

1

PRC

# Cancer cachexia -a short overview

Trondheim, 27th September 2019  
Tora Skeidsvoll Solheim MD, PhD

[www.ntnu.no/prc](http://www.ntnu.no/prc)

European Palliative Care Research Centre (PRC)

2

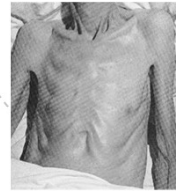
- What is cachexia and why is it important?
- What is the pathophysiology of cachexia?
- Which interventions are of importance?

[www.ntnu.no/prc](http://www.ntnu.no/prc)

European Palliative Care Research Centre (PRC)

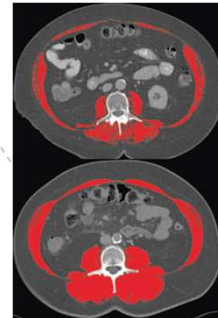
## Why focus on weight loss?

- Progressive weight loss interferes with cancer therapy
- Responsible for a poor quality of life and decreased function
- Patients with weight loss live shorter irrespective of tumour mass or the presence of metastasis
- Will often cause significant psychological distress, affecting also patients' next of kin



## Definition of cachexia

- Cancer cachexia is a multidimensional syndrome with on-going muscle loss (and often fat loss)
- It cannot be cured by conventional nutrition alone
- Leads to progressive functional impairment

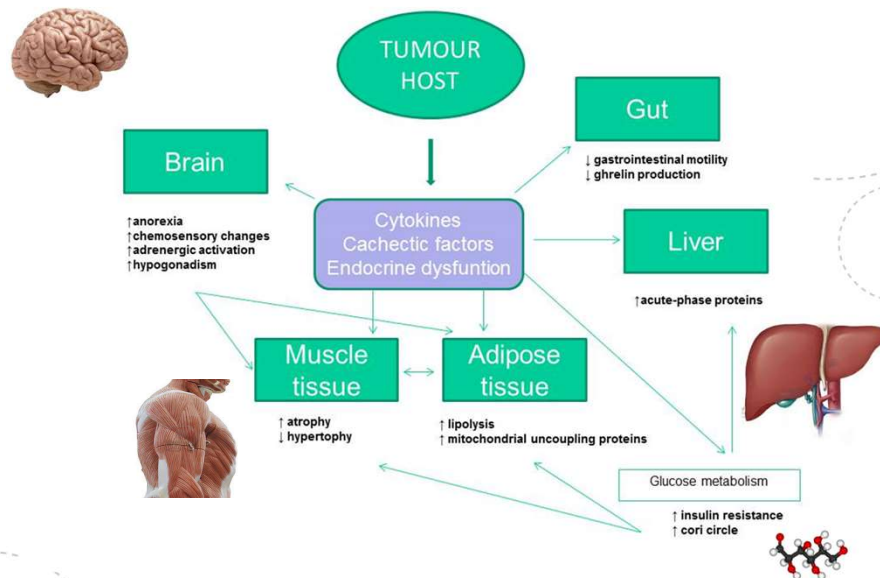


5


[www.ntnu.no/prc](http://www.ntnu.no/prc)

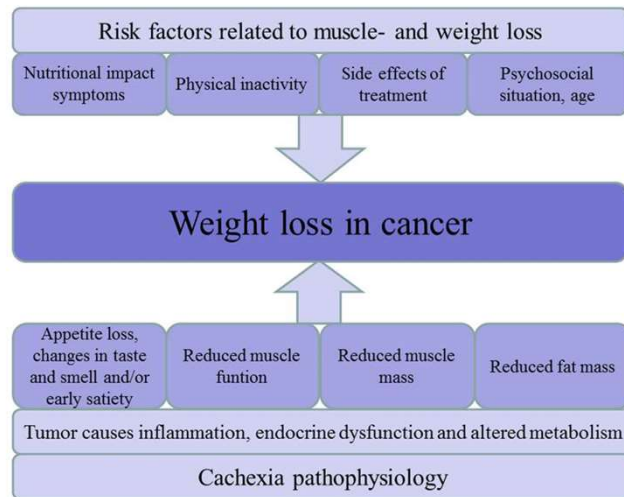
European Palliative Care Research Centre (PRC)

6


[www.ntnu.no/prc](http://www.ntnu.no/prc)

European Palliative Care Research Centre (PRC)

