ESMO Vienna 2012 - ESMO-MASCC Joint symposium 30. Sept. 16:15 / L-M
Integration between medical oncology and supportive care: Two sides of the same coin

Development of rational therapeutic strategies for patients with pre-cachexia and cachexia through the integration of oncology and palliative care and collaborative clinical trials (EAPC-Research Network)

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MASCC Working Group Nutrition and Cachexia
ESMO Palliative Care Working Group
Eur **A**ssoc **P**all **C**are TF Integrated Oncol & Pall Care; **EAPC-RN**
Society **S**arcop **C**achexia **W**asting **D**iseases
Intl **A**ssoc **H**ospice **P**all **C**are
ESPEN

Disclosure Slide

Unrestricted grants for clinical research

- Bachem (bulk Ghrelin)
- Celgene (Lenalidomide Cachexia trial)
- Fresenius (Survey parenteral nutrition malignant bowel obstruction)
- Grünenthal (opioid rotation trial)

Participation in clinical cachexia trials

- Novartis (BYM338 cachexia trial)

Punctual Advisorship

Acacia, Alder, Amgen, Baxter, Fresenius, Helsinn, Nutricia, GSK, Otsuka, Ono, Pfizer, Santhera, Solvay, Teva, Wyeth

No: Mono-sponsored Industry Sattelite meetings

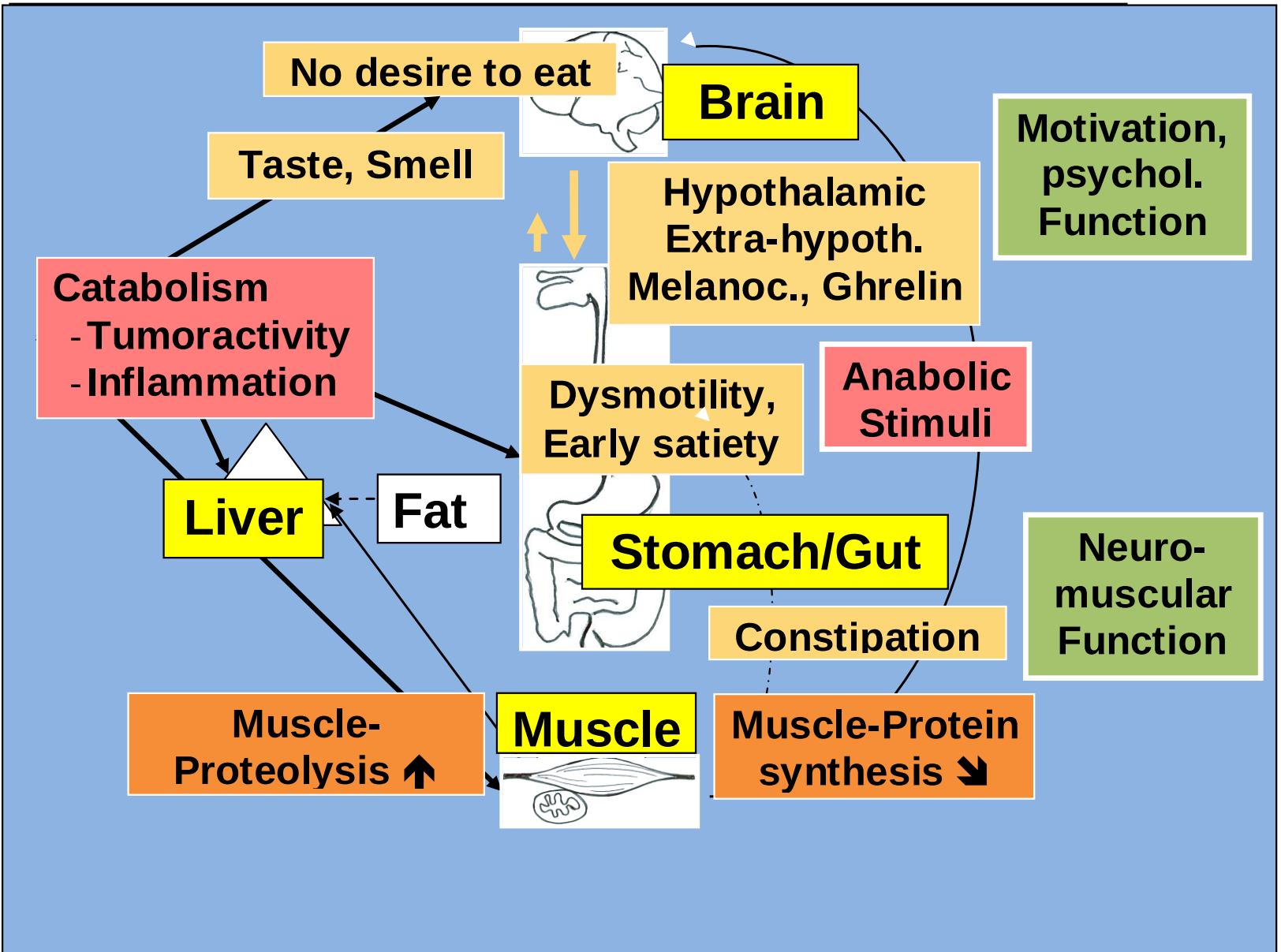
No: Personal financial interest (stocks, private use of honoraria, ..)

