2018

VIENNA, AUSTRIA

SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

28-30 JUNE 2018

MASCC/ISOO

ANNUAL MEETING ON SUPPORTIVE CARE IN CANCER

MASCC Multinational Association of Supportive Care in Cancer

ISOO International Society of Oral Oncology

www.mascc.org/meeting

#MASCC18

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Predictive/prognostic value of anorexia-cachexia

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Prognostic value of Anorexia-Cachexia

Relationship between Prognosis

- Weight
- Appetite
- Nutritional Impact Symptoms
- Body Composition
- Multiple Domains of cachexia

uncertainty

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- Wide variation in guidelines[1] and use of weight loss criteria
- Systematic review of cachexia domains and weight loss criteria[2]

  5% loss [n = 12] 10% [n = 20] specific % [n = 29] kg lost [n = 10]

  time period 6 months [n = 18], 3 months [n = 4], unspecified [n = 16]
- Oncologists unclear which cut-offs are clinically significant [3,4]

1.Mauri BMJ Supp Pall 2014 2.Blum Crit Rev Onc Hem 2011 2.Spiro BJC 2006 3.Del Fabbro JSO 2015

Definition of Cancer Cachexia

- Multi-factorial syndrome
  - Characterized by ongoing loss of skeletal muscle mass ± loss of fat mass
  - Cannot be reversed fully by conventional nutritional support
  - Leads to progressive functional impairment

Weight loss >5% over 6 mo that cannot be attributed to simple starvation

or

BMI <20 + weight loss >2%

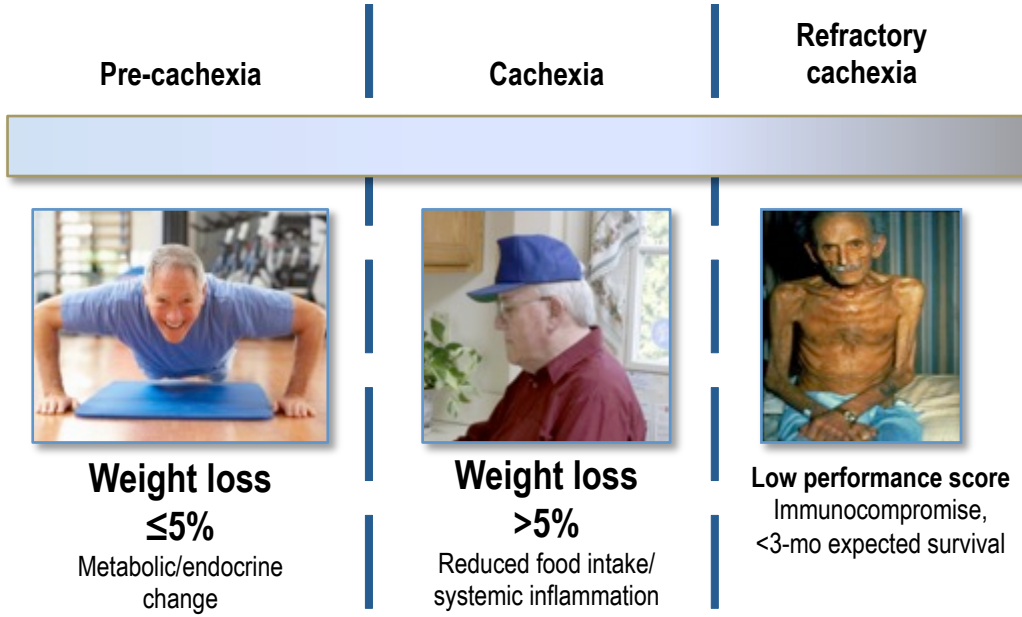
or

Appendicular skeletal muscle mass index consistent with **sarcopenia + weight loss >2%**

- **BMI,** body mass index.

Fearon K, et al. *Lancet Oncol*. 2011;12:489-495 .

Stages of Cancer Cachexia



"In the beginning of the malady it is easy to cure but difficult to detect, but in the course of time, not having been either detected or treated in the beginning, it becomes easy to detect but difficult to cure."

Niccolo Machiavelli

Fearon K, et al. *Lancet Oncol*. 2011;12:489-495.

