Nutritional evaluation and support of pancreatic cancer patients

Moon Jae Chung
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Contents

- *Definition of Cancer Cachexia*
- *Clinical Implications of Cancer Cachexia*
- *Diagnosis of Cancer Cachexia*
- *Pathogenesis of Cancer Cachexia*
- *Current Therapies of Cancer Cachexia*
- *CT imaging for Nutritional Assessment in Pancreatic Cancer*

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What is Cachexia ?

The origin of "Cachexia"

kakos ("bad") + hexis ("condition")

● *Physical wasting with loss of skeletal and visceral muscle mass in the presence of underlying inflammation*

● Multi-factorial syndrome defined by

1. an ongoing loss of skeletal muscle mass
(with or without loss of fat mass)
2. that cannot be fully reversed by conventional nutritional support
3. and leads to progressive functional impairment.

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The prevalence of cachexia in cancers

Lei Sun, et al. Nutrition and Cancer, 67(7), 1056–1062
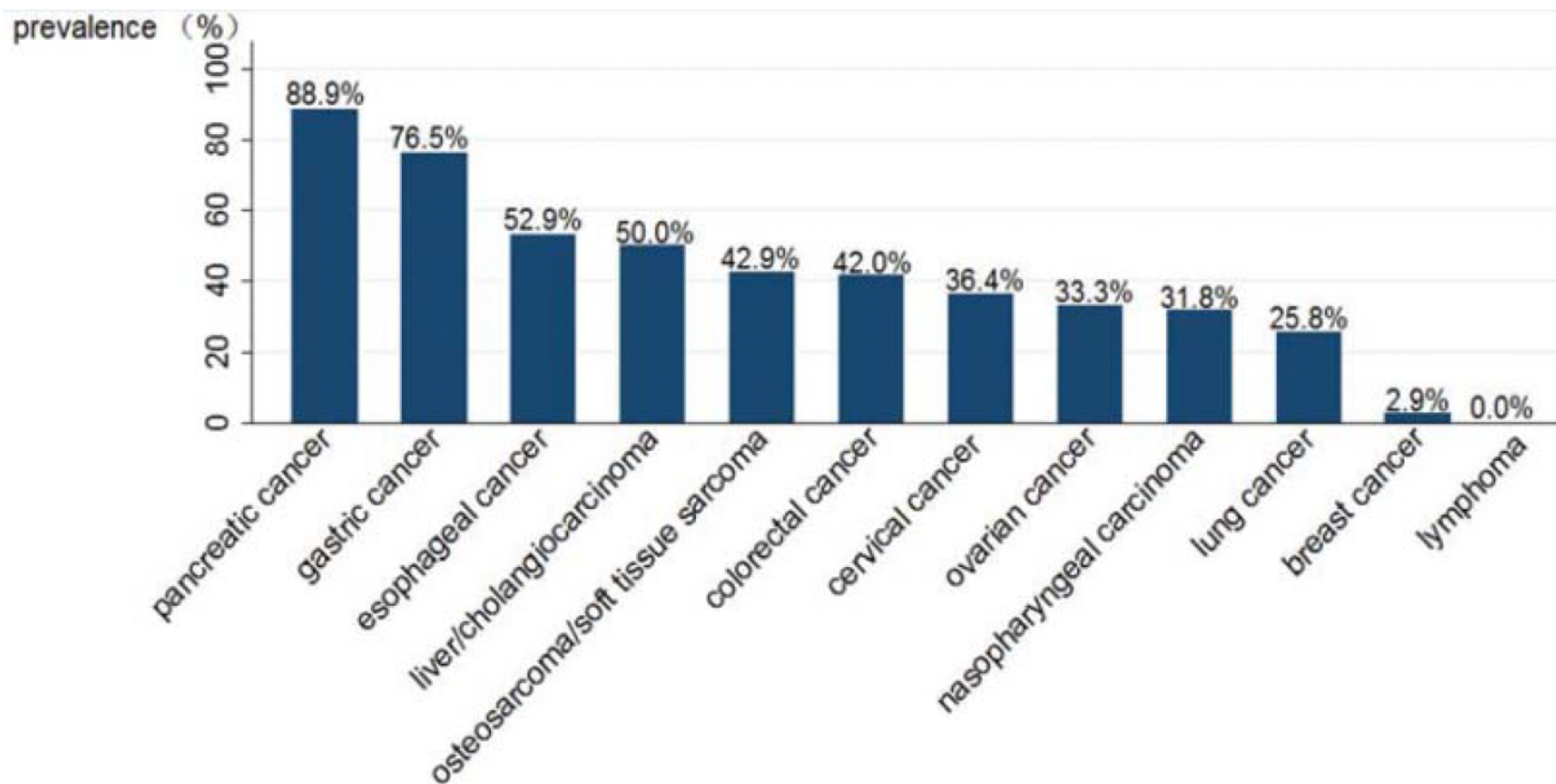
Clinical Implications of Cancer Cachexia

Clinical outcomes of cancer cachexia

Metabolic abnormalities induced by proinflammatory cytokines

inadequate energy intake

↑ energy expenditure

Anorexia, Muscle proteolysis, Asthenia (weakness), Hypoalbuminemia, Emaciation, Immune system impairment, Metabolic dysfunction, Autonomic failure

Failure of anti-cancer treatment

Increased treatment toxicity

Delayed treatment initiation

Early treatment termination

Shorter survival

Psychosocial distress

Muscle wasting shorten survival

High weight loss, muscle depletion, and low muscle attenuation on CT were independent prognostic factor of survival in lung & pancreatic cancer.
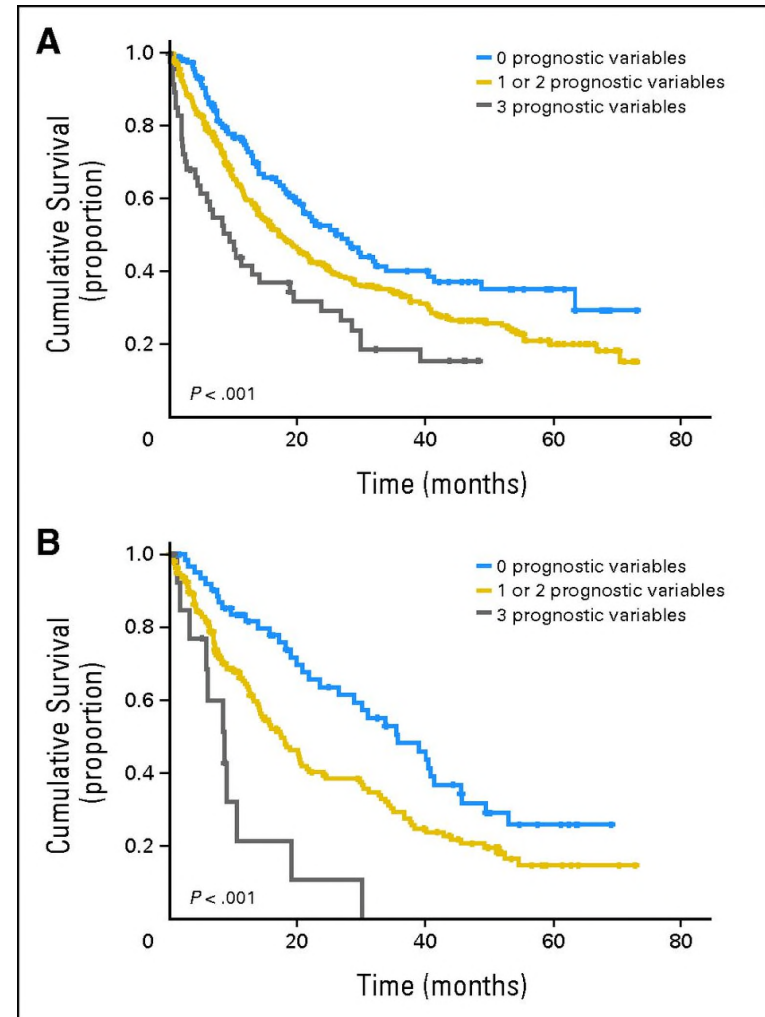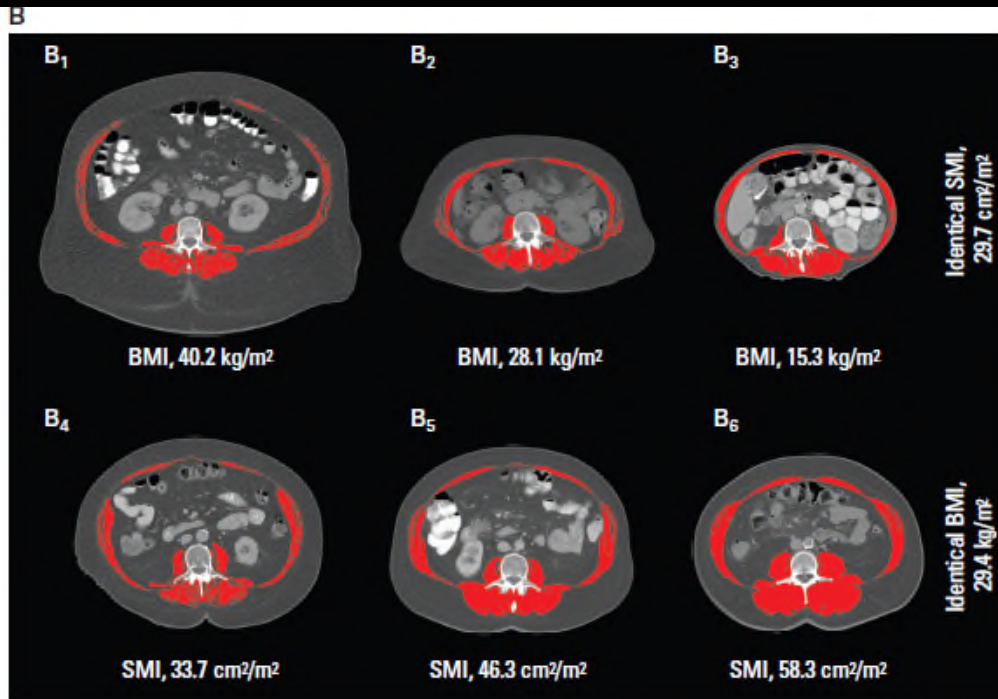
Martin L et al. JCO 2013;31:1539-1547

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Diagnosis of Cancer Cachexia

Diagnostic criteria by international panel of experts

Unintentional weight loss (≥5%) within 6 months

or

BMI <20 and any degree of weight loss >2%

or

Appendicular skeletal muscle index consistent with sarcopenia (males <7.26 kg/m^2; females <5.45 kg/m^2)* and any degree of weight loss >2%

* Appendicular skeletal muscle index determined by dual energy x-ray absorptiometry