Mr K, 72-j, Pancreas-adenocarcinoma liver-mets
Gemcitabine weekly first-line, since 3 weeks

„How are you“: swollen legs, people do nothing about it.
Am tired and weak, I want to go home, when can i go?

What is our therapeutic strategy?

Why does this happen to me? Mechanism of cancer cachexia



Strasser F.
Oxford Textbook of Palliative Medicine, 4th Edition, Chapter 10.3.2

Key features of cancer cachexia

The domains to „always“ consider:

- 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

For phenotyping patients:
prospective cohort studies and phase II/III trials needed
→ **Intl. consensus project** for common datasets and on outcomes for clinical trials: 11.2012-7-2013

“What” is NOT cancer cachexia ?

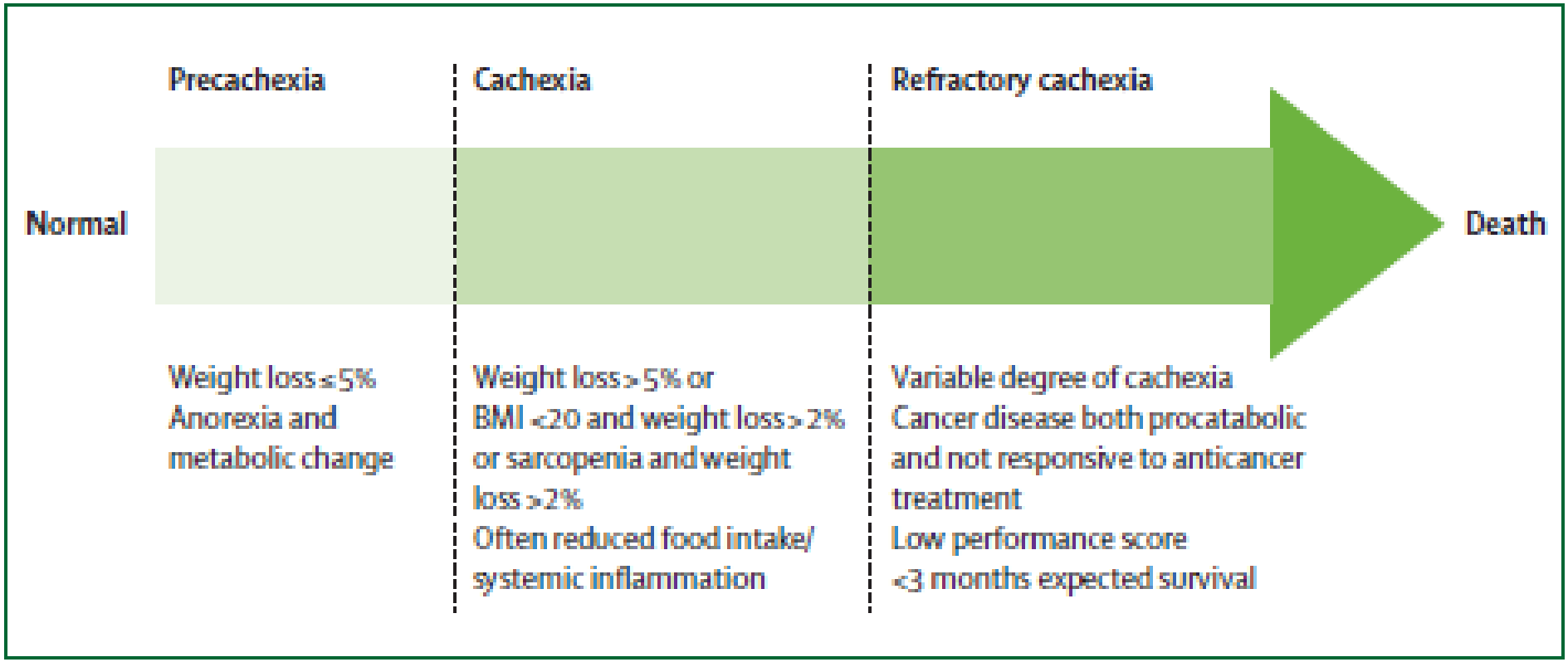
Patients “neglected” for maintenance of adequate nutritional intake

- **Diet mistakes / misconceptions: too healthy, ..**
- **Periods of nausea/vomiting, mucositis, diarrhea, constipation**
- **(partial) bowel obstruction, dysphagia**
- **Periods of “no eating” due to procedures**

….

→ The “epidemy” of Malnutrition [ESPEN et al.]

The faces of cancer cachexia: a spectrum



Main Goal: Prevention Muscles, function Alleviation

Fearon K & Strasser F, et al. Lancet Oncol 2011 ;12(5):489-95

How to identify patients with cancer cachexia in daily practice?

Screening

- physical fatigue[1]
- perceived problems with appetite/eating
- weight loss

Diagnosing[2]

- 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

→ **Intl. consensus project** minimal common datasets 11.2012-7-2013

1: Käser I et al., JPSM 2009;38:505-14

2: Fearon K & Strasser F, et al. Lancet Oncol 2011 ;12(5):489-95

Why treat patients with cachexia?
Impact on Survival

1473 canadian patients (lung, gastrointestinal), obese: Weight loss (WL), low lumbar skeletal muscle index (MI)*, altered mean muscle attenuation (MA)*, and BMI.

- BMI not prognostic for survival
- If WL + MI + MA below/above defined thresholds: survival 8 mts, if no prognostic fct: 28 mts ($p<0.001$)

* Assessed from routine lumbar computed tomography (CT).

