

Cancer cachexia

-a short overview

Trondheim, 26th November 2021

Tora Skeidsvoll Solheim

Consultant oncology/professor palliative care

- Why focus on weight loss?
- What is cachexia and why is it important?
- What is the pathophysiology of cachexia?
- Which interventions are of importance?

General malnutrition definition

- Lack of energy and protein results in weight loss and reduced muscle mass
 - leads to worsened physical or mental function and poorer outcome in case of illness

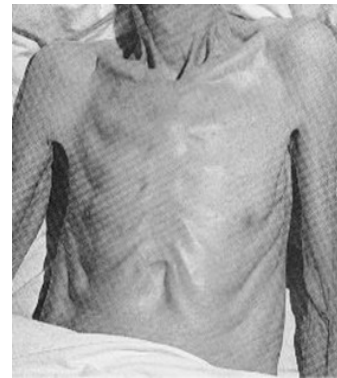
In general

-Why is malnutrition important in patient care?

- Increased risk of infections
- Reduced muscle strength
 - difficult mobilization, poor coughing power
- Reduced wound healing
 - wound rupture and anastomosis failure
- Psychological functions
 - lethargy, malaise, memory loss, depression, personality changes, apathy and fatigue
- Delayed rehabilitation

What are the consequences of weight loss in cancer?

- 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



Conclusion:

- Nutrition and weight are important!
- Think about it early!
 - Ask about food intake and what prevents patients from eating
 - Weight change
 - Physical activity
 - Cancer stage, prognosis and expected effect of tumor treatment
- There are several different tools for screening and diagnostics
 - MUST, NRS-02, MNT, PG-SGA etc

Cause of weight loss in patients with cancer?

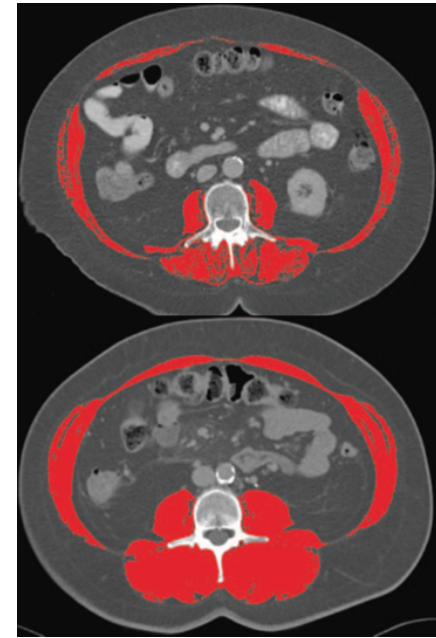
- Symptoms and conditions that reduce food intake
- Reduced gastrointestinal absorption
- Protein loss
- Treatment
- Economics / psychosocial conditions
- Decreased muscle activity
- Cancer related cachexia
- Increased catabolism (e.g. cachexia due to COPD)



