Recognition of cachexia and fatigue in routine daily oncology practice and embedded in cancer clinical trials
Current evidence of routine screening of pre-cachexia, fatigue, malnutrition, cachexia, and physical function decline

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Disclosure Slide (last 5 years)

**Unrestricted industry-grants for clinical research**
- Bachem (bulk Ghrelin)
- Celgene (Lenalidomide Cachexia trial)
- Fresenius (Survey parenteral nutrition malignant bowel obstruction)
- Grünenthal (opioid rotation trial)

**Participation in company-lead clinical cachexia trials**
- Novartis (BYM338 cachexia trial)

**Punctual Advisorship** (Boards, Expert meetings)
Acacia, Alder, Amgen, Baxter, Fresenius, Helsinn, Nutricia, GSK, Otsuka, Ono, Pfizer, Santhera, Solvay, Teva, Wyeth

*No: Mono-sponsored industry-controlled Satellite meetings*
*No: Personal financial interest (stocks, private use of honoraria, ...)*
In which settings, which patients, shall we screen for Fatigue & Cachexia?

- Time in trajectory of incurable cancer
- Location: in-, out-patient, specialized clinics,...
- Professions involved: model of care
- Risk assessment before anticancer treatments
- Candidates for clinical trials
- ...

MASCC Berlin 27.6.2013 / F. Strasser
In **which settings, which patients**, shall we screen for Fatigue & Cachexia?

**Time in trajectory of incurable cancer**

- At first diagnosis of advanced, incurable cancer → very variable situations depending on tumor type
- During advanced, incurable cancer → increasingly longer survival, many new treatments

![Colorectal cancer patients: Median Survival (Months)](chart.png)
In which settings, which patients, shall we screen for Fatigue & Cachexia?

**Time in trajectory of incurable cancer**

- Last 6 months of advanced, incurable cancer

In which settings, which patients, shall we screen for Fatigue & Cachexia?

Professions involved: model of care

Multidisciplinary health care professionals' perceptions of the use and utility of a symptom assessment system for oncology patients

Self-completed surveys (n=120)

ESAS in clinic either "always" or "most of the time": nurses (89%), physicians (55%), and other providers (57%)

The no-users: more efficient to talk to the patient or do their own assessment to determine symptom issues.

Acknowledge perceived roles of all multidisciplinary team members, including physicians.

In which settings, which patients, shall we screen for Fatigue & Cachexia?

Candidates for clinical trials

Systematic monitoring and treatment of physical symptoms to alleviate fatigue in patients with advanced cancer: a randomized controlled trial

Patients were eligible:
solid malignancy, treatment with palliative intention, fatigue score $\geq 4$ on a numeric rating scale (0 to 10), ECOG PS $<2$, life expectancy $>4$ months

Intervention:
Protocolized patient-tailored treatment of symptoms

Why should we recognize / screen for Fatigue & Cachexia?

- Unmet clinical need of patients: (re-) prioritize care
  - perceived fatigue
  - perceived loss of appetite, early satiety, chronic nausea
- Availability of effective interventions *(see part 2 of WS)*
- Impact of fatigue/cachexia on anticancer treatment toxicity, survival, response-stabilisation *(see talk 5)*

Barriers to screen:
- No clinical practice tools to screen
- Burden and impact not clear: „why bother“
- No interventions for my current patient, no specialists
What domains of Fatigue & Cachexia shall we screen?

### Cachexia
- Depletion of reserves: muscle mass *and* fat mass
- Nutritional intake *and* „gut-brain axis“ symptoms appetite
- Inflammation *and* tumor dynamics
- Neuro-muscular *and* emotional-cognitive function

### Fatigue
- Physical fatigue: Malnutrition or Cachexia or other
- Emotional fatigue: depression, existential issues
- Cognitive fatigue: delirium, side-effect drugs, etc.
How shall we screen for Fatigue & Cachexia?

Phenotypic approach: Fatigue Domains*

- Cognitive  
  SQIDS, m-MMSQ, DOS
- Emotional  
  HSWS (J.Holland), HADS
- Physical  
  Muscles (weight?), physical. Fct.

