UNIVERSITÄT LEIPZIG

Medizinische Fakultät

Universitätsklinikum Leipzig

Medizin ist unsere Berufung.

Cancer Cachexia

in Patients with Lung Cancer

A multi-factorial and multi-professional problem

Armin Frille

Dept. for Respiratory Medicine, University Hospital Leipzig, Germany

21 SEP 2023

AGENDA

1. Lung cancer: clinical perspective
2. Malnutrition and cachexia
3. Pathophysiology: focus on inflammation
4. Management and treatment strategies

Lung cancer

- ESMO Clinical Practice Guidelines, 2023

  Hendricks LE et al., ESMO 2023: PMID: 36872130, 36669645

- NCCN Clinical Practice Guidelines in Oncology, 2023

  Version 3.2023, 04/13/23 © 2023 National Comprehensive Cancer Network® (NCCN®)

Cancer cachexia and malnutrition

- Definition and classification of cancer cachexia, 2011

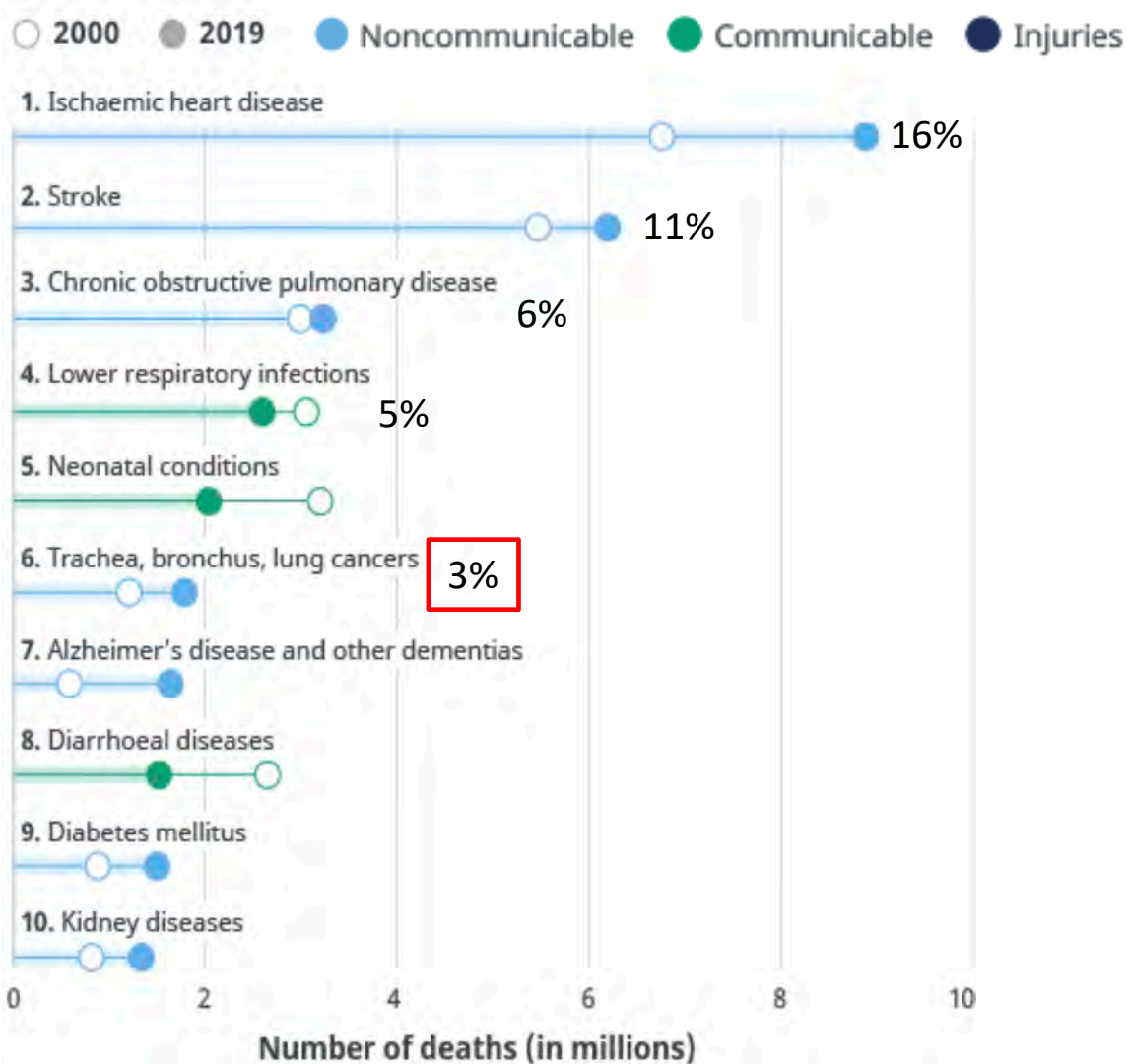
  Fearon K et al., Lancet Oncol. 2011: PMID: 21296615

- Cancer cachexia in adult patients, 2021

  Arends J et al., ESMO open. 2021: PMID: 34144781

- ESPEN guideline: Clinical Nutrition in cancer, 2021

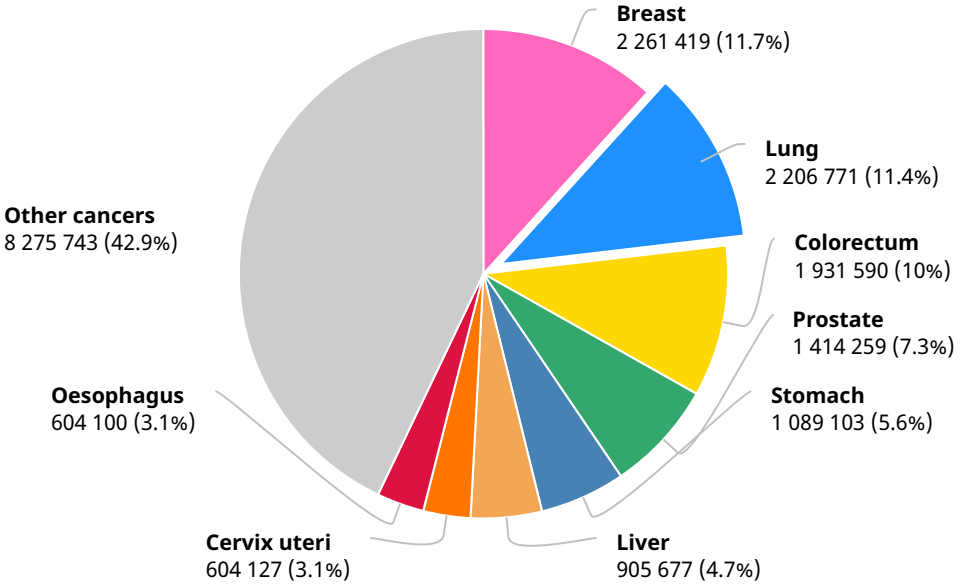
  Muscaritoli M et al., Clin Nutr. 2021: PMID: 33946039