Stage of Cancer Cachexia
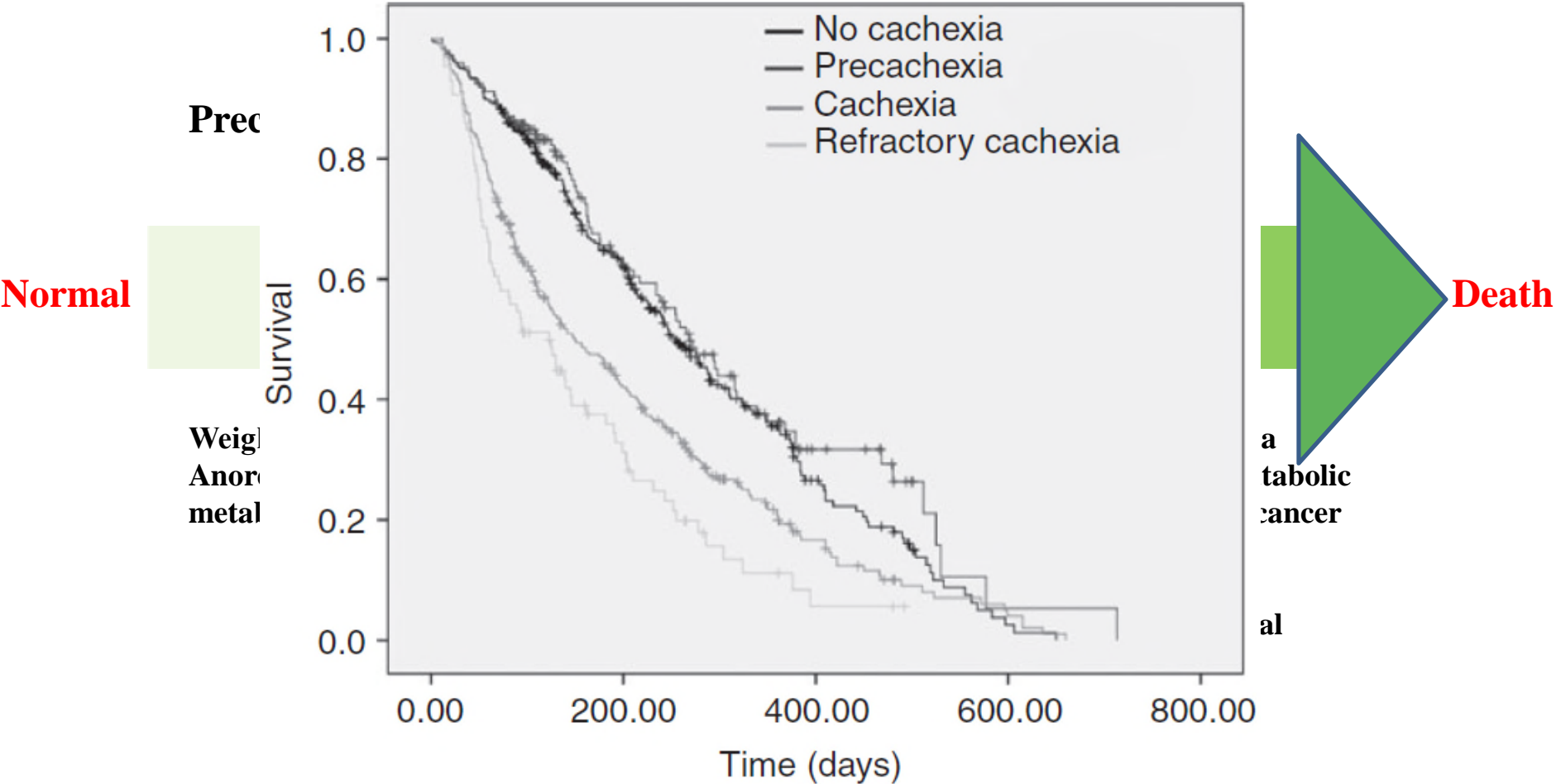
Normal

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Death

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Pathogenesis of Cancer Cachexia

Multi-factorial syndrome

Tumor

Tumor factors

Proteolysis-inducing factor (PIF)
Lipid-mobilizing factor (LMF)

Metabolic change:
- **Proteolysis**
- **Lipolysis**
- **Gluconeogenesis**
- **Glucose turnover**

Insulin resistance counter-regulatory hormones (catecholamines, cortisol, glucagon)

Humoral factors

Cytokines:
  TNF-α
  IL-1
  IL-6
  IFN-γ
Neuropeptide:
  Neuropeptide Y
Hormone
  Insulin

Digestive factors

Dysgeusia
Early satiation
Nausea
Dysphagia
Odynophagia
Mucositis
Constipation
Gastric infiltration
Bowel obstruction

Anorexia

Food intake ↓

CACHEXIA

Crit Rev Oncol Hematol 2013;88:625-36
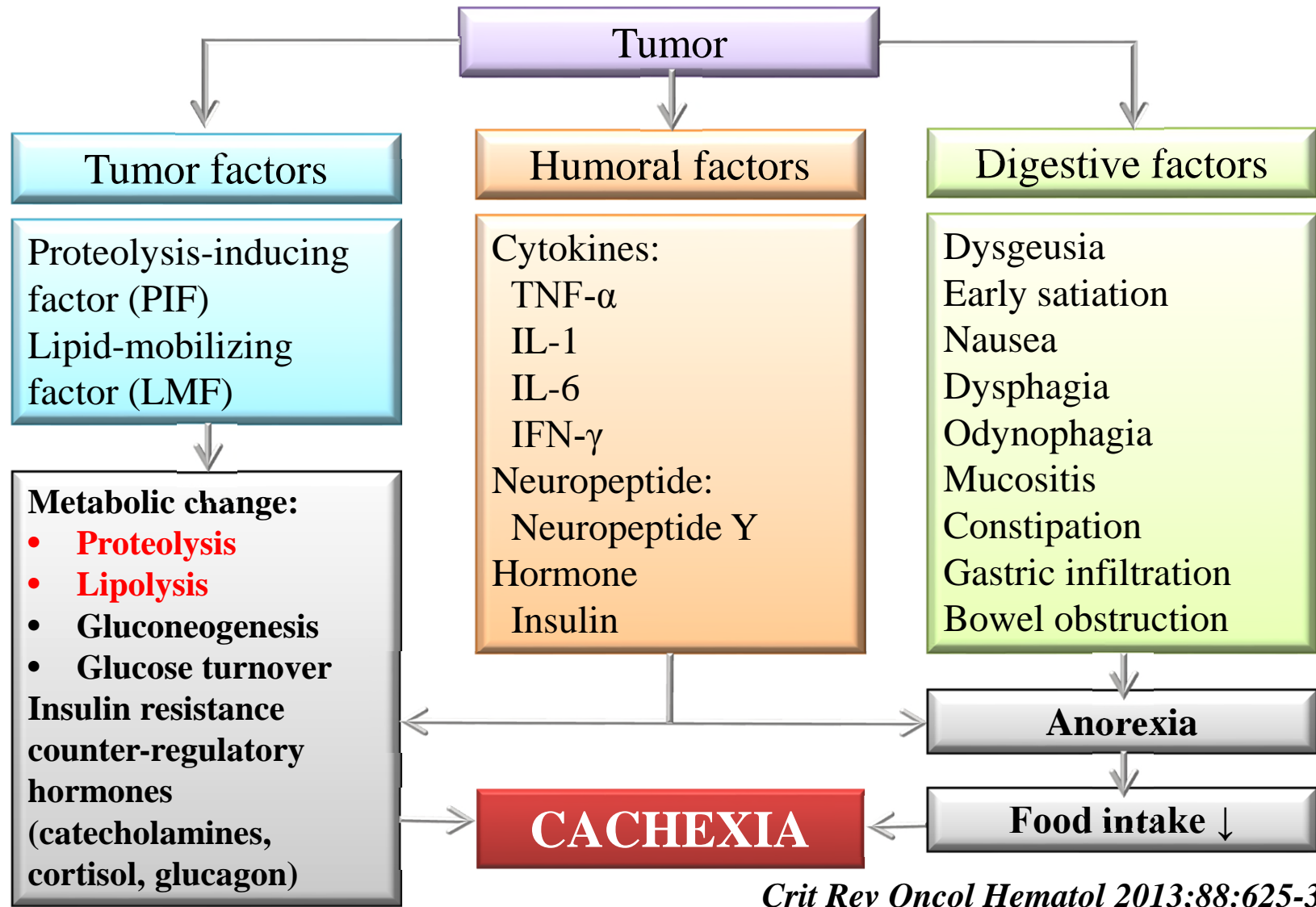
Understanding the molecular basis

- **Energy wasting syndrome**
- **Muscle wasting and atrophy**
- **Adipose tissue wasting**
- **Tumor-driven inflammation**
- **Multi-organ syndrome**