(Other studies: Thoresen L et al. Clin Nutr. 2012 Jun 11)

Martin L et al. J Clin Oncol 2012, in press

Why treat patients with cachexia?
A supportive care need – anticancer tx toxicity

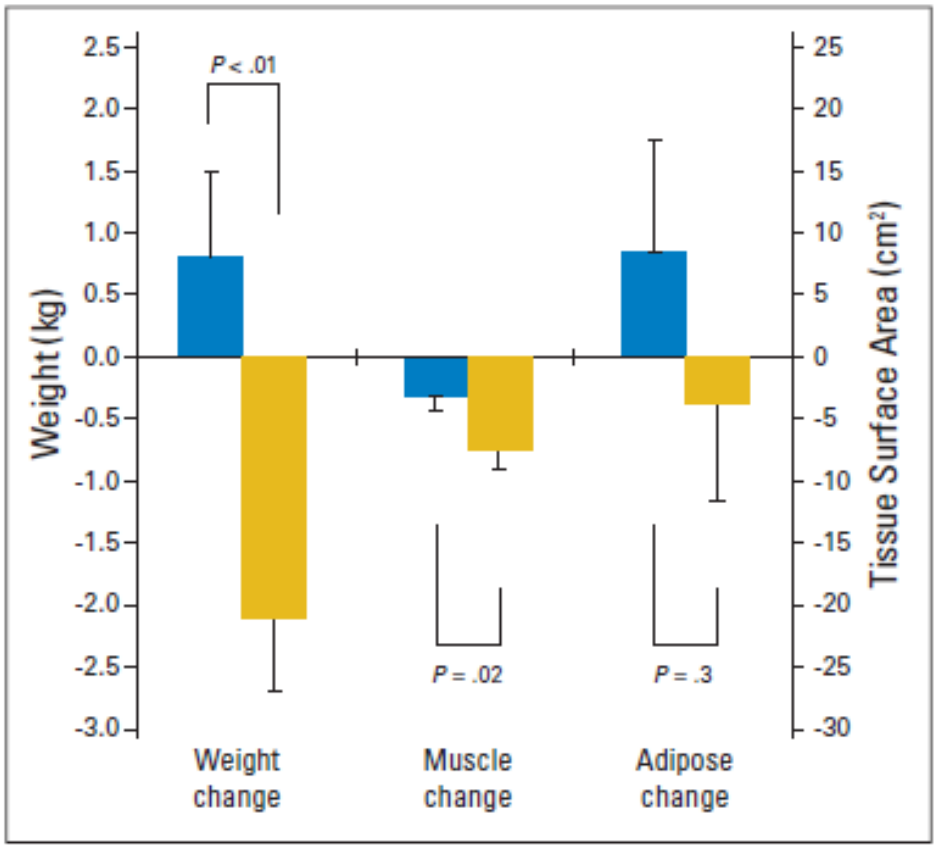


Fig 2. Evolution of body weight, muscle area, and adipose area during 6 months of treatment with sorafenib (gold; n = 48) *v* placebo (blue; n = 32). Statistical indications are for unpaired *t* test were as follows (mean ± SE; black error bars above and below color blocks indicate SE): body weight (in kilograms), 0.8 ± 0.7 *v* −2.1 ± 0.6 (*P* < .01); and skeletal muscle area (in square centimeters), −3.1 ± 1.3 *v* −7.4 ± 1.7 (*P* = .02).

Metastatic renal cell cancer, resistant to standard therapy (n=80): sorafenib 400 mg b.i.d. or placebo

Muscle mass loss:
- 6 mts (4.9%; P .01)
-12 mts (8.0%; P .01)

→ Independent of tumor response

Antoun S et al.
J Clin Oncol 2010;28(6):1054-60

Why treat patients with cachexia?
Impact on oncology anticancer drug toxicity

Preliminary data suggest significant association of muscle mass with chemotherapy toxicity

24 breast cancer receiving adjuvant intravenous 5-FU: Lean Body Mass in patients with versus without chemotherpay toxicity: 41.6 vs. 56.2 kg, P = 0.002.[1]

55 women with metastatic breast cancer, caepcitabine: 25% were sarcopenic: toxicity 50% vs 20%, P = 0.03.[2]

(Barret M et al. J Clin Oncol 30, 2012 (suppl; abstr 9026)

1: Prado CM et al. Cancer Chemother Pharmacol 2011;67(1):93-101.
2: Prado CM et al. Clin Cancer Res 2009;15(8):2920-6.

Why treat patients with cachexia?
Palliative cancer care needs from diagnosis to death

Abundant data on association of weight loss / cancer cachexia on deterioration of
- physical function, performance status, fatigue
- breathlessness
- psychosocial distress of patient & family members
- distressing cachexia/related symptoms (anorexia, chronic nausea, early satiety, constipation, etc.)