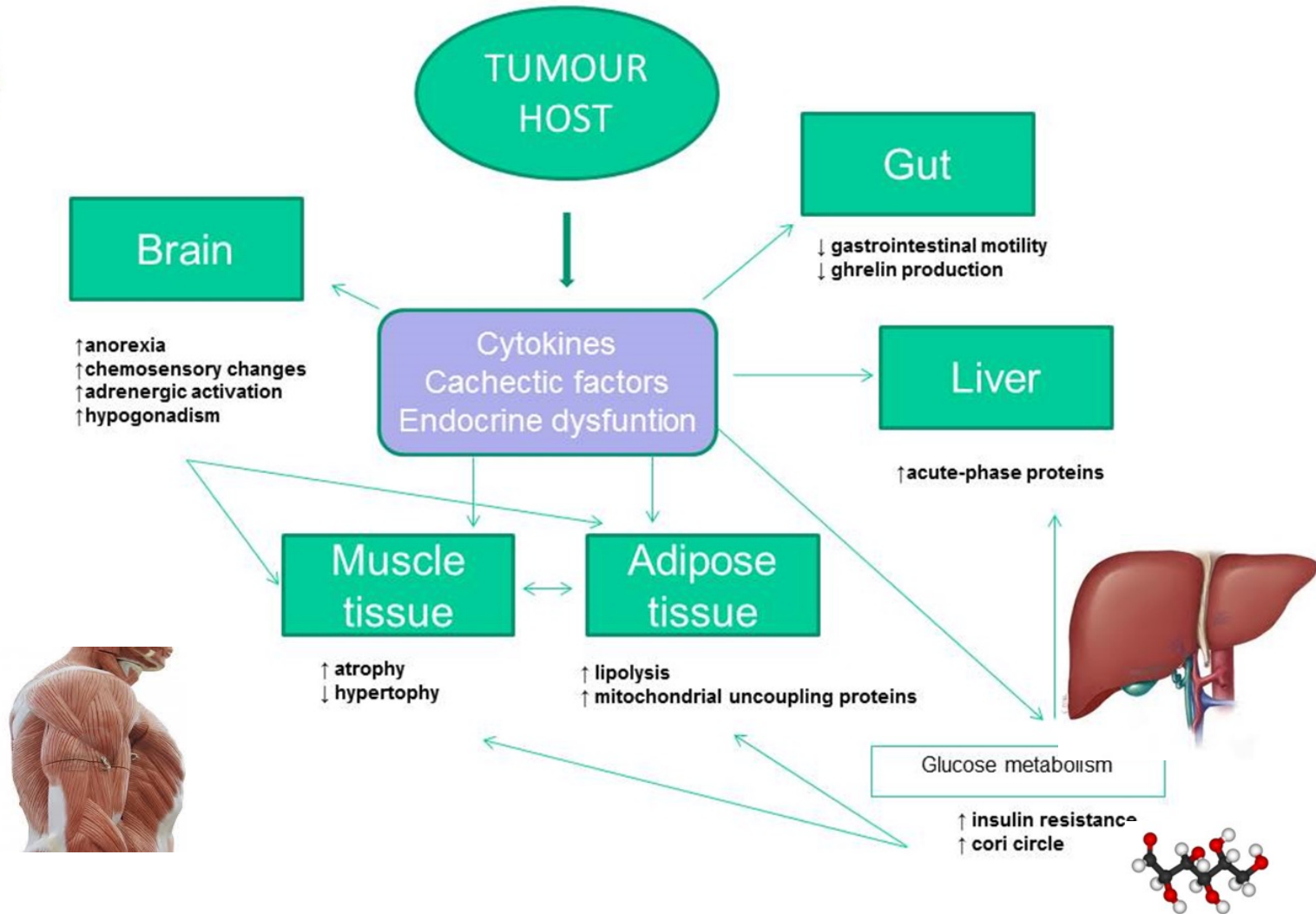


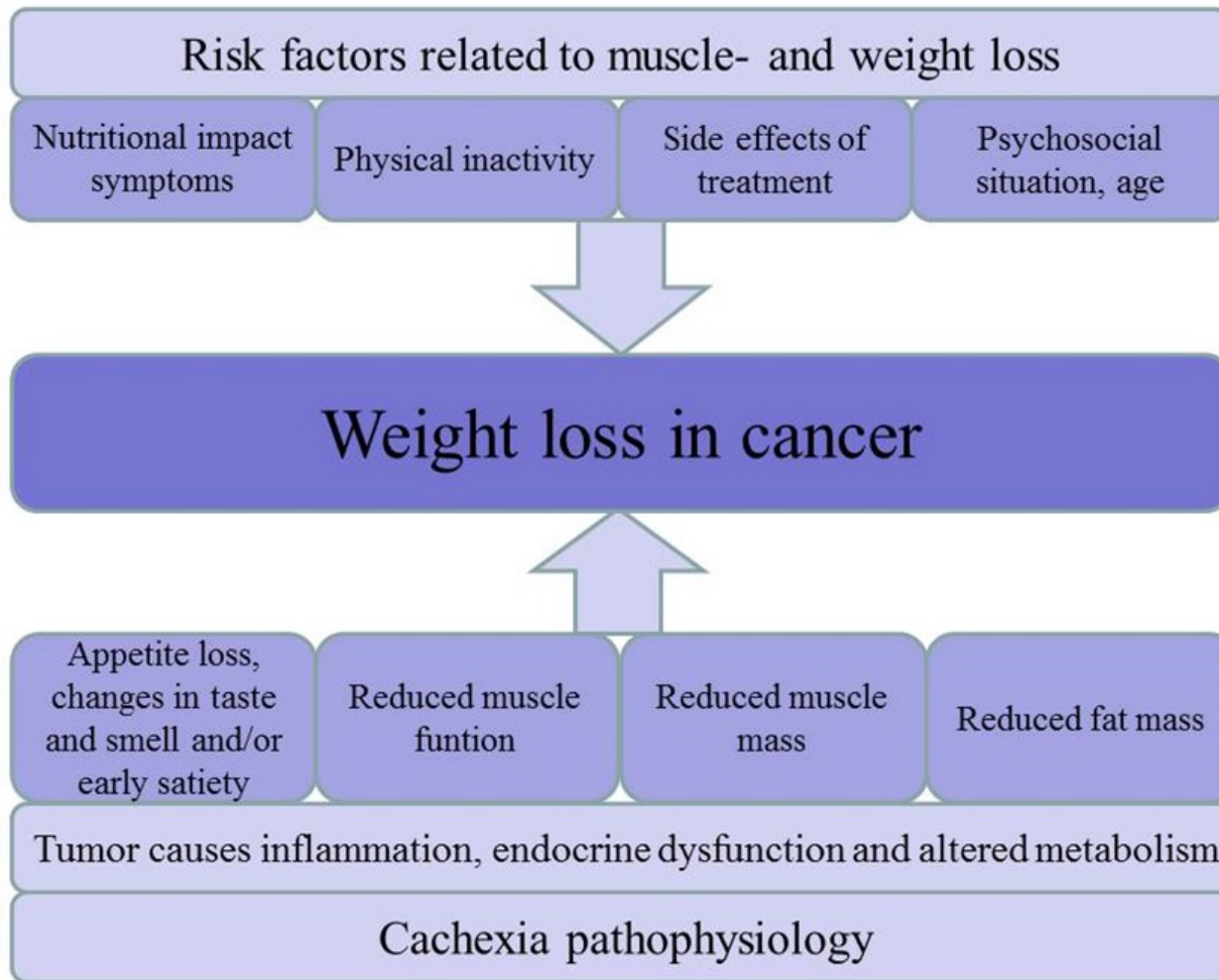
Definition of cachexia

- 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



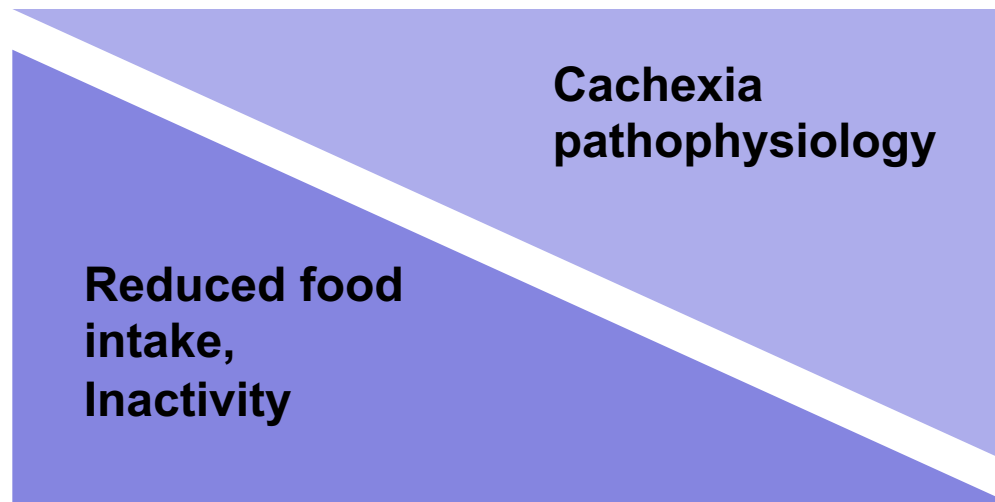
Fearon K, *et al.* Definition and classification of cancer cachexia: An international consensus. *Lancet Oncology* 2011





With the patient in front of you, what is the contribution of cachexia?

