 50 mg/dL</td>
</tr>
<tr>
<td><strong>NRI</strong></td>
<td>≥ 97.5</td>
<td>83.5-97.5</td>
<td>≤ 83.5</td>
</tr>
</tbody>
</table>

*NRI = 1,519 x albumine (g/l) + 0,417 x Pds actuel/Pds habituel x 100*
Nutritional assessment: The French Decision Tree

(adapted from Hasselmann M. et al. Nutr Clin Metabol 2003; 17: 218-26)

Step 1

- BMI > 18
  - No WL

Step 2

- NRI ≥ 97.5
  - Surveillance

- BMI ≤ 18
  - And/or weight loss

Step 3

- Alb < 35 g/L or 83.5 < NRI < 97.5
  - Dietician exercise, Oral nutritional supplements

- Alb < 30 g/L or NRI < 83.5
  - EN or/and PN

- Albumin ?
  - NRI * ?

BMI ?
- WL ?
Modified Glasgow Prognostic Score
«an inflammation-based prognostic score»

<table>
<thead>
<tr>
<th>Biochemical measure</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>C-reactive protein ≤10 mg/L + Albumin ≥35 g/L</td>
<td>0</td>
</tr>
<tr>
<td>C-reactive protein ≤10 mg/L + Albumin &lt;35 g/L</td>
<td>0</td>
</tr>
<tr>
<td>C-reactive protein &gt;10 mg/L</td>
<td>1</td>
</tr>
<tr>
<td>C-reactive protein &gt;10 mg/L + Albumin &lt;35 g/L</td>
<td>2</td>
</tr>
</tbody>
</table>

McMillan DC, Curr Opin Clin Nutr Metab Care, 2009; 12: 223-6
Prevalence of Muscle Loss (i.e. Sarcopenia)

The typical cancer patient is more likely to be overweight or obese and sarcopenic, than to be clinically underweight.
Why being interested in body composition, muscle mass in cancer?

PATIENT A
68 year old man
Small bowel Cancer
Body Mass Index (weight/height$^2$) 24.4 kg/m$^2$
Skeletal Muscle area = 31.7 cm$^2$
Adipose tissue area = 575.5 cm$^2$

PATIENT B
54 year old man
Pancreatic cancer
Body Mass Index (weight/height$^2$) 24.2 kg/m$^2$
Skeletal Muscle area = 177.0 cm$^2$
Adipose tissue area = 303.1 cm$^2$
New definition of cancer cachexia

“a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat”

This feature is crucial to explore the link between sarcopenia and chemotherapy toxicities.
Sarcopenia / Chemotherapy Toxicity

Metastatic renal cell cancer receiving Sorafenib n=55

% Patients with Dose Limiting Toxicity

- Non sarcopenic men (5.5%) vs sarcopenic men (37%)
- Non sarcopenic men BMI>25 (10%) vs sarcopenic men BMI<25 (71%)
- Total non sarcopenic BMI>25 (12%) vs total sarcopenic BMI<25 (47%)

Antoun, Ann Oncol 2010
Sarcopenia and drug toxicity

All Dose Limiting Toxicities (DLT)

- Incidence of DLT (%)
  - Sarcopenic: 80%
  - Non-sarcopenic: 20%

Diarrhea (grade 3/4)

- Incidence of DLT (%)
  - Sarcopenic: 60%
  - Non-sarcopenic: 20%

Mir, PLoS ONE, 2012
First conclusions

- Malnutrition/cachexia is *per se* a major pronostic factor of Cancer.
- Nutritional assessment is easy ...
- But is not part of the clinical routine of oncologists!
- It could lead to better and earlier prescription aiming at fighting against cachexia.
The learning curve: how and... does it work?

- Prevalence and prognosis
- Nutritional assessment
- Nutritional support: modalities and results
Nutrition and Tumor Growth?

- Yes, in animal models
- No proof in clinical nutrition with concomitant anti-cancer treatments!!

First, try to maintain oral feeding asap during the course of cancer:

The utmost value of dietetic counseling and ONS
Why is it so crucial?

Because eating, like breathing, is synonym of life!...
Favor Spontaneous Oral Feeding, Promote Dieticians!

- Take care of the location, the schedule and the conviviality of the meals:
  - Meals must be fractionated (4 to 6 small portions per day)
  - Favourite food should be presented
  - ‘Rich’ food (sugar, butter, cream, eggs, cheese) is recommended
  - Feed the patient when hungry; gently encourage
  - Ambiance of meals should be quiet; make meal times social, convivial and enjoyable
  - Maintain some level of activity
  - ...