7



*In prep: ESMO guidelines for treatment of cancer cachexia*

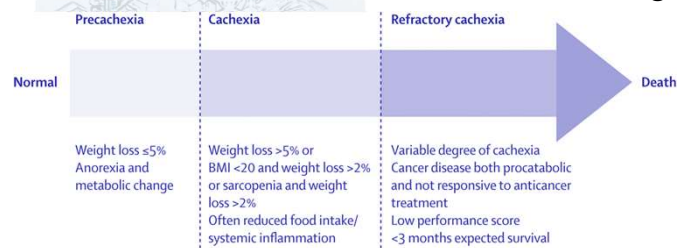
[www.ntnu.no/prc](http://www.ntnu.no/prc)

European Palliative Care Research Centre (PRC)

8



## Different treatment aims at different stages



ref. Fearon K, *et al.* 2008

[www.ntnu.no/prc](http://www.ntnu.no/prc)

European Palliative Care Research Centre (PRC)

## Assessment

- Think about it- early
  - Screen for weight loss, ask about appetite loss and nutritional intake
  - Cancer stage, prognosis and expected effect of tumor treatment
  - Physical status
  - Several different tools available for assessment/screening of nutritional status:
    - MUST, NRS-02, MNT, PG-SGA etc

## Treatment

- No consensus on how to treat cancer cachexia
- Doubtful that major treatment achievements are to be reached using unimodal therapy



## Pathophysiology

Inflammation and  
catabolic changes

Reduced food intake  
Reduced physical  
activity

Cancer

## Intervention

Targeted  
cachexia  
intervention

Sufficient nutrition  
Physical exercise

Symptom  
management  
Cancer treatment

## Complex interventions for cachexia

Targeted cachexia treatment

Sufficient nutrition  
Exercise/physical activity

Symptom management  
**Cancer treatment**

## Optimal cancer treatment for all

- Curing the cancer is still the only way to cure cancer cachexia
- But, cancer treatment might also increase muscle breakdown

## Complex interventions for cachexia

Targeted cachexia treatment

Exercise/physical activity  
Sufficient nutrition

**Symptom management**  
Cancer treatment



## Symptom management



- It is imperative to treat symptoms or conditions that interfere with nutritional intake
- Perhaps its not mainly cachexia, perhaps the patient is starving?
  - Nausea, pain, bowel obstruction, wrong diet etc

## Symptom management

- But symptom relief is not always *adding* a pharmacological treatment
- Always keep scrupulous attention to whether the patient really need the prescribed drug – or if the dose can be reduced



## Symptom management



- A lot of side effects mimic common symptoms in advanced cancer / refractory cachexia
- What drugs do you most commonly consider affecting fatigue/cachexia?
  - **Opioids:** nausea, constipation, sedation, dry mouth, reduced appetite
  - **Benzodiazepam:** sedation, dizziness
  - **5-HT3R antagonists:** constipation
  - **Dipyridamol:** dizziness, nausea
  - **Statins:** headache, difficulty sleeping, muscle aches, drowsiness, dizziness, myopathy

## Symptom management includes communication

- Lack of focus on cachexia from health care professionals is common
  - This increases patients' and relatives' confusion, anxiety and concern
  - Patients need their weight loss to be acknowledged, need to receive information and to get advice on how to intervene

• *Ref Reid et al 2009*

## Communication

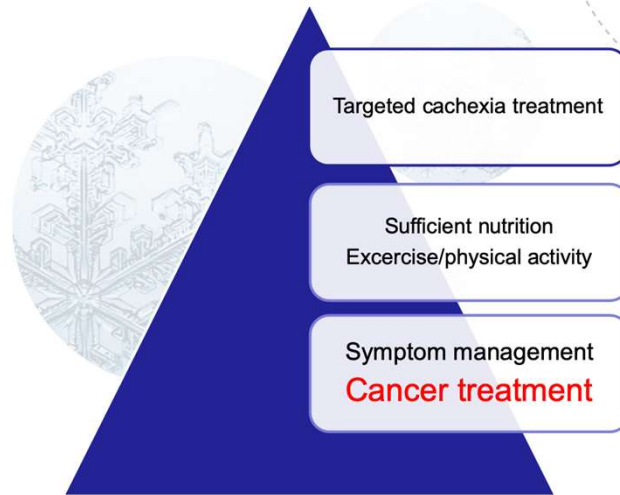


- Both patient and relatives
- Open questions, empathizing, actively listening
- Information on cachexia mechanisms
- Interventions/approach and reasonable goals

## Information to relatives/patients

- How to reply:
  - Why do you let my mother starve? She is nothing but skin and bones!!
  - Has she decided that she wants to die from me? She does not eat all the good things I make for her!
  - How much can I pressure her to eat?
  - What can I do for my mother now when I can't support her by giving her treats?