WHO Global Health Estimates, 2020

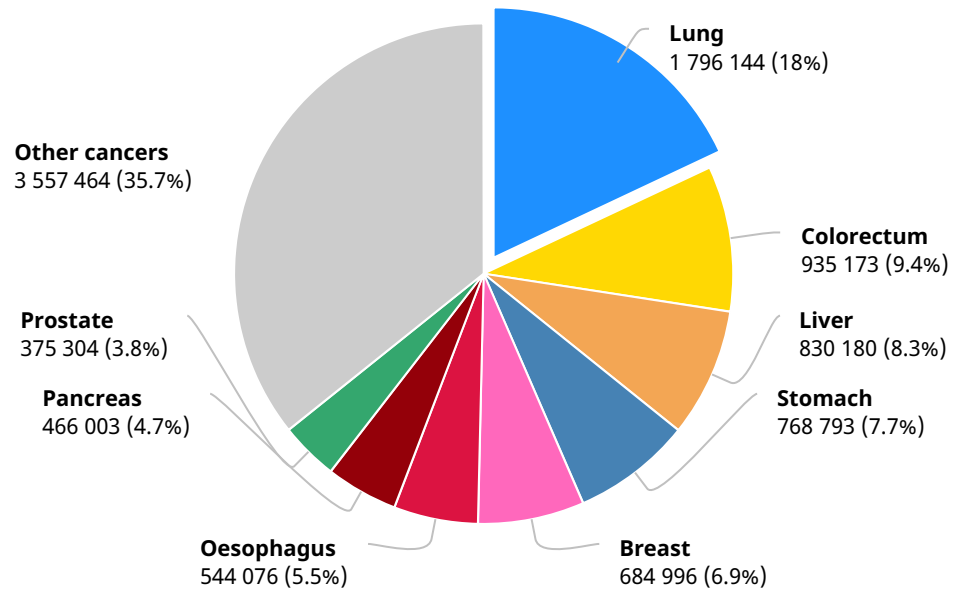
Worldwide cases in 2020

New cases



Total: 19 292 789 cases

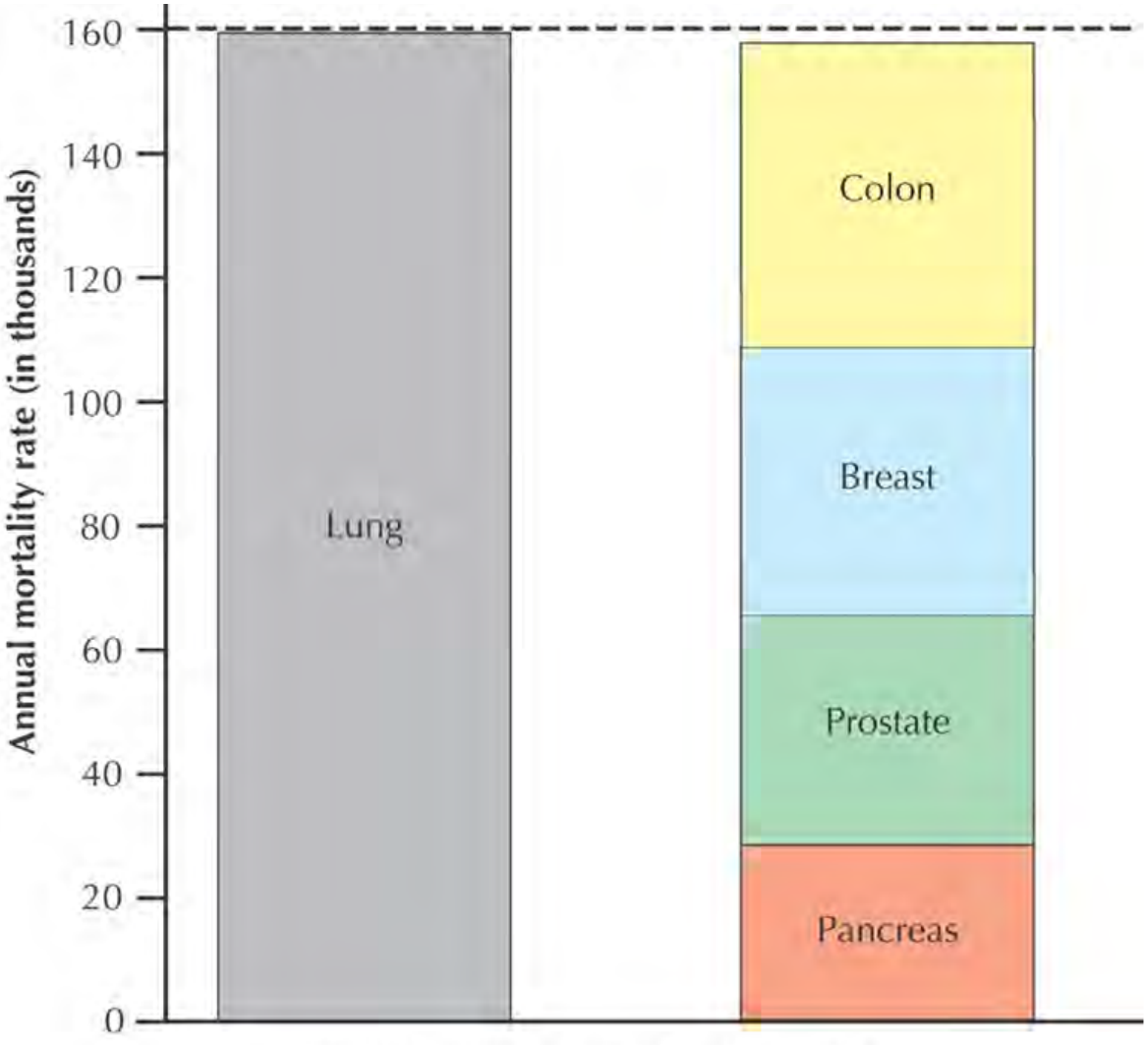
Deaths



Total: 9 958 133 deaths

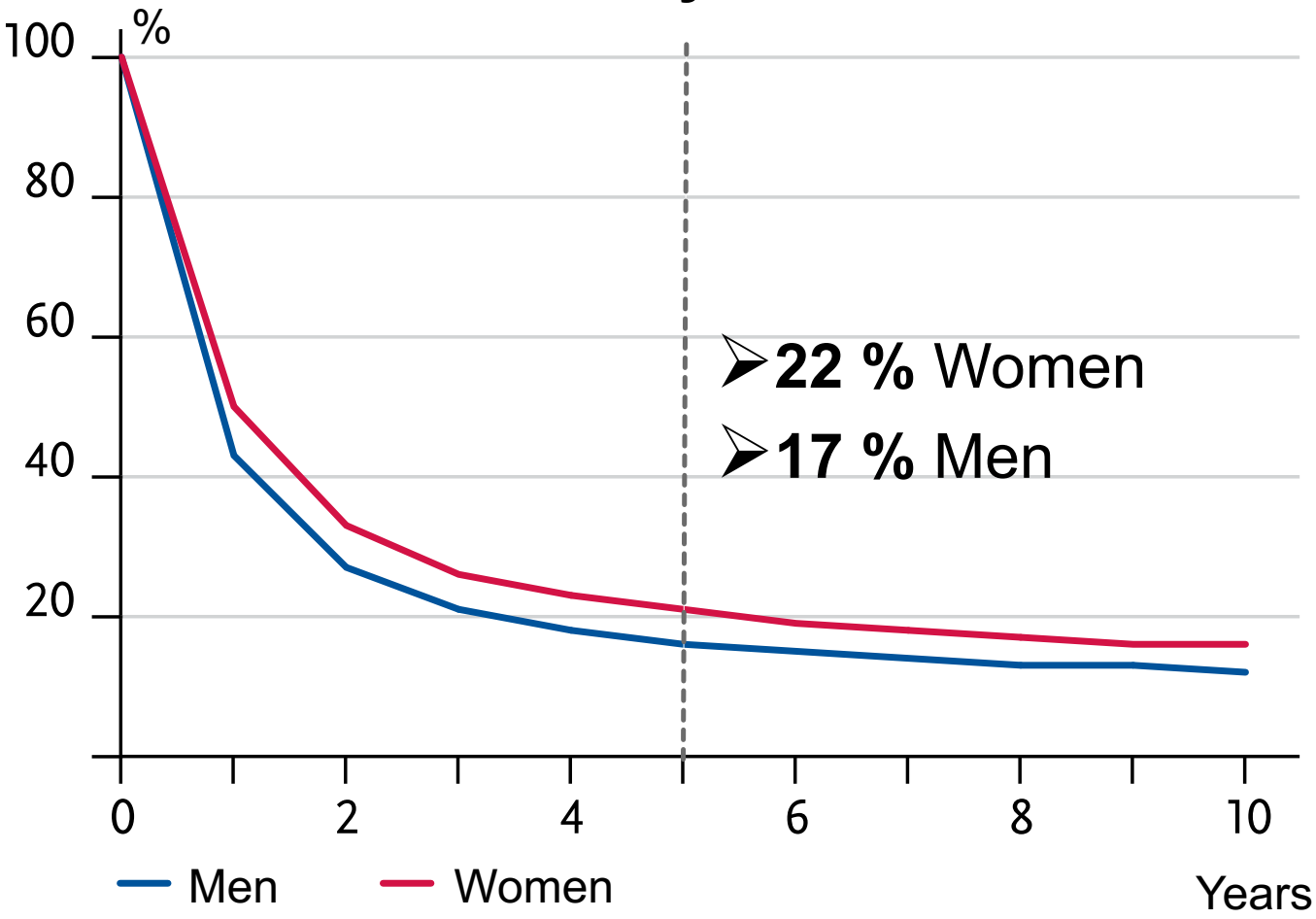
Sung H et al. Global cancer statistics 2020: GLOBOCAN. CA Cancer J Clin 2021

Annual death rate in the US



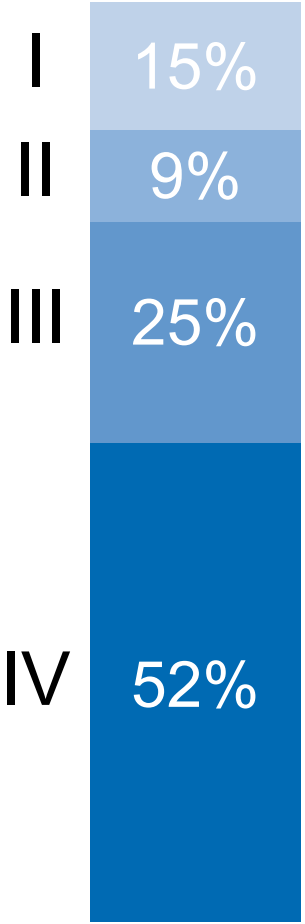
Netter, Netter's Internal Medicine, 2008.

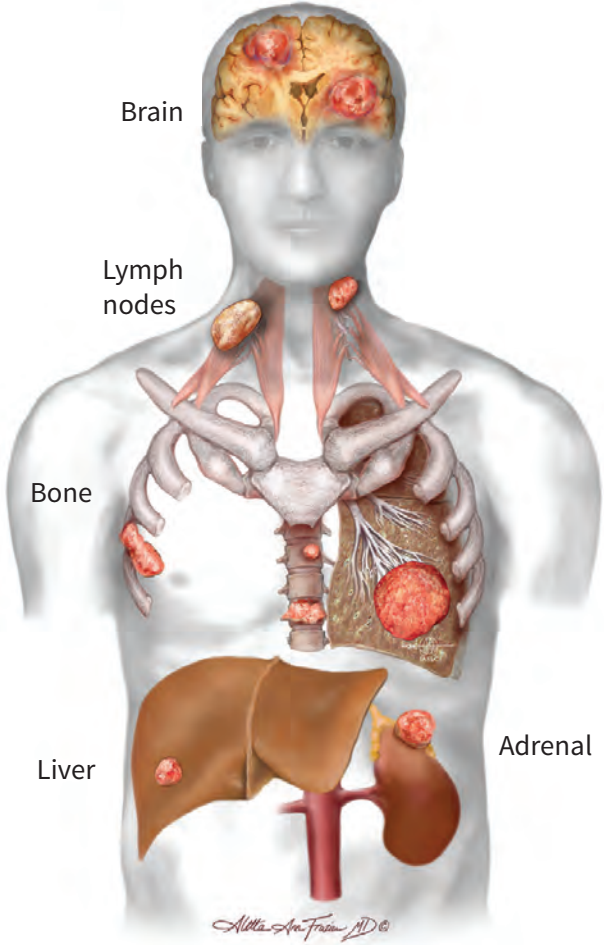
Low relative 5-year survival



Krebs in Deutschland 2017/2018, RKI 2021

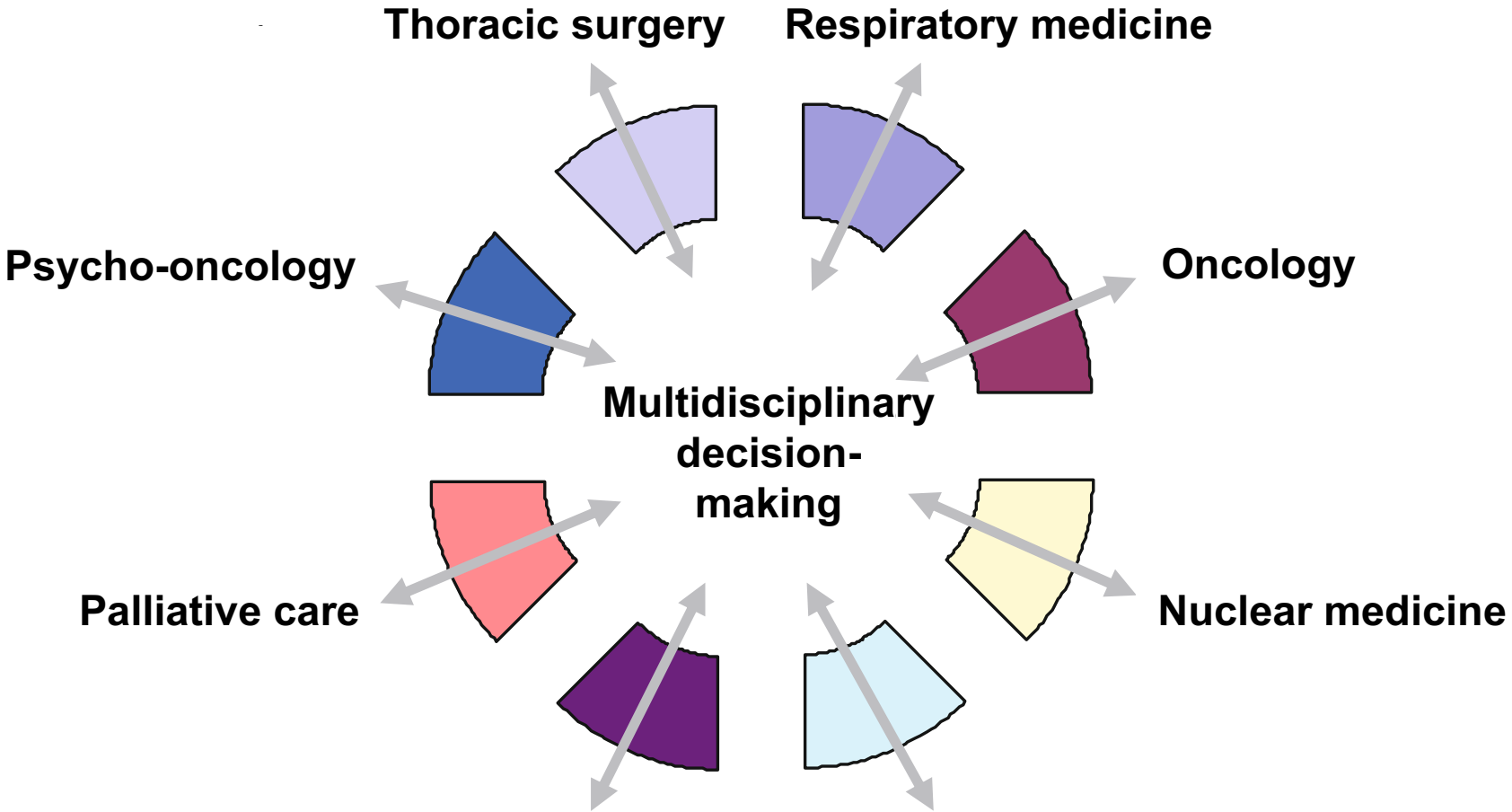
Tumour stage distribution





Krebs in Deutschland 2017/2018, RKI 2021; **Rami-Porta R** et al, Staging Manual in Thoracic Oncology, IASLC, 2016.

Multidisciplinary team discussion



Hardavella G, Frille A et al., Breathe, 2020

- **65-yo female patient, stage IV lung cancer**

- Loss of appetite, bloated

- Height 1,68 m, weight 50 kg, BMI 17,7 kg/m^2

- Weight loss (6 months):

  -10 kg (ca. 16%)

  (60 kg → 50 kg)

- Laboratory workup:

  CRP 20 mg/L (<5 mg/L),

  Albumin 35 g/L (>30 g/L),

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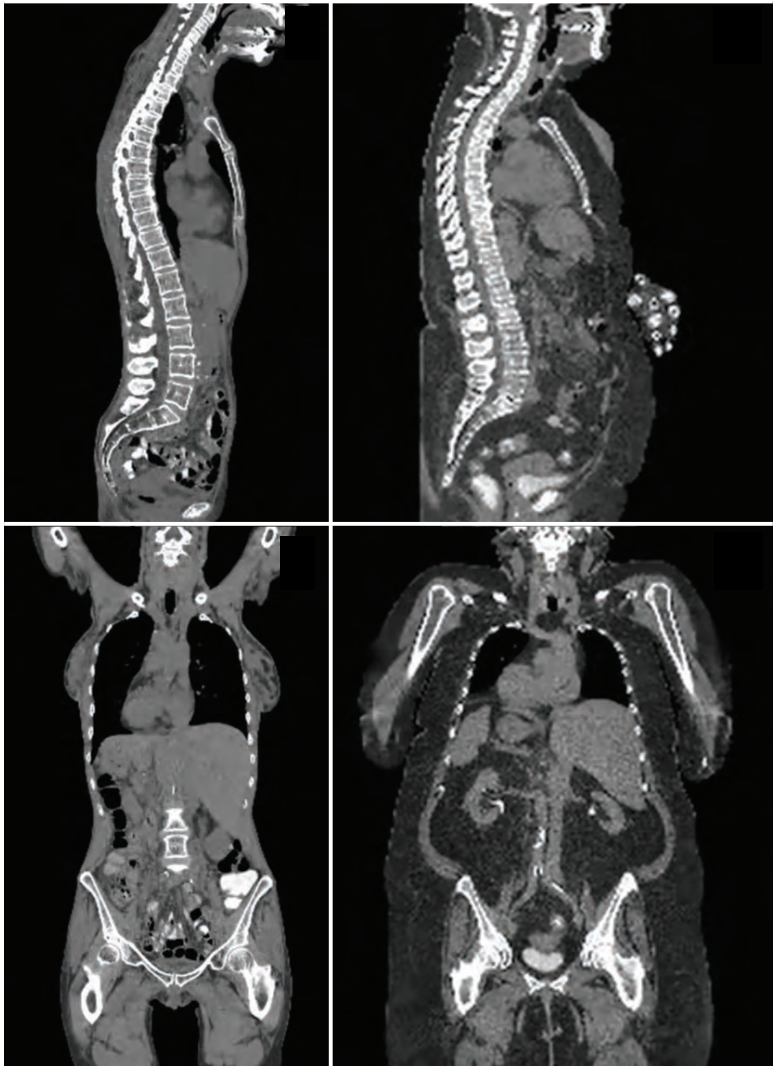
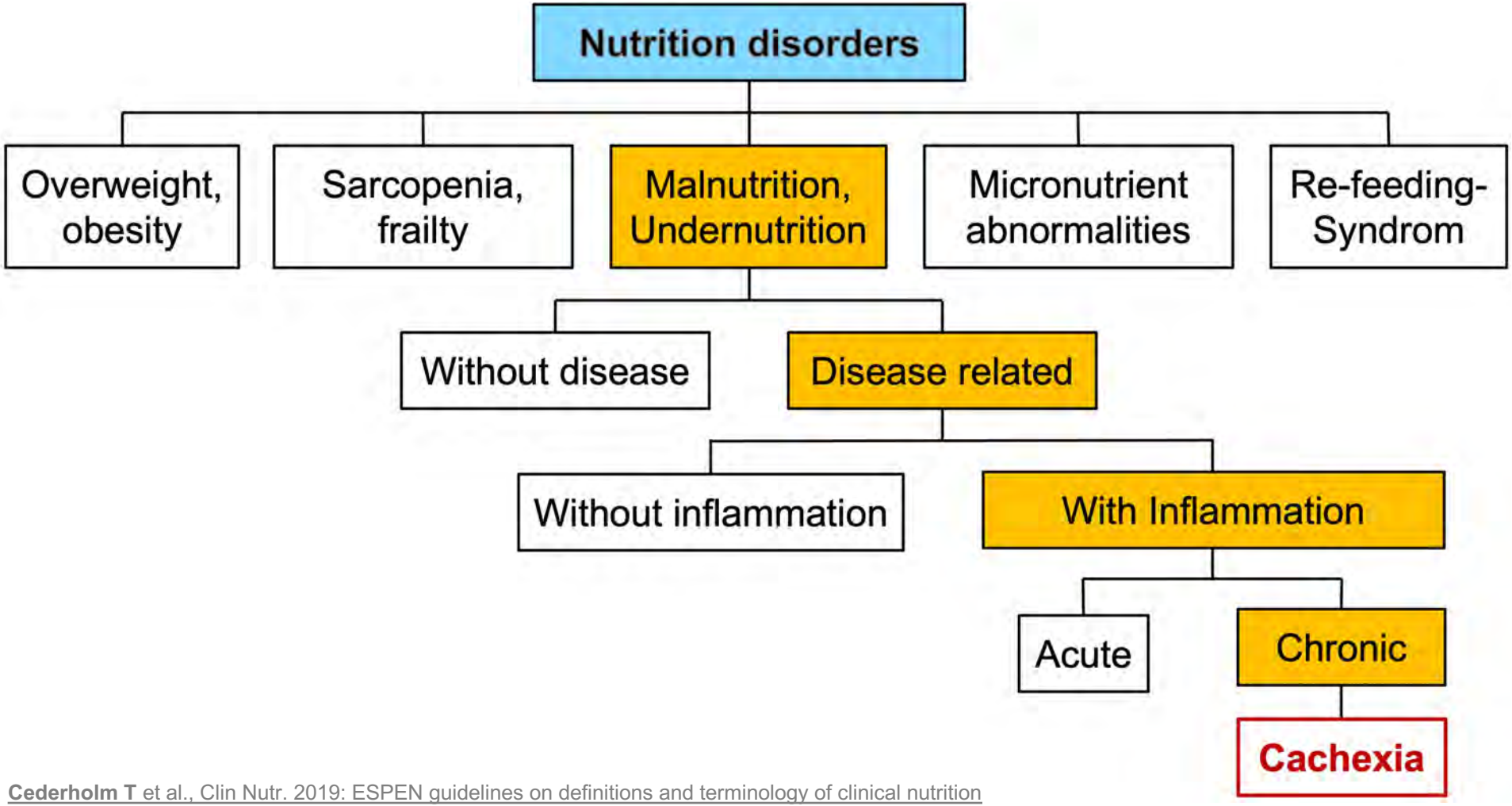