Pathogenesis of Cancer Cachexia

Metabolic alterations associated with tumor burden

Pathogenesis of Cancer Cachexia

Skeletal muscle wasting during cachexia
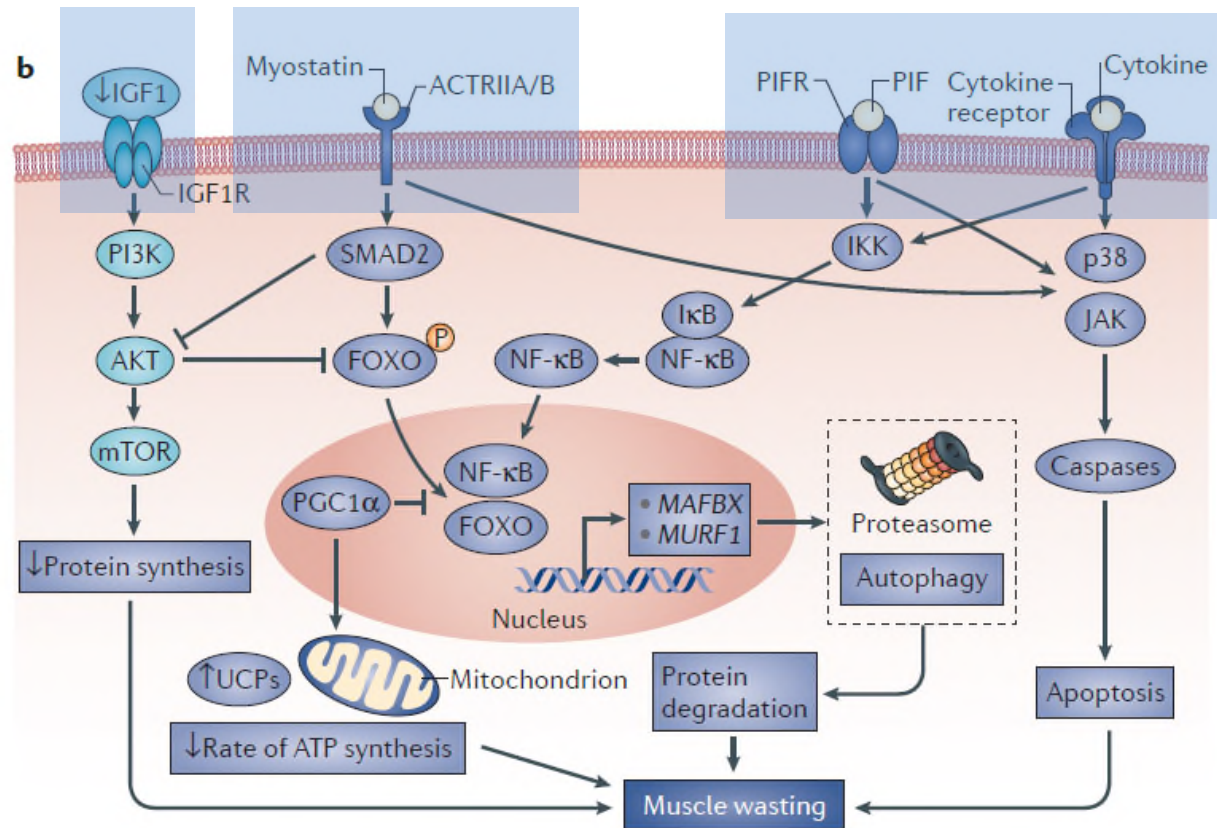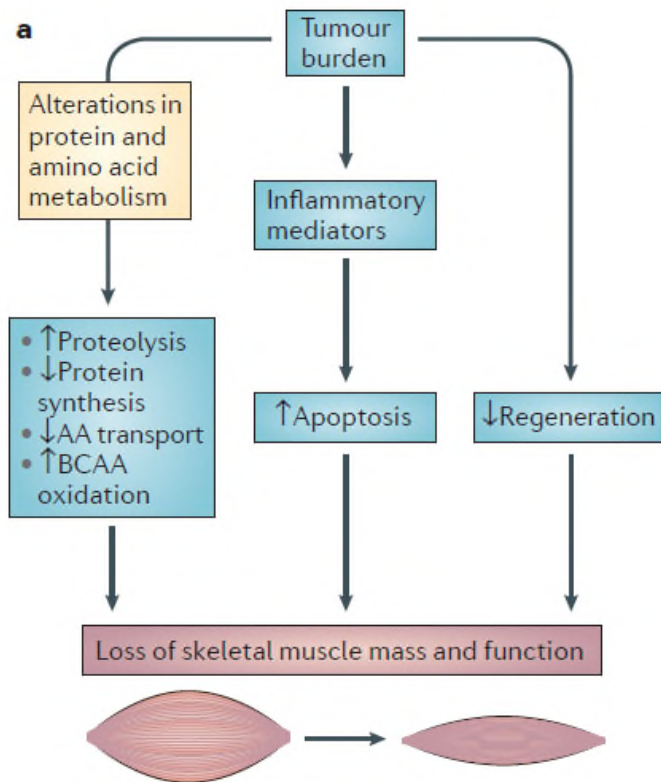
Browning of white adipose tissue in cachexia

Nat Rev Cancer 2014;14:754-62
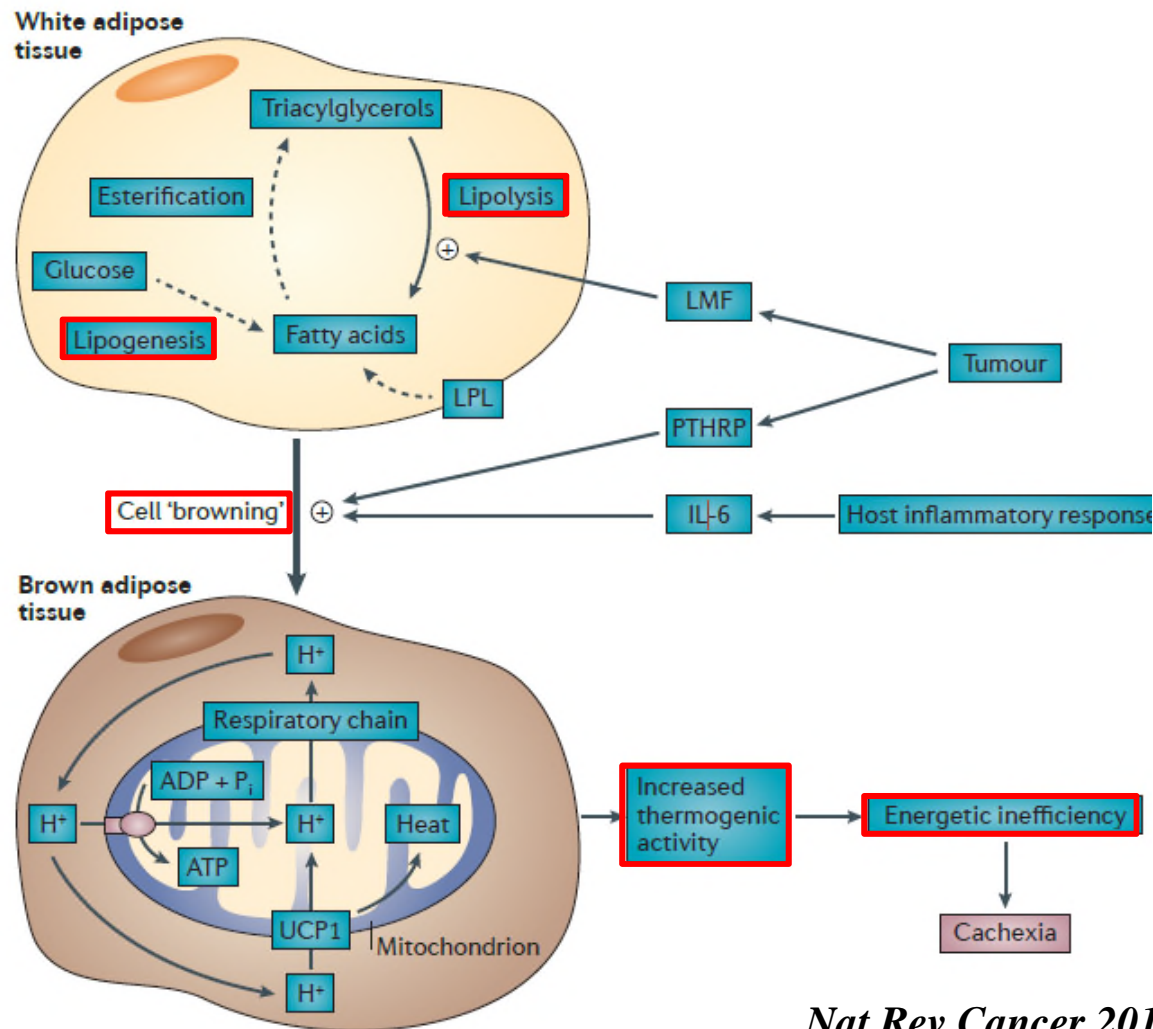
Cachexia as multi-organ syndrome

Brain
- Altered pattern of hypothalamic mediators
- Loss of appetite
- Hyposmia
- Hypogeusia

Anorexia

White adipose tissue
- Increased lipolysis
- Release of fatty acids
- Release of inflammatory mediators?

Wasting

Brown adipose tissue
Energetic inefficiency

Thermogenesis

Skeletal muscle

Wasting

Liver
- Release of acute-phase proteins
- Reduced albumin synthesis
- Release of inflammatory mediators?

Acute-phase response

Heart
- Atrophy
- Decreased innervation
- Increased energy consumption
- Release of inflammatory mediators?

Cardiac dysfunction

Gut
- Gut-barrier dysfunction
- Altered ghrelin production
- Release of inflammatory mediators

Malabsorption

Nat Rev Cancer 2014;14:754-6.

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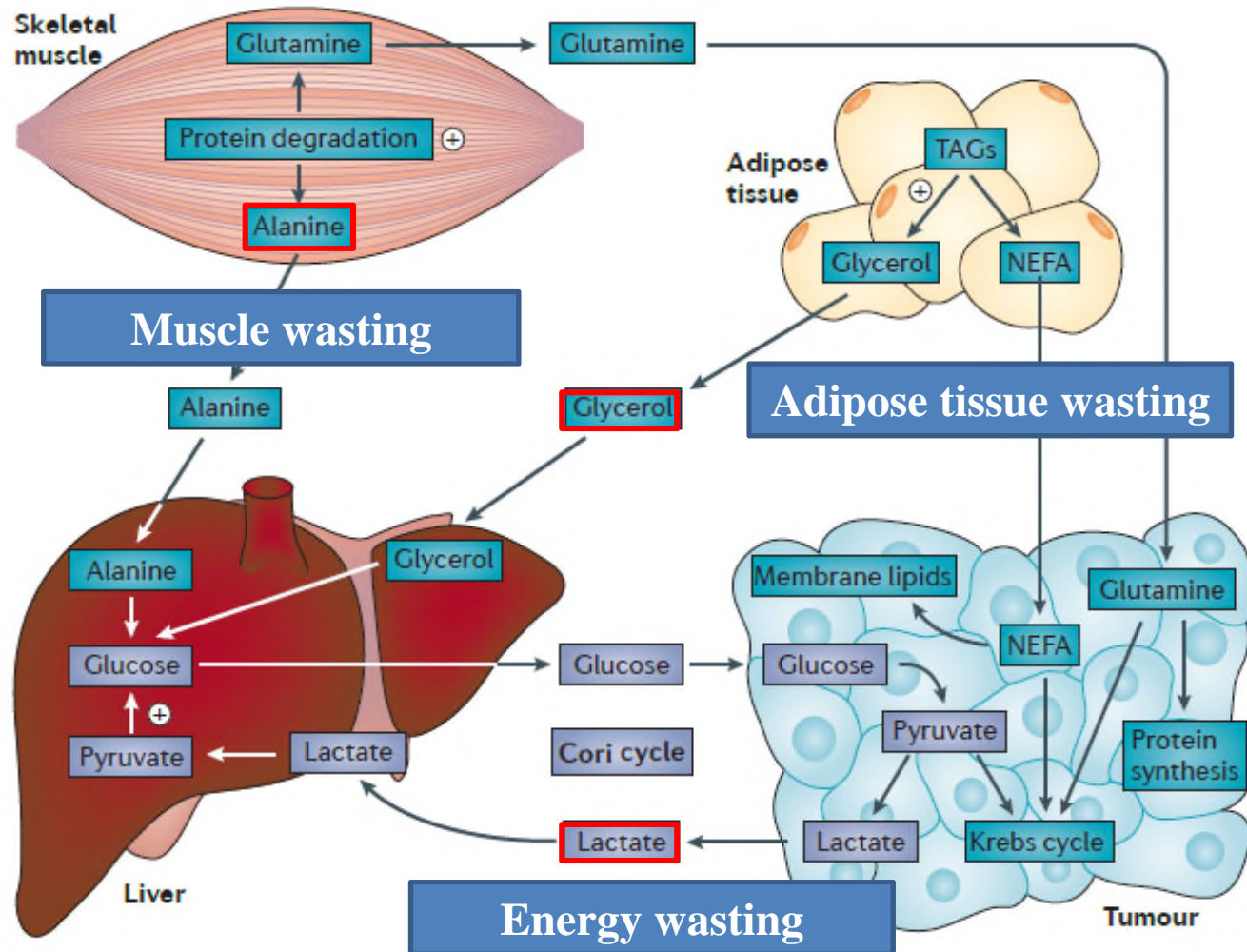- *CT imaging for Nutritional Assessment in Pancreatic Cancer*

Strategies for intervention in cachexia

Comprehensive management

- Influencing the **primary cause**, such as cancer

- Alleviating **aggravating factors**

- Providing appropriate **nutritional support**

- Considering **pharmacological systemic treatment**

- Delivering compassionate **counseling** and support.