## Complex interventions for cachexia



## Nutrition



- Many cancer patients' dietary intake is insufficient to support energy and protein balance
- Relevant to all cancer patients:
  - Energy requirements: 25-30 kcal/kg/day
  - Protein intake: >1 g/kg/day, if possible up to 1.5 g/kg/day
  - High fat/carbohydrate ratio diet to patients with insulin resistance
  - Vitamins and trace elements supplied equal to RDA
    - ESPEN guidelines 2017: strong recommendation, low and moderate LOE

## Nutrition

– Intervention in the following order (if indicated):

- Counselling and use of oral nutritional supplements
- Enteral nutrition (tube feeding, PEG)
- Parenteral nutrition

## Nutritional counseling

- Energy dense food
- High in proteins
- Small, appetizing meals
- Increased meal frequency
- People eat more of what they enjoy to eat
- No proven benefit of “A healthy diet” (5 a day fruit and vegetables, high fibers, low fat) in advanced cancer
- ONS



## Nutrition

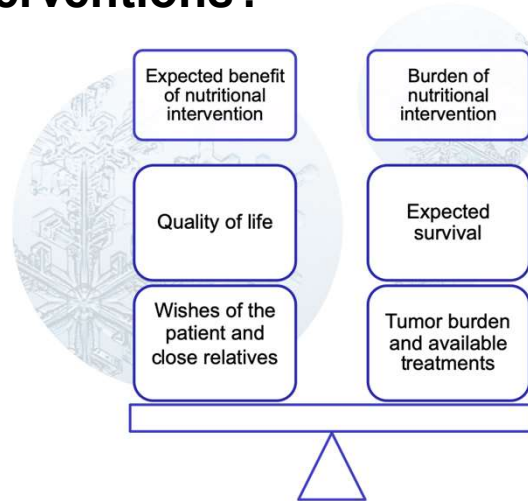
- Meta analysis (13 studies, 1414 patients):
  - Nutritional intervention associated with
    - Increased energy intake (430Kcal/d)
    - Some weight gain (1.86 kg)
    - Exploratory data suggesting effects on overall quality of life
    - No effect on mortality
- *Ref: Baldwin C, 2012*

## Nutrition

- Dietary counselling in advanced cancer makes it possible to maintain or increase energy and protein intake
  - ref: Balstad et al 2014*
  - But nutrition *alone* seems not to be enough



## More «aggressive» nutritional interventions?



## Medical nutrition



- Unconditional artificial nutrition during chemotherapy is associated with more harm than benefit
  - Ref: PN in patients undergoing chemotherapy, a metaanalysis, *Nutrition* **1990**
- Only one RCT presenting effect on survival
  - Ref: Lundholm 2004
- Two, underpowered, RCTs has been performed in patients with advanced cancer

## Medical nutrition

- Some observational studies

**Table 2.** Patients' scores for the EORTC QLQ-C30 scales at different time-points.

Time-points	T0	T1	T2	T3	T4
Number of available measures	111/111 (100%)	97/111 (87.4%)	76/111 (68.5%)	54/111 (48.6%)	49/111 (44.1%)
Global QoL <sup>1</sup>	52 (17)	58 (17)	66 (17)	71 (14)	66 (16)
PF <sup>1</sup>	38 (22)	42 (22)	46 (21)	55 (16)	52 (17)
RF <sup>1</sup>	33 (24)	38 (26)	41 (24)	48 (19)	45 (20)
EF <sup>1</sup>	47 (16)	51 (17)	52 (13)	56 (12)	55 (12)
CF <sup>1</sup>	58 (17)	59 (18)	62 (16)	62 (17)	63 (12)
SF <sup>1</sup>	53 (21)	54 (20)	56 (21)	60 (16)	57 (21)
AP <sup>2</sup>	79 (26)	77 (23)	74 (22)	63 (26)	64 (24)
FA <sup>2</sup>	77 (17)	75 (16)	73 (17)	73 (18)	71 (16)
NV <sup>2</sup>	56 (25)	52 (20)	54 (20)	54 (18)	54 (20)
FI <sup>2</sup>	36 (21)	36 (19)	36 (19)	34 (15)	35 (16)



## Medical nutrition



- Current parenteral nutrition treatment in patients with advanced cancer is understudied and the level of evidence is weak
  - Tobberup et al, *Crit Rev Oncol Hematol*, 2019
- Conflicting guidelines and not much evidence for the effect of intravenous or enteral nutritional treatment
  - Varying clinical practice

## Case 1

- 65 Year old woman with metastatic breast cancer, gradually developed ileus, medically treated. Weight loss 20% last 6 months, fatigue, is in bed or in a chair 50% of the day.
- How many would give intravenous nutrition?
- For how long time would you give it?