- **60-yo female patient, stage IV lung cancer**
- neither appetite, nor energy, bedridden
- Height 1,65 m, weight 85 kg, BMI 31.2 kg/m^2
- Weight loss (6 months):
  -15 kg (ca. 15%)
  (100 kg → 85 kg)
- Laboratory workup:
  CRP 60 mg/L (<5 mg/L),
  Albumin 25 g/L (>30 g/L),

Definitions



Cederholm T et al., Clin Nutr. 2019: ESPEN guidelines on definitions and terminology of clinical nutrition

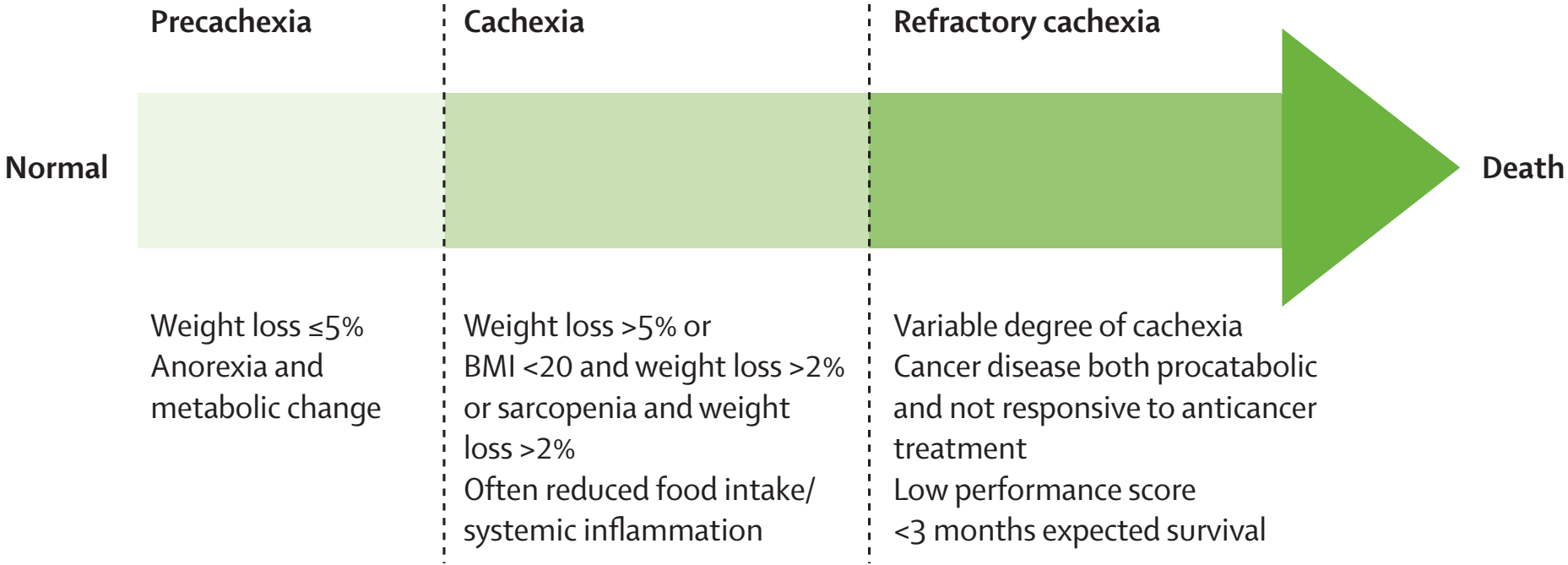
Cachexia – „bad condition“

- Multifactorial syndrome, **chronic** disease-related **malnutrition** with **inflammation**
- Ongoing and unintended loss of skeletal muscle mass (± loss of fat mass)
- That cannot be fully reversed by conventional nutritional support

- Progressive functional impairment (↓ mobility)
- Can be aggravated by tumor therapy
- ↓ quality of life
- ↑ mortality

Fearon K et al, Lancet Oncol, 2011, Muscaritoli M et al., Clinical Nutrition, 2023

Cachexia – consensus criteria

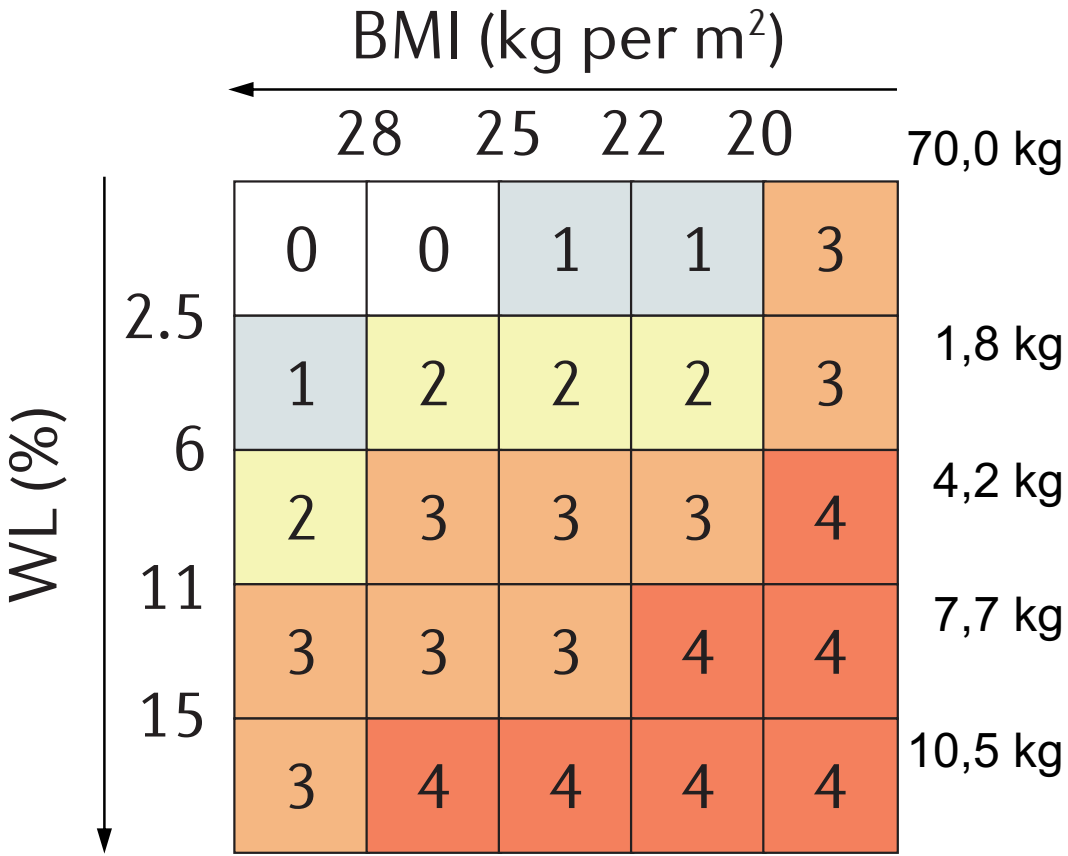


Fearon K et al, Lancet Oncol 2011

BMI – weight loss – survival – correlation

Martin L et al., Journal of Clinical Oncology, 2015.

BMI – weight loss – survival – correlation



Martin L et al., Journal of Clinical Oncology, 2015.

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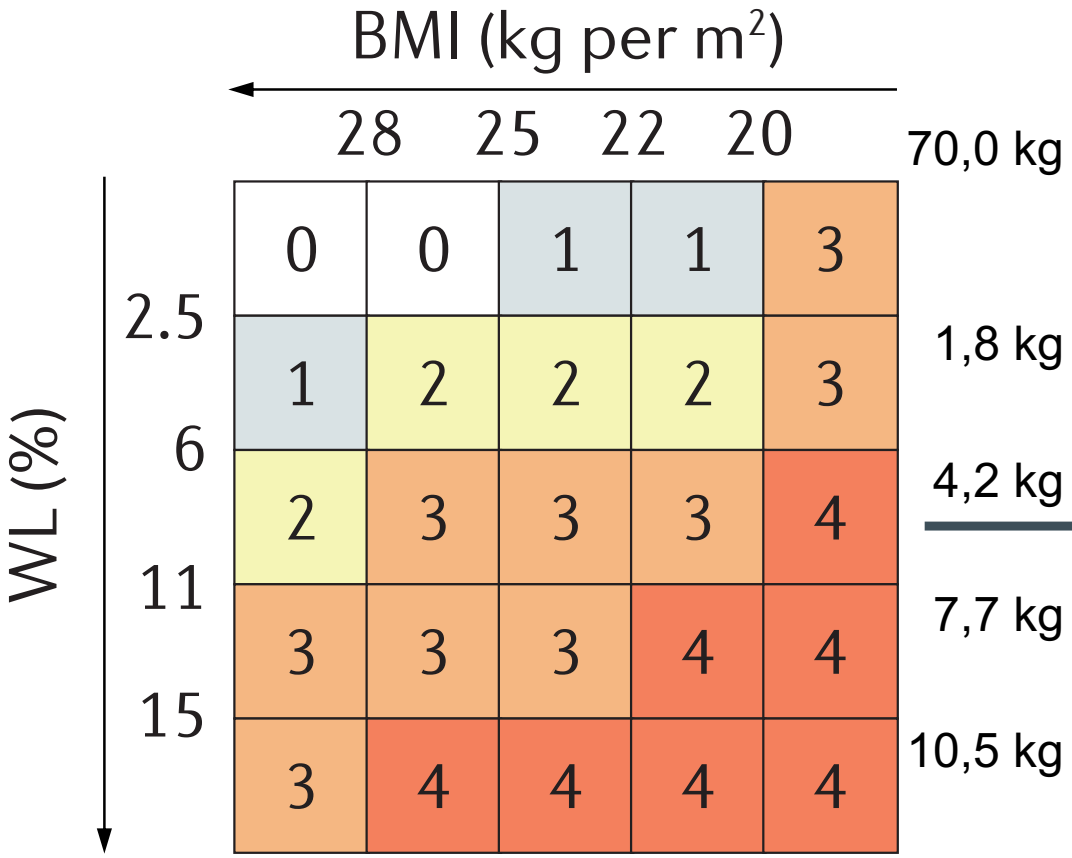
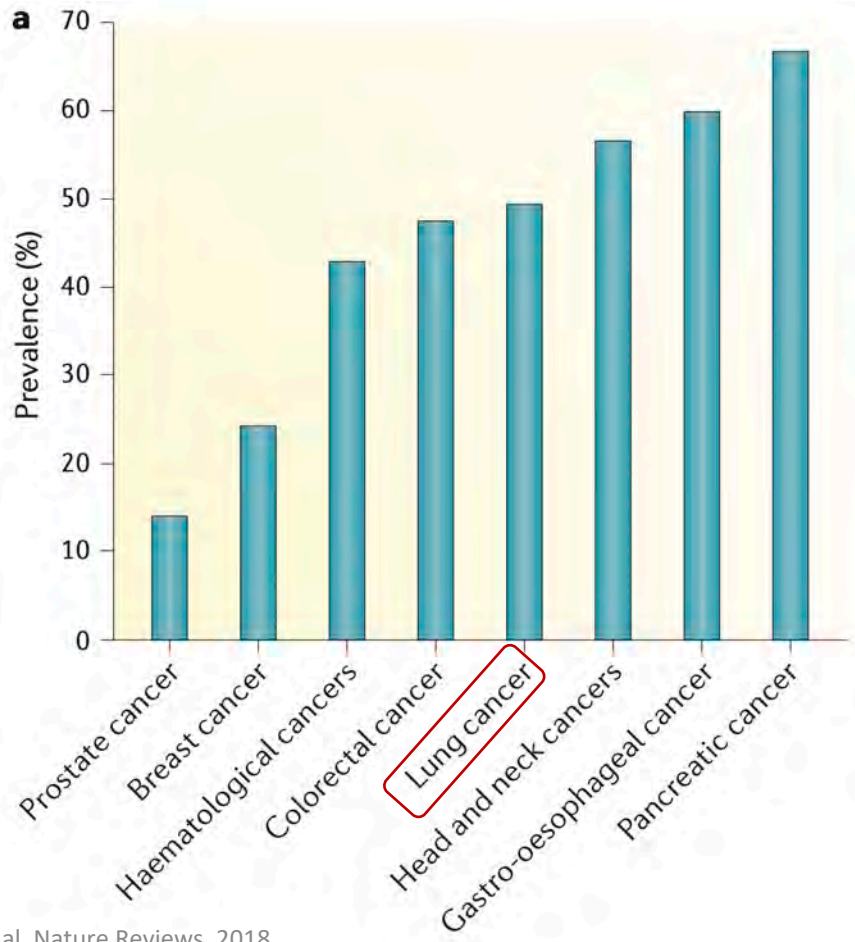
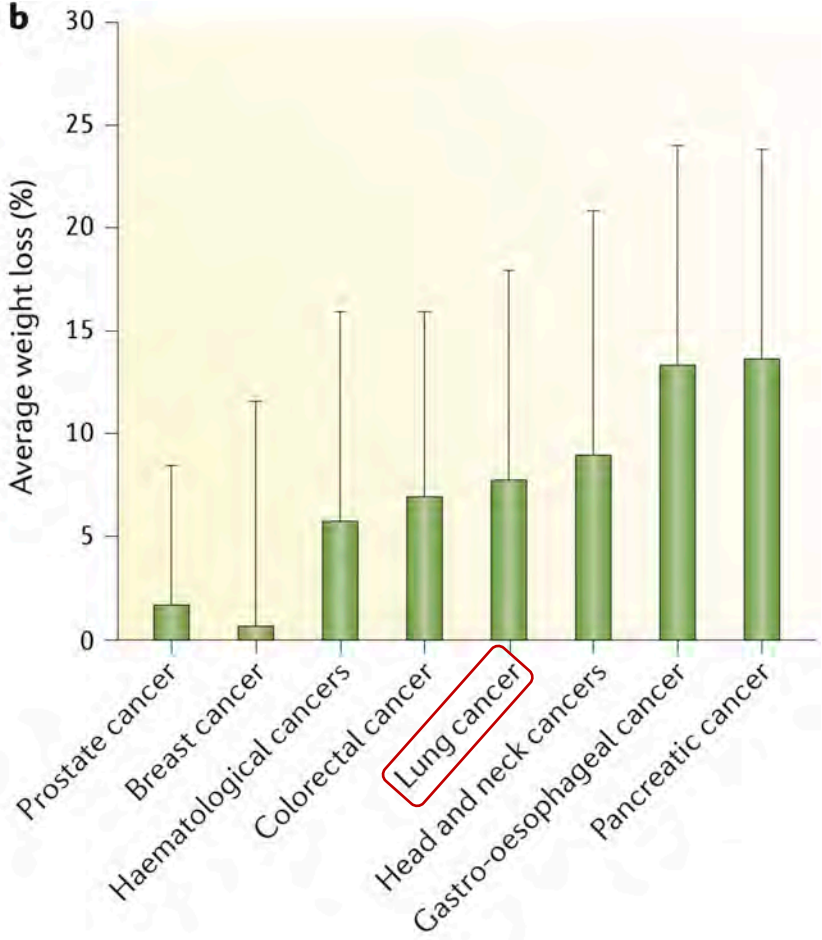