Example: Patient with Non Small Cell Lung Cancer



NSCLC receiving RT against trachea

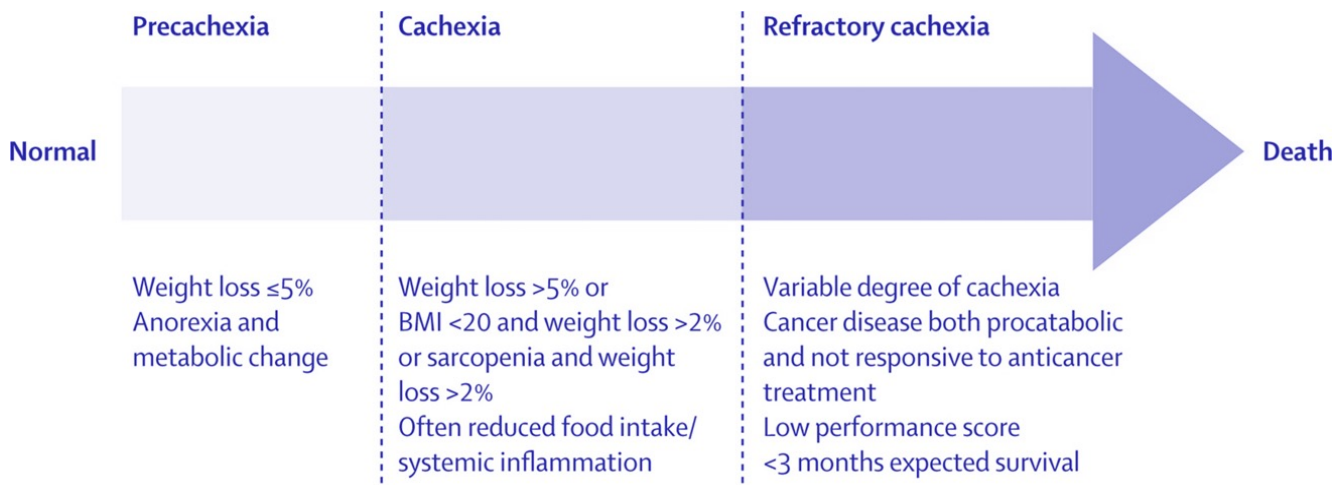
Stage IIIb NSCLC receiving chemotherapy

Stage IV NSCLC progressing

Modified from Fearon, Arends, Baracos. Nature Reviews Clinical Oncology 2013



Different treatment aims at different stages



ref. Fearon K, et al. 2008

Treatment

- No consensus on how to treat cancer cachexia
- Doubtful that major treatment achievements are to be reached using unimodal therapy
 - When we approach a patient loosing weight, think broadly