## Case 2

- 35 year old male with aggressive metastatic sarcoma, rapidly developing disease without more tumor treatment available. CRP 65 without infection, albumin 29.
- In bed > 50% of the day. Weight loss 10% last 6 months. No gastrointestinal obstruction.
- Appetite loss, last week he has eaten less than 60% of required calculated calories.
- How many would recommend medical nutrition?

## Case 3

- 73 year old man with metastatic prostate cancer on 3<sup>rd</sup> line treatment
- 10% weight loss developed gradually last year. No nutritional impact symptoms but appetite loss, and has eaten less than 60% of required calculated calories
- Conflict in family, patients think the situation is OK, relatives terrified because of the weight loss
- Would you give medical nutritional treatment?

- Scientific data to support nutritional interventions treating cachexia are conflicting
- For refractory cachexia; make attention not to increase eating related distress

## Complex interventions for cachexia

Targeted cachexia treatment

Exercise/physical activity  
Sufficient nutrition

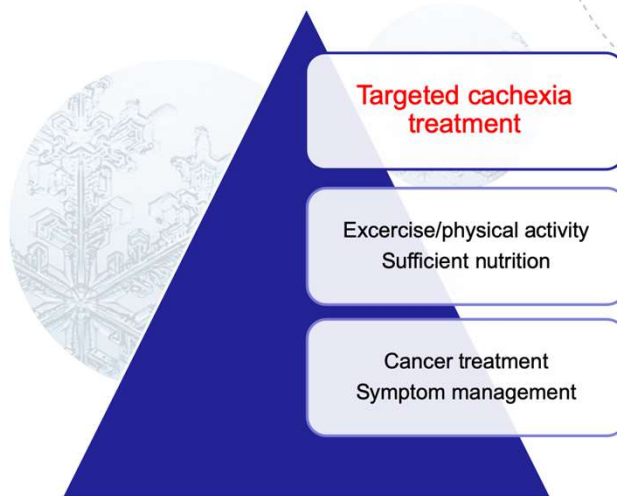
**Symptom management**  
Cancer treatment