BMI–WL grade	Median survival (months)
0	20.9
1	14.6
2	10.8
3	7.6
4	4.3

Martin L et al., Journal of Clinical Oncology, 2015.

Prevalence of weight loss in cancer patients

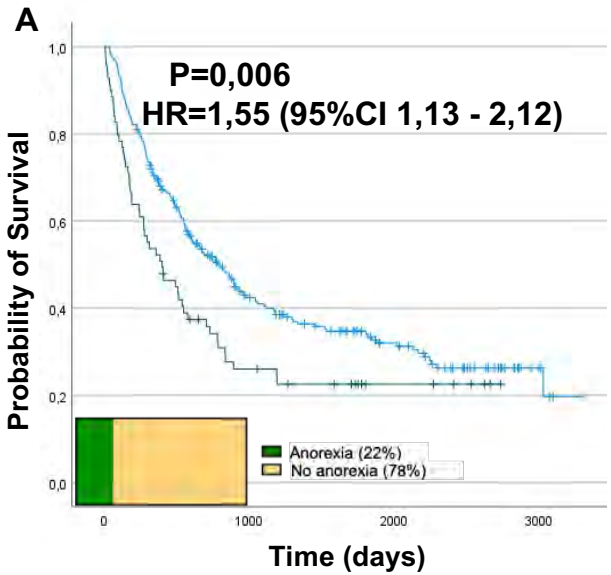




Baracos VE et al, Nature Reviews, 2018

Patients with lung cancer in Leipzig

Anorexia



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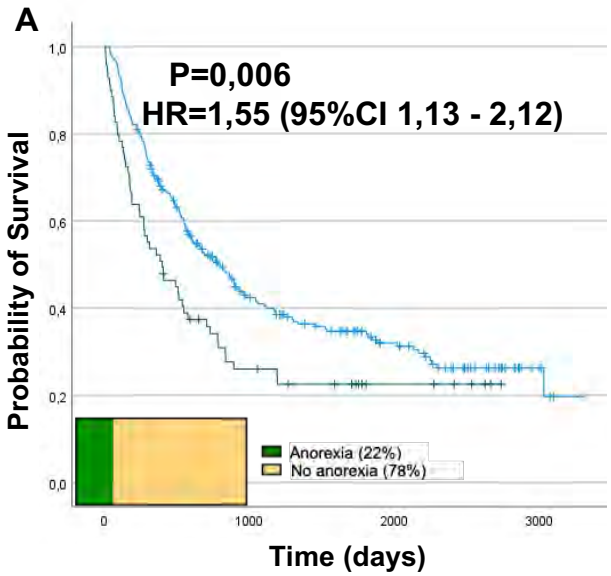
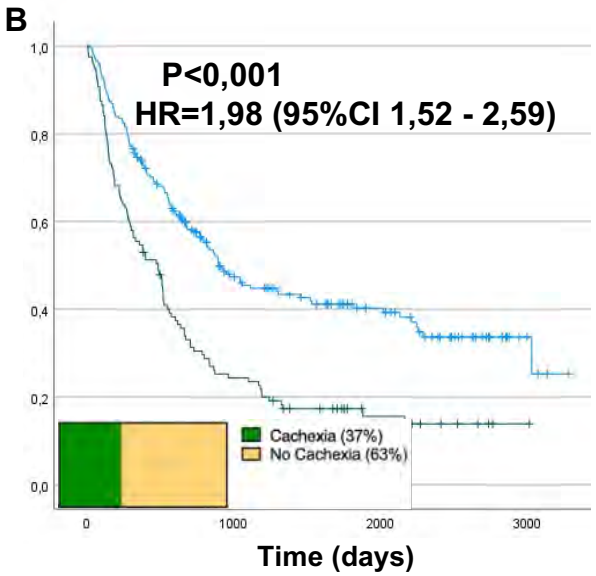


Cachexia



Median OS:

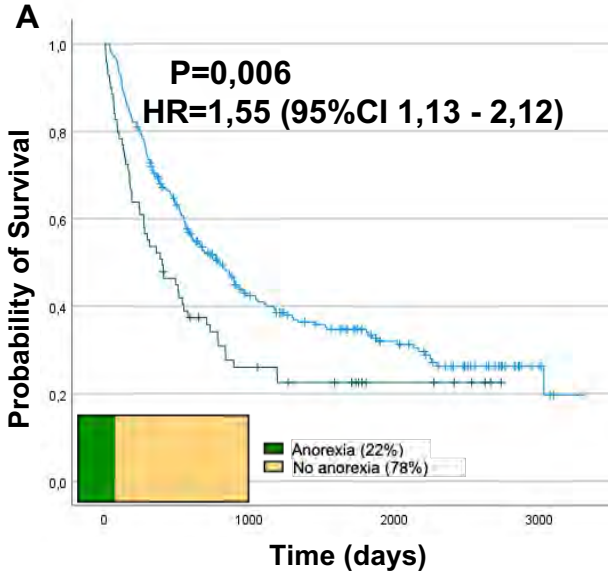
No: **898 days**

Yes: **486 days**

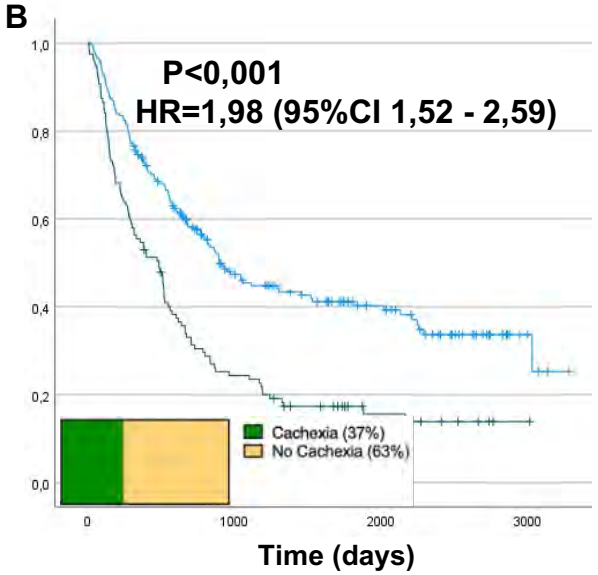
Frille A et al., DGP 2022, in preparation

Patients with lung cancer in Leipzig

Anorexia



Cachexia



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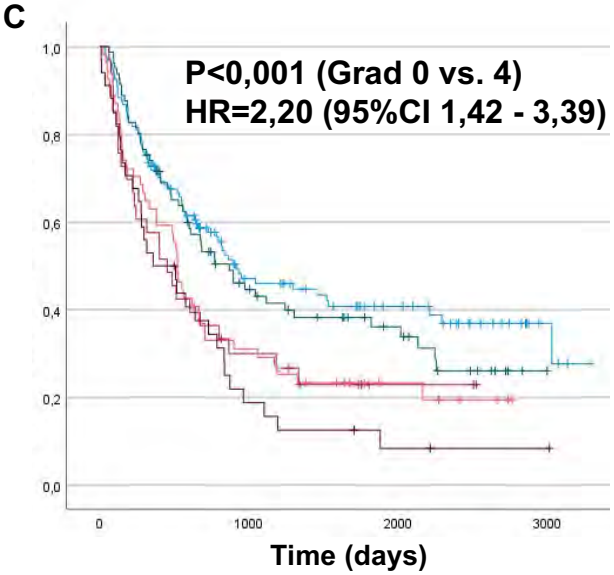
BMI-WL



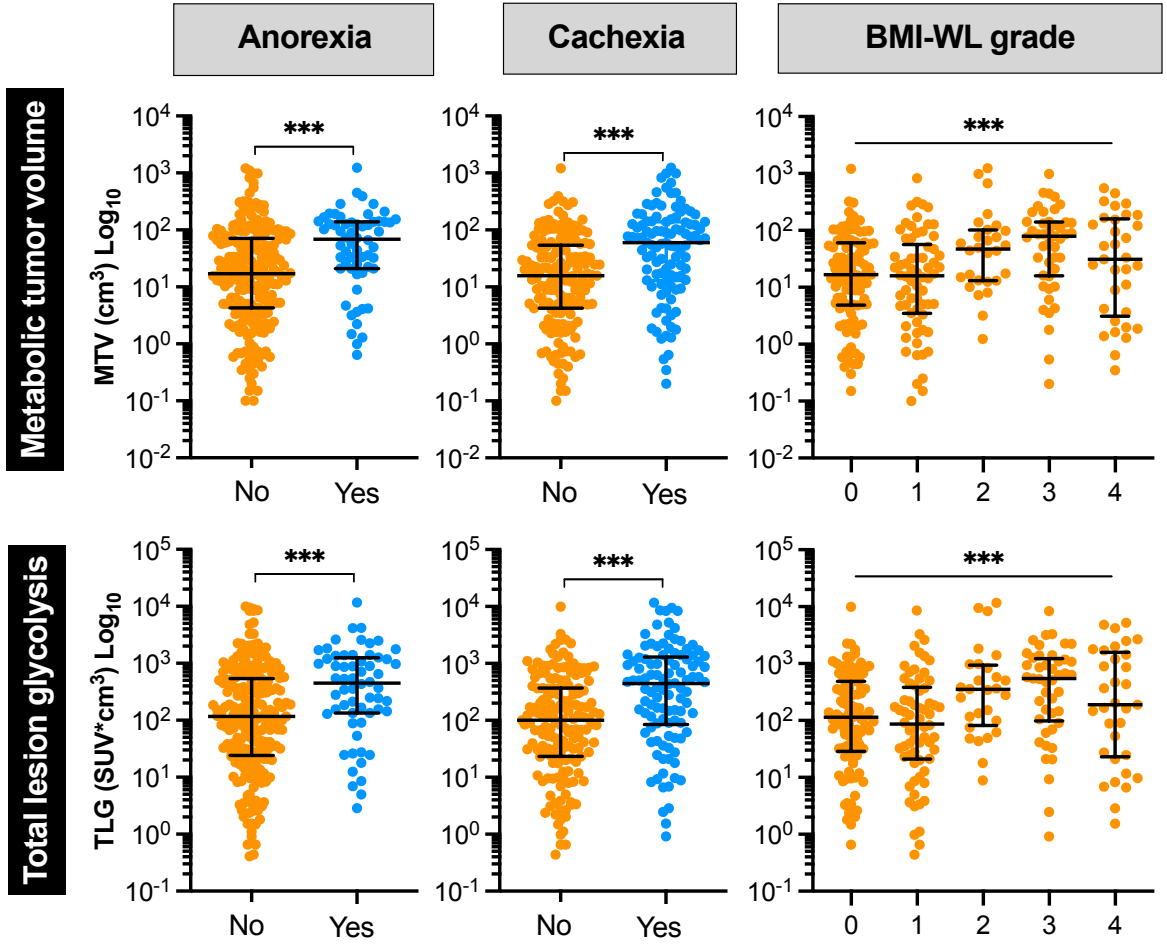
Median OS:

Grade 0: **915 days**

Grade 4: **358 days**

Frille A et al., in preparation

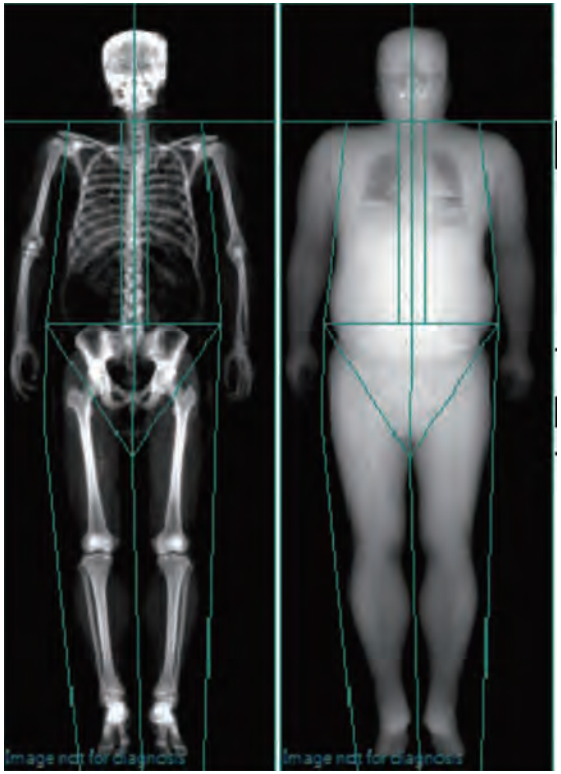
Metabolic characteristics of patients with lung cancer



Frille A et al., in preparation

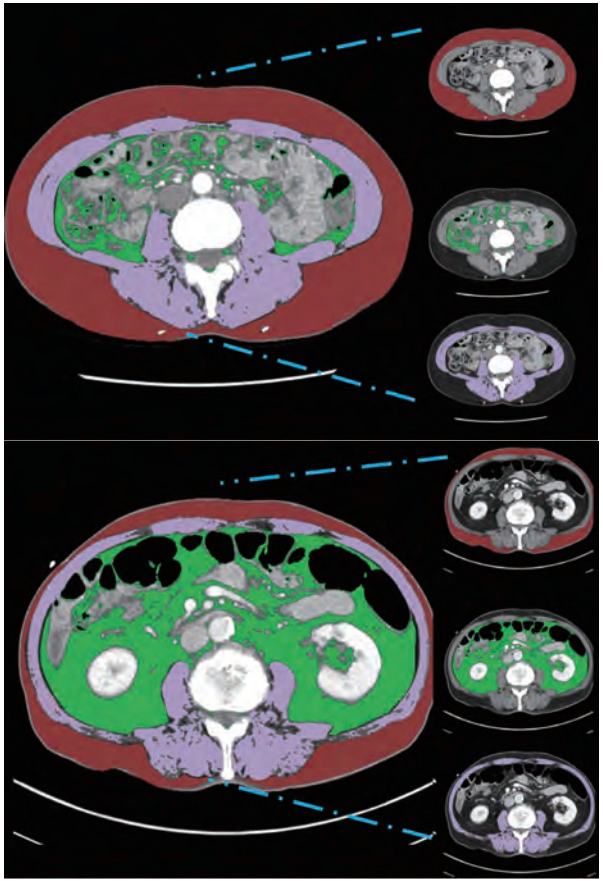
Body composition modalities

DXA



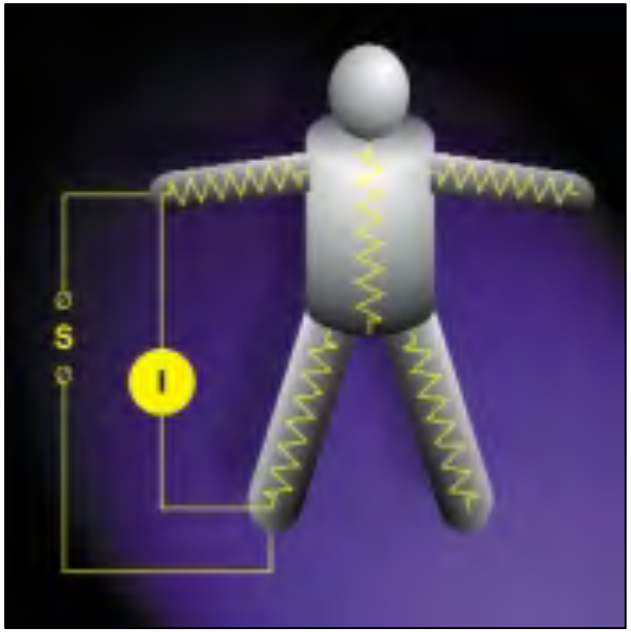
Lee K et al., The Korean Society of Radiology, 2019

CT



Skeletal muscle Visceral fat Subcutaneous fat

BIA

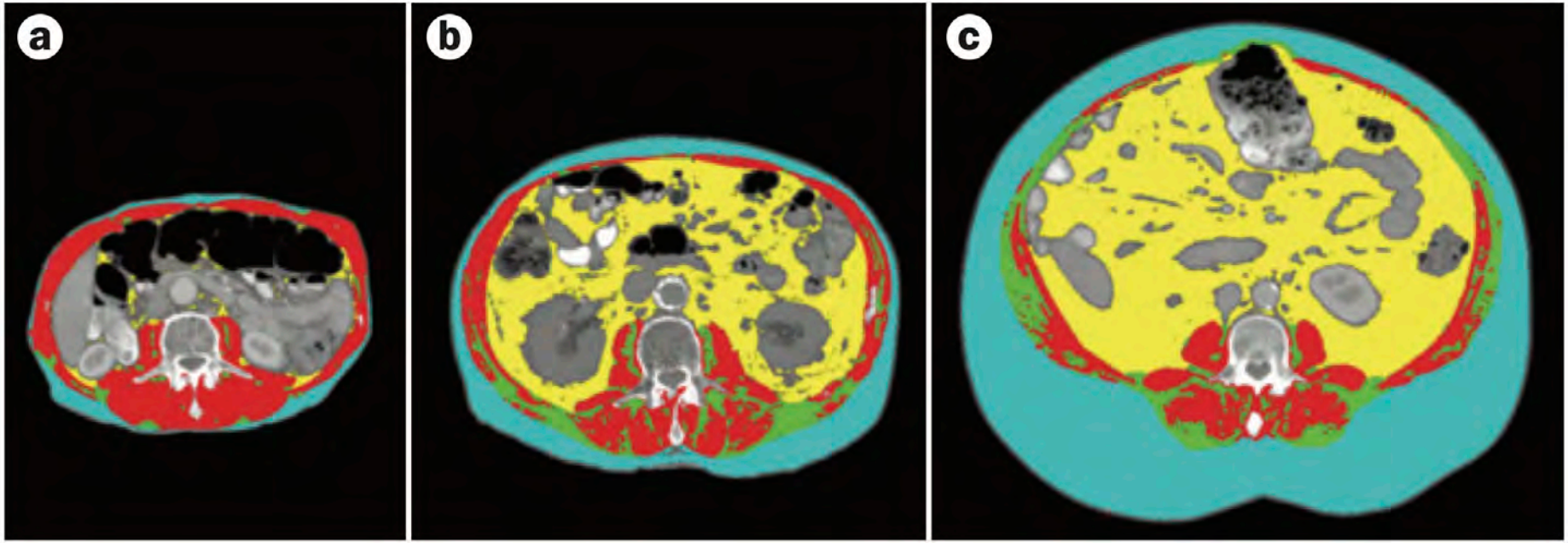


Data Input GmbH, Das B.I.A. – Kompendium, 2002

Body composition

CT

BMI 17 kg/m^2 | BMI 25 kg/m^2 | BMI 38 kg/m^2



- Total skeletal muscle (parapinal, psoas, transverse/oblique abdominus, rectus abdominus)
- Visceral adipose tissue
- Subcutaneal adipose tissue
- Intermuscular adipose tissue

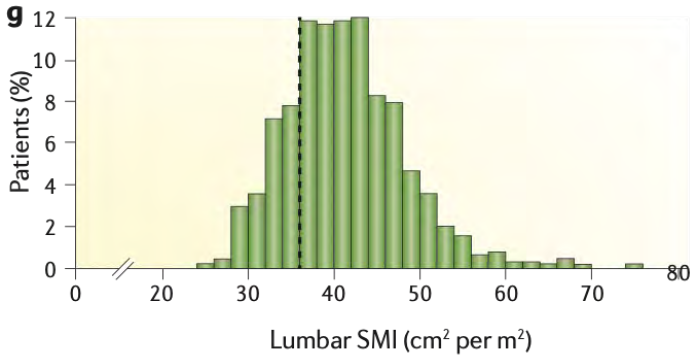
Fearon K et al., Nat. Rev. Clin. Oncol., 2012