Global challenge with increasing cancer burden,
In ressource-challenged countries more patients present with stage IV disease

The challenge of therapeutic strategies for cancer cachexia

- A multidimensional problem requires a multi-modal and multi-disciplinary approach
- For mono-dimensional interventions, the other domains need to be standardized
- Treatment and outcomes are different for the three cachexia phases
- A close interaction between palliative cancer care and (medical) oncology management is required
- A consensual phenotyping of cancer cachexia pts (also necessary for molecular profiling) pts is missing: work in progress (consensus project)

Common Cachexia interventions delivered by multiprofessional teams

- Various anti-cachexia drugs (soon?; still experimental)
- Tumor control - slowering progression / activity[1]
- Nutritional intake optimize (own habits, ONS, educate)[2]
- Physical activity increase & maintenance
- Coping with disease, life goals, support of and by family
- Alleviate eating-, weight loss related distress[3]

1: Köberle D et al. J Clin Oncol. 2008;26(22):3702-8; Au H-J et al. J Clin Oncol 2009;27
2: Strasser F, Demmer R, Böhme C, et al. The Oncologist, 2008;13:337-346
3: Strasser F, Binswanger J, et al. Palliative Medicine 2007;21:129-37

Example of a «mono-dimensional» cachexia trial exploring a muscle specific agent

Main outcomes: muscle mass & muscle function (Ph II)

Standardize

- Nutritional intake (e.g. ≥ 20kcal, 0.6 Prot/ kgBW; pragmatic)
- Physical activity (e.g. maintain Borg ≥ 4)
- Tumorsituation and its treatment (e.g. estimate cancer-related prognosis, anticancer treatment tolerability proven)
- Inflammation (e.g.defined treatment, no active infection)
- Emotional & social participation (e.g., life goals, coping)

Treatment and outcomes are different for the three cachexia phases

Pre-cachexia*	Stabilisation of muscle mass & function „Oncology outcomes“: toxicity, RR, OAS
Cachexia	≥ 1 domain-specific effect** Patient functions*** improve - stabilize Oncology outcomes
Refract cachexia	Alleviation of burdensome symptoms

* NOT equal to a muscle mass & function stable patient without neuro-hormonal / inflammatory / metabolic alterations

** The other domains are controlled for with defined management

*** Physical function, emotional function, „Quality of life“

A close interaction between palliative cancer care and (medical) oncology management is required

- Palliative Cancer Care starts early in the trajectory[1]

- Anticancer treatments can (and shall) a patient-derived clinical benefit: weight & function gain[2]

- The quality of “Best Supportive Care” may impact outcomes, and can be defined[3]

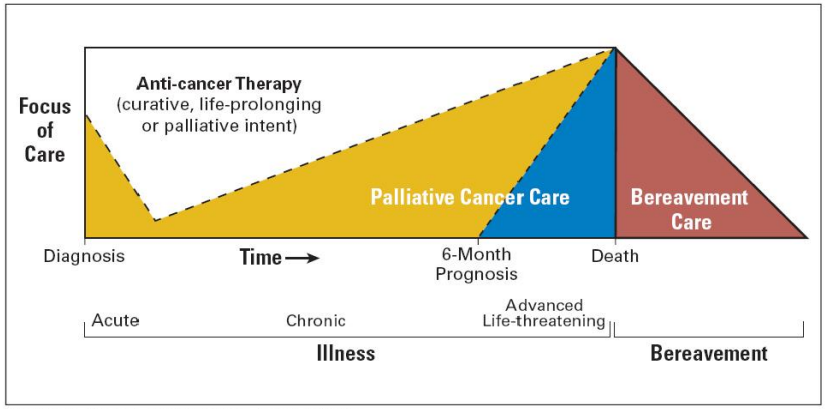


Figure 1. Model of Palliative Cancer Care.

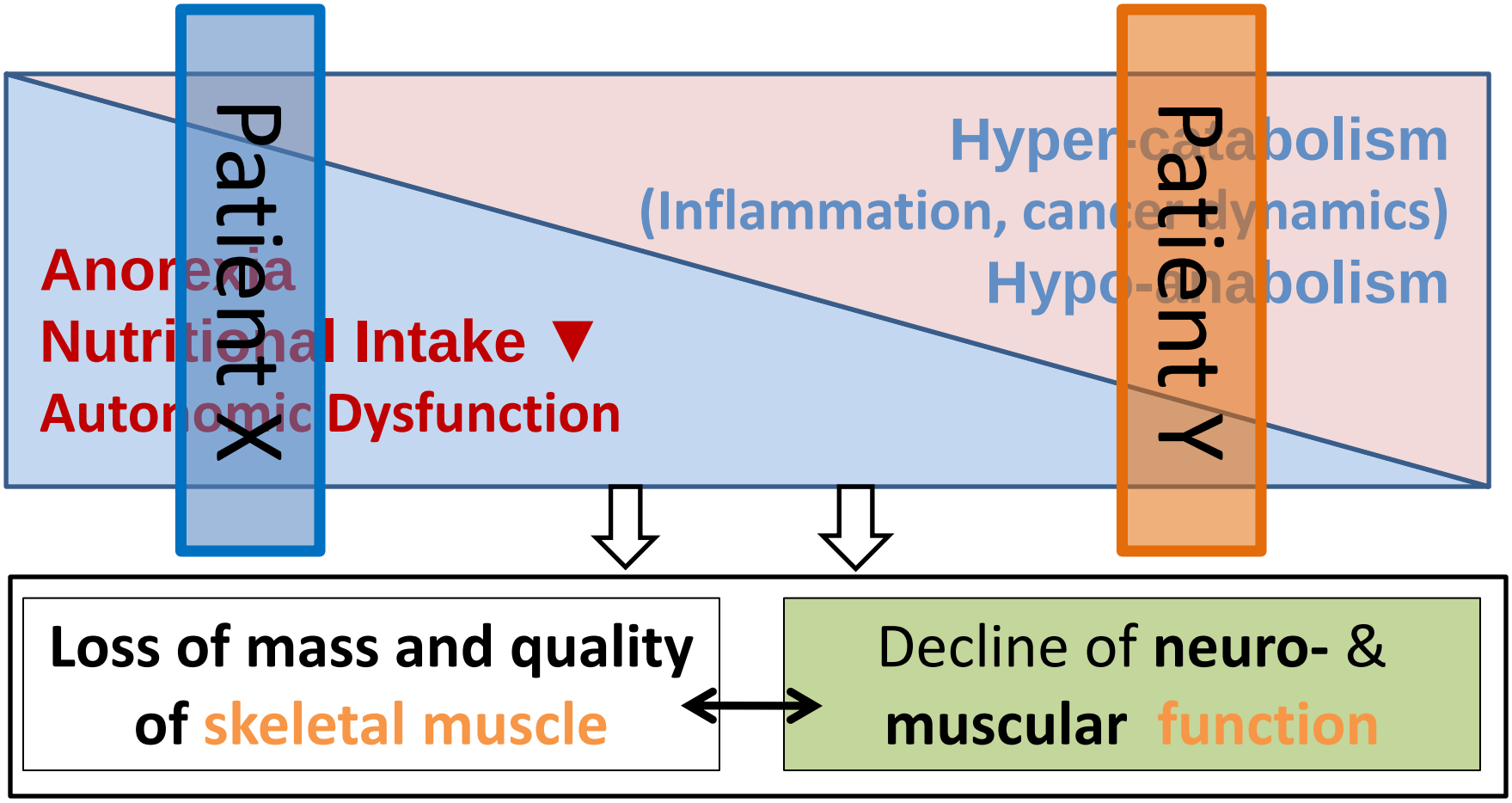
1: Ferris FS et al. J Clin Oncol 2009;27:3052-8