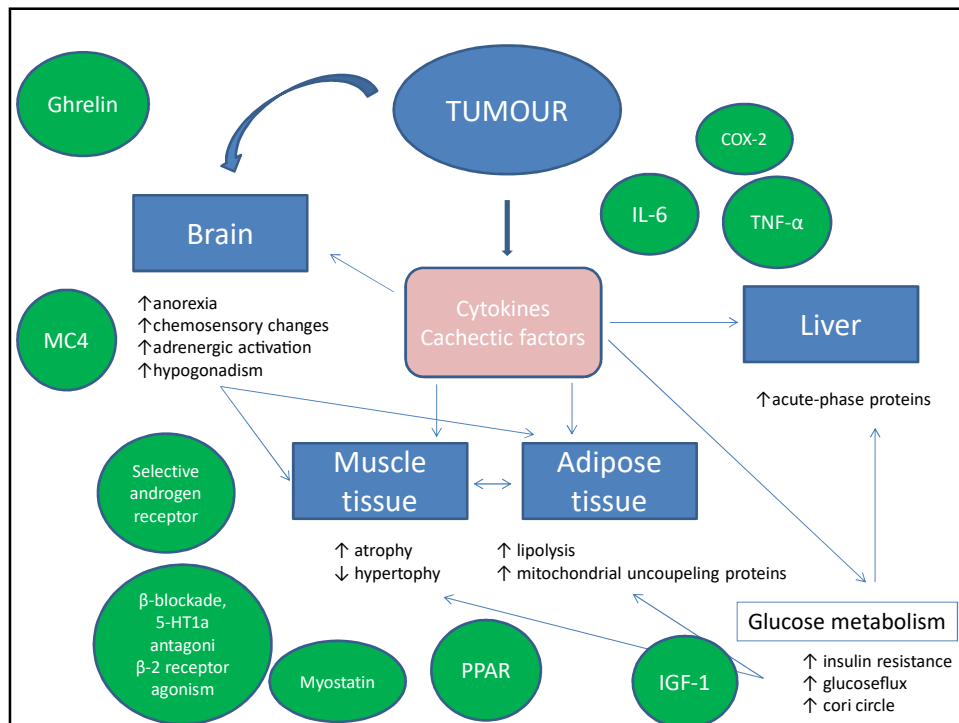
## Exercise



- Physical exercise in order to:
  - Counter-balance inactivity atrophy
  - Reduce fatigue
  - Improve Quality of Life
  - Decrease muscle catabolism, increase anabolism
  - Might reduce inflammation

## Complex interventions for cachexia





40

## Pharmacological symptom relief in refractory cachexia – most important agents

- Only **progestins** and **corticosteroids** were found to have sufficient evidence to support their use in improvement of **appetite**

– Ref: Yavuzsen 2005



## Progestines

- RR appetite improvement: 2.57 (1.48-4.49)
- RR weight improvement: 1.55 (1.08-2.26)
- Increased risk; impotence, dyspnoea, oedema, thromboembolism

*Ref: Ruiz Garcia V et al 2005, 2013, and 2018*

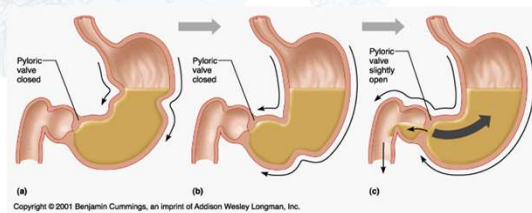
- Optimal dose is 160-800 mg/d (?)
- For short-intermediate term appetite stimulation and increase of weight but not muscle mass

## Corticosteroids

- Can improve QoL, appetite, vomiting, wellbeing, fatigue
  - Weight is often not significantly affected
- Side effects: myopathy, hyperglycemia, mood changes and immunosuppression
- For short duration (1-2 weeks), improvement in appetite

## Metoclopramide

- Fewer patients included in studies
- Can help in patients with early satiety, chronic gastro paresis and nausea

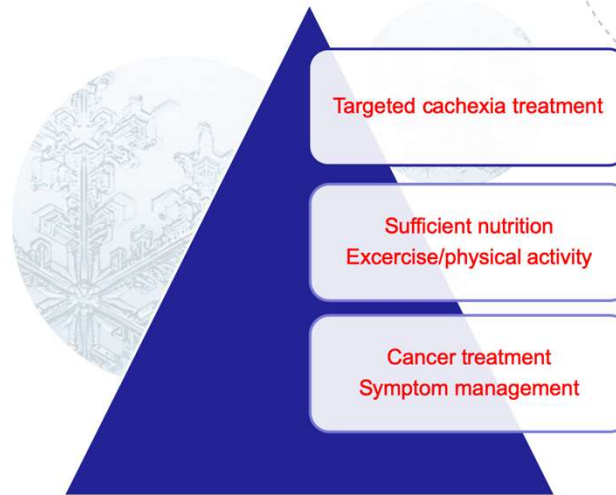


## Upcoming drugs?

- Anamorelin (Ghrelin-analogue)
- Enobosarm (selective androgen receptor modulator)
- Other
  - Cannabinoids, androgens, olanzapine, fometerol, NSAID..



## Complex interventions for cachexia



## Complex interventions

- Observational data from cachexia clinics show some benefit in programs treating symptoms impeding food intake, recommending exercise and give nutritional advice

• Ref: Del Fabbro et al (2011). Clinical outcomes and contributors to weight loss in a cancer cachexia clinic. Parmar et al. (2013). Weight changes correlate with alterations in subjective physical function in advanced cancer patients referred to a specialized nutrition and rehabilitation team.

- Feasibility study (preMENAC) shows that complex intervention is feasible and that patients are willing to participate

• Solheim et al. 2017

## Questions for research?

- Dosing and content of nutritional intervention?
- Which patients benefit from intravenous nutrition/enteral nutrition?
- Which patients have no benefit from intravenous nutrition/enteral nutrition?
  - When to stop?
- When stop screening?
- What are the expected benefits of nutritional interventions?
- Exercise regimens, and doses..?