National Comprehensive Cancer Network®

**NCCN Guidelines Version 1.2018
Palliative Care**

NCCN Guidelines Index
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ANOREXIA/CACHEXIA

ESTIMATED LIFE EXPECTANCY	INTERVENTIONS[h]		REASSESSMENT

Years → See Interventions (PAL-13)

Year to months

- Treat reversible causes of anorexia (See PAL-13)
- Assess anorexia/cachexia severity and associated symptoms
- Educate patient/family/caregiver on patient's condition and risk/benefits of treatment options
- Consider appetite stimulant
- Focus on patient goals and preferences
- Provide family/caregiver(s) with alternate ways of caring for the patient
- Treat reversible causes

Months to weeks

- Provide education and emotional support to patient/family/caregiver regarding natural history of disease, including the following points:
  ‣ Absence of hunger and thirst is normal in the dying patient
  ‣ Nutritional support may not reverse weight loss in patients with advanced cancer

Weeks to days (Dying patient)

‣ There are risks associated with artificial nutrition and hydration, including fluid overload, infection, and hastened death

‣ Symptoms like dry mouth should be treated with local measures (eg, mouth care, small amounts of liquids)
‣ Withholding or withdrawing nutrition is ethically permissible and may improve some symptoms.

Acceptable outcomes:
- Adequate anorexia/cachexia symptom management
- Reduction of patient/family/caregiver distress
- Acceptable sense of control
- Relief of caregiver burden
- Strengthened relationships
- Optimized quality of life
- Personal growth and enhanced meaning

→ Continue to treat and monitor symptoms and quality of life

If unacceptable →
- Re-evaluate palliative care interventions and intensify as possible
- Consult or refer to specialized palliative care services or hospice

Ongoing reassessment

[h]See Drug Appendix (PAL-A) for specific recommendations for medical management of symptoms.

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Palliative Care

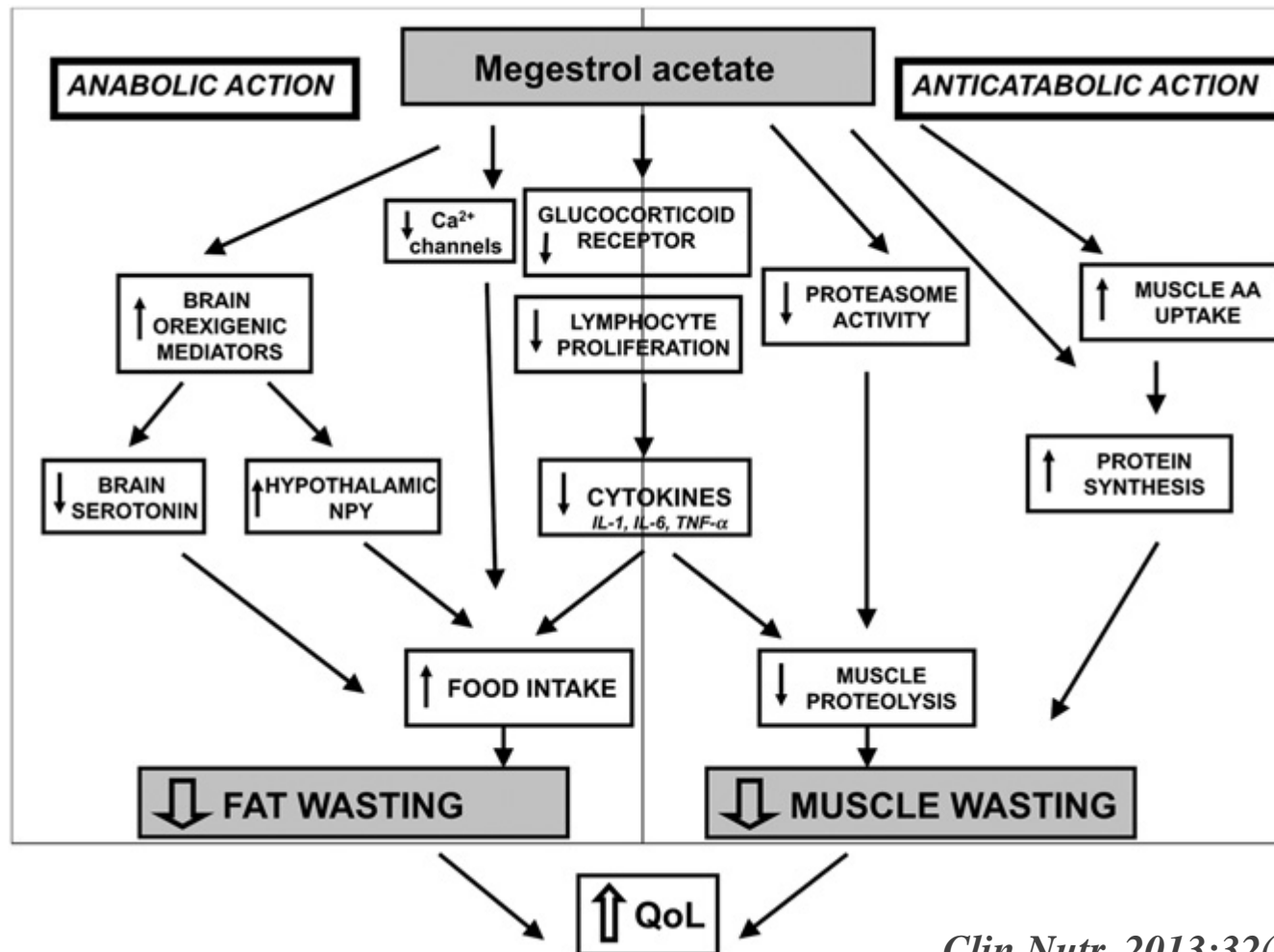NCCN Guidelines Index
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PALLIATIVE CARE DRUG APPENDIX

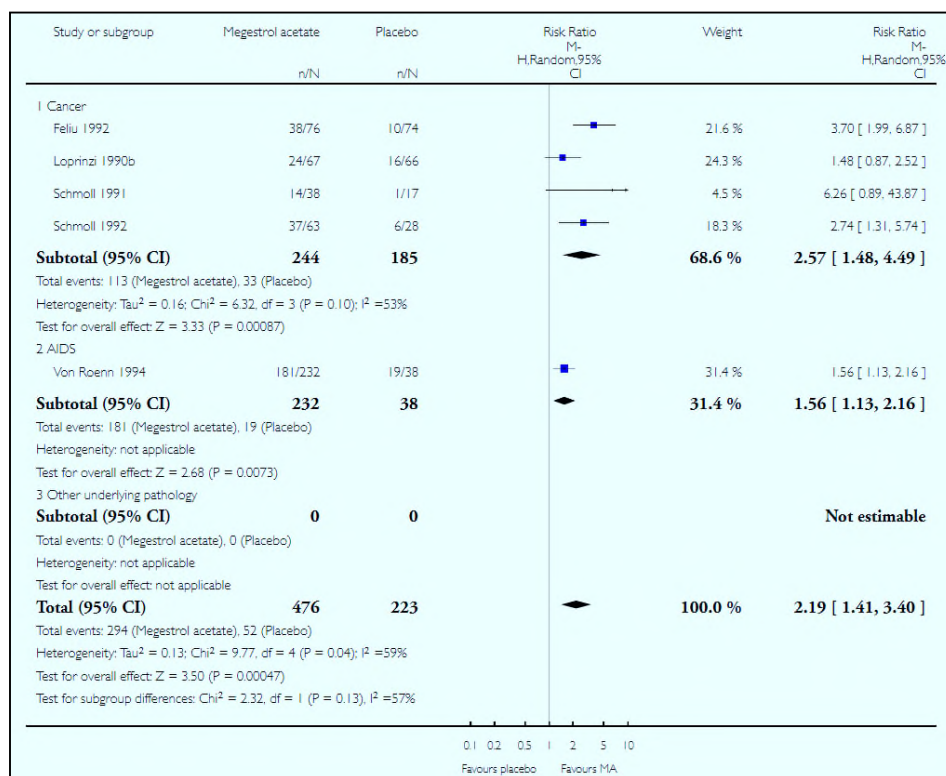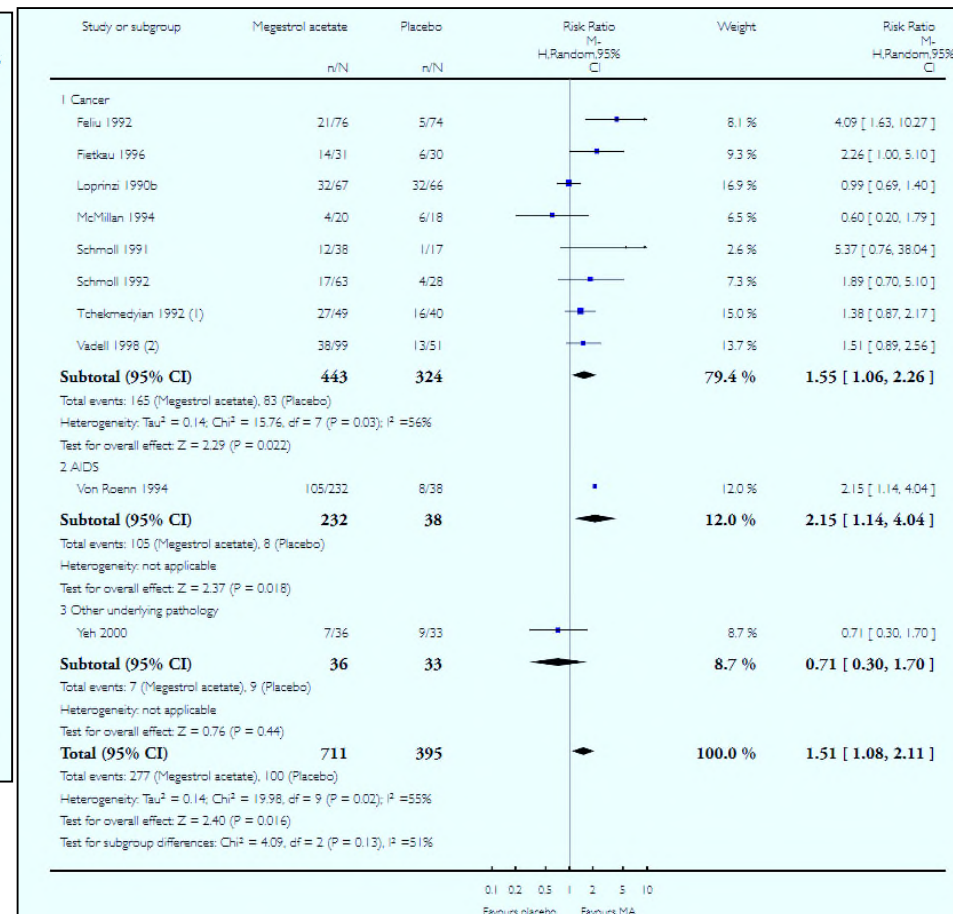| Condition	Recommended Agents and Dosage by Estimated Life Expectancy and Symptom Etiology
Dyspnea (PAL-11)	Life Expectancy: Years; Year to Months; and Months to Weeks • General: Morphine, 2.5–10 mg PO q2h PRN or 1–3 mg IV q2h PRN for opioid naïve, increase dose by 25% for non-opioid naïve ▸ For acute progressive dyspnea, or for patients who are not opioid naïve, more aggressive titration may be required • Anxiety: Lorazepam, 0.25–1 mg PO q4h PRN for benzodiazepine naïve
Dyspnea (PAL-12)	Life Expectancy: Weeks to Days (dying patient) • General: Morphine, 2.5–10 mg PO q2h PRN or 1–3 mg IV q2h PRN if opioid naïve, increase dose by 25% for non-opioid naïve ▸ For acute progressive dyspnea, or for patients who are not opioid naïve, more aggressive titration may be required • Anxiety: Lorazepam, 0.25–1 mg PO q4h PRN if benzodiazepine naïve • Fluid overload: Furosemide
Secretions (PAL-12)	• Excessive secretions: Scopolamine, 0.4 mg SC q4h PRN/1.5 mg patches, 1–3 patches q 3 OR atropine, 1% ophthalmic solution 1–2 drops SL q4h PRN OR glycopyrrolate, 0.2–0.4 mg IV or SC q4h PRN
Anorexia/ Cachexia (PAL-13)	Life Expectancy: Years; Year to Months • Depression/anorexia: Mirtazapine, 7.5–30 mg QHS • Gastroparesis (early satiety): Metoclopramide 5–10 mg PO QID 30 min before meals and at bedtime • Low/no appetite: Megestrol acetate, 400–800 mg/d
Anorexia/ Cachexia (PAL-14)	Life Expectancy: Months to Weeks; Weeks to Days (dying patient) • Offer education to patient • Low/no appetite: Megestrol acetate, 400–800 mg/d OR olanzapine, 5 mg/d OR dexamethasone, 4–8 mg/d OR consider cannabinoid • Depression: Mirtazapine, 7.5–30 mg QHS