Pathophysiology

Inflammation and
catabolic changes

Reduced food intake
Reduced physical
activity

Cancer

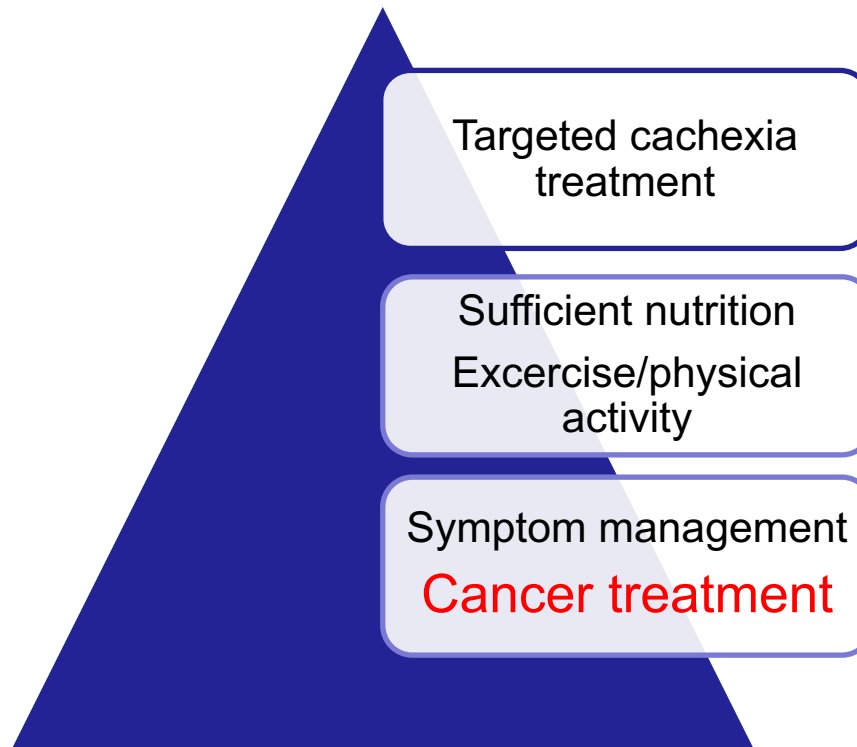
Intervention

Targeted
cachexia
intervention

Sufficient nutrition
Physical exercise

Symptom
management
Cancer treatment

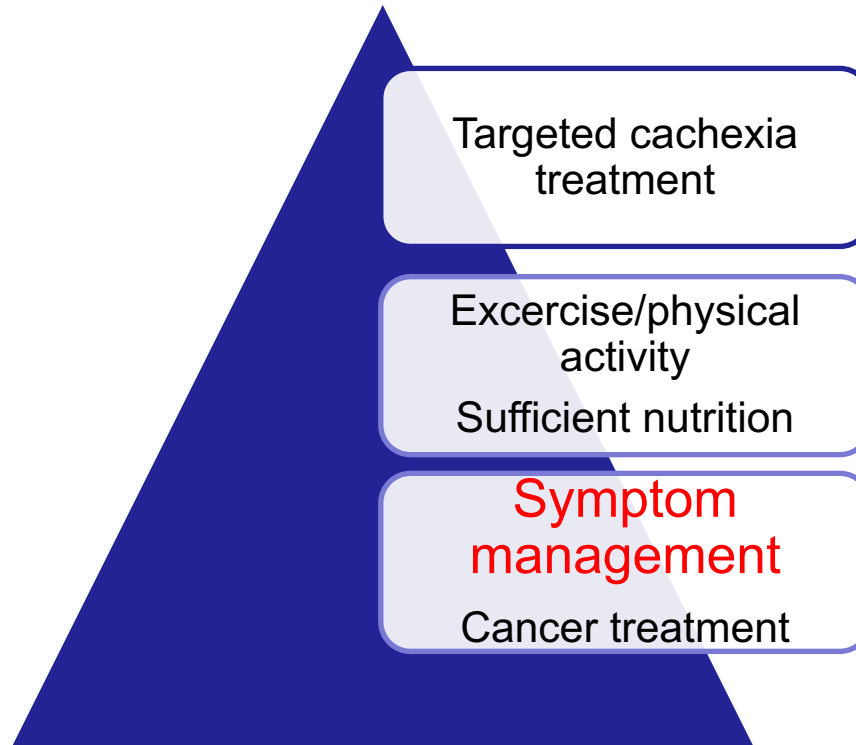
Complex interventions for cachexia



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



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

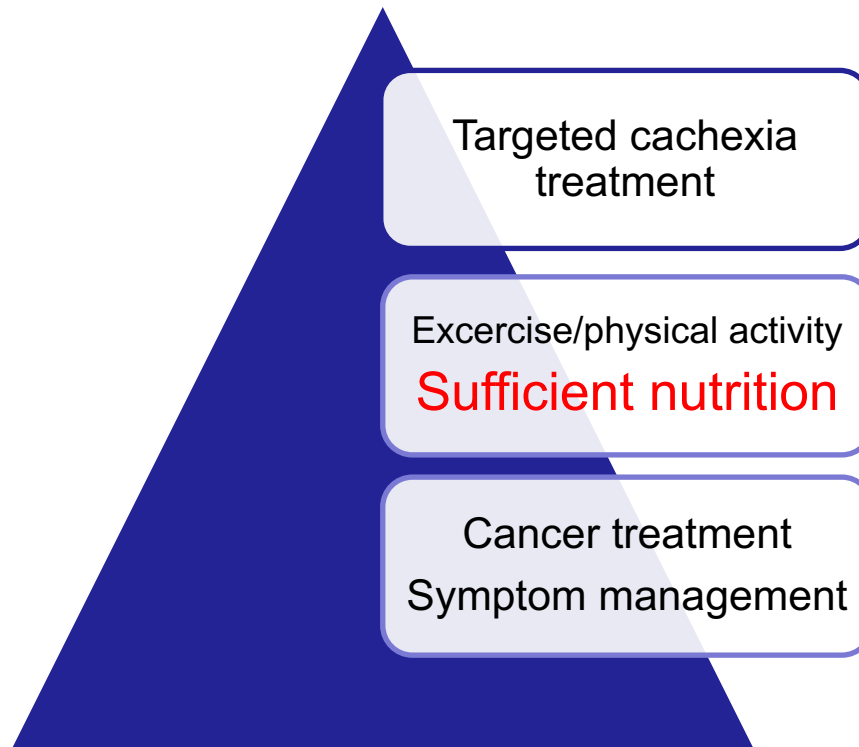
- Both patient and relatives
- Open questions, empathizing, actively listening
- Information on cachexia mechanisms
- Interventions/approach and reasonable goals



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



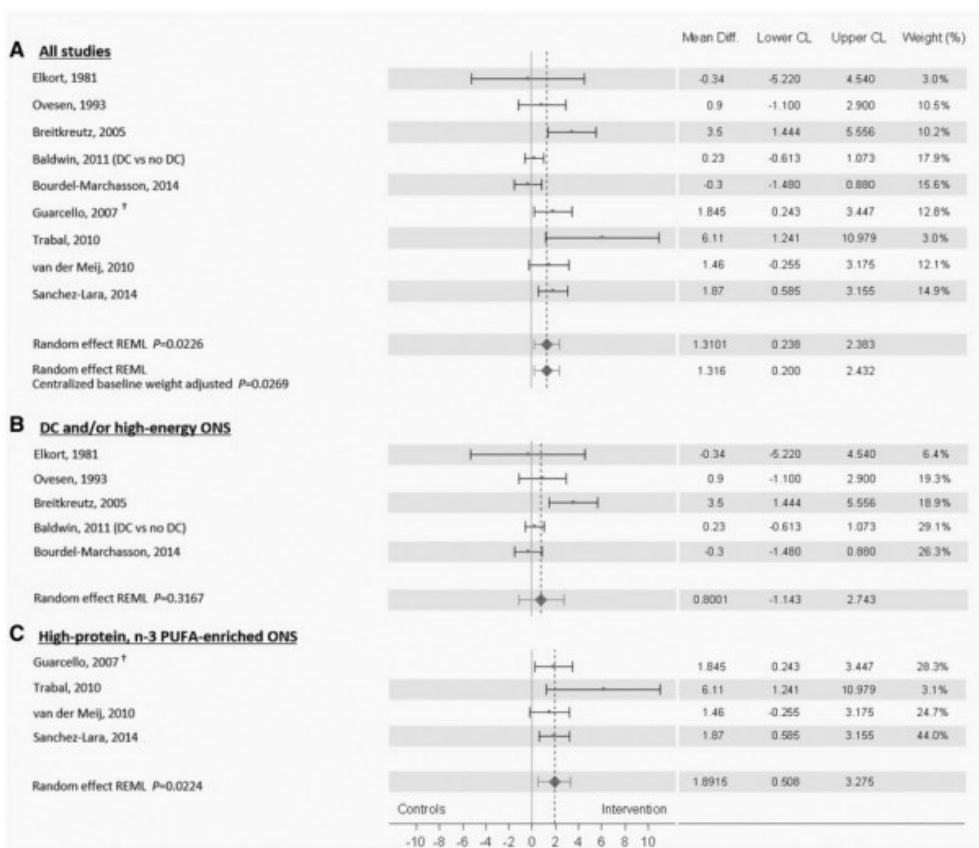
Nutrition



- 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

Ernæring

- 11 RCT (1981-2015) ONS and/or nutritional advice



REVIEW

Systematic review and meta-analysis of the evidence for oral nutritional intervention on nutritional and clinical outcomes during chemo(radio)therapy: current evidence and guidance for design of future trials

M. A. E. de van der Schueren^{1,2*}, A. Laviano³, H. Blanchard⁴, M. Jourdan⁴, J. Arends⁵ & V. E. Baracos⁶

Annals of Oncology 29: 1141-1153, 2018
doi:10.1093/annonc/mdy114
Published online 18 April 2018

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*
- New RCT from inpatient cancer patients in Switzerland
 - Standard care vs individualized nutritional support
 - 30 day mortality 14.1% vs 19.9%
 - *Ref: Bargetzi L et al. Annals of Oncology 2021*