2: Koeberle D et al., J Clin Oncol 2008; 26(22):3702-8: Ohorodnyk P et al. Eur J Cancer 2009:45(13):2249-52

3: Cherny N et al. J Clin Oncol 2009;27:5476-86 Zafar Y et al., Lancet Oncology Feb 2012

Check: E-learning www.ESMO.org

Can cancer cachexia phenotypes *(and genotypes?[1])* **be differentiated?** *--> prospective, consensual work needed*



European Association Palliative Care - Research Network 2012 // **1:** Tan BH et al. EMBO Mol Med 2012;4(6):462-71; **1:** Solheim TS et al. Br J Cancer. 2011;105(8):1244-51.

Examples of planned phase „specific“ clinical trials: pre-cachexia and refractory cachexia

MENAC[1]: Multimodal Exercise/Nutrition/Anti-inflammatory treatment for Cancer Cachexia
Patient Eligibility: new diagnosed stage IV solid tumor
→ Mixed pre-cachexia & cachexia study

Family Approach to Weight and Eating (FAWE)[2]:
a new psycho-educational intervention for people affected by refractory cachexia
→ Focus on mainly refractory patients

1: European Association of Palliative Care Research Network
2: Cardiff University, Jane Hopkinson et al.

emerging therapeutic approaches for cachexia

- Melanocortin Receptor 4-antagonists
- Ghrelin & its analogues
- Androgen (SARMs, ...), β2-mimetics,...
- Muscle pathways (anti-myostatin, ActRIIB,..)
- Anti-inflammatory agents (IL-1, Il-6, TNF, Lenalidom, ...)
- many other promises [1]

C-steroids, progestins, prokinetics

Olanzapine, Mirtazapine

Cannabinoids

1: Cancer cachexia conference Boston September 2012

Conclusions

A rational therapeutic strategy for cancer cachexia is based on the defined phase of cancer cachexia and its target domains, treatments and outcomes are different.

To optimize personalized cancer care for tis multidimen-sional problem, a close interplay of medical oncology and palliative cancer care interventions is required.

A close collaboration between oncology, palliative, supportive, nutritional, cachexia and other societies is mandated for necessary consensus projects, prospective cohort studies and intervention trials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Backup Slides

Physical function interventions in palliative care?

- Exercise in elderly: long-term benefits on muscle function, less falls, more independence, QoL[1]
- Physical exercise: reduce fatigue, improve QoL and physical functioning in cancer patients[2]
  - mostly survivors, breast cancer: large effects
  - with chemotherapy moderate effects: QOL, physical activity levels, aerobic fitness, muscular strength
  - palliative patients: phase II studien positive trends[3]
    RCT (n=231), superv. PA 60 min 2x/w x 8 w; 70% complete
    Fatigue nicht (Fatigue Quest.), physical fct (SWT/HGS) besser[4]

1: Singh MA, et al. J Gerontol A Biol Sci Med Sci 2002;57:M262-82. Lynch GS. Expert Opin Emerg Drugs 2004;9:345-61. Lynch GS. Intern Med J 2004;34:294-6.
2: Conn VS et al. Support Care Cancer 2006;14:699-712. Schmitz KH, et al. Cancer Epidemiol Biomarkers Prev 2005;14:1588-95 (survivors, meta-analysis). Speck RM et al. J Cancer Surviv;2010:6.
3: Lowe SS, et al. J Support Oncol 2009;7:27-34; 4: Oldervoll LM et al., The oncologist 2011; Sep 26

The evolution of clinical trial design in cancer cachexia: a systematic review based on the novel classification and definition criteria