Megestrol acetate

Clin Nutr. 2013;32(3):319-24

Current Therapies of Cancer Cachexia

Megestrol acetate

Appetite improvement

Study or subgroup	Megestrol acetate n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Cancer					
Feliu 1992	38/76	10/74		21.6 %	3.70 [1.99, 6.87]
Loprinzi 1990b	24/67	16/66		24.3 %	1.48 [0.87, 2.52]
Schmoll 1991	14/38	1/17		4.5 %	6.26 [0.89, 43.87]
Schmoll 1992	37/63	6/28		18.3 %	2.74 [1.31, 5.74]
Subtotal (95% CI)	**244**	**185**		**68.6 %**	**2.57 [1.48, 4.49]**
Total events: 113 (Megestrol acetate), 33 (Placebo)					
Heterogeneity: Tau² = 0.16; Chi² = 6.32, df = 3 (P = 0.10); I² =53%					
Test for overall effect: Z = 3.33 (P = 0.00087)					
2 AIDS					
Von Roenn 1994	181/232	19/38		31.4%	1.56 [1.13, 2.16]
Subtotal (95% CI)	**232**	**38**		**31.4 %**	**1.56 [1.13, 2.16]**
Total events: 181 (Megestrol acetate), 19 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.68 (P = 0.0073)					
3 Other underlying pathology					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol acetate), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**476**	**223**		**100.0 %**	**2.19 [1.41, 3.40]**
Total events: 294 (Megestrol acetate), 52 (Placebo)					
Heterogeneity: Tau² = 0.13; Chi² = 9.77, df = 4 (P = 0.04); I² =59%					
Test for overall effect: Z = 3.50 (P = 0.00047)					
Test for subgroup differences: Chi² = 2.32, df = 1 (P = 0.13), I² =57%					

0.1 0.2 0.5 1 2 5 10
Favours placebo   Favours MA

Weight improvement

Study or subgroup	Megestrol acetate n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Cancer					
Feliu 1992	21/76	5/74		8.1 %	4.09 [1.63, 10.27]
Fietkau 1996	14/31	6/30		9.3 %	2.26 [1.00, 5.10]
Loprinzi 1990b	32/67	32/66		16.9 %	0.99 [0.69, 1.40]
McMillan 1994	4/20	6/18		6.5 %	0.60 [0.20, 1.79]
Schmoll 1991	12/38	1/17		2.6 %	5.37 [0.76, 38.04]
Schmoll 1992	17/63	4/28		7.3 %	1.89 [0.70, 5.10]
Tchekmedyian 1992 (1)	27/49	16/40		15.0 %	1.38 [0.87, 2.17]
Vadell 1998 (2)	38/99	13/51		13.7 %	1.51 [0.89, 2.56]
Subtotal (95% CI)	**443**	**324**		**79.4 %**	**1.55 [1.06, 2.26]**
Total events: 165 (Megestrol acetate), 83 (Placebo)					
Heterogeneity: Tau² = 0.14; Chi² = 15.76, df = 7 (P = 0.03); I² =56%					
Test for overall effect: Z = 2.29 (P = 0.022)					
2 AIDS					
Von Roenn 1994	105/232	8/38		12.0 %	2.15 [1.14, 4.04]
Subtotal (95% CI)	**232**	**38**		**12.0 %**	**2.15 [1.14, 4.04]**
Total events: 105 (Megestrol acetate), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.37 (P = 0.018)					
3 Other underlying pathology					
Yeh 2000	7/36	9/33		8.7 %	0.71 [0.30, 1.70]
Subtotal (95% CI)	**36**	**33**		**8.7 %**	**0.71 [0.30, 1.70]**
Total events: 7 (Megestrol acetate), 9 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.76 (P = 0.44)					
Total (95% CI)	**711**	**395**		**100.0 %**	**1.51 [1.08, 2.11]**
Total events: 277 (Megestrol acetate), 100 (Placebo)					
Heterogeneity: Tau² = 0.14; Chi² = 19.98, df = 9 (P = 0.02); I² =55%					
Test for overall effect: Z = 2.40 (P = 0.016)					
Test for subgroup differences: Chi² = 4.09, df = 2 (P = 0.13), I² =51%					

0.1 0.2 0.5 1 2 5 10
Favours placebo   Favours MA
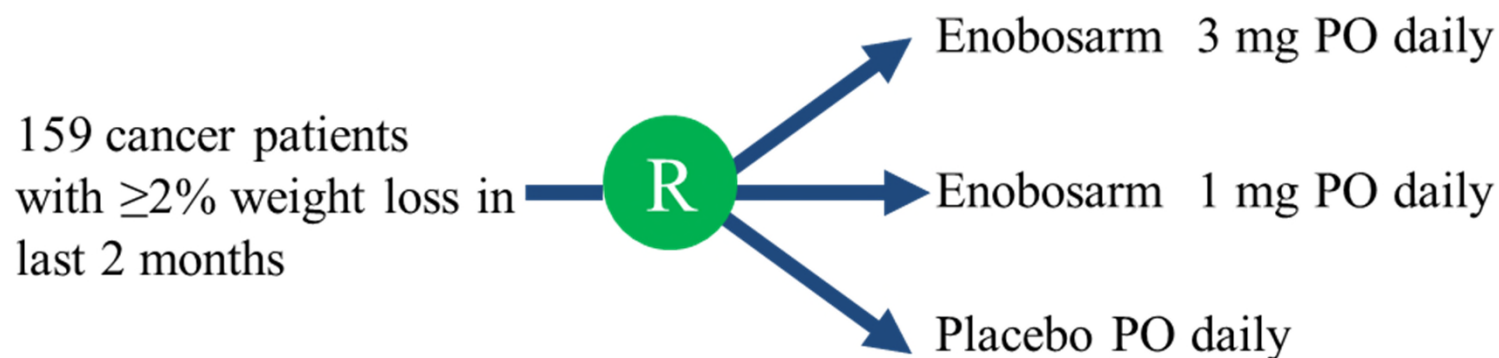
Current Therapies of Cancer Cachexia

Enobosarm (selective androgen receptor modulators, SARMs)

159 cancer patients with ≥2% weight loss in last 2 months → **R** →

- Enobosarm 3 mg PO daily
- Enobosarm 1 mg PO daily
- Placebo PO daily

Change in total lean body mass at day 113 or end of study compared with baseline

	Placebo	Enobosarm 1 mg	Enobosarm 3 mg
N	34	32	34
Mean (SD), kg	0·1 (2·7)	1·5 (2·7)	1·3 (3·5)
Median (range), kg	0·02 (−5·8 to 6·7)	1·5 (−2·1 to 12·6)	1·0 (−4·8 to 11·5)
p value[*]	0·88	0·0012	0·046

Current Therapies of Cancer Cachexia

MABp1 (Anti-interleukin 1α Monoclonal Antibody)