Nutrition

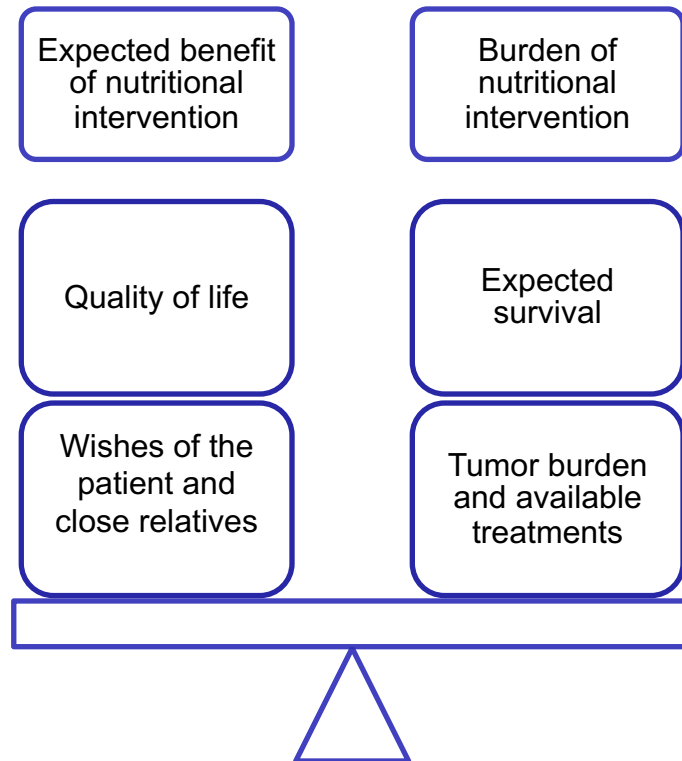
- Dietary counselling in advanced cancer makes it possible to maintain or increase energy and protein intake

ref: Balstad et al 2014

- But nutrition *alone* seems not to be enough



More «aggressive» nutritional interventions?



Sonde-ernæring/intravenøs ernæring

When?



Parenteral nutrition in patients with advanced cancer: Tobberup R et al Crit Rev Oncol hematol 2019

Three small RCTs on the use of IV nutrition 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 ¹	52 (17)	58 (17)	66 (17)	71 (14)	66 (16)
PF ¹	38 (22)	42 (22)	46 (21)	55 (16)	52 (17)
RF ¹	33 (24)	38 (26)	41 (24)	48 (19)	45 (20)
EF ¹	47 (16)	51 (17)	52 (13)	56 (12)	55 (12)
CF ¹	58 (17)	59 (18)	62 (16)	62 (17)	63 (12)
SF ¹	53 (21)	54 (20)	56 (21)	60 (16)	57 (21)
AP ²	79 (26)	77 (23)	74 (22)	63 (26)	64 (24)
FA ²	77 (17)	75 (16)	73 (17)	73 (18)	71 (16)
NV ²	56 (25)	52 (20)	54 (20)	54 (18)	54 (20)
FI ²	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



Multinational Association of Supportive Care in Cancer (MASCC) expert opinion/guidance on the use of clinically assisted nutrition in patients with advanced cancer

Bryony Alderman¹ · Lindsey Allan¹ · Koji Amano² · Carole Bouleuc³ · Mellar Davis⁴ · Stephanie Lister-Flynn⁵ · Sandip Mukhopadhyay⁶ · Andrew Davies^{7,8,9} 

Received: 1 September 2021 / Accepted: 3 October 2021
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Results The Subgroup produced 11 suggestions, and 1 recommendation (due to the paucity of evidence). These outcomes relate to assessment of patients, indications for CAN, contraindications for CAN, procedures for initiating CAN, and re-assessment of patients.

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?

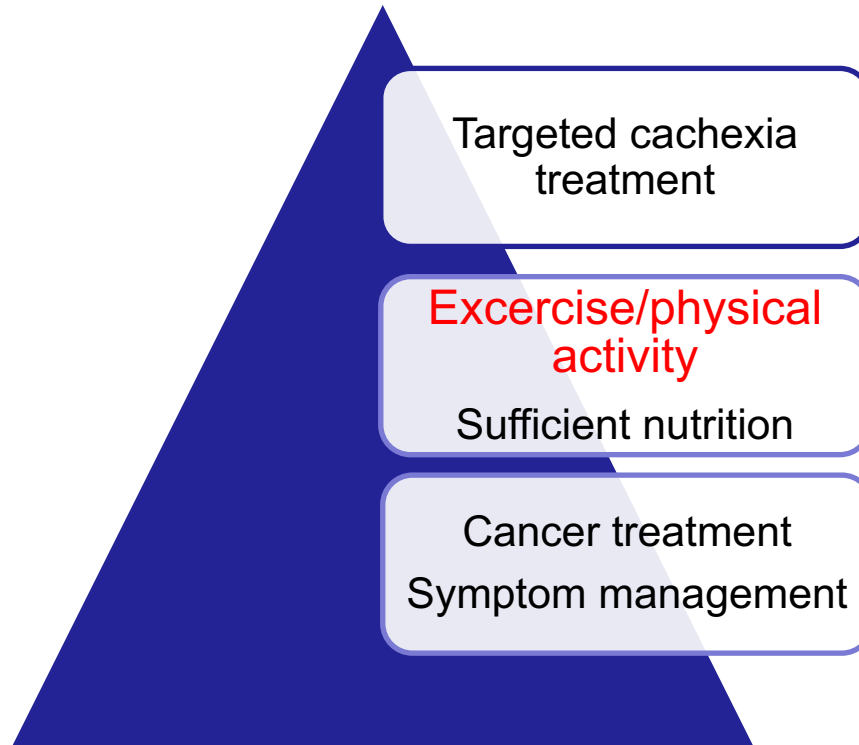
Case 2

- 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 3rd 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?