Next level simple assessment:
- SQIDS: single question in Delirium\(^1\)
- s-MMSQ : short mini-mental state exam\(^2\)
- DOS: Delirium observation scale\(^3\)
- HGWS: hopelessness, guilt, worthlessness, suicidal\(^4\)
- HADS: Hospital Anxiety Depression Scale\(^5\)
- Muscle: visual, Mid-Arm-Circumf. <5 percentile\(^6\)

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* Single-item Fatigue (Käser I et al. JPSM 2009)
Single-Item Fatigue

Kognitiv – Emotional - Körperlich

<table>
<thead>
<tr>
<th></th>
<th>Kopf</th>
<th>Stimmung</th>
<th>Kraft</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2</strong></td>
<td>Ich fühle mich <strong>müde, weil</strong> ich „im Kopf“ müde bin, weil ich Mühe habe mich zu konzentrieren, weil meine Auffassungsgabe verlangsamt ist:</td>
<td></td>
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<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
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<tr>
<td><strong>3</strong></td>
<td>Ich fühle mich <strong>müde, weil</strong> ich „keine Freude“ verspüre, weil ich keine Lust habe, weil ich keinen Antrieb habe, weil „es“ keinen Sinn (mehr) macht:</td>
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<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
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<tr>
<td><strong>4</strong></td>
<td>Ich fühle mich <strong>müde, weil</strong> ich „keine Kraft“ mehr habe, weil mein Körper schwach ist, meine Muskeln schwach sind:</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Käser I et al., JPSM 2009;38:505-14
Correlations with FAQ, EORTC QLQ c30

Käser I et al., JPSM 2009;38:505-14
How shall we screen for Fatigue & Cachexia?

Mechanistic approach: search for causes

- Dehydration
- metabolic alterations in Malnutrition
- Elektrolytes: Phosphat, Ca++, Na?, Mg?
- Organ-Functions: renal, liver, heart, lung
- Infection (or tumor-assoz. inflammation)
- Endocrine: TSH, Testosteron (M)
- Medications: Opiates, Benzo, Neuro-leptics, ...
- Anemia, iron-deficiency
- Chemotherapy, biologicals
- Cancer cachexia
- Malnutrition
- Depression
- Sleep-problems
- ...
Screen for Malnutrition in routine daily (hospital) care

**NRS-2000**

Measure: BMI, weight loss, perceived dietary intake

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
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<tbody>
<tr>
<td>1</td>
<td>Is BMI &lt; 20.5?</td>
</tr>
<tr>
<td>2</td>
<td>Has the patient lost weight within the last 3 months?</td>
</tr>
<tr>
<td>3</td>
<td>Has the patient had a reduced dietary intake in the last week?</td>
</tr>
<tr>
<td>4</td>
<td>Is the patient severely ill? (e.g. in intensive therapy)</td>
</tr>
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Yes: If the answer is ‘Yes’ to any question, the screening in Table 2 is performed.

→ Many patients with advanced, incurable (solid) cancer

Screen for Malnutrition in routine daily (hospital) care

<table>
<thead>
<tr>
<th>Impaired nutritional status</th>
<th>Severity of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal nutritional status</td>
<td>Normal nutritional requirements</td>
</tr>
<tr>
<td>0. Wt loss &gt;5% in 3 mths or Food intake below 50–75% of normal requirement in preceding week</td>
<td>0. Normal nutritional requirements</td>
</tr>
<tr>
<td>1. Wt loss &gt;5% in 2 mths or BMI 18.5 – 20.5 + impaired general condition or Food intake 25–60% of normal requirement in preceding week</td>
<td>1. Hip fracture* Chronic patients, in particular with acute complications: cirrhosis*, COPD*. Chronic hemodialysis, diabetes, oncology</td>
</tr>
<tr>
<td>2. Wt loss &gt;5% in 1 mth (&gt;15% in 3 mths) or BMI &lt;18.5 + impaired general condition or Food intake 0-25% of normal requirement in preceding week</td>
<td>2. Major abdominal surgery* Stroke* Severe pneumonia, hematologic malignancy</td>
</tr>
<tr>
<td>3. Wt loss &gt;5% in 1 mth (&gt;15% in 3 mths) or BMI &lt;18.5 + impaired general condition or Food intake 0-25% of normal requirement in preceding week</td>
<td>3. Head injury* Bone marrow transplantation* Intensive care patients (APACHE &gt;10).</td>
</tr>
</tbody>
</table>

→ „nutritional plan“ indicated for score ≥ 3

With Malnutrition Screening we identify both patients with „simple starvation“ and cancer cachexia

BUT:

● Cancer cachexia can occur earlier in the cancer trajectory, before BMI is very low, patients lost lots of weight, and before patients eat significantly less: pre-cachexia

● Increase of nutritional intake is important, but will alone (per definition) not reverse cancer cachexia: multi-modal cachexia management is required

● In far advanced cancer patients, attempts to increase nutritional intake may worsen suffering of patients and family members: refractory cachexia
How to identify patients with cancer cachexia in daily practice?