Weight-Related Outcomes in Patients with Cancer

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- Increased risk for complications, death[1]
- Decreased treatment response [2]
- Greater failure to complete cycles of therapy[2,6]
- Increased toxicity[3]
- Increased fatigue[4]
- Lower QoL[5,8]
- Decreased Performance status
- Low testsoterone

1. DeWys WB, et al. *Am J Med*. 1980;69:491-497; 2. Ross PJ, et al. *Br J Cancer*. 2004;90:1905-1911; 3. Kazemi-Bajestani SM. *Semin cell Dev 2016*; 4. Parmar MP, et al. *Support Care Cancer*. 2013;21:2049-2057; 5. Mariani L, et al. *Support Care Cancer*. 2012;20:301-309; 6 *Andreyev Eur J Cancer 1998;7 Chlebowski,8. Thoresen* Eur J Cancer Care 2012

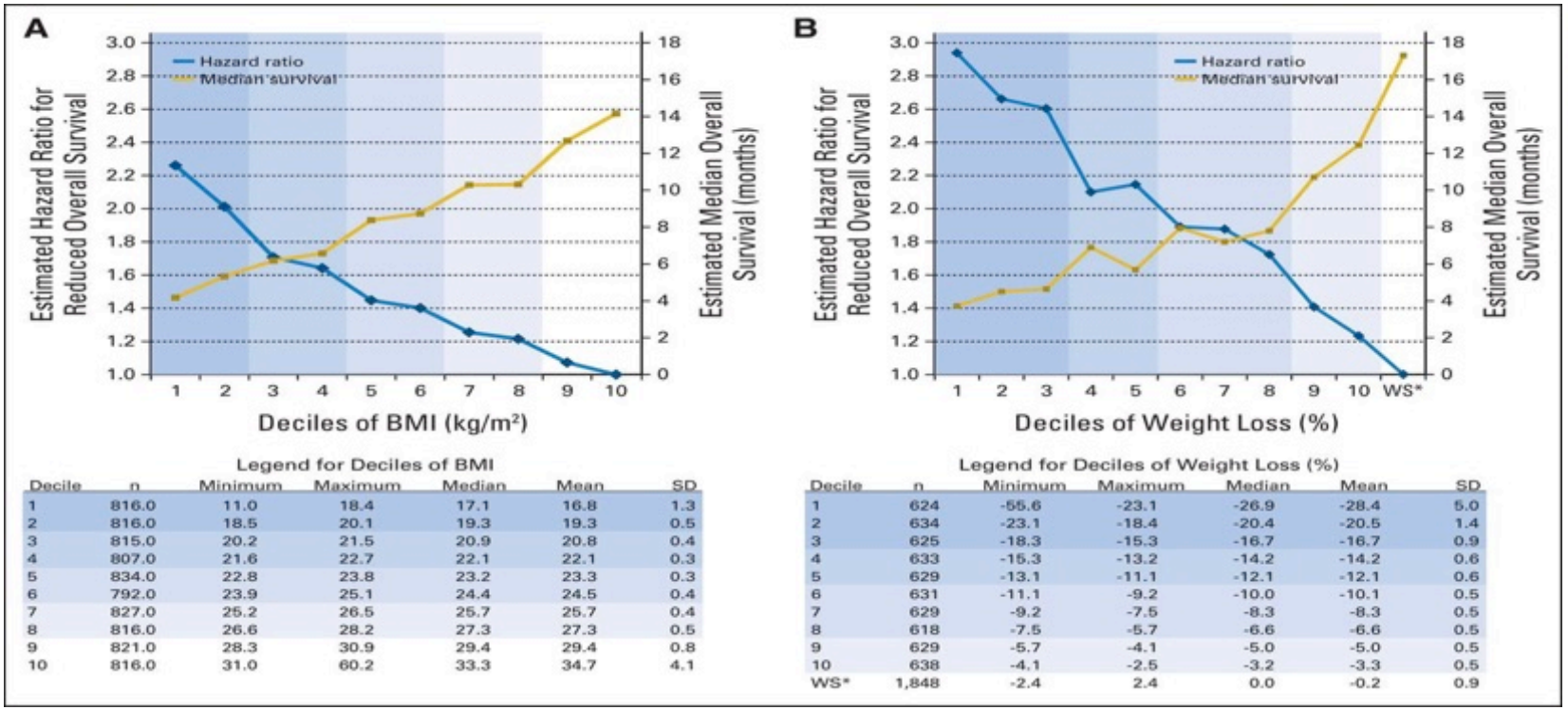
Weight loss and prognosis

- Obesity increasing worldwide
- Classification of Weight loss based on *contemporary* data
- European and Canadian study of 8160 patients
- Prognostic significance of **Weight loss** in patients