Complex interventions for cachexia



Exercise

- Potential effect:
 - Inhibition of inflammation, increase anabolism
 - Prevents inactivity-induced sarcopenia
 - Better quality of life, fatigue and muscle mass
- Evidence:
 - Despite strong clinical rationale, not enough studies have been conducted to assess efficacy in patients with cachexia
 - Grande AJ 2015, Cochrane Collaboration systematic review
- Exercise can improve QoL and relieve fatigue, insomnia, dyspnoea and physical and social functioning for patients with advanced cancer
 - Ya-jing Chen 2020, Systematic review and meta-analysis (15 RCTs, 1208 patients)

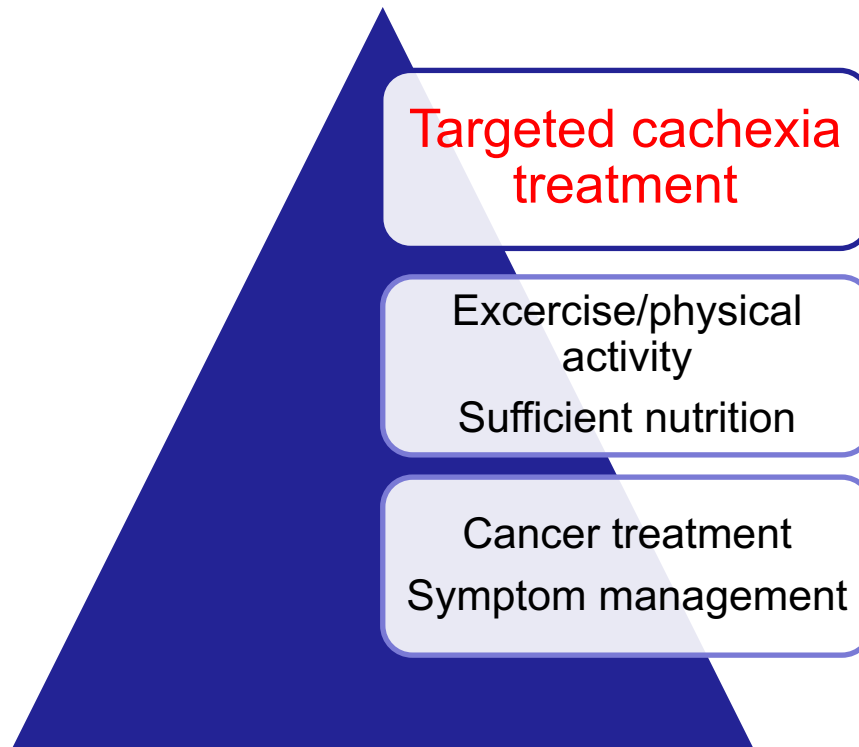


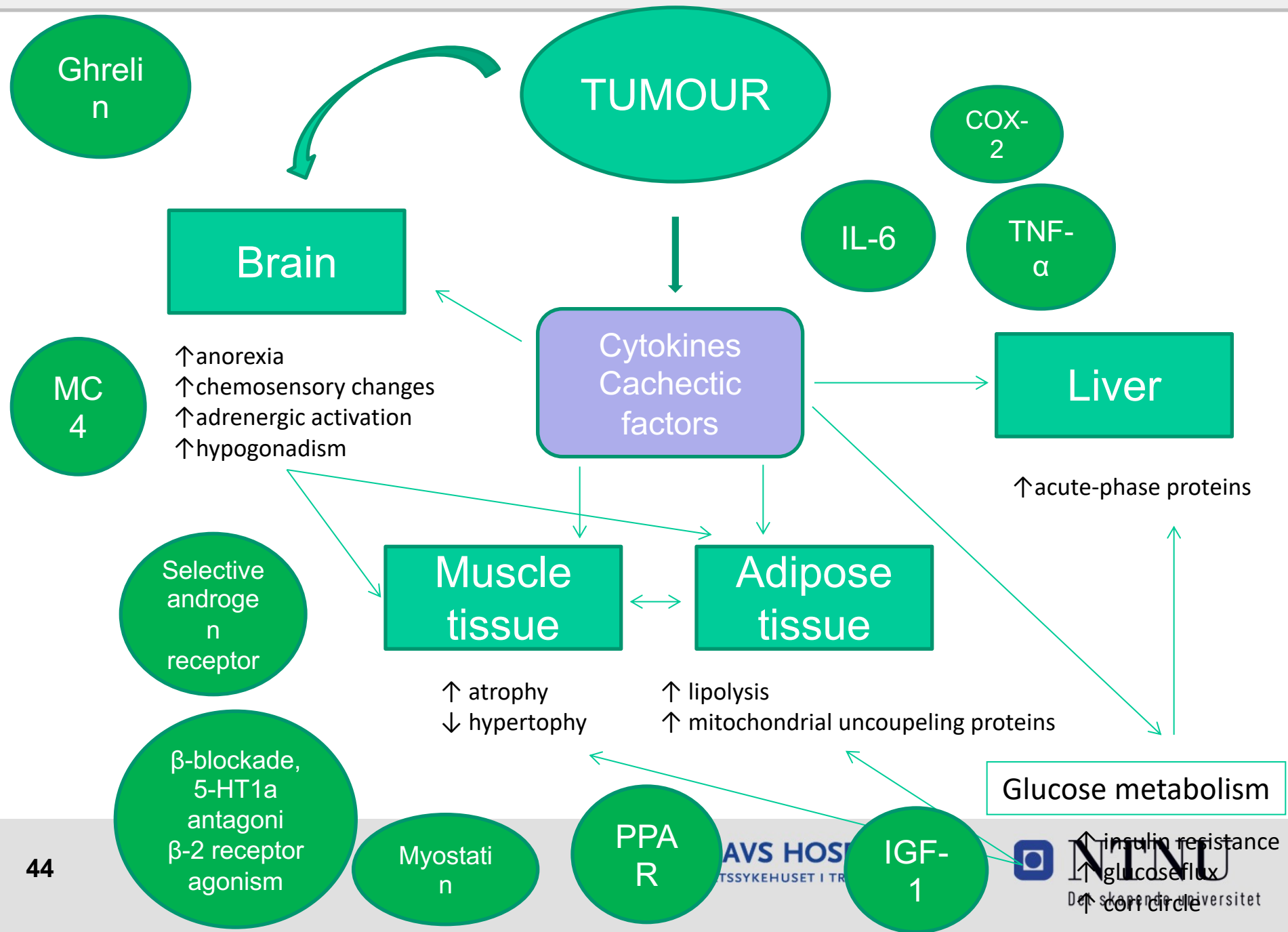
Physical exercise

- How?
- What “dose”?