Screening

- **physical fatigue**¹ (not [only] emotional or cognitive fatigue)
- perceived problems with appetite/eating²
- weight loss²

Diagnosing³

- pre-cachexia: no standard yet
- cachexia: 5% weight loss 6 mts (no fluid retention) or 2% and [BMI<20 or sarcopenia]
- refractory cachexia: no standard yet

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A possible approach to assess cachexia (to be refined)

<table>
<thead>
<tr>
<th>SCREEN</th>
<th>DIAGNOSIS</th>
<th>RESEARCH</th>
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<tbody>
<tr>
<td>Daily Practice</td>
<td>Specialized Practice</td>
<td>Clinical Trials and Studies</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>STORAGE</th>
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<tbody>
<tr>
<td>Weight loss % last 2-6 mts</td>
</tr>
<tr>
<td>Body Mass Index</td>
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<table>
<thead>
<tr>
<th>INTAKE</th>
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<tbody>
<tr>
<td>Perceived eating problems</td>
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<tr>
<td>Simple Starvation ruled out</td>
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</tbody>
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<table>
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<tr>
<th>POTENTIAL treatments</th>
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<tr>
<td>Stage IV cancer</td>
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</table>

<table>
<thead>
<tr>
<th>PERFORMANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer related KPS ≤ 70</td>
</tr>
<tr>
<td>Physical Fatigue</td>
</tr>
<tr>
<td>Cachexia, a care priority</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRP &gt; 10mg/l, without clinical infection</th>
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<tbody>
<tr>
<td>Physical function measurement (muscle strength, physical functioning)</td>
</tr>
<tr>
<td>Psychosocial distress: weight, eating</td>
</tr>
<tr>
<td>Decisions towards care goals</td>
</tr>
</tbody>
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<tr>
<th>History of anticancer</th>
</tr>
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<tr>
<td>Cytokines, hormones</td>
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<table>
<thead>
<tr>
<th>Muscle power, 6-MWT, et al.</th>
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<tr>
<td>Body worn sensor tests</td>
</tr>
<tr>
<td>Comprehensive item pools</td>
</tr>
<tr>
<td>Prognosis tools</td>
</tr>
</tbody>
</table>
What is the evidence for routine screening of symptoms (fatigue & cachexia)?

Change of symptom management when symptom is “seen“
Symptom-Assessment: improvement of related symptoms
In busy practice standard tools needed
Fatigue and appetite are underestimated by oncologist
Intervention trials: few (example: E-MOSAIC)
Does symptom severity trigger clinical intervention?

Retrospective chart reviews (symptom documentation, symptom-related action(s) taken within 1 week) on cancer patient visits (n=912) at a regional cancer center.

Positive association but symptom-related actions in a minority of visits with severe symptoms

Figure 1. Pain and shortness of breath outcomes for all patient visits. ESAS, Edmonton Symptom Assessment Scale. (*) Sample size by ESAS score category: pain: 0 (n = 263), 1-3 (n = 236), 4-6 (n = 221), 7-10 (n = 192); shortness of breath: 0 (n = 242); 1-3 (n = 228); 4-6 (n = 226); 7-10 (n = 216).

Does systematic symptom assessment and specialized palliative care improve symptoms?

Table 6  Associations of response\(^a\) of ESAS nausea to treatment with response\(^b\) of other ESAS items (univariate; \(N=112\))

<table>
<thead>
<tr>
<th>ESAS response (^b)</th>
<th>Odds ratio</th>
<th>95 % CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>1.74</td>
<td>(0.71–4.25)</td>
<td>0.2265</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4.53</td>
<td>(1.58–13.00)</td>
<td>0.0049</td>
</tr>
<tr>
<td>Depression</td>
<td>2.12</td>
<td>(0.95–4.73)</td>
<td>0.0670</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.90</td>
<td>(0.86–4.21)</td>
<td>0.1114</td>
</tr>
<tr>
<td>Lack of appetite</td>
<td>3.41</td>
<td>(1.52–7.64)</td>
<td>0.0029</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>3.03</td>
<td>(1.11–8.23)</td>
<td>0.0298</td>
</tr>
<tr>
<td>Impaired feeling of well-being</td>
<td>2.67</td>
<td>(1.18–6.03)</td>
<td>0.0185</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>2.53</td>
<td>(1.08–5.93)</td>
<td>0.0331</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>1.38</td>
<td>(0.63–3.01)</td>
<td>0.4159</td>
</tr>
</tbody>
</table>

\(^a\) Responder defined as 30 % improvement on ESAS nausea item score at follow-up for patients with baseline moderate/severe nausea

\(^b\) Thirty percent improvement on ESAS item score at follow-up

Improvement of nausea at 1st follow-up visit: improvement of appetite and fatigue (not the other symptoms)

Rhondali W et al. Support Care Cancer 2013 Apr 16. [Epub ]
Does systematic symptom assessment and specialized palliative care improve symptoms?