who initially have a low, intermediate, or high **BMI**

Published in: Lisa Martin; Pierre Senesse; Ioannis Gioulbasanis; Sami Antoun; Federico Bozzetti; Chris Deans; Florian Strasser; Lene Thoresen; R. Thomas Jagoe; Martin Chasen; Kent Lundholm; Ingvar Bosaeus; Kenneth H. Fearon; Vickie E. Baracos; *JCO* **2015,** 33, 90-99.

Weight loss, BMI ,prognosis



Legend for Deciles of BMI

Decile	n	Minimum	Maximum	Median	Mean	SD
1	816.0	11.0	18.4	17.1	16.8	1.3
2	816.0	18.5	20.1	19.3	19.3	0.5
3	815.0	20.2	21.5	20.9	20.8	0.4
4	807.0	21.6	22.7	22.1	22.1	0.3
5	834.0	22.8	23.8	23.2	23.3	0.3
6	792.0	23.9	25.1	24.4	24.5	0.4
7	827.0	25.2	26.5	25.7	25.7	0.4
8	816.0	26.6	28.2	27.3	27.3	0.5
9	821.0	28.3	30.9	29.4	29.4	0.8
10	816.0	31.0	60.2	33.3	34.7	4.1

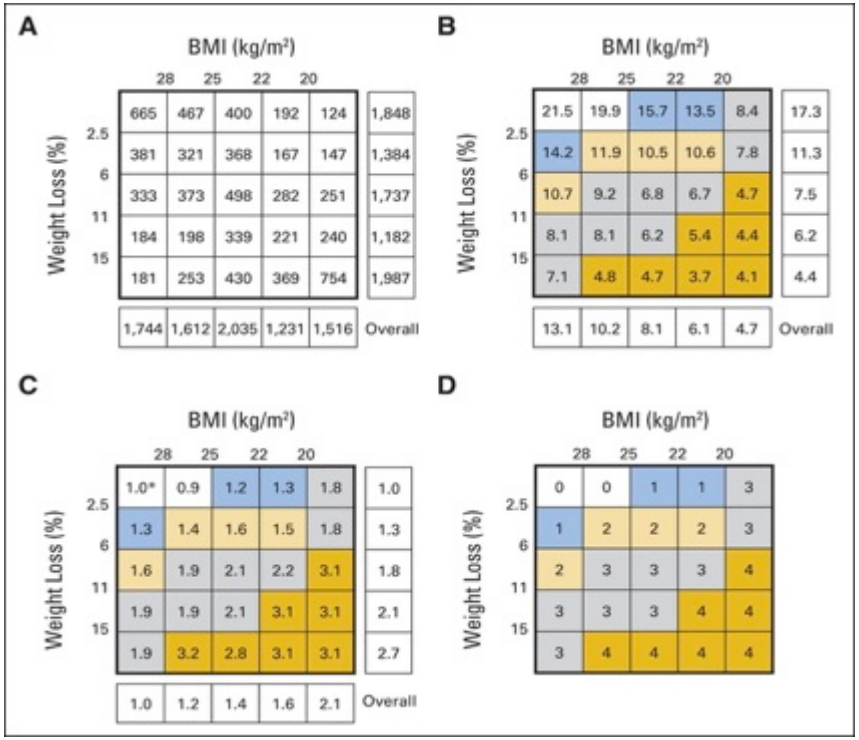
Legend for Deciles of Weight Loss (%)