## Summary: For refractory cachexia consider

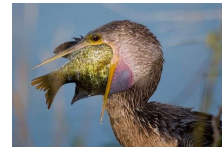
- Other reasons/contributing factors for weight loss
- Appetizing food/ONS and physical activity in a setting that does not cause distress and does not give false hope or goals
- Communication/information
- Corticosteroids for 1-2 weeks
- Progesteron short time for improving appetite

## Very advanced terminal phase

- Treatment based on comfort:
  - Artificial hydration and nutrition are unlikely to provide any benefit for most patients
  - Food and artificial nutrition may have social, emotional and existential significance for the individual patient and family members

## Cachexia - why is it important?

- Neglection of cachexia:
  - No treatment of reversible causes
  - No multimodal approach to counteract complex pathophysiology (nutrition, pharmacology, exercise, information)
- Overtreatment:
  - To "aggressive" nutrition
  - Family/patient misunderstands cachexia mechanisms
  - Lack of alternative intervention to deal with hope, dignity and closure



## PATIENT HISTORY

**Presentation:** 55 years, 94 kg, 178 cm; married, 2 children  
engineer in appliance company, hobbies: golf (uses golf cart)

**Medical History:** Hypertension (2 drugs), COPD GOLD grade 2, group B, smoking history 30 pack years  
Last two months anorexia, fatigue, more coughing.

**Radiology:** Chest X-ray: right hilar lesion; ultrasound: pleural effusion 4 cm.  
CT chest/abdomen: 4 cm tumor, ipsilateral mediastinal lymph nodes 2 cm  
no distant metastases

## PATIENT HISTORY

**Bronchoscopy and cytology:** Adeno carcinoma, pleural effusion positive for tumor cells

**Diagnosis:** Non small cell lung cancer, adenocarcinoma, stage IV (cT2a cN2 cM1a)

**Further typing:** No driver mutations

**MDT:** ECOG 1, palliative chemotherapy (carboplatin + pemetrexed)

## Q1. WHAT SHOULD BE THE NEXT STEP?

1. Proceed directly to oncologic treatment
2. Explain that fortunately no nutritional risks are to be considered
3. Perform screening for, and if necessary assessment, of malnutrition
4. Initiate obesity program to reduce body weight

(one answer)

## Q1. WHAT SHOULD BE THE NEXT STEP?

1. Proceed directly to oncologic treatment
2. Explain that fortunately no nutritional risks are to be considered
3. **Perform screening for and if necessary assessment of malnutrition**
4. Initiate obesity program to reduce body weight

(one answer)

## Q2. HOW TO SCREEN FOR MALNUTRITION?

1. Ask for weight loss during last 3 months.
2. Ask for food intake as compared to usual amount.
3. Calculate Body Mass Index (WT/HT<sup>2</sup>).
4. Ask for physical performance
5. All of the above

(one answer)

## Q2. HOW TO SCREEN FOR MALNUTRITION?

1. Ask for weight loss during last 3 months.
2. Ask for food intake as compared to usual amount.
3. Calculate Body Mass Index (WT/HT<sup>2</sup>).
4. Ask for physical performance
5. **All of the above** (→ use screening tool, e.g. NRS = Nutrition Risk Screening)

(one answer)

## SCREENING

Points	Nutritional status			Age	Severity of disease (≈ metabolic stress)
	Food intake % of normal last 3 months	Weight loss if PS>1	BMI (kg/m <sup>2</sup> )		
1	50-75%	>5%	18.5-20.5	≥70 y	Chronic disease ( <b>oncology</b> , diabetes, ..) Severely acute ill (pneumonia, stroke, <b>hematologic malignancy</b> , ..) Intensive care (sepsis, bone marrow transplant, ..)
2	25-50%	>7.5%	18.5-20.5		
3	0-25%	>15%	<18.5		

① ② ③ ④ ⑤ ⑥ ⑦

→ Nutritional support

## SCREENING

Points	Nutritional status			Age	Severity of disease (≈ metabolic stress)
	Food intake % of normal last 3 months	Weight loss if PS>1	BMI (kg/m <sup>2</sup> )		
1	50-75%	>5%	18.5-20.5	≥70 y	Chronic disease ( <b>oncology</b> , diabetes, ..) Severely acute ill (pneumonia, stroke, <b>hematologic malignancy</b> , ..) Intensive care (sepsis, bone marrow transplant, ..)
2	25-50%	>7.5%	18.5-20.5		
3	0-25%	>15%	<18.5		

70%

8%

(BMI 30.0)