Adapted from Acreman (2009); Nitenberg and Raynard (2000)
Compensate the handicaps

Adapted eating utensils

Convenient help

Attractive serving tray

Unacceptable!
Be aware of taste alterations!

54 cancer patients (mean age: 53 y), including 77% with advanced cancer
And a mean WL of -3.0 ± 1.1 kg.

... oral nutritional supplements (ONS)

- Nutritional compounds for oral nutrition
- Supplement = *non exclusive oral intake* +++
- Complete = CH, lipids, proteins (or CH + P)
ONS : The 10 Commandments

Thou shall ensure a correct indication
Thou shall encourage patient’s motivation
Thou shall respect patient’s taste
Thou shall care about patient’s handicap
Thou shall distribute ONS distant to the meals
Thou shall give one ONS at a time
Thou shall serve it at the good temperature
Thou shall help patient to take the ONS
Thou shall avoid ONS monotony
Thou shall ensure compliance with the prescription
Oral Nutritional Interventions in Malnourished Pts W/Ca: A Systematic Review and Meta-Analysis

- 13 studies, 1414 patients
- Variability in quality and considerable clinical and statistical heterogeneity.
- After removing the main sources of heterogeneity:
  - no statistically significant difference in weight gain or energy intake.
  - Beneficial effect on some aspects of QOL (emotional functioning, dyspnea, loss of appetite, and global QOL)
  - no effect on mortality (relative risk = 1.06, 95% CI = 0.92 to 1.22, p = .43).
### Oral nutritional intervention & global QoL meta-analysis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention Mean</th>
<th>Intervention SD</th>
<th>Intervention Total</th>
<th>No intervention Mean</th>
<th>No intervention SD</th>
<th>No intervention Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Baldwin et al. 2008a (17)</td>
<td>-0.03</td>
<td>5.77</td>
<td>60</td>
<td>-0.05</td>
<td>6.27</td>
<td>21</td>
<td>9.5%</td>
<td>0.02 [-3.03-3.07]</td>
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<tr>
<td>Baldwin et al. 2008b (17)</td>
<td>0.29</td>
<td>5.93</td>
<td>58</td>
<td>-0.05</td>
<td>6.27</td>
<td>21</td>
<td>9.4%</td>
<td>0.34 [-2.75-3.43]</td>
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<tr>
<td>Baldwin et al. 2008c (17)</td>
<td>0.89</td>
<td>6.31</td>
<td>55</td>
<td>-0.05</td>
<td>6.27</td>
<td>22</td>
<td>9.4%</td>
<td>0.94 [-2.17-4.05]</td>
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<td>Elkort et al. 1980 (25)</td>
<td>2.6</td>
<td>15</td>
<td>12</td>
<td>3.4</td>
<td>13</td>
<td>14</td>
<td>1.9%</td>
<td>-0.80 [-11.68-10.08]</td>
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<tr>
<td>Isenring et al. 2004 (27)</td>
<td>-0.38</td>
<td>3.42</td>
<td>25</td>
<td>-4.7</td>
<td>4.69</td>
<td>29</td>
<td>11.4%</td>
<td>4.32 [2.15-6.49]</td>
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<tr>
<td>Lovik et al. 1996 (28)</td>
<td>-0.9</td>
<td>3.1</td>
<td>24</td>
<td>-2</td>
<td>4.2</td>
<td>25</td>
<td>11.7%</td>
<td>1.10 [-0.96-3.16]</td>
</tr>
<tr>
<td>Ovesen et al. 1993 (30)</td>
<td>1</td>
<td>5.6</td>
<td>57</td>
<td>0.1</td>
<td>4.7</td>
<td>48</td>
<td>11.9%</td>
<td>0.90 [-1.07-2.87]</td>
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<tr>
<td>Persson et al. 2002 (18)</td>
<td>1.29</td>
<td>2.9</td>
<td>24</td>
<td>1.6</td>
<td>3.2</td>
<td>35</td>
<td>12.7%</td>
<td>-0.60 [-2.17-0.97]</td>
</tr>
<tr>
<td>Ravasco et al. 2005a (19)</td>
<td>4</td>
<td>3</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>Not estimable</td>
<td></td>
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<tr>
<td>Ravasco et al. 2005b (19)</td>
<td>0</td>
<td>0</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Ravasco et al. 2005c (20)</td>
<td>5</td>
<td>2</td>
<td>37</td>
<td>-2</td>
<td>5</td>
<td>18</td>
<td>10.9%</td>
<td>7.00 [4.60-9.40]</td>
</tr>
<tr>
<td>Ravasco et al. 2005d (20)</td>
<td>1</td>
<td>1</td>
<td>37</td>
<td>-2</td>
<td>5</td>
<td>19</td>
<td>11.2%</td>
<td>3.00 [0.73-5.27]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>439</td>
<td>277</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.86 [0.25-3.47]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 4.69$; $\chi^2 = 37.15$, df = 9 ($P < .0001$); $I^2 = 76$