Complex interventions for cachexia





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

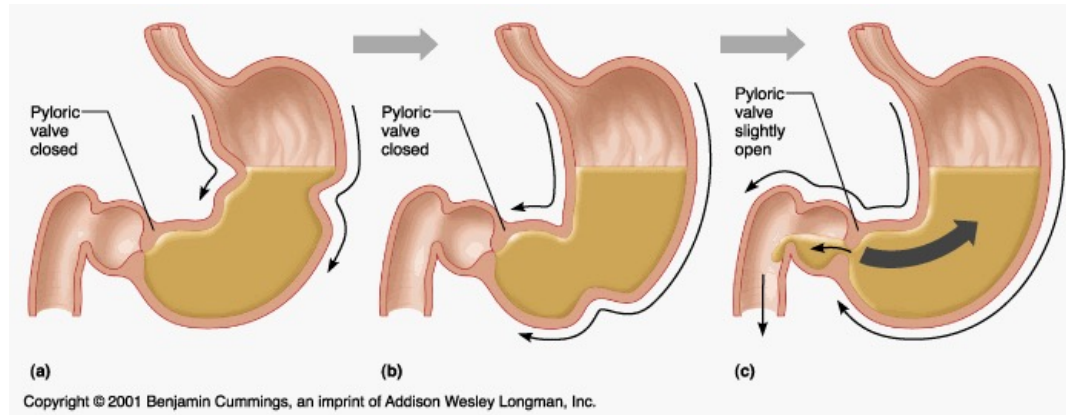
- Optimal dose is 160-800 mg/d (?)
- For short-intermediate term appetite stimulation and increase of weight but not muscle mass

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

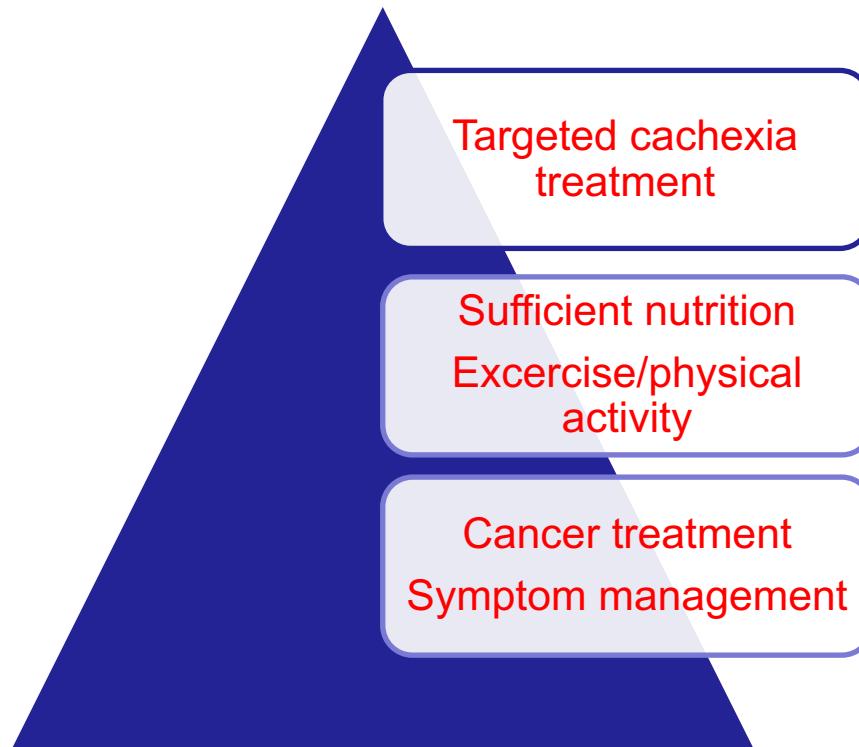
- Fewer patients included in studies
- Can help in patients with early satiety, chronic gastro paresis and nausea



Upcoming drugs?

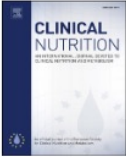
- Anamorelin (Ghrelin-analogue)
- Enobosarm (selective androgen receptor modulator)
- Other
 - Cannaboinoids, androgens, olanzapine, fometerol, NSAID..