Decile	n	Minimum	Maximum	Median	Mean	SD
1	624	-55.6	-23.1	-26.9	-28.4	5.0
2	634	-23.1	-18.4	-20.4	-20.5	1.4
3	625	-18.3	-15.3	-16.7	-16.7	0.9
4	633	-15.3	-13.2	-14.2	-14.2	0.6
5	629	-13.1	-11.1	-12.1	-12.1	0.6
6	631	-11.1	-9.2	-10.0	-10.1	0.5
7	629	-9.2	-7.5	-8.3	-8.3	0.5
8	618	-7.5	-5.7	-6.6	-6.6	0.5
9	629	-5.7	-4.1	-5.0	-5.0	0.5
10	638	-4.1	-2.5	-3.2	-3.3	0.5
WS*	1,848	-2.4	2.4	0.0	-0.2	0.9

Fig 1. Line graphs representing the relationships between deciles of (A) body mass index (BMI) and (B) percent weight loss (%WL) to overall survival. Decile 1 represents (A) the lowest BMI and (B) the highest %WL. Decile 10 represents (A) the highest BMI and (B) the lowest %WL. Blue lines represent unadjusted estimated hazard ratios (HRs) associated with reduced overall survival. Reference categories are BMI decile 10 (BMI > 30.9 kg/m2; HR, 1.0) and weight stable (WS; ± 2.4%; HR, 1.0). Risk of reduced survival increases with decreasing BMI and increasing %WL. Gold lines represent the estimated median overall survival in months. Median survival decreases with decreasing BMI and increasing %WL. Different shades of blue in the figures indicate significant differences (P < .05) in median survival between deciles. (*) WS is ± 2.4%.

Published in: Lisa Martin; Pierre Senesse; Ioannis Gioulbasanis; Sami Antoun; Federico Bozzetti; Chris Deans; Florian Strasser; Lene Thoresen; R. Thomas Jagoe; Martin Chasen; Kent Lundholm; Ingvar Bosaeus; Kenneth H. Fearon; Vickie E. Baracos. *JCO* **2015,** 33, 90-99.