Test for overall effect: $Z = 2.26$ ($P = .02$)

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Individualized nutrition intervention in colorectal cancer pts: a randomized controlled trial


G1: individualized counseling (n=34)
G2: ONS + usual diet (n=29)
G3: usual diet (n=26)

Comparisons adjusted for cancer stage, age, follow-up time, disease recurrence, adjuvant treatments, survival, and number of patients in each group.

p< 0.006

p< 0.001
Individualized nutrition intervention in colorectal ca pts: late radiotherapy toxicity

G1: individualized counseling (n=34)
G2: ONS + usual diet (n=29)
G3: usual diet (n=26)

p = 0.002
Individualized nutrition intervention in colorectal cancer pts: disease-specific survival

G1: individualized counseling (n=34)
G2: ONS + usual diet (n=29)
G3: usual diet (n=26)

n-3 PUFAs and Cachexia

Diagram showing the relationship between n-3 fatty acids (n-3 FA) and cachexia, involving adipose tissue, muscle, liver, and tumor cells. The process includes TNF-α and PIF signaling pathways.
n-3 PUFAs and NFκB activity

Graph showing the relationship between Omega 3 product in diet (% w/w) and NFκB activation (density x area). The graph displays a downward trend as the Omega 3 product increases.
EPA level and Lean Body Mass

Omega-3 fatty acids in Cancer: key points

- Omega-3 FA may:
  - Reverse cancer cachexia
  - Improve muscle mass and LBM
  - Promote weight maintenance

- Although *limited evidence* ... their use has been demonstrated in small studies:
  - to improve nutritional status and function
  - *To possibly reduce cancer treatment toxicities*
  - *To possibly increase response rates*

What about appetite stimulants?  
Megestrol Acetate

- True appetite stimulant effect
- Improve oral intake
- **Weight gain or stabilization, but …**
  - Water retention (oedema)
  - Increase in fat mass
  - No improvement of LBM
  - Small but significant risk of thromboembolism
- No difference in quality of life or survival

In case of failure,
Propose Enteral Nutrition
In summary, a decision tree for nutritional support

- Oral intake < 1000-1200 kcal/j
  - Yes: Functional gut?
    - Yes: Enteral Nutrition
      - Duration > 30 d?
        - No: Nasogastric tube
        - Yes: Specific cases
          - Nasoduodenal tube
    - No: Gastrostomy
  - No: Parenteral Nutrition
    - nutrition > 14 j and/or TPN and/or Central line in place
      - Yes: Central
      - No: Peripheral max 1000 kcal/d

+ call the dietician or/and nutritionist!!
The learning curve: looking for the future

- Prevalence and prognosis
- Nutritional assessment
- Nutritional support: modalities and results
INHIBITORS OF CYTOKINE SYNTHESIS AND/OR RELEASE: PENTOXIFYLLINE, THALIDOMIDE, STATINS, ACE-INHIBITORS, ANTI-COX2, EPA

ANTI-CYTOKINES ANTIBODIES: ANTI-IL-6; ANTI-TNF

ANTI-INFLAMMATORY CYTOKINES IL-12; IL-15

CATABOLISM ATTENUATION

PROGESTAGENS, CANNABINOIDS, GLUCOCORTICOIDS, SEROTONIN SYNTHESIS/RELEASE INHIBITORS

IMPROVING ANOREXIA

ATTENUATION OF PIF CACHETIC EFFECTS

BODY WEIGHT

NUTRITIONAL SUPPORT

ANABOLISM STIMULATION

EPA

A similar approach for targeted anticancer therapies and targeted « nutrition » ?
Resveratrol affects the activity of multiple signaling pathways.
Conclusions (simple but robust)

Nutritional Support is a major part of the supportive care of the cancer patient and should be considered in curative as well as in palliative situations.

1. Perform nutritional assessment very early in the course of the disease and at each step of the cancer treatment.

2. Nutrition is part of the holistic care of the patient to improve treatment tolerance and minimize side-effects of drugs.

3. Oral nutrition, including prescription of ONS, should be favored and followed by a « nutrition team ».

4. In case of failure, enteral nutrition is feasible and well tolerated in the majority of cancer patients.

5. Consider to « just say no » for artificial nutrition at the end of life.
• **Doctors are people who prescribe medicine few things of which they know to cure diseases which they know even less ... at human beings of whom they know nothing.**

Voltaire (1694-1778)