Lisa Martin [1,2], Aurelius Omlin[1], Vickie Baracos[2], Kenneth C. H. Fearon[3], Florian Strasser[1]

Systematic literature review: all papers and ongoing clinical trials ≥ 2000

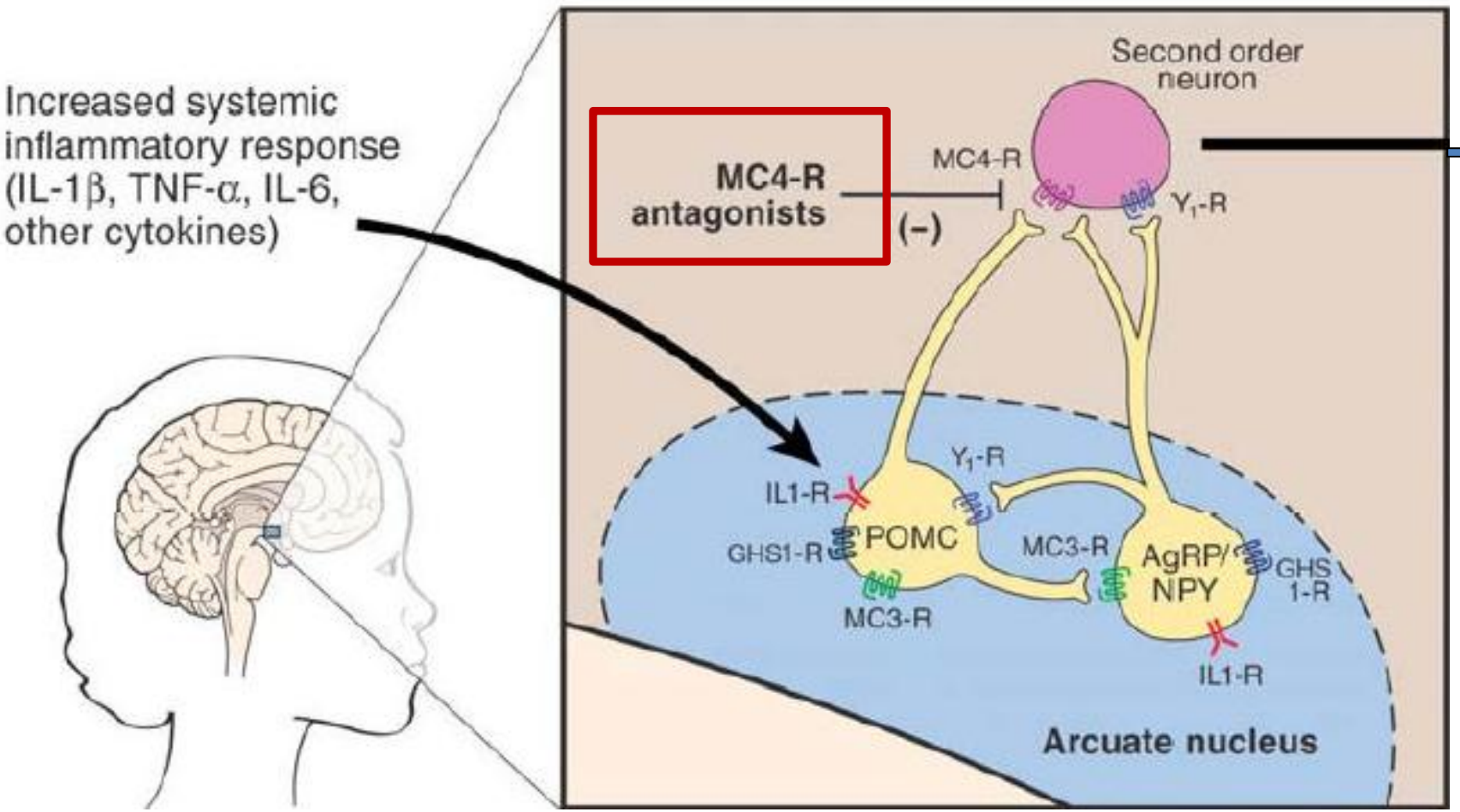
RESULTS	Studies #	Studies %
Domain I. Depletion of Reserves	86	87%
Body Weight	72	73%
Body Composition	60	61%
CT	2	2%
DEXA	9	9%
Anthropometrics	14	14%
BIA	33	33%
Muscle Strength	21	21%
upper limb hand-grip dynamometry	14	14%
lower limb extension	3	3%
Domain II. Limitations to Nutrtional Intake	72	73%
Food Intake	33	33%
Patient-reported food records (calculated)	26	26%
Subjective categorical classification	7	7%
Nutrition Impact Symptoms	53	54%
Appetite	43	43%
Domain III. Catabolic Drive	40	40%
Inflammation	32	32%
CRP	21	21%
Altered Metabolism (REE, indirect calorimetry)	13	13%
Response to chemotherapy	5	5%
Domain IV. Functional/Psychosocial Effects	73	74%
Physical Function	41	41%
Physician reported (ECOG, KPS, WHO, etc.)	27	27%
Objective measures (PA, exercise capacity)	12	12%
Patient-reported	8	8%
Quality of Life	53	54%
Fatigue	18	18%
Distress (depress., anxiety, mood, well being)	9	9%

Large heterogenity

- domains „missing“
- cachexia phases & severity

Preliminary results presented @ Cachexia conference Milano 2011

Melanocortin Receptor 4-antagonists



DeBoer MD. Nutrition 2010;26(2):146-51.