Reduced survival = a function of body mass index & percent weight loss

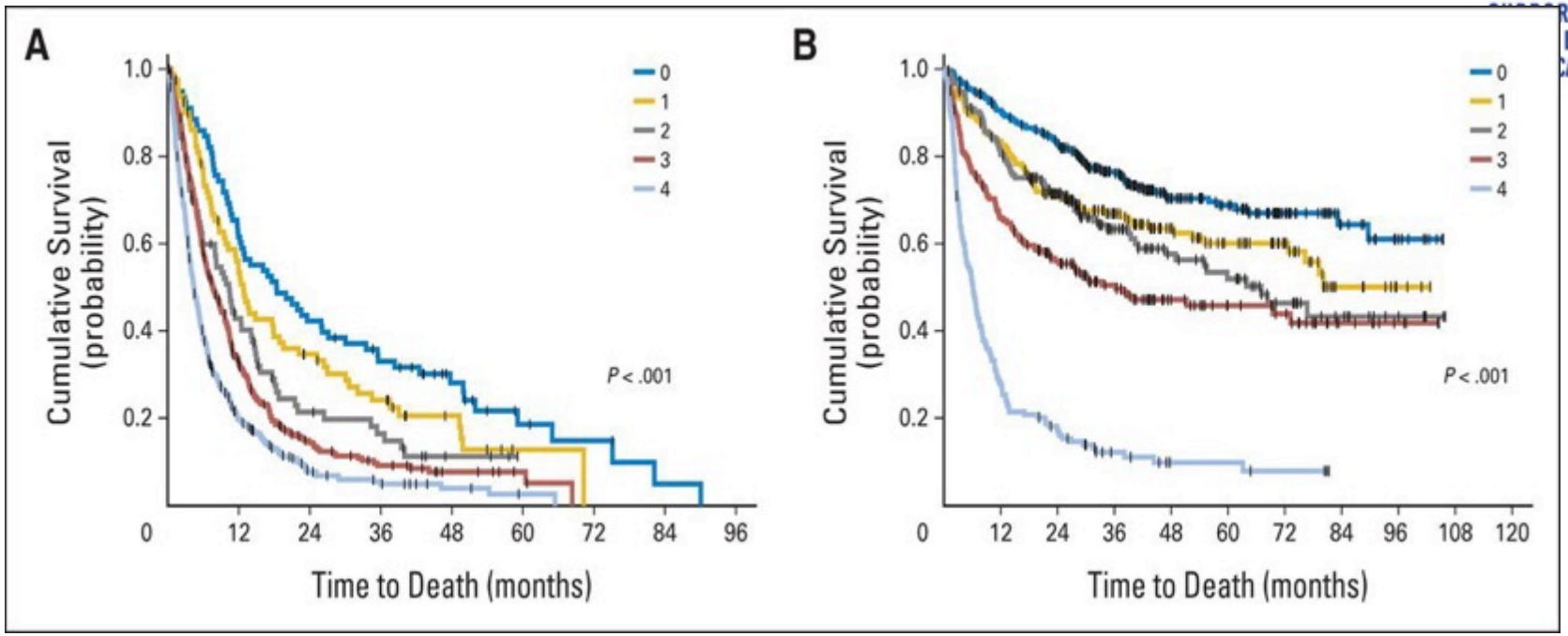


Median survival by grade
0=20.9 months
1=14.6
2=10.8
3=7.6
4=4.3

Panels A to C represent a 5 × 5 matrix analysis of the five categories of BMI and five categories of %WL for a total of 25 possible combinations. The (A) sample size, (B) median overall survival (months), and (C) unadjusted estimated hazard ratios (HRs; HR, 1.0) are presented for each cell. (*) Reference categories are BMI ≥ 28.0 kg/m2 and weight stable ± 2.4%. Different colors represent significant differences (P < .05) in median overall survival and HRs within and between cells of the matrix. Panel D represents the BMI-adjusted WL grading system (grades 0 to 4)

Lisa Martin; Pierre Senesse; Ioannis Gioulbasanis; Sami Antoun; Federico Bozzetti; Chris Deans; Florian Strasser; Lene Thoresen; R. Thomas Jagoe; Martin Chasen; Kent Lundholm; Ingvar Bosaeus; Kenneth H. Fearon; Vickie E. Baracos; *JCO* **2015,** 33, 90-99.

Survival curves from the subgroup analysis for (A) gastroesophageal and (B) head and neck cancers by grade



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JCO **2015,** 33, 90-99.
DOI: 10.1200/JCO.2014.56.1894

Grading system for weight loss in cancer

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- Function of % weight loss and BMI
- Prognosis Independent of cancer site, stage or performance status
- Implications for clinical trial enrollment
- Limitations