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*

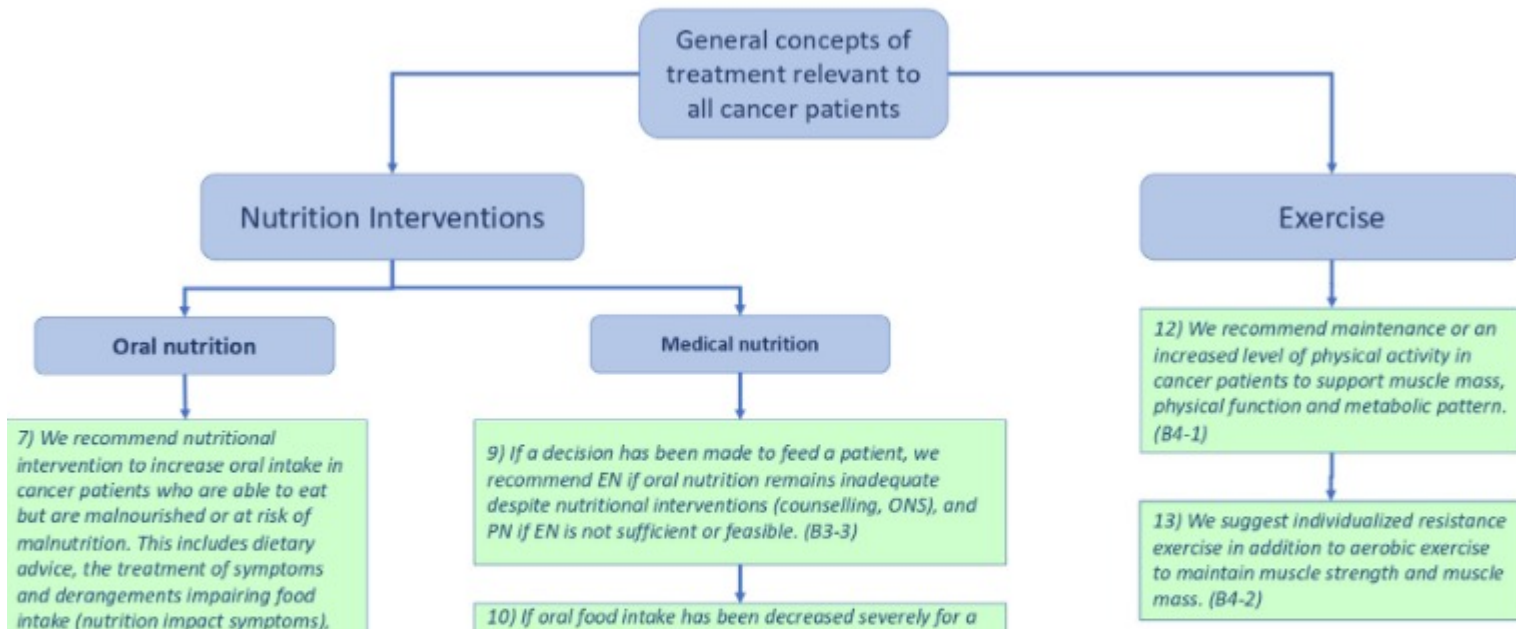


Guidelines

ESPEN Guideline

ESPEN practical guideline: Clinical Nutrition in cancer

Maurizio Muscaritoli ^{a,*}, Jann Arends ^b, Patrick Bachmann ^c, Vickie Baracos ^d, Nicole Barthelemy ^e, Hartmut Bertz ^b, Federico Bozzetti ^f, Elisabeth Hütterer ^g, Elizabeth Isenring ^h, Stein Kaasa ⁱ, Zeljko Krznaric ^j, Barry Laird ^k, Maria Larsson ^l, Alessandro Laviano ^a, Stefan Mühlebach ^m, Line Oldervoll ⁿ, Paula Ravasco ^o, Tora S. Solheim ^p, Florian Strasser ^q, Marian de van der Schueren ^{r,s}, Jean-Charles Preiser ^t, Stephan C. Bischoff ^u



Guidelines



SPECIAL ARTICLE

Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines[☆]

J. Arends¹, F. Strasser^{2,3}, S. Gonella^{4,5}, T. S. Solheim^{6,7}, C. Madeddu⁸, P. Ravasco^{9,10,11}, L. Buonaccorso¹², M. A. E. de van der Schueren^{13,14}, C. Baldwin¹⁵, M. Chasen^{16,17,18} & C. I. Ripamonti¹⁹, on behalf of the ESMO Guidelines Committee

Cachexia treatment requires a multimodal approach aimed at relieving symptoms impacting on food intake, ensuring adequate energy and nutrient intake, minimising catabolic alterations, supporting muscle training and offering psychological and social support [II, B].

Guidelines

Management of Cancer Cachexia: ASCO Guideline

Eric J. Roeland, MD¹; Kari Bohlke, ScD²; Vickie E. Baracos, PhD³; Eduardo Bruera, MD⁴; Egidio del Fabbro, MD⁵; Suzanne Dixon, MPH, MS, RD⁶; Marie Fallon, MD⁷; Jørn Herrstedt, MD, DMSci⁸; Harold Lau, MD⁹; Mary Platak, PhD, MS, RD¹⁰; Hope S. Rugo, MD¹¹; Hester H. Schnipper, LICSW, BCD, OSW-C¹²; Thomas J. Smith, MD¹³; Winston Tan, MD¹⁴; and Charles L. Loprinzi, MD¹⁵

Recommendation 1.1. Clinicians may refer patients with advanced cancer and loss of appetite and/or body weight to a registered dietitian for assessment and counseling, with the goals of providing patients and caregivers with practical and safe advice for feeding; education regarding high-protein, high-calorie, nutrient-dense food; and advice against fad diets and other unproven or extreme diets (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 2.1. Evidence remains insufficient to strongly endorse any pharmacologic agent to improve cancer cachexia outcomes; clinicians may choose not to offer medications for the treatment of cancer cachexia. There are currently no FDA-approved medications for the indication of cancer cachexia (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3. Outside the context of a clinical trial, no recommendation can be made for other interventions, such as exercise, for the management of cancer cachexia.

Summary: For refractory cachexia consider

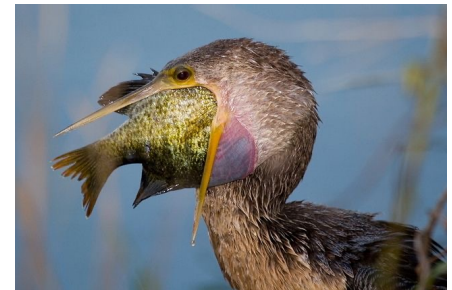
- Other reasons/contributing factors for weight loss
- Appetizing food/ONS and physical activity in a setting that does not cause distress and does not give false hope or goals
- Communication/information
- Corticosteroids for 1-2 weeks
- Progesteron short time for improving appetite

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?

- **Neglect 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?

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- **3. Perform screening for and if necessary assessment of malnutrition**
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- (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/HT²).
- 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/HT²).
- 4. Ask for physical performance
- **5. All of the above** (→ use screening tool, e.g. NRS = Nutrition Risk Screening)
- (one answer)

SCREENING

Nutrition Risk Screening. Kondrup et al., Clin Nutr 2013

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



Nutritional support

SCREENING

Nutrition Risk Screening. Kondrup et al., Clin Nutr 2013

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70%
8%
(BMI 30.0)
(55 y)
lung cancer heading for chemotherapy



Nutritional support

Q3. How to ASSESS for Malnutrition?

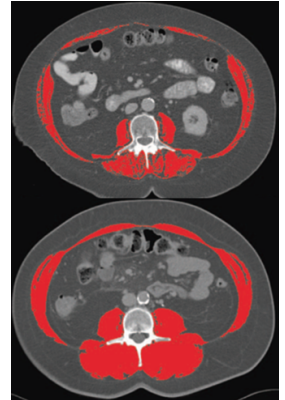
- 1. Ask for nutrition impact symptoms, e.g. nausea, early satiety
- 2. Estimate food intake
- 3. Assess degree of systemic inflammation
- 4. Measure muscle mass
- 5. All of the above
- (one answer)

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)

Assessment of nutritional status

- Performed by nutrition expert
- Nutrition impact symptoms: anorexia, early satiety
- Food diary: 1750 kcal (70%)
- Body composition: BMI 30 kg/m³, 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**

Q4. WHAT NUTRITIONAL SUPPORT SHOULD THE PATIENT RECEIVE?

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- 8. Advice on individualised *exercise training*
- 9. **Options 5-8**

Patient history

- The patient receives chemotherapy (carboplatin / pemetrexed)
- The oncology team has focus on NIS, and he has relatively few challenges with pain and nausea
- He continues golfing, but more often walks than takes 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

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)
- All of the above

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)
- **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

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

Q6: What could BE a possible next step?

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

Consider a trial with:

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

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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

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

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Thank you for your attention