(55 y)

lung cancer heading for chemotherapy

① ② ③ ④ ⑤ ⑥ ⑦

→ Nutritional support



### Q3. HOW TO ASSESS FOR MALNUTRITION?

1. Ask for nutrition impact symptoms, e.g. nausea, early satiety
  2. Estimate food intake
  3. Assess degree of systemic inflammation
  4. Measure muscle mass
  5. All of the above
- (one answer)

### Q3. HOW TO ASSESS FOR MALNUTRITION?

1. Ask for nutrition impact symptoms, e.g. nausea, early satiety
  2. Estimate food intake
  3. Assess degree of systemic inflammation
  4. Measure muscle mass
  5. All of the above
- (one answer)

## Slide 60

---

**TSS4** Tora Skeidsvoll Solheim; 03.09.2018

**TSS5** In our ESMO GL text so far we include (p6) " Assessment of nutritional status should include objective assessment of BW, weight change during the preceding months, body composition with a focus on muscle mass, food intake with a focus on energy and protein, PS and physical activity, as well as information on the presence and degree of systemic inflammation."

We should be strong on muscle mass to present sarcopenic obesity as a major problem!

Tora Skeidsvoll Solheim; 03.09.2018

## ASSESSMENT OF NUTRITIONAL STATUS

*Performed by nutrition expert*

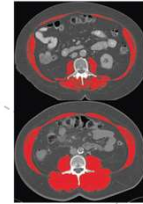
Nutrition impact symptoms: anorexia, early satiety

Food diary: 1750 kcal (70%)

Body composition: BMI 30 kg/m<sup>2</sup>, weight loss 8%  
muscle mass (AMA) 27 kg (sarcopenia)

Performance status: ECOG PS=1 (some 2 hours rest required during day)

Metabolism: systemic inflammation, CRP 60mg/l, albumin 34 g/l



## Q4. WHAT NUTRITIONAL SUPPORT SHOULD THE PATIENT RECEIVE?

1. **None** at this time
2. **Parenteral nutrition** with high fat ratio
3. **Glucocorticosteroids** to improve appetite
4. **Melatonin** to improve appetite
5. **Nutritional advice** to increase calorie and protein intake
6. Consider **metoclopramide** to see if this reduces early satiety
7. Consider **oral Nutritional Supplements** (ONS)
8. Advice on individualised **exercise training**
9. **Options 5-8**

## Slide 62

---

**TSS3**

looks good to me!

Tora Skeidsvoll Solheim; 03.09.2018

#### Q4. WHAT NUTRITIONAL SUPPORT SHOULD THE PATIENT RECEIVE?

1. None at this time
2. *Parenteral nutrition* with high fat ratio
3. *Glucocorticosteroids* to improve appetite
4. *Melatonin* to improve appetite
5. *Nutritional advice* to increase calorie and protein intake
6. Consider *metoclopramide* to see if this reduces early satiety
7. Consider *oral Nutritional Supplements* (ONS)
8. Advice on individualised *exercise training*
9. Options 5-8

#### PATIENT HISTORY

The patients receives chemotherapy (carboplatin / pemetrexed)

- The oncology team have focus on NIS, and he has relatively few challenges with pain and nausea
- He continues golfing, but more often walk than take the cart
- He manages to increase energy and protein intake with the help of protein- and *n-3* PUFA-enriched ONS, and the weight stabilizes (94kg)
- After 4 cycles of chemotherapy evaluation shows PR, 2 more cycles given

TSS7

## Slide 64

---

**TSS7**

what does the GL say, but you could discuss whether the choice of N-3/protein rich was evidence based

Tora Skeidsvoll Solheim; 03.09.2018

## PATIENT HISTORY

After 6 cycles chemotherapy patient is assigned to follow-up

- During follow-up he starts to develop pain in his back
- MRI presents several metastatic bone lesions, but one large affecting medulla in TH1
- Radiotherapy is offered and started, subsequent systemic therapy is planned
- Halfway through radiotherapy he starts to get pain when swallowing, he feels very tired and anxious, ECOG PS 2

## Q5. WHAT SHOULD BE THE NEXT STEP?

- Assessment of weight, nutritional intake and other nutritional impact symptoms
- Nutritional advice to increase energy and protein intake
- ONS
- Symptomatic treatment (pain, psychological support) TSS8
- All of the above



## Slide 66

---

### TSS8

- You are right about only rare esophagitis; so due to time we should skip this but you may mention that tube feeding is an option in severe esophagitis, especially in other settings with radio-chemotherapy