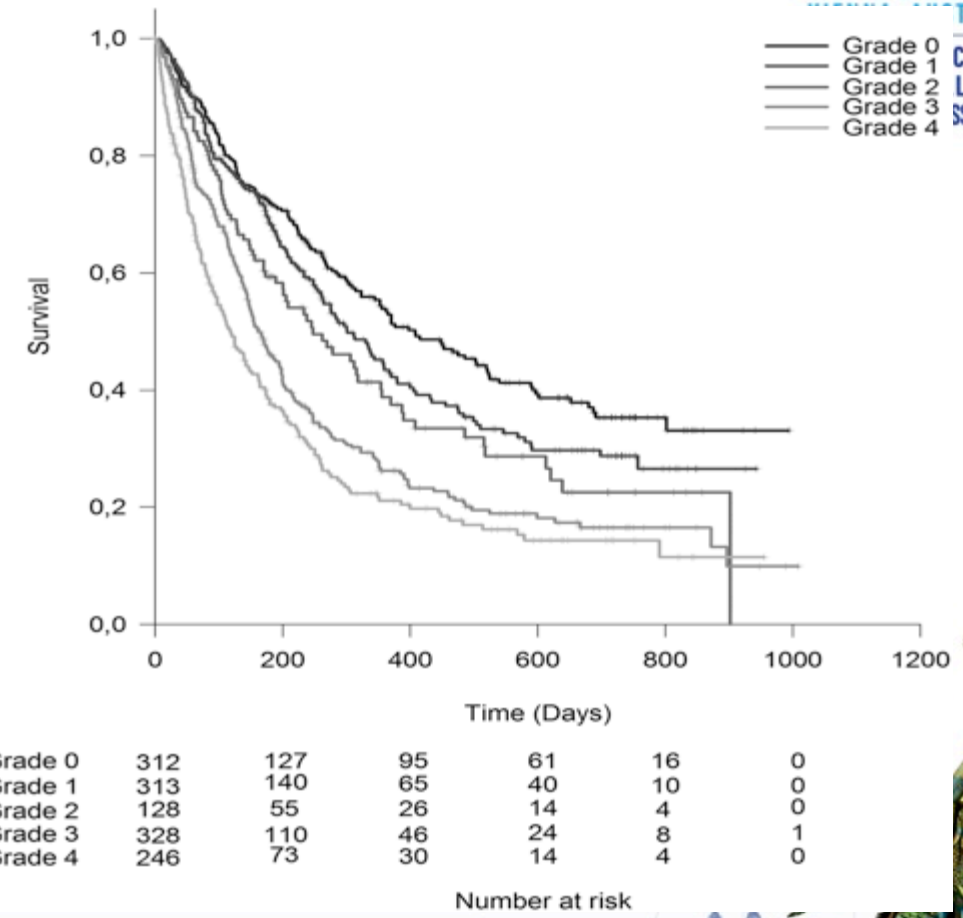
  time frame of weight loss

  performance status measures

  type of chemo

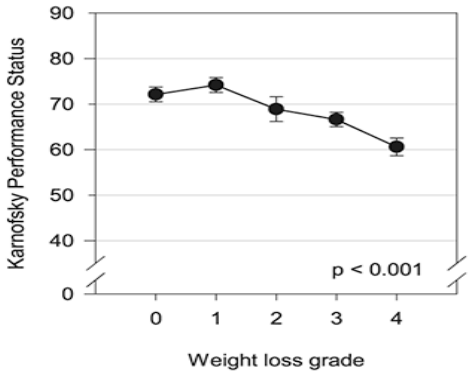
Applicability of a weight loss grading system in cancer cachexia: a longitudinal analysis

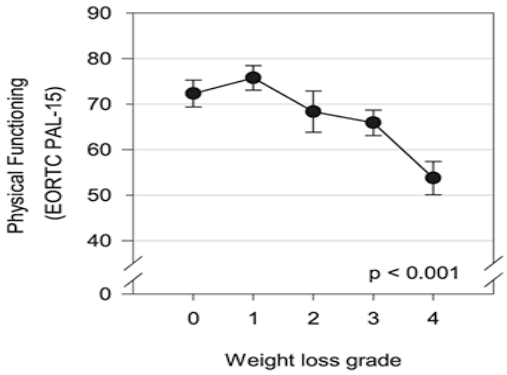
Confirm the system‘s prognostic validity
Relationship to cachexia domains
Ability to predict cachexia progression

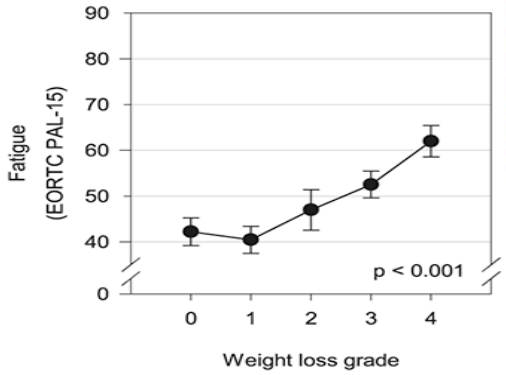


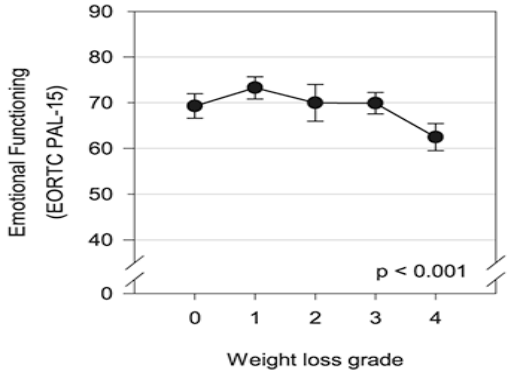
Journal of Cachexia, Sarcopenia and Muscle
Volume 8, Issue 5, pages 789-797, 18 JUN 2017