Inflammation → MC4R activity ▲ → cachexia

Ghrelin → GHS-1 Rec → AgRP ▲ → MC4R▼

(Extra)-hypothalamic Ghrelin actions

Serotonergic inputs to the hippocampus → neurogenesis, learning, memory

Mesolimbic dopaminergic system → hedonic & incentive value of food

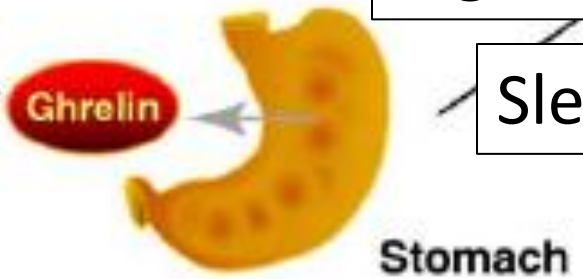
Hypothalamic
energy metabolism
appetite regulation
glucose homeostasis
GH release
body weight regulation

learning and memory
reward and motivation
neuro
mood regulation

Neuroprotection

Modulation of anxiety and regulation of mood

Sleep-wake regulation



Andrews ZB. Trends Neurosc. 2011;34:1

Steiger A et al., Moll Cell Endoc 2011;340:88-96

Cancer Cachexia Framework: key features

From „anorexia/cachexia syndrome“ to cancer cachexia

„Muscle loss relevant for physical function, not reversible by nutrition, caused by decreased intake and alt. metabolism“

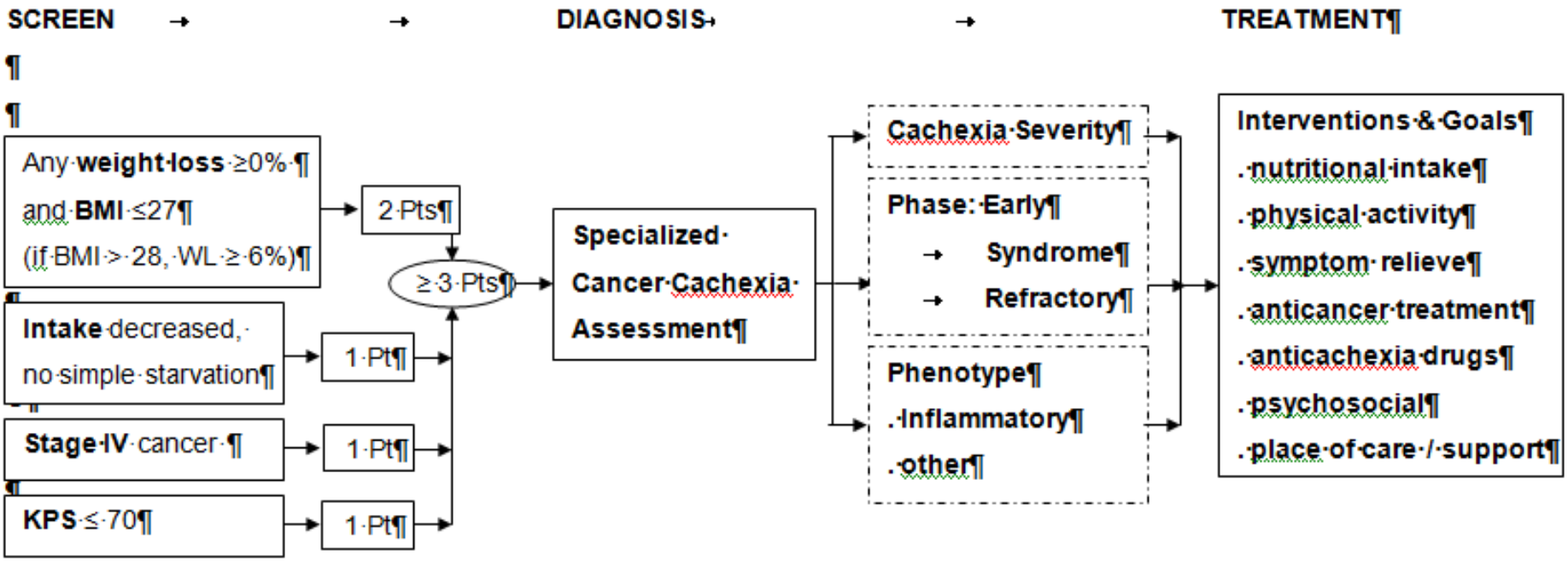
Diagnostic criteria: based on weight loss and BMI

Domains: Muscle/(Fat)
Nutritional Intake & „Appetite“-Symptoms
Catabolic tumor, inflammation, and hormones
Neuro-muscular and emotional function