Figure 3: Change in lean body mass between baseline and week 8
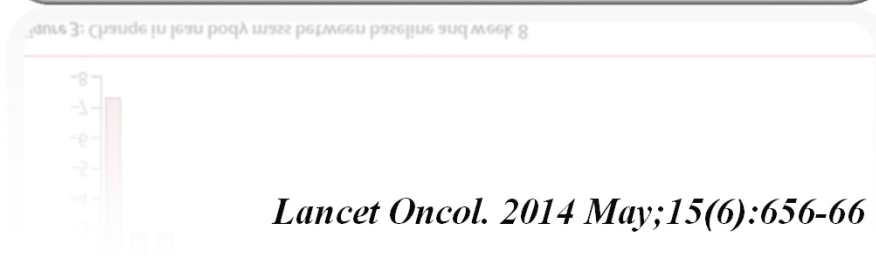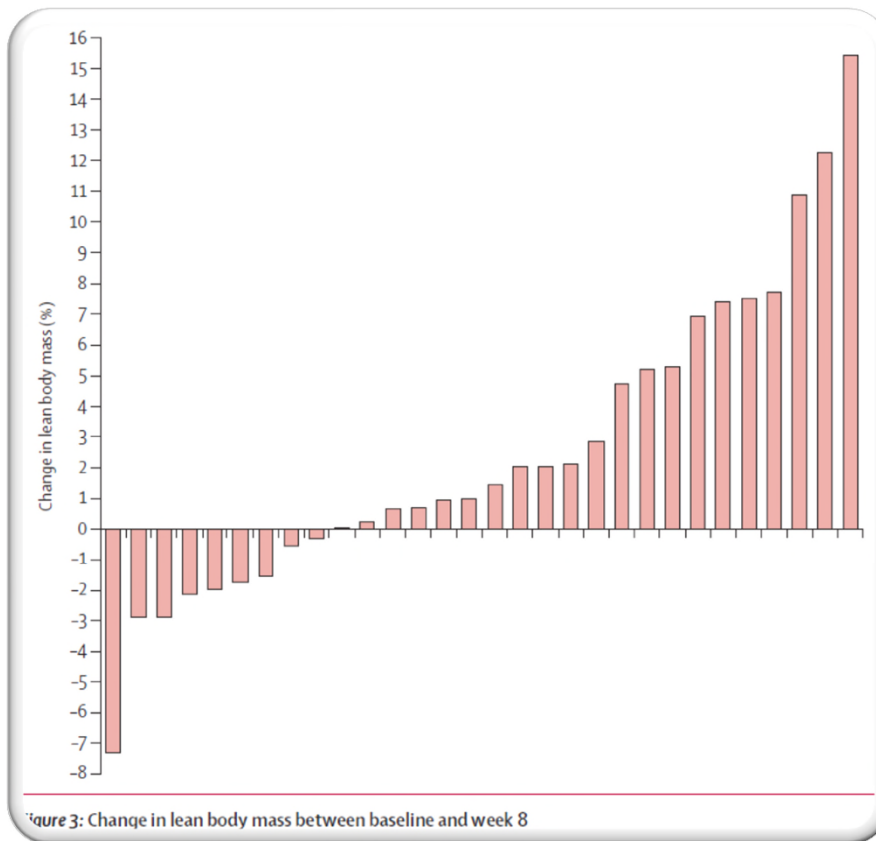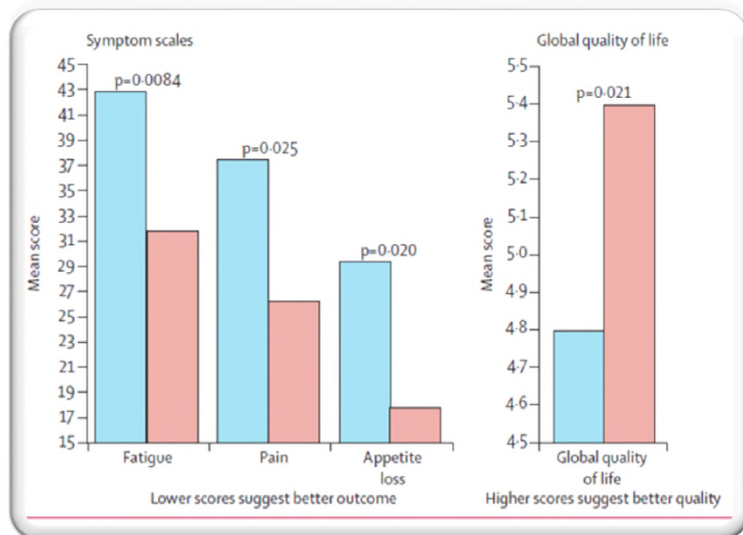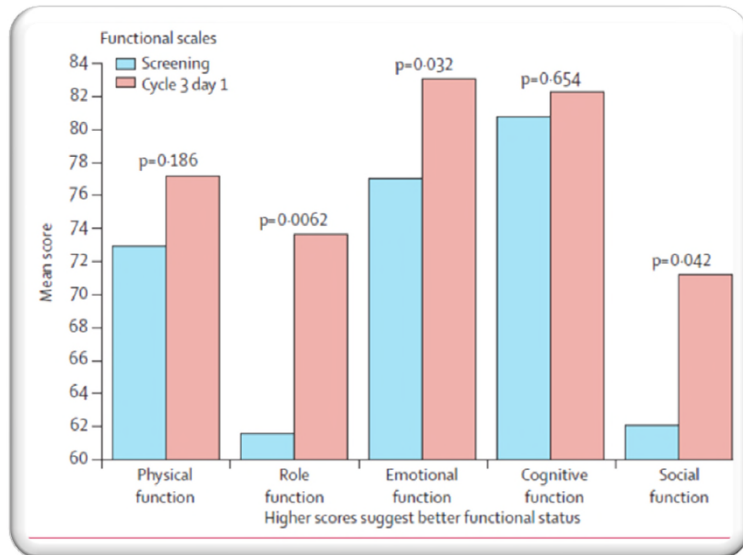
Current Therapies of Cancer Cachexia

Anamorelin (ghrelin mimetic)

- *Analysis of change in lean body mass (kg) from baseline over 12 weeks by subgroup*

ROMANA 1	Number of patients				p value
	Placebo	Anamorelin	— Placebo — Anamorelin		
Study population	158	316			<0·0001
Sex					
Male	119	242			<0·0001
Female	39	74			0·62
Age					
≤65 years	104	211			<0·0001
>65 years	54	105			0·093
Weight loss					
≤10%	96	190			0·0006
>10%	62	126			0·0058
Body-mass index					
≤18·5 kg/m²	15	30			0·060
>18·5 kg/m²	143	286			<0·0001
Chemotherapy or radiation therapy					
No chemotherapy or radiation therapy	94	191			<0·0001
With chemotherapy or radiation therapy	64	125			0·054
ECOG					
0–1	133	252			<0·0001
2	25	64			0·12

Pharmacologic treatments

Corticosteroids *are beneficial in treating anorexia in palliative care patients with malignancies; There is insufficient evidence to recommend any particular corticosteroid drug over another, or to recommend a dosing regimen.*

Use of corticosteroids for anorexia in palliative medicine: a systematic review.
J Palliat Med. 2014;17(4):482-5

Olanzapine *(atypical antipsychotic) had only a modest effect in altering the trajectory of weight loss.*

Olanzapine for cachexia in patients with advanced cancer
:an exploratory study of effects on weight and metabolic cytokines.
Support Care Cancer. 2015 Sep;23(9):2649-54

After 4 weeks of **mirtazapine** *(a tetracyclic antidepressant), 24% of patients gained 1 kg or more, 24% and 6% improved appetite and health-related quality of life.*

Phase II trial of mirtazapine for cancer-related cachexia and anorexia.
Am J Hosp Palliat Care. 2010 ;27(2):106-10

Human antibody to ActRIIB

Muscle Wasting is a new target of pharmaceutical development !
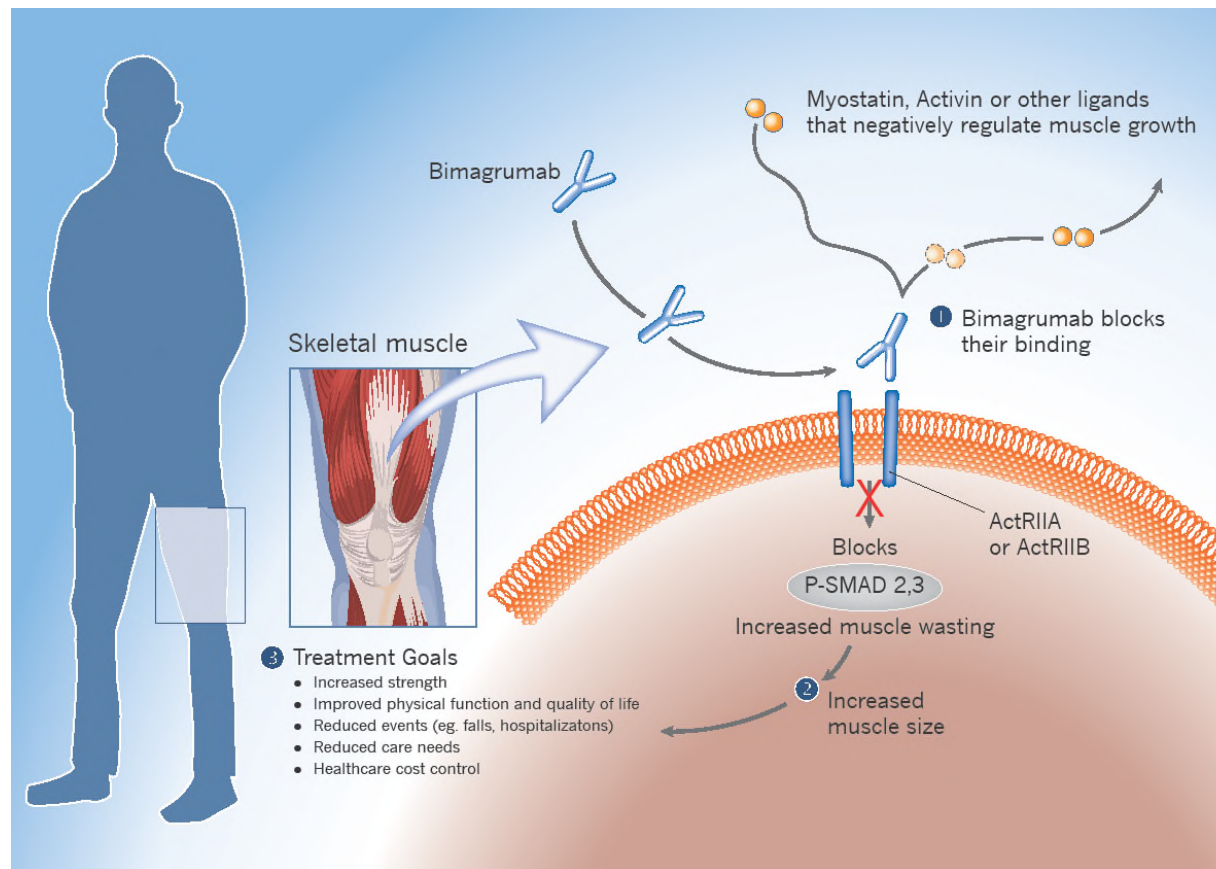
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Personalized Nutrition in Pancreatic Cancer Patients

Subjects : Pancreatic Cancer Patients (N=413), diagnosed and deceased in SEVERANCE

Aim : To identify **the Factors the differences in muscle mass, subcutaneous and visceral fat between two different CT evaluation**

Nutritional status or supplements ?
Medications ?
Lab (CBC, Chemistry) ?