Rhondali W et al. Support Care Cancer 2013 Apr 16. [Epub ]
Exploration of oncologists' attitudes toward and perceived value of patient-reported outcomes

Practicing oncologists (n=20) acknowledged (focus groups)
- that PRO measures were more appropriate for assessing patient symptoms and treatment response.
- clinical efficacy and toxicity data were of primary importance, but PROs become increasingly important when multiple treatments are available, in advanced or incurable disease, and in palliative care.

Several issues prevented oncologists from being able to draw meaningful conclusions from PRO data:
- lack of familiarity with PRO measures
- being presented with too much data to process,
- lack of clarity: meaningful change in PRO measure scores,
- lack of standardization in the use of PRO measures.
Cut points on 0-10 numeric rating scales for symptoms included in the Edmonton symptom assessment scale in cancer patients: a systematic review.


Cut point: lower bound of the scores representing moderate and severe burden.

Pain, cut point 5 and 7
Tiredness, cut point 4 and both 7 and 8
Nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath: lack of evidence
Few studies suggested a cut point below 4.

Cautious about strongly recommending a certain cut point in guidelines and as quality indicators

Oldenmenger WH et al. J Pain Symptom Manage 2013:1083-93
Oncologists' recognition of supportive care needs and symptoms: breast cancer outpatient consultation.

Table 2. Supportive care needs and symptoms: patients’ report vs. oncologists’ perceptions (n = 408)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Prevalence (%) reported by</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Oncologists</td>
<td>Patients</td>
</tr>
<tr>
<td>Fatigue</td>
<td>76.5</td>
<td>24.8</td>
<td>28.2</td>
</tr>
<tr>
<td>Pain</td>
<td>57.6</td>
<td>46.3</td>
<td>11.2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>46.2</td>
<td>9.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>41.4</td>
<td>16.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Numbness</td>
<td>39.7</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>39.6</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>32.4</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Appetite loss</td>
<td>23.3</td>
<td>8.6</td>
<td>17.9</td>
</tr>
</tbody>
</table>

Psychological symptoms

- Anxiety (borderline/clinical): 20.8/74.0
- Depression (borderline/clinical): 16.9/26.5

Bringing advanced cancer patients’ experiences to the oncology outpatient care

Monitoring patient experiences in busy clinics is a time and resources challenge → clinical practice tools

Clinical practice tools embedded in daily routine care

- collection of patients’ symptoms
- palliative care needs
- review of systems
- general concerns and questions

Missing: Monitoring of clinical benefit criteria

The E-MOSAIC tool

Symptoms VAS
● 9 ESAS
● ≤ 3 optional (list of 20)

Nutritional intake VAS

Nurse-assisted
● Symptom Medications
  - Opioids, NSAR
  - Methylph., blood, Epo
  - Nutritional supplements
● Karnofsky PS
● Weight loss (% , time)

Feasibility (n=54): test-retest, paper vs palm, time
The Intervention: LoMoS (symptoms, symptom mgmt, clinical benefit parameters)

- Advanced, incurable cancer outpatients seen first by nurses
- E-MOSAIC palm-assessment
- Longitudinal Monitoring Sheet - cumulative weekly data

- Given to the oncologist - at routine visits, with labs
  - No additional education
  - Routine chart documentation
- After visits removed from chart
Results: Primary endpoint

between-arm difference of the “difference in G-QOL”
Results: Secondary endpoints
ITT-analysis (≥4 visits): Intervention (IV) vs control (ctrl)

**Symptom distress** score, Δ BL to week 6

**Physician compassion**, Δ BL to week 6

Patients having *no* visits with high symptom load *without* immediate **oncologists’ symptom mgmt** intervention

Exploratory EP: Coping & Burden of treatment
Conclusion

● Education of oncologists, nurses, patients about the mechanisms and impact of fatigue & cachexia

● Communicate available evidence and experiences of improvements if apply individualized interventions - expand from symptom to broader early palliative care
Palliative Care Interventions

Standard interventions:
- Illness understanding
  (Prognosis, Therapy-goals)
- Symptom control
  (bio-psycho-social)
- Decision processes
  (cancer-specific, Nutrition)
- End of life preparation
  (incl. Family; double Way)
- Support-Network
  (whole trajectories)

National Consensus Project (& Clinical Practice Guidelines) for Quality Palliative Care; 2009. USA

Conclusion

- **Education** of oncologists, nurses, patients about the mechanisms and impact of fatigue & cachexia
- **Communicate** available evidence and experiences of improvements if apply *individualized interventions* - expand from symptom to broader early palliative care
- **Apply** *clinical practice tools* appropriately in the clinical settings and multiprofessional teams
- Consider a simple fatigue phenotype approach to screen with defined, also simple, next step assessment - amend with specialist-leaders for in-depth assessment - do clinical trials focused on fatigue / cachexia