Phases: from early to cachexia to refractory cachexia

Severity described by weight loss and BMI

How could an Assessment – Approach look like



The Cancer Cachexia Assessment: proposal to be further refined by consensus

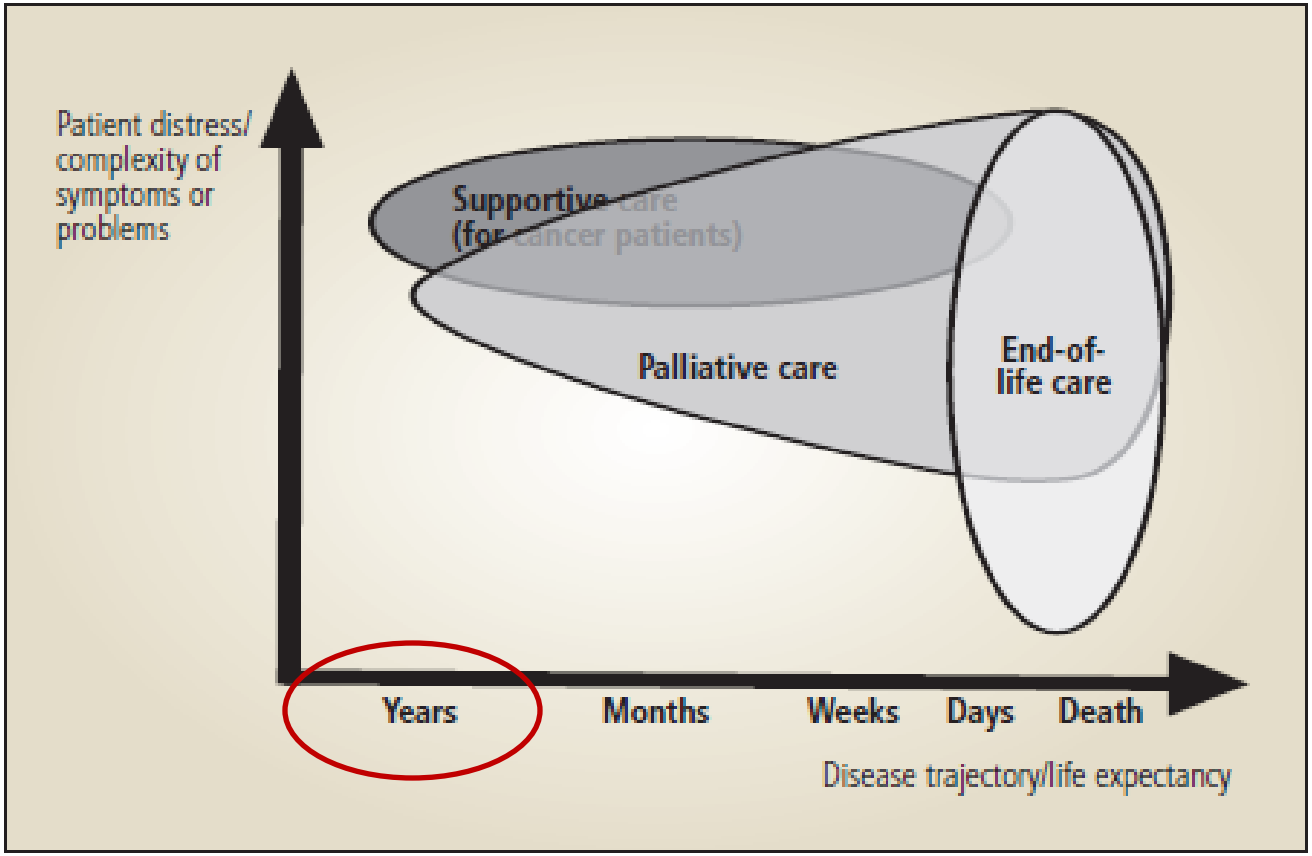
integrates information from the Patients' Past, Present and Future

	SCREEN Daily Practice	DIAGNOSIS Specialized Practice	RESEARCH Clinical Trials and Studies
STORAGE	**Weight loss % last 2-6 mts** **Body Mass Index**	**Detailed weight loss history** **if fluid retention: CT L3/4 or DEXA**	**MRI thigh / DEXA / CT L3-4** **(mass of muscle, fat**
INTAKE	**Perceived eating problems** **Simple Starvation ruled out**	**2 day diet diary, % kcal/protein / needs** **Secondary nutrition impact symptoms** **Symptoms: appetite, early satiety, etc.** (instruments: FAACT, et al.)	**Food weight, components** **Response to treatment of S-NIS** **Comprehensive item pools**
POTENTIAL	**Stage IV cancer**	**Tumor dynamics** . responsive to anticancer treatment . symptomatic progression < 3 months **CRP > 10mg/l, without clinical infection**	**History of anticancer treatments** . Past and expected responses . Short term muscle loss response **Cytokines, hormones**
PERFORMANCE	**Cancer related KPS ≤ 70** **Cachexia, a care priority**	**Physical function measurement** (muscle strength, physical functioning) **Psychosocial distress: weight, eating** **Decisions towards care goals**	**Muscle power, 6-MWT, et al.** Body worn sensor tests **Comprehensive item pools** **Prognosis tools**

Refractory (late) cancer cachexia

Advanced muscle wasting (with or without loss of fat) due to progressive cancer, not anymore responding to anticancer treatment.
Patients have a low performance status and short life expectancy (<3months). It is evident that the burden of artificial nutritional support would outweigh any potential benefit.
Therapeutic interventions focus typically on alleviating the consequences/complications of cachexia, e.g. symptom control (appetite stimulation, nausea), eating-related distress of patients and families.

When should palliative care interventions start?



Main area of care provision for palliative care, supportive care and end-of-life care (using a narrow definition of end-of-life care)

European Association of Palliative Care (EAPC): year(s) before death

Radbruch L et al. EUROPEAN JOURNAL OF PALLIATIVE CARE, 2009; 16(6)