Muscle mass
Subcutaneous fat
Visceral fat

Muscle mass
Subcutaneous fat
Visceral fat

Diagnosis　　　　　　　　　**CT Follow-up**　　　　　　　　　**CT Follow-up**
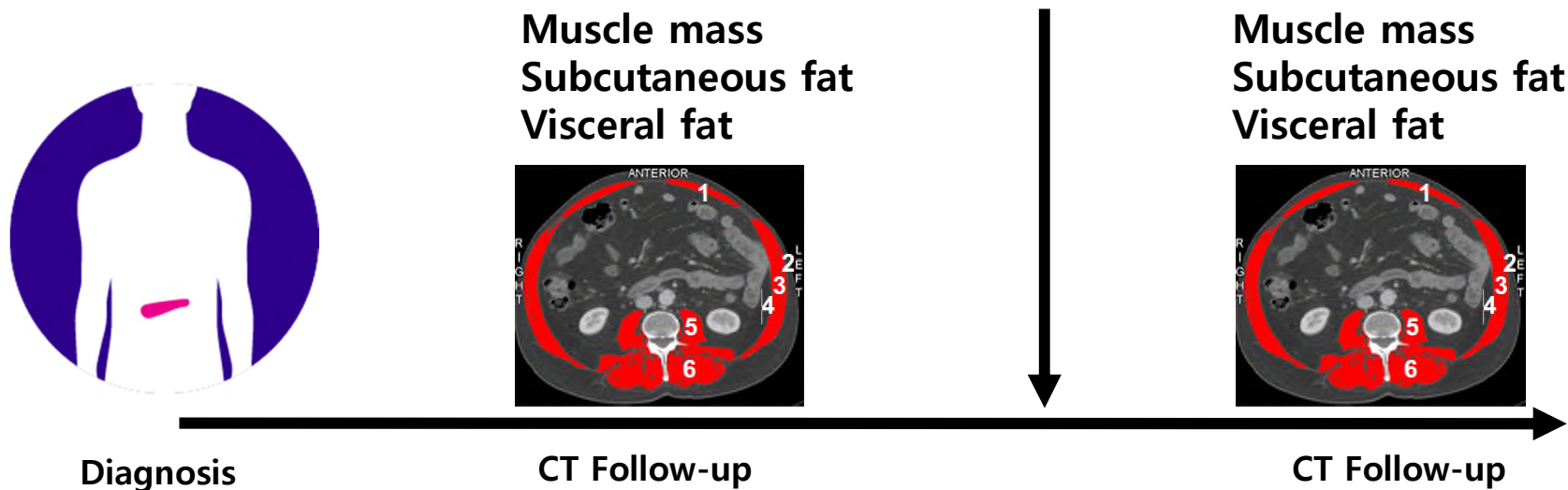
Methods : Potential Factors

Enteral Nutrition   Parenteral Nutrition   Lab
(CBC, General Chemistry, Inflammatory)   Drugs
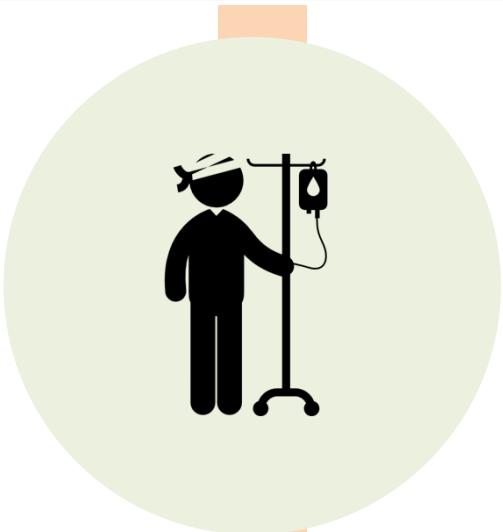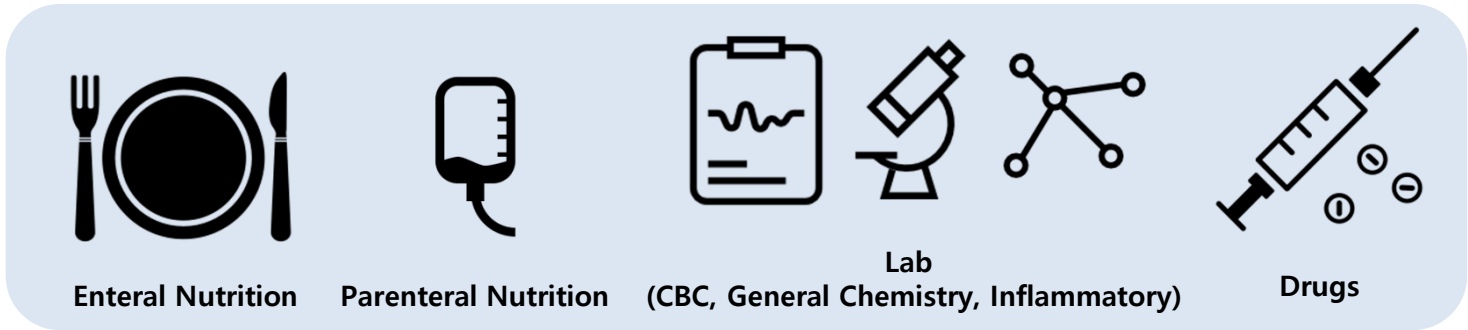
Antidepressant
Antiemetics
Antilipidemics
Anti-inflammatory
Hormone
DM medication
HTN medication
Nutrition (Pancreatic Enzyme, L-carnitine)
Analgesics
Chemotherpeutic agents
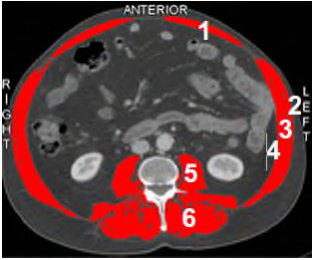
Visceral Adipose Tissue Area
Subcutaneous Adipose Tissue Areas
Smooth Muscle Area
Skeletal Muscle Area
Index : FFM/FM/Muscle Index/Sarcopenia

Methods : Lean tissue imaging (CT L3 Level)

Fat (subQ)　　　　　Fat (visceral)　　　　　Muscle

-190 ~ -30 HU　　　　-150 ~ -50 HU　　　　Low, fatty -29 ~ 29 HU
　　　　　　　　　　　　　　　　　　　　　　Normal 30 ~ 150 HU

Aquarius iNtuition ver.4.4.12.185.3539 TeraRecon, Foster City, CA, USA

Visceral Adipose Tissue Area
Subcutaneous Adipose Tissue Areas
Skeletal Muscle Area

FFM (kg) =0.3 x (skeletal muscle cross-sectional area at L3 (cm2))
FM (kg) =0.042 x ((visceral fat area at L3 (cm2))
　　　　　　　　　+(subcutaneous fat area at L3 (cm2)))
VF% = VFA/TFA x 100
Skeletal Muscle Index
= (skeletal muscle cross-sectional area at L3 (cm2))/(Height)^2(m^2)

Results : Baseline Characteristics

|	n = 413
Age, mean ± SD	66 ± 10.2
Gender male, N	239 (57.9)
Body mass index (kg/m^2), median (IQR)	**22.3 (20.3-24.3)**
<20.0 (underweight), N(%)	41 (9.9)
20.0-24.9 (normal weight), N(%)	288 (69.7)
>25.0 (overweight, obese), N(%)	82 (19.9)
Alcohol consumption, N (%)	
Never / Former / Current	219(53) / 110 (26.6) / 74 (17.9)
> 8 glass / week	104
Smoking status, N(%)	
Never / Former / Current	245 (59.3) / 110 (26.6) / 46 (11.1)
Comorbidity, N (%)	
Diabetes (yes/no)	151 (36.6)
Hypertension (yes/no)	201 (48.7)
Resectability	
Resectable	53 (12.8)
Borderline resectable	46 (11.1)
Locally advanced	57 (13.8)
Advanced	256 (62.3)

Results : Baseline Characteristics

	n = 413
Body Composition Variable	
SMI (cm^2/m^2), median(IQR)	40.9 (35.7-46.7)
MA(HU), median (IQR)	40.6 (34.6-46.1)
VF (%), median (IQR)	44 (35-55.1)
FFM (cm^2), median (IQR)	38.2 (33-44.5)
FM (cm^2), median (IQR)	17.3 (14.8-20.1)

Results : Skeletal Muscle Attenuation

Variable	Beta	S.E	P-value
ECOG 1	6.06187	2.45367	0.0145
ECOG 3	-12.11517	4.36487	0.0061
Hemoglobin	1.40586	0.42894	0.0013
WBC	-0.63782	0.20876	0.0026
Neutrophil	-0.00075	0.00022	0.0010
NLR	-0.46910	0.15319	0.0026
Albumin	3.52572	1.07867	0.0013
CRP	-0.04846	0.01928	0.0131

# Results : Skeletal Muscle Attenuation
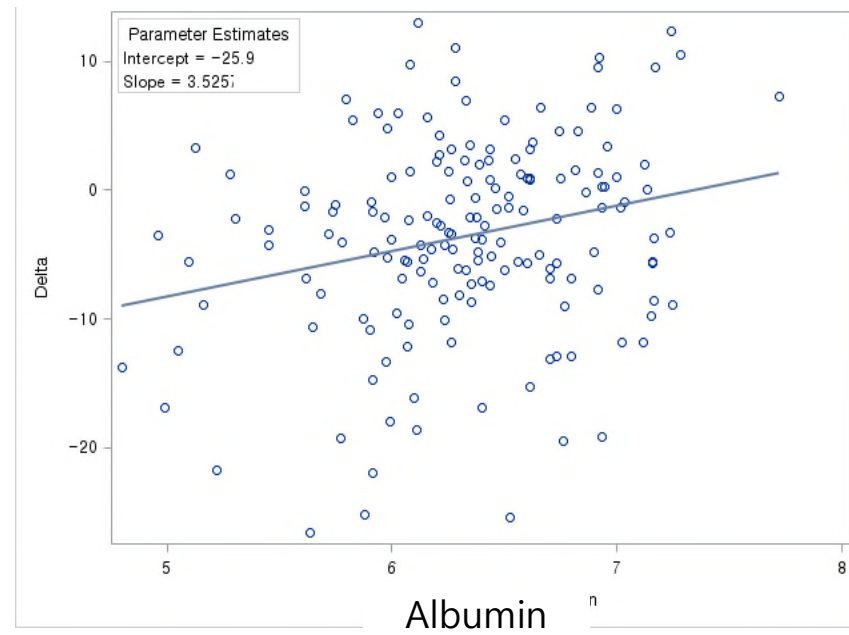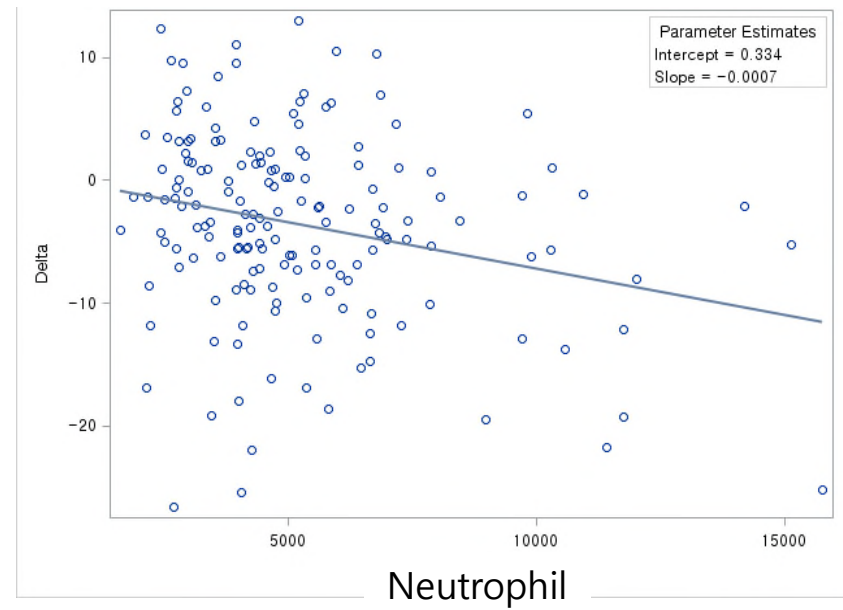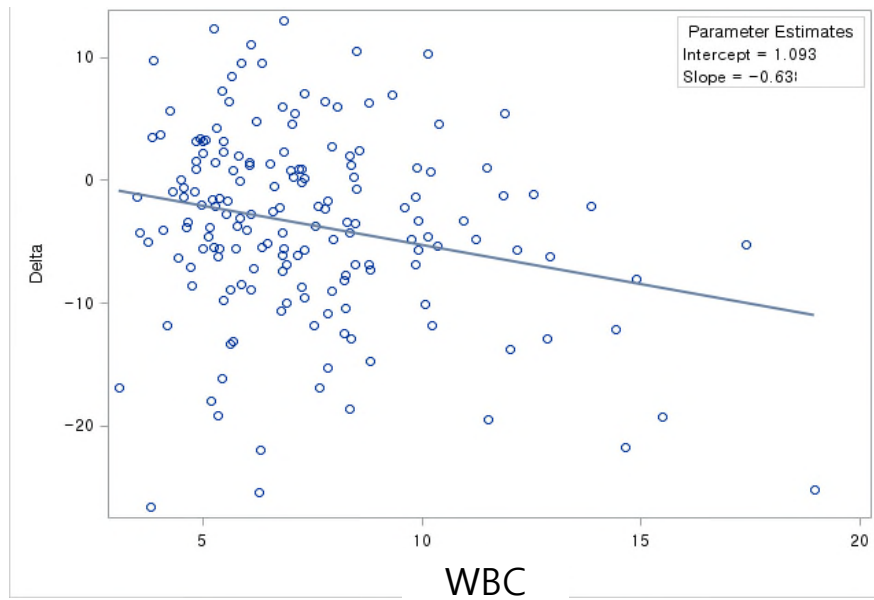
Summery & Conclusions