Tora Skeidsvoll Solheim; 03.09.2018

## Q5. WHAT SHOULD BE THE NEXT STEP?

- Assessment of weight, nutritional intake and other nutritional impact symptoms
- Nutritional advice to increase energy and protein intake
- ONS
- Symptomatic treatment (pain, psychological support) TSS8
- **All of the above**

## PATIENT HISTORY

After radiotherapy the patient is started on immunotherapy (nivolumab)

- His weight is 86 kg and he eats 60% of estimated requirement
- He receives pain treatment, psychological contact as well as nutritional counselling and ONS
- Weight remains stable
- Follow-up at 2 and 4 months shows only minor progress at some locations

## Slide 67

---

### TSS8

- You are right about only rare esophagitis; so due to time we should skip this but you may mention that tube feeding is an option in severe esophagitis, especially in other settings with radio-chemotherapy

Tora Skeidsvoll Solheim; 03.09.2018

## PATIENT HISTORY

6 months into nivolumab treatment..

- .. the patients starts to lose weight again, appetite decreases
- Nutritional intake is less than 40% even after nutritional counselling and ONS
- The patient and his close family are very preoccupied with his lack of food intake and they all are very distressed by this
- Evaluation shows progressive disease in liver and lung, PS 2, weight 80 kg

The patient and his family receive renewed information on cancer cachexia and weight loss mechanisms.

TSS9

## Q6: WHAT COULD BE A POSSIBLE NEXT STEP?

Consider a trial with:

1. Corticosteroids
2. Cannabinoids
3. NSAID
4. Testosteron
5. Parenteral or enteral nutrition

## Slide 70

---

### TSS9

With the answer to the question you will need to very briefly say a word to all options:

- steroids. consider survival, pain on liver capsule
- cannabinoids might be worth an individual trial after all
- NSAID might be an option to include with analgesics
- testosterone would be measured by MD Anderson and Florian and substituted if low levels found
- PN would require port system (would be available) and EN would require tube

So, any answer by the audience might be ok. Which is important to mention the range of options. So we might allow all answers. Our patient however would receive PN

Tora Skeidsvoll Solheim; 03.09.2018

The patient and his family receive renewed information on cancer cachexia and weight loss mechanisms.

TSS9

### Q6: WHAT COULD BE A POSSIBLE NEXT STEP?

Consider a trial with:

1. **Corticosteroids**
2. **Cannabinoids**
3. **NSAID**
4. **Testosterone**
5. **Parenteral or enteral nutrition**

## PATIENT HISTORY

- Parenteral nutrition is initiated (gradually increased to 30 kcal/kg/day) and delivered at home during the night, an agreement is made to evaluate the treatment in 2 weeks, and then at given intervals after that
  - The patient feels strongly about parenteral nutrition and will not accept a nasogastric tube
- The patient is started on weekly docetaxel treatment for his lung cancer

## Slide 71

---

### TSS9

With the answer to the question you will need to very briefly say a word to all options:

- steroids. consider survival, pain on liver capsule
- cannabinoids might be worth an individual trial after all
- NSAID might be an option to include with analgesics
- testosterone would be measured by MD Anderson and Florian and substituted if low levels found
- PN would require port system (would be available) and EN would require tube

So, any answer by the audience might be ok. Which is important to mention the range of options. So we might allow all answers. Our patient however would receive PN

Tora Skeidsvoll Solheim; 03.09.2018

## PATIENT HISTORY

- After 8 weeks of docetaxel treatment he has rapid clinical decline
- CT shows further progressive disease
- PS 3, weight 75 kg
- He is getting ascites and is bothered by his swollen feet
- He would like to get to celebrate his daughters wedding in a neighboring town in the weekend

## Q7: WHAT SHOULD THE NEXT STEP BE

1. Increase parenteral nutrition to 40 kcal/kg/day
2. Stress that it is important that he should eat more if he would like to live longer
3. Ask him to do exercises to get fit for his daughters wedding
4. After discussions with patients and his family, terminate parenteral nutrition and give him a short trial of glucocorticoids
5. Start high dose progestins



### Q7: WHAT SHOULD THE NEXT STEP BE

1. Increase parenteral nutrition to 40 kcal/kg/day
2. Stress that it is important that he should eat more if he would like to live longer
3. Ask him to do exercises to get fit for his daughters wedding
4. **After discussions with patients and his family, terminate parenteral nutrition and give him a short trial of glucocorticoids**
5. Start high dose progestins

## Thank you for your attention