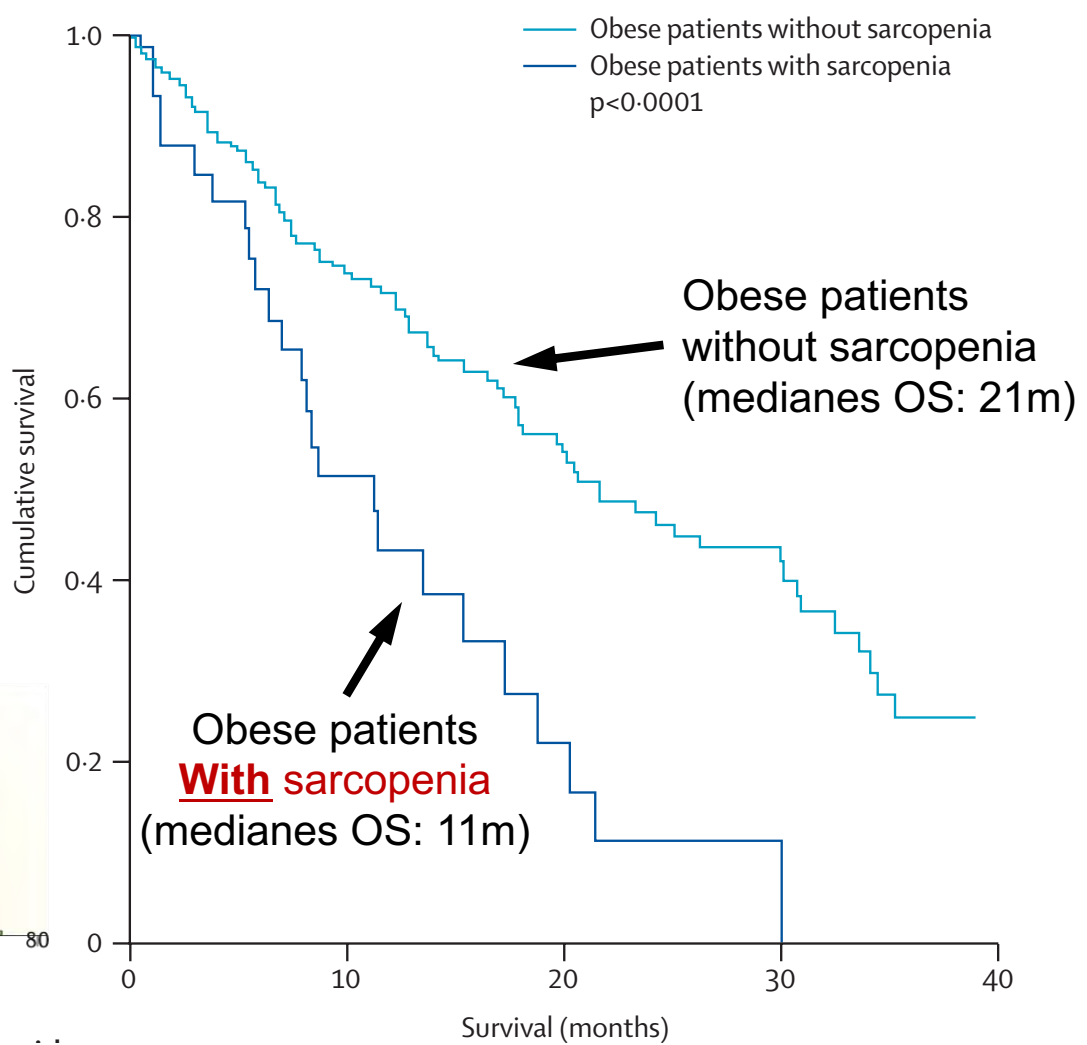
Body composition

Sarcopene obesity

Lumbar SMI cutoffs

Men	52.4 cm^2/m^2
Women	38.5 cm^2/m^2

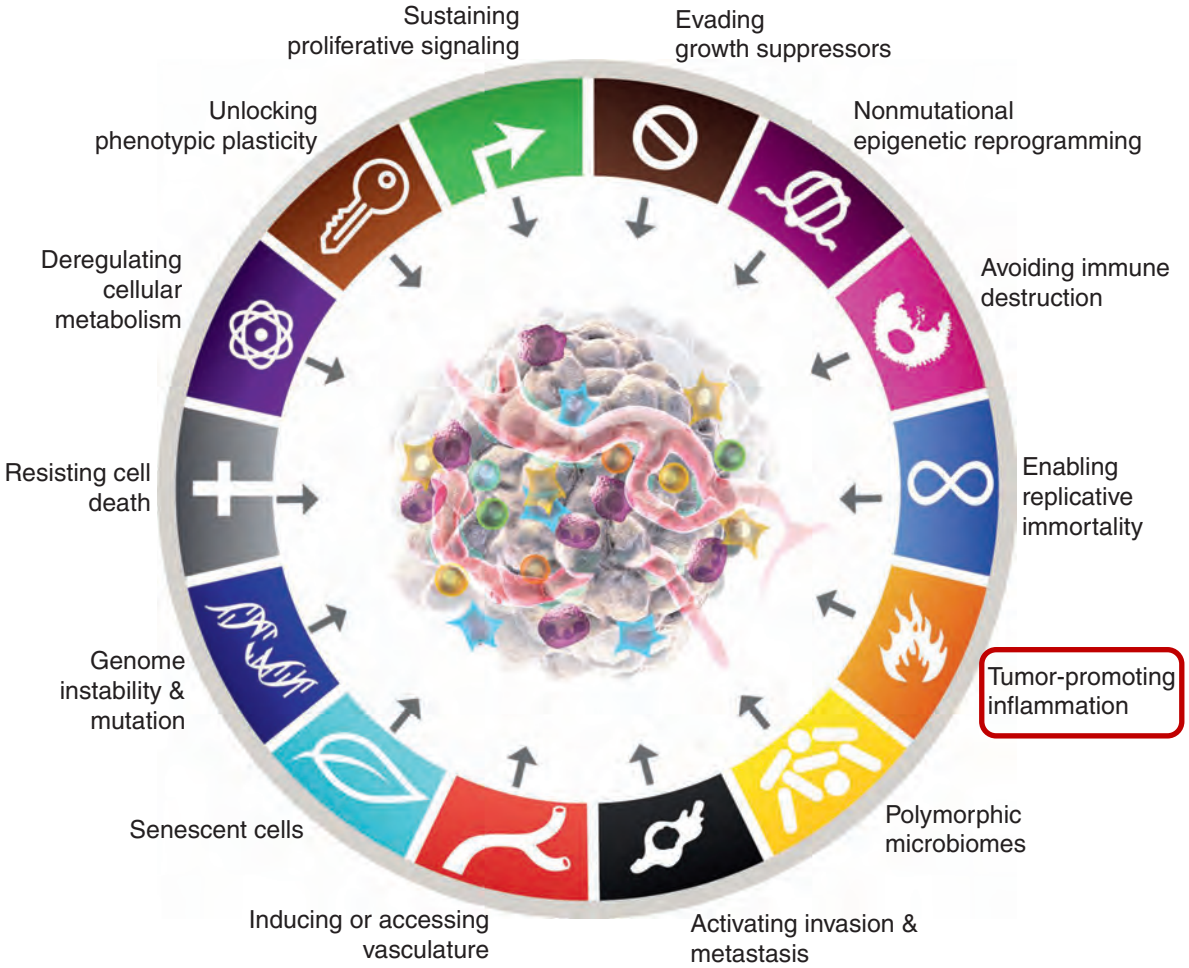




Prado CMM et al, Lancet Oncol, 2008

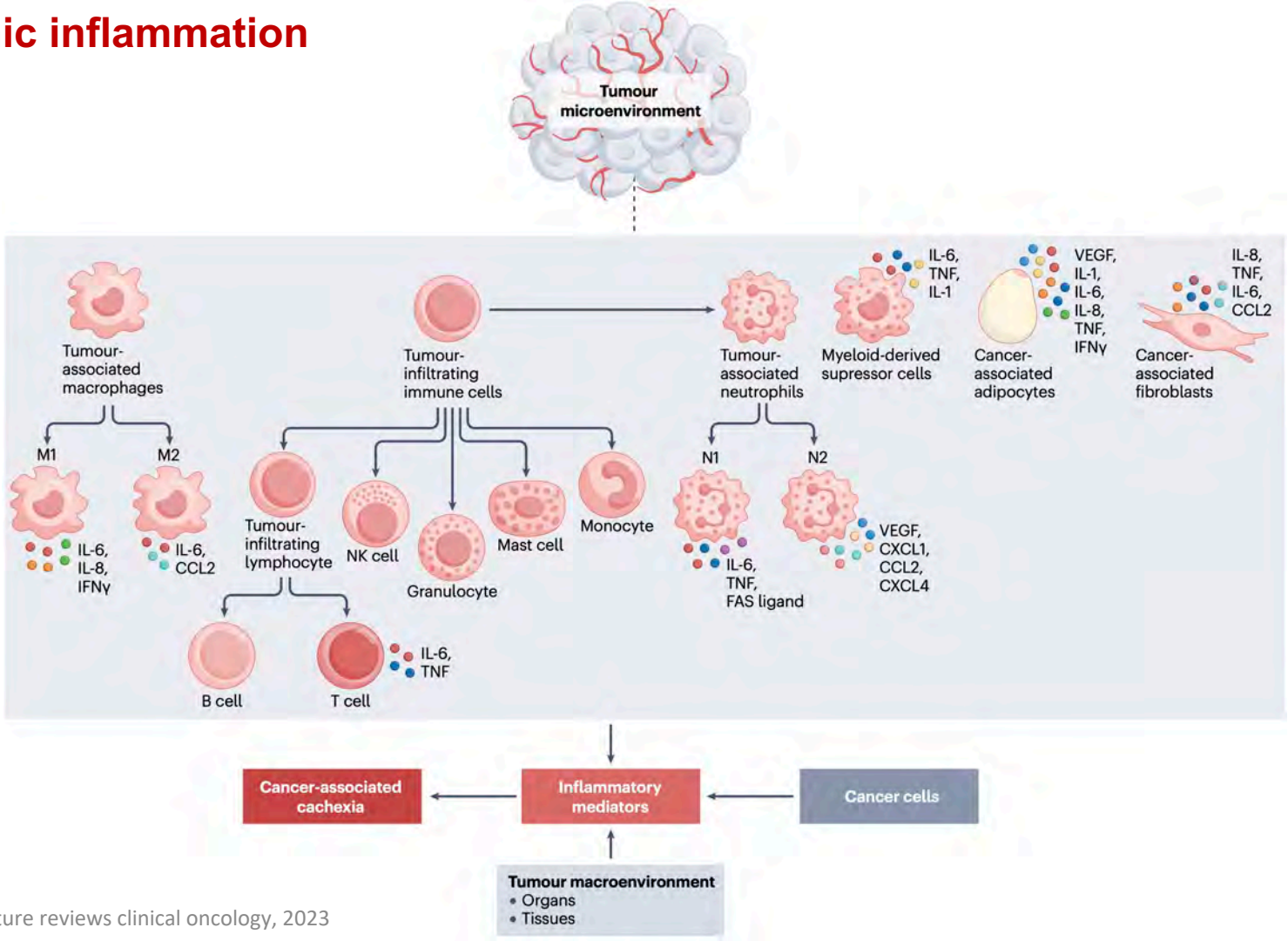
Systemic inflammation – a hallmark of cancer

Systemic inflammation – a hallmark of cancer



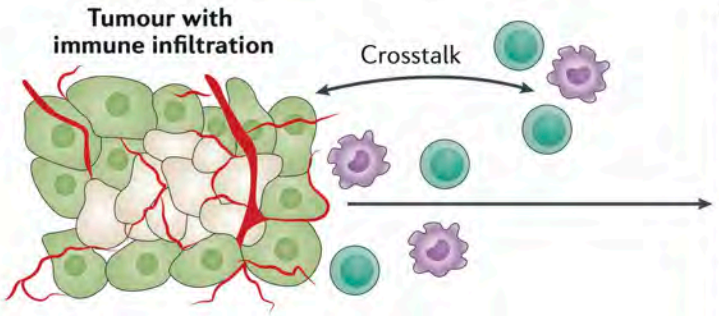
Hanahan D et al, CANCER DISCOVERY, 2022; **Hanahan D & Weinberg RA**, Cell, 2011

Systemic inflammation



Argilés JM et al, nature reviews clinical oncology, 2023

Systemic inflammation



Tumour-derived catabolic factors

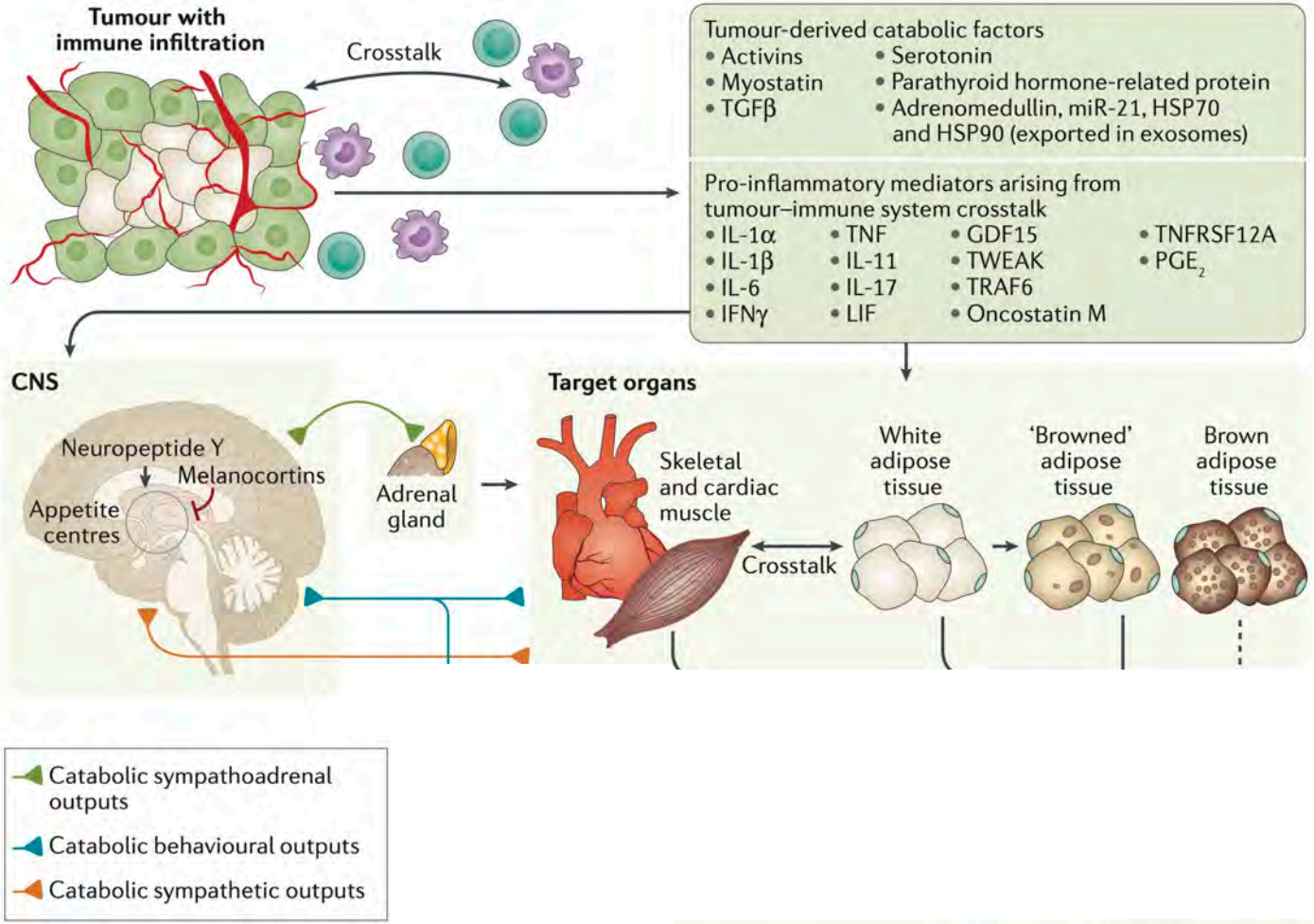
- Activins
- Myostatin
- TGFβ
- Serotonin
- Parathyroid hormone-related protein
- Adrenomedullin, miR-21, HSP70 and HSP90 (exported in exosomes)

Pro-inflammatory mediators arising from tumour–immune system crosstalk

- IL-1α
- IL-1β
- IL-6
- IFNγ
- TNF
- IL-11
- IL-17
- LIF
- GDF15
- TWEAK
- TRAF6
- Oncostatin M
- TNFRSF12A
- PGE_2