◆ **Cancer cachexia occurs most often in gastrointestinal cancer compared to cancers in other sites. In pancreatic cancer and gastric cancer, cachexia occurs in over 80% of cases.**

◆ **The pathophysiology of cachexia includes complex metabolic mechanisms directly linked to the tumor-host interaction.**

◆ **Current diagnosis of cancer cachexia comprise weight loss, body mass index (BMI) and levels of muscle mass (sarcopenia).**

◆ **Cancer cachexia leads to shortened survival, early & frequent treatment toxicities, and poor functional status.**

◆ **An expanded multimodality approach including specific anti-cachexia pharmacological interventions, nutritional counseling, exercise is may be more effective than the use of any of these treatment alone.**

Methods : Lean tissue imaging
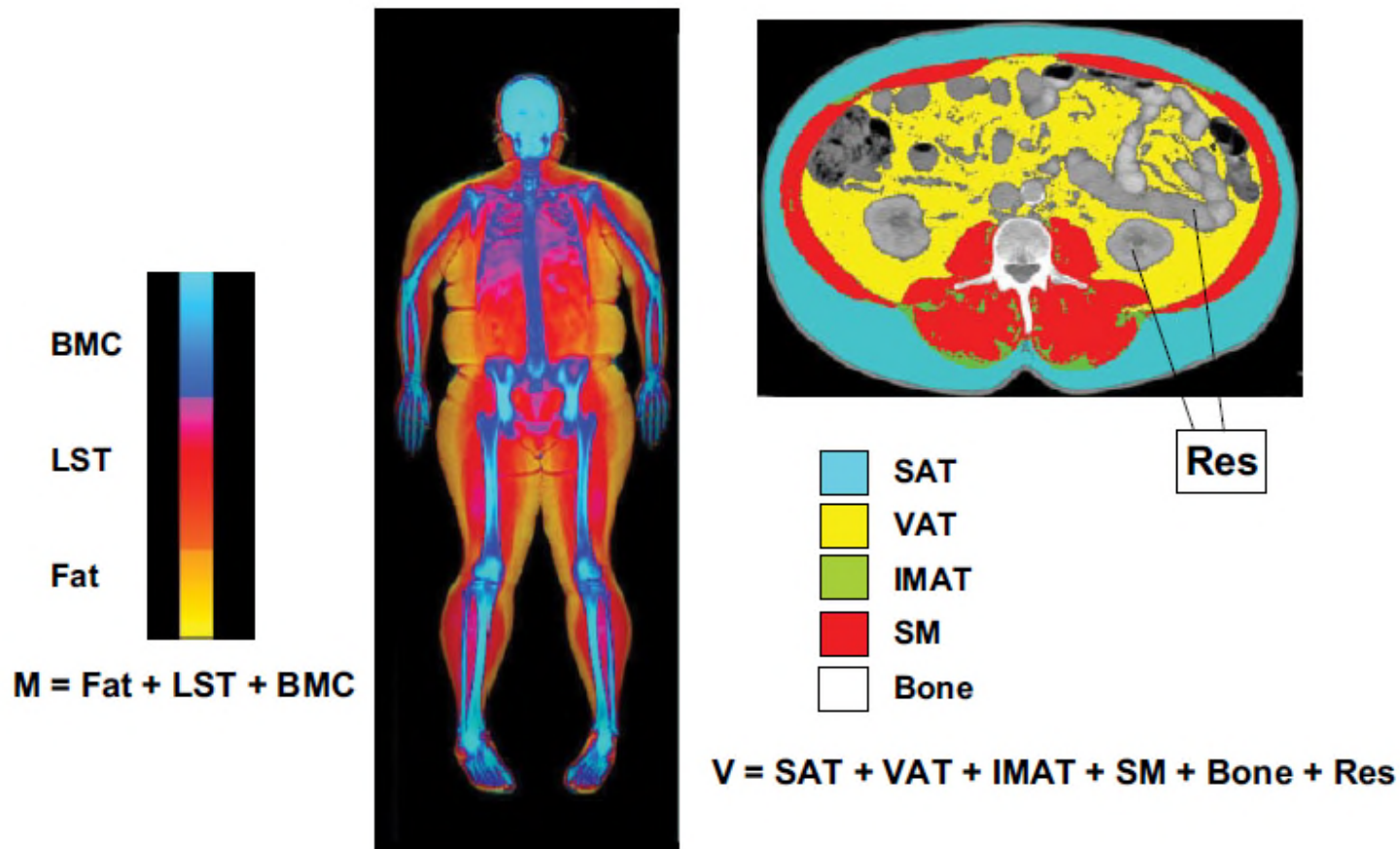
Figure 2. Selected body composition components measured by dual-energy x-ray absorptiometry (DXA; left) and magnetic resonance imaging (MRI; right). Body mass (M) and volume (V) represent the sum of these components for DXA and MRI, respectively. BMC, bone mineral content; IMAT, intermuscular adipose tissue; LST, lean soft tissue; Res, residual mass (organs and tissues remaining after subtracting skeletal muscle, bone, and adipose tissue volumes); SAT, subcutaneous adipose tissue; SM, skeletal muscle; VAT, visceral adipose tissue.

Methods : Lean tissue imaging
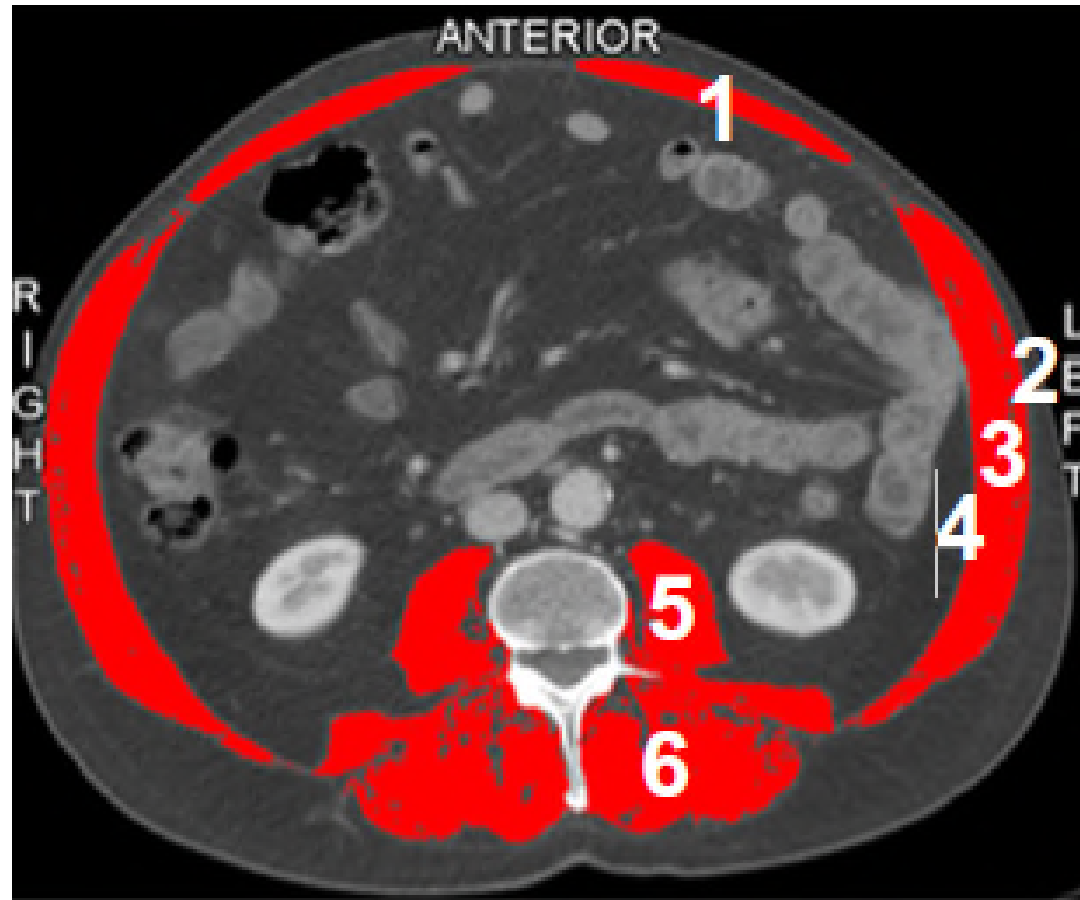
1 rectus abdominis, 2 external oblique, 3 internal oblique, 4 transverse abdominal, 5 psoas, 6 paraspinal