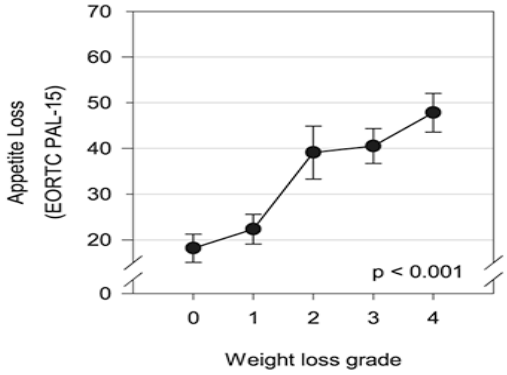
The applicability of a weight loss grading system in cancer cachexia: a longitudinal analysis

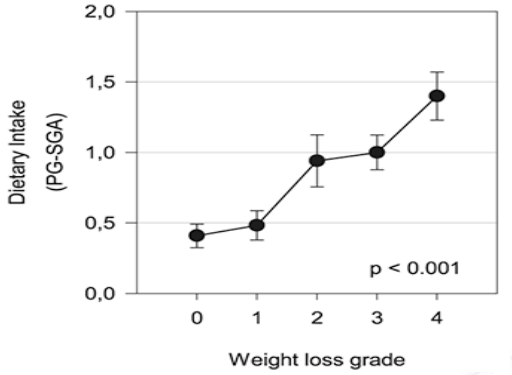








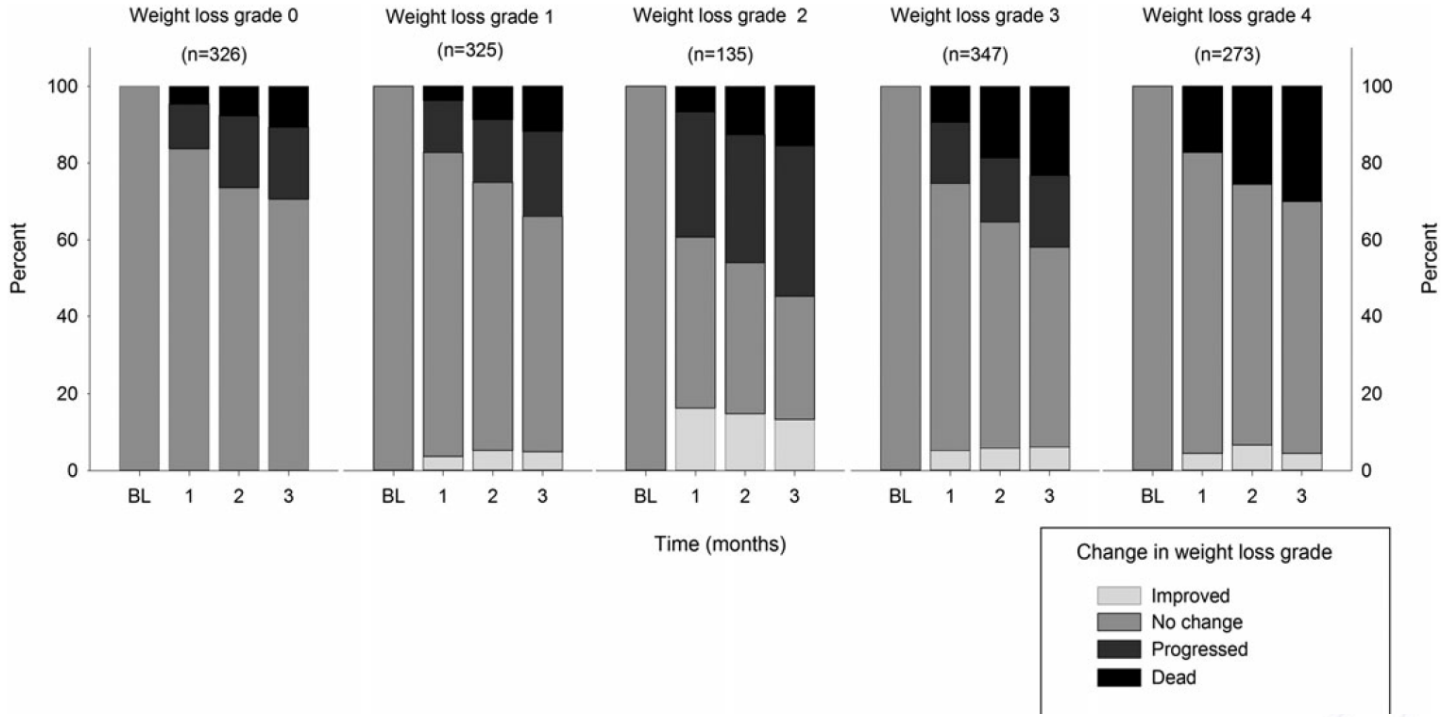




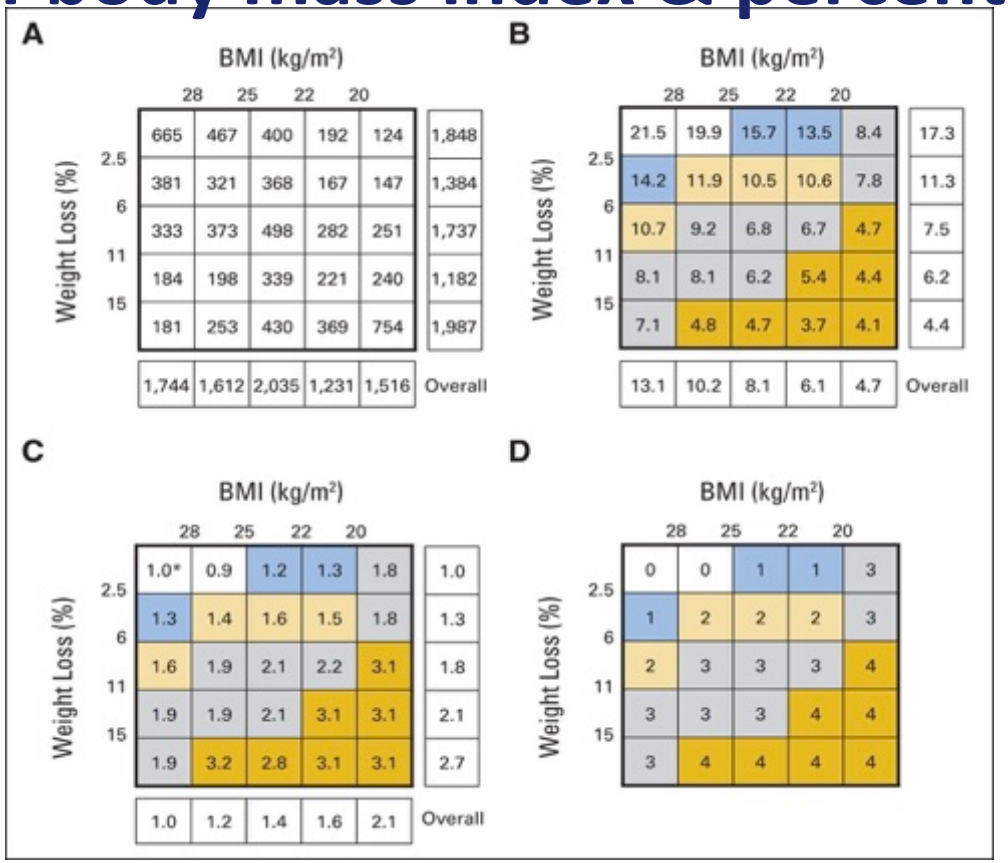
Journal of Cachexia, Sarcopenia and Muscle
Volume 8, Issue 5, pages 789-797, 18 JUN 2017

Identifying progression or reversibility

Figure 4 Bar charts for each baseline weight loss grade (0–4) showing the likelihood of improvement to preceding or progress to subsequent grades death at 1, 2, and 3 months of follow-up.



Reduced survival =
Function of body mass index & percent weight loss



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Additional domains

- Body composition[1]
- Patient reported outcomes

  Appetite[2]

  Nutrition Impact symptoms [3,4]

  Fatigue and function[5]
- Dietary intake[6]
- Physical Function[7]
- Chronic inflammation[8]
- Other- chemo & endocrine dysfunction[9]

1.Prado .Proc nutr Soc 2016 Quinten Lancet Oncology 2011. 2. Farhangfar 2010 Oral Onc. 3.Zhou JPSM 2017 4.Del Fabbro JPM 2010 6. Nasrah Clin Nutr. 2016 9.Burney JCEM2012

Body composition and prognosis

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