Baracos VE et al, Nature Reviews, 2018

Systemic inflammation



Baracos VE et al, Nature Reviews, 2018

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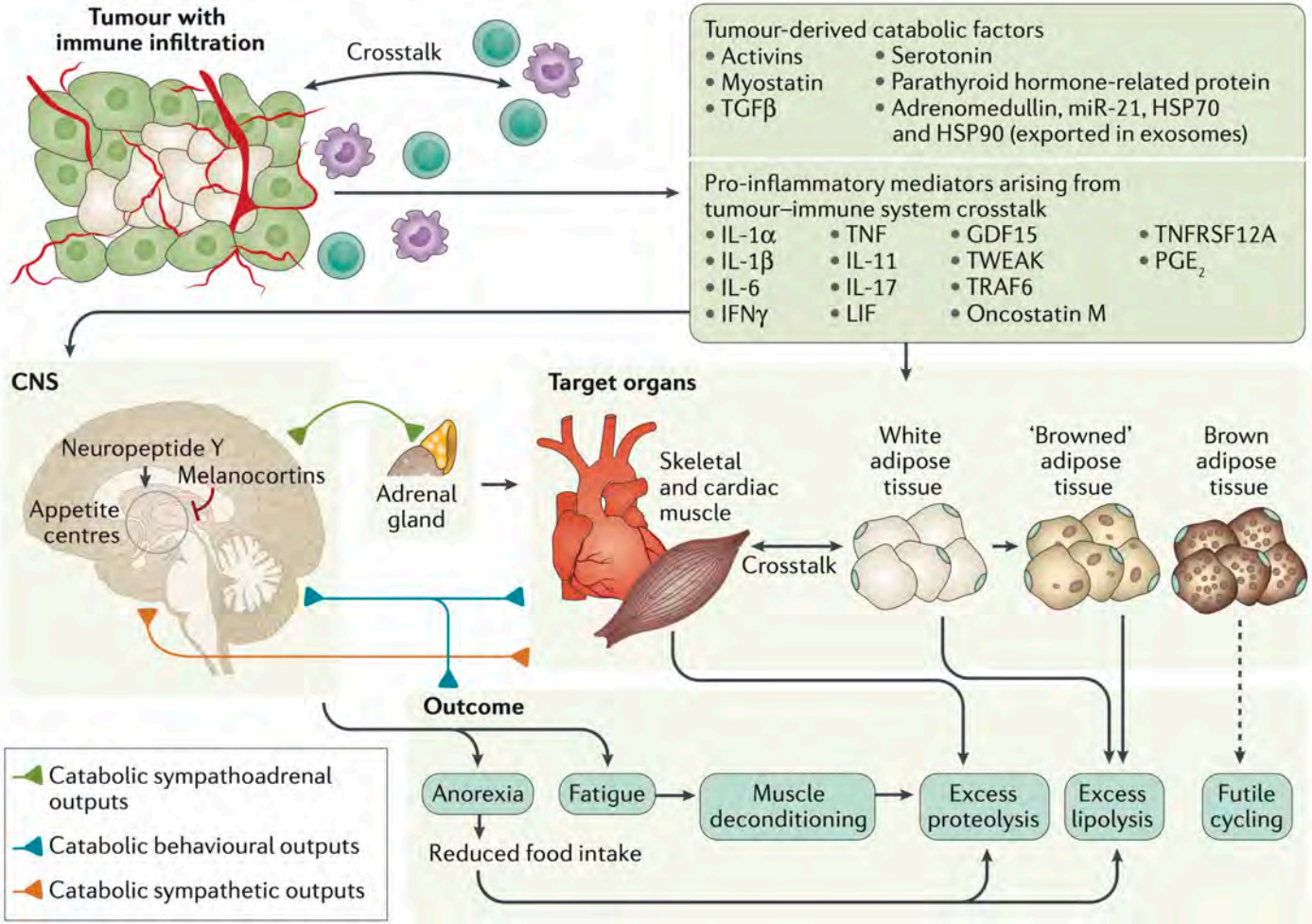
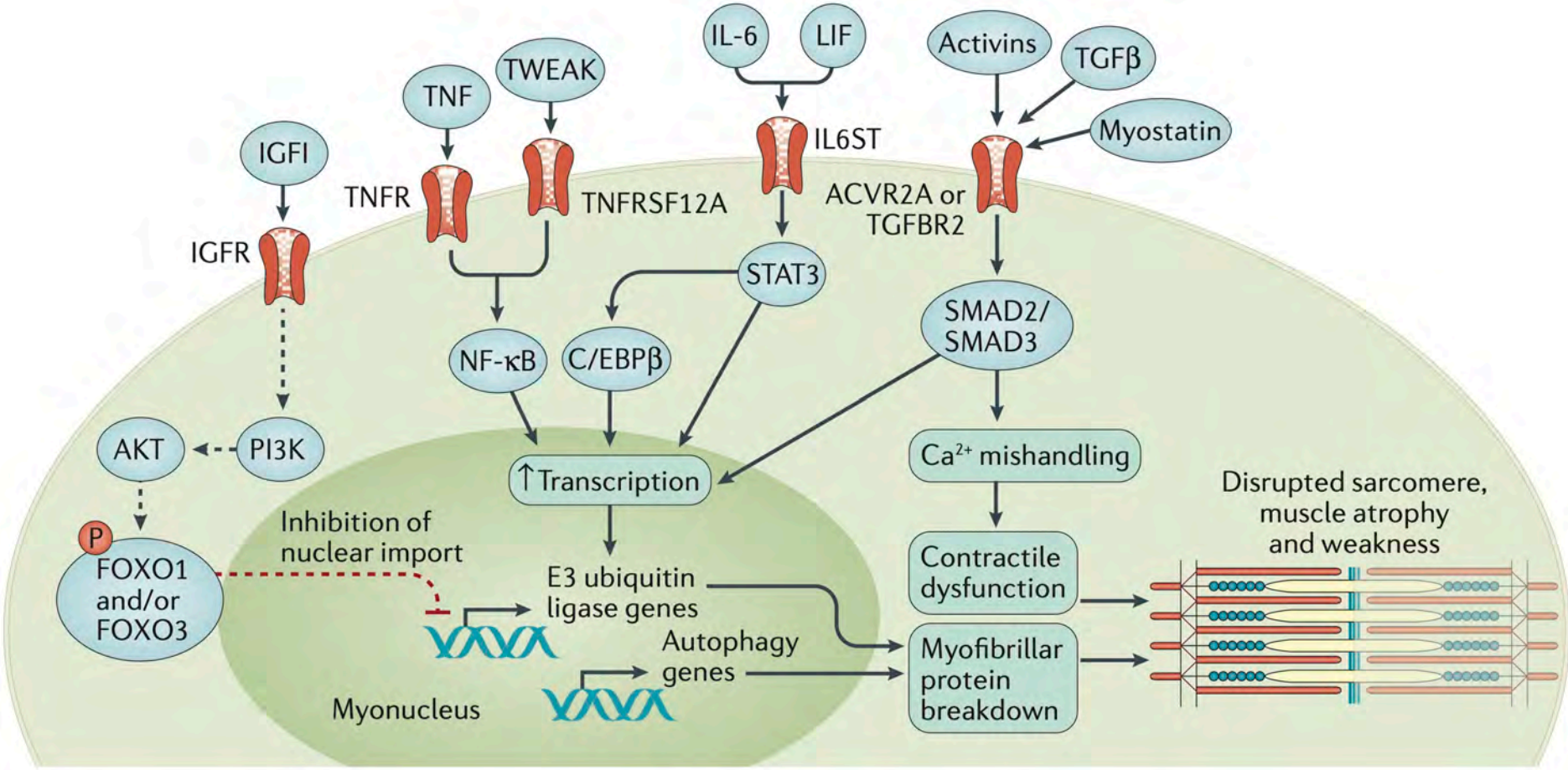


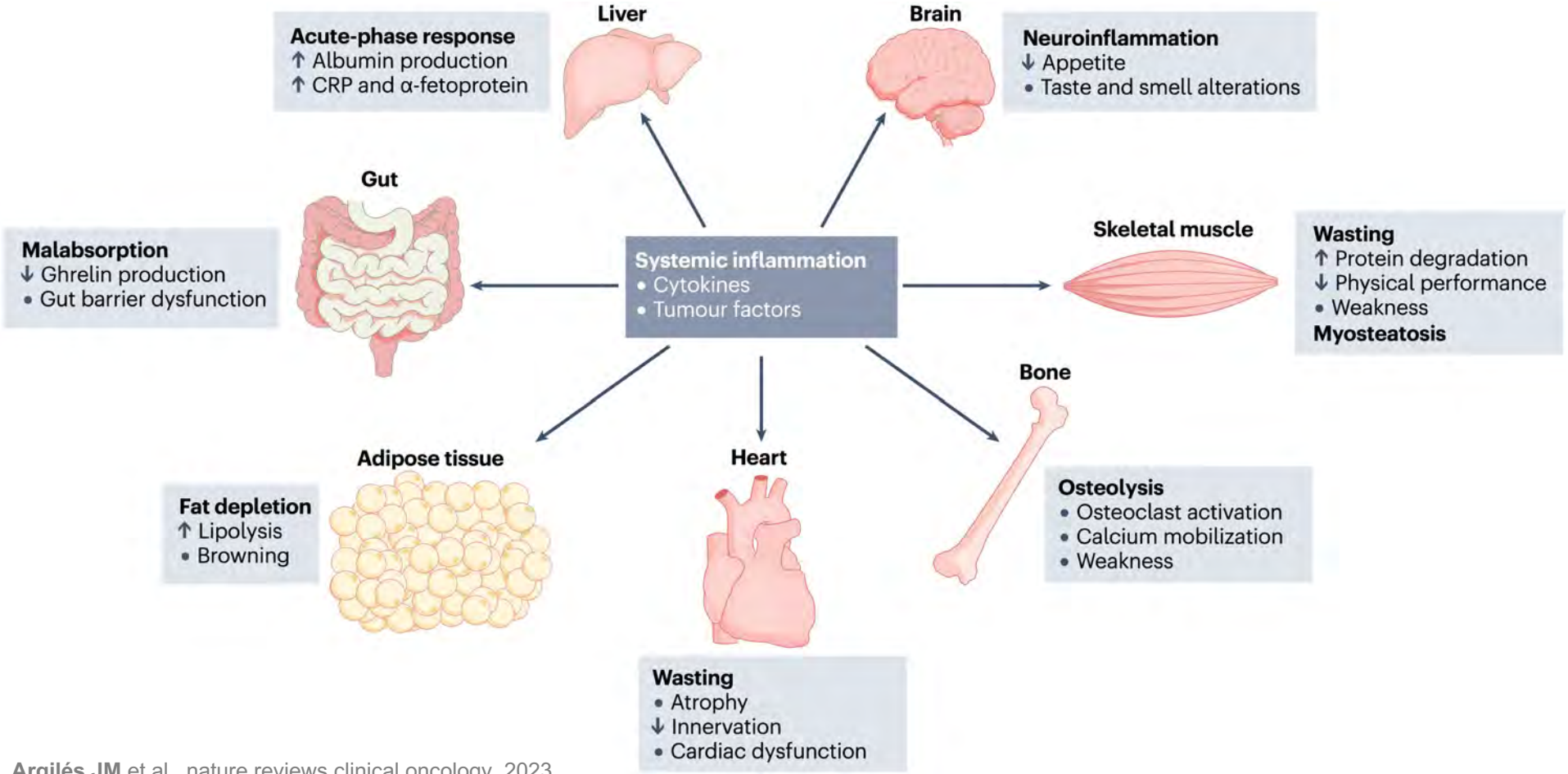
Baracos VE et al, Nature Reviews, 2018

Systemic inflammation



Baracos VE et al, Nature Reviews, 2018

Systemic inflammation - Tumour macroenvironment and cachexia



Argilés JM et al., nature reviews clinical oncology, 2023

Systemic inflammation

- IL-6, IL-1, CRP, TNFa
- Modified Glasgow Prognostic Score (mGPS)

Laird BJ et al., Clin Cancer Res, 2013

Systemic inflammation

- IL-6, IL-1, CRP, TNFa
- Modified Glasgow Prognostic Score (mGPS)

mGPS	CRP (mg/L)	albumin (g/L)
0	↓ ≤10	↑ ≥35
1	↑ >10	↑ ≥35
2	↑ >10	↓ <35

Laird BJ et al., Clin Cancer Res, 2013

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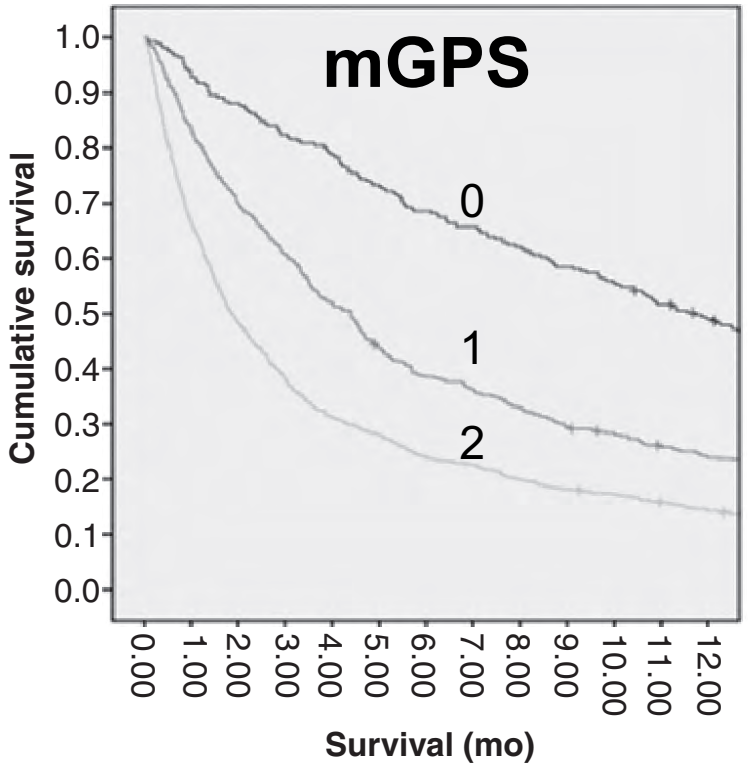
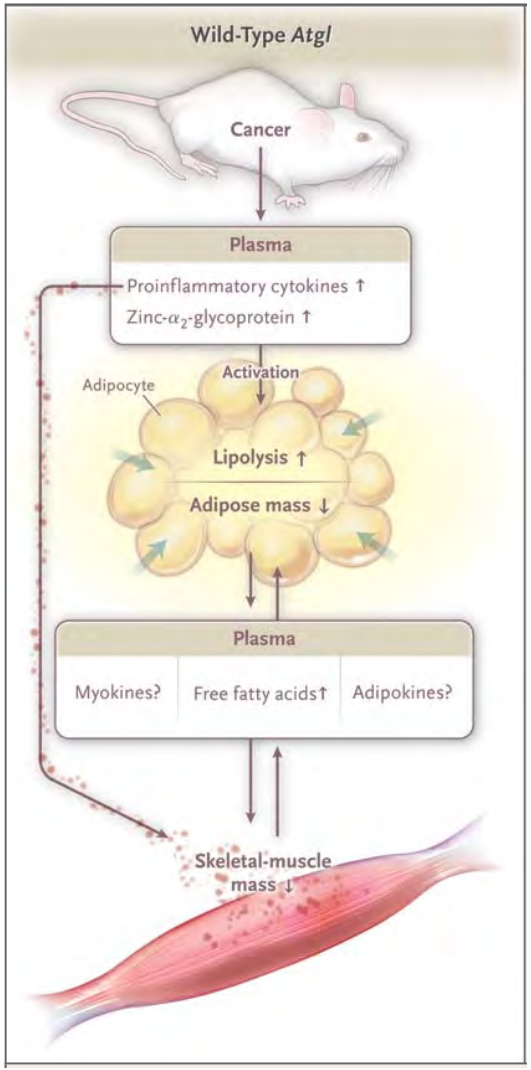


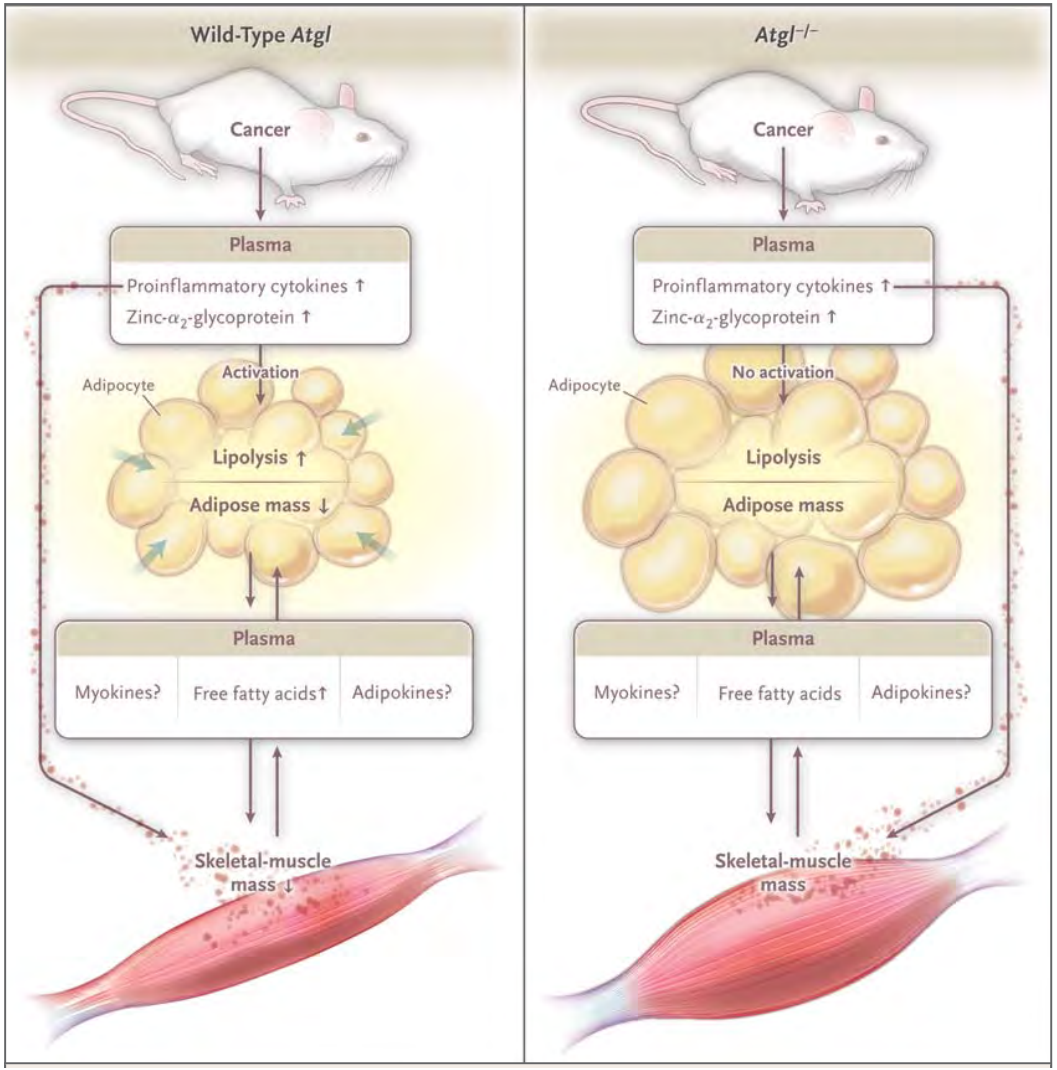
mGPS (0, 1, 2 from top to bottom).
Log-rank $P < 0.001$

Adipocyte triglyceride lipase



Fearon K et al., New England Journal of Medicine, 2011.
Das SK et al., Science, 2011.

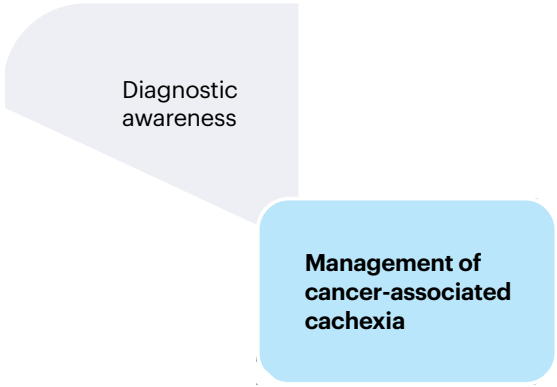
Adipocyte triglyceride lipase



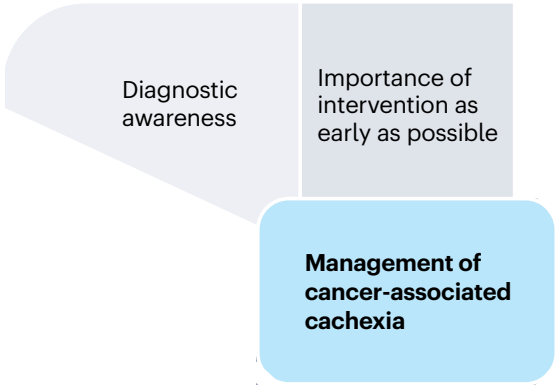
Fearon K et al., New England Journal of Medicine, 2011.
Das SK et al., Science, 2011.

Management of cancer-associated cachexia

Argilés JM et al., nature reviews clinical oncology, 2023



Argilés JM et al., nature reviews clinical oncology, 2023



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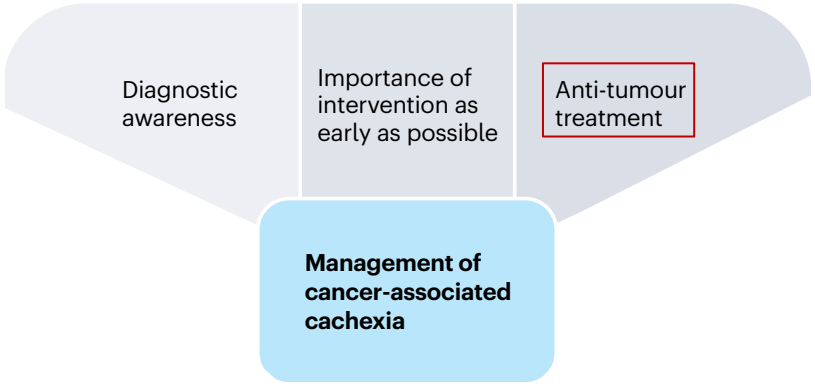

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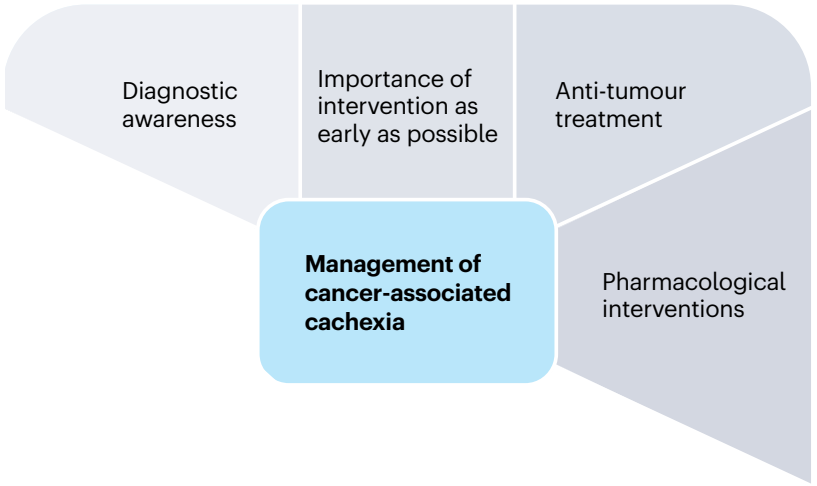

Drugs that modulate appetite

- Megestrol acetate (= progesterone)
- Ghrelin mimetics
- Cannabinoids

Drugs that block inflammation

- Bermekimab (= anti-IL-1 alpha)
- Tocilizumab (= anti-IL-6 receptor)
- Clazakizumab (= anti-IL-6)
- Ruxolitinib (= JAK ½ TKI)
- NSAIDs
- Etanercept (= TNF alpha/beta
- Infliximab (= anti-TNF alpha)
- Anti-GDF15 antibodies

Drugs that counteract metabolic abnormalities

- β_2-Adrenergic receptor blockers
- β_2-Adrenergic receptor agonists
- SARMs (= anti-TNF alpha)
- Anti-myostatin strategies
- MEK inhibitors
- Erythropoietin
- Angiotensin receptor blockers
- Proteasome inhibitors
- Physiactisome
- MitoQ

Tested in clinical studies

Tested in preclinical studies

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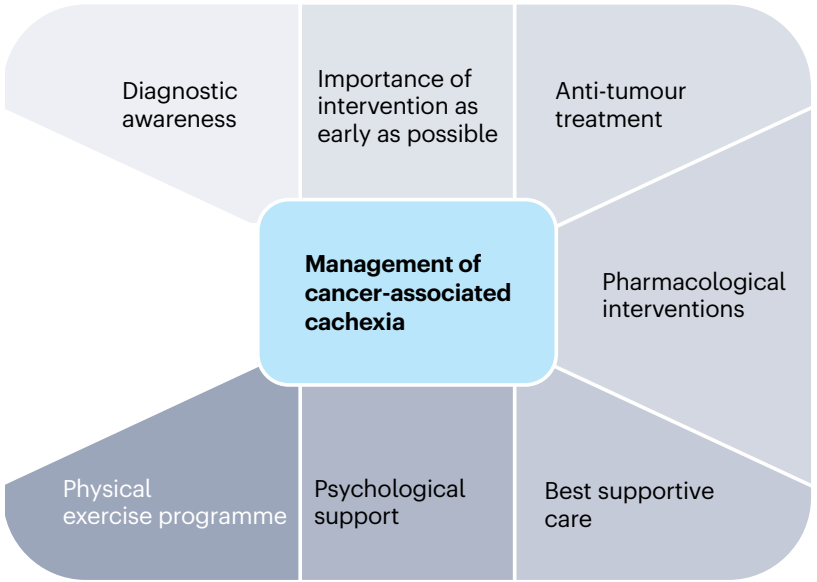

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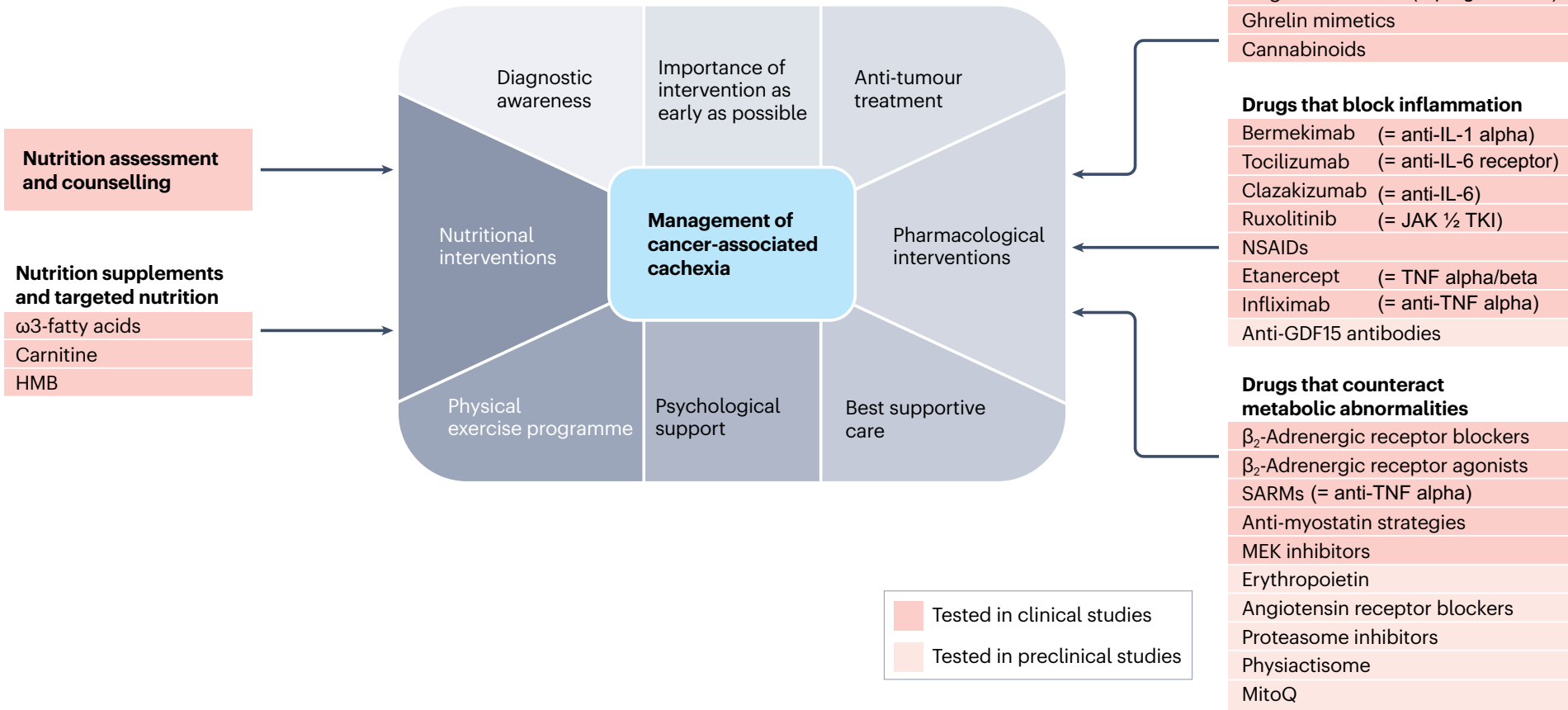

Argilés JM et al., nature reviews clinical oncology, 2023

- **Corticosteroids**
  - Increase appetite, intended for 2-3 weeks (I, B)
- **Synthetic Gestagene** (Medroxyprogesteron and Megestrol)
  - Increase appetite and weight, but not muscle mass, QoL, mobility (I, B)
- **Olanzapin**
  - Increase appetite, reduce nausea (II, B)
- **Androgenes**
  - Not recommended (II, D)
- **Insufficient data**: Cannabis, NSAR, MCP, Domperidon,
- **Ghrelin receptor agonist**
  - Increase appetite, & lean body weight, but not grip strength or survival, approved only in Japan

Muscaritoli M et al., Clin Nutr. 2021. **Arends J** et al., ESMO Open, 2021

Conclusions

- Cancer associated cachexia is a multifactorial syndrome with huge impact on prognosis
- Systemic inflammation affects many organ systems (mGPS)
- Repeated screening for malnutrition
- Adequate multi-professional nutrition counselling with multimodal treatment strategy
- **<u>Unmet needs</u>: early detection of cachexia, molecular basis for improving treatment options**

Thank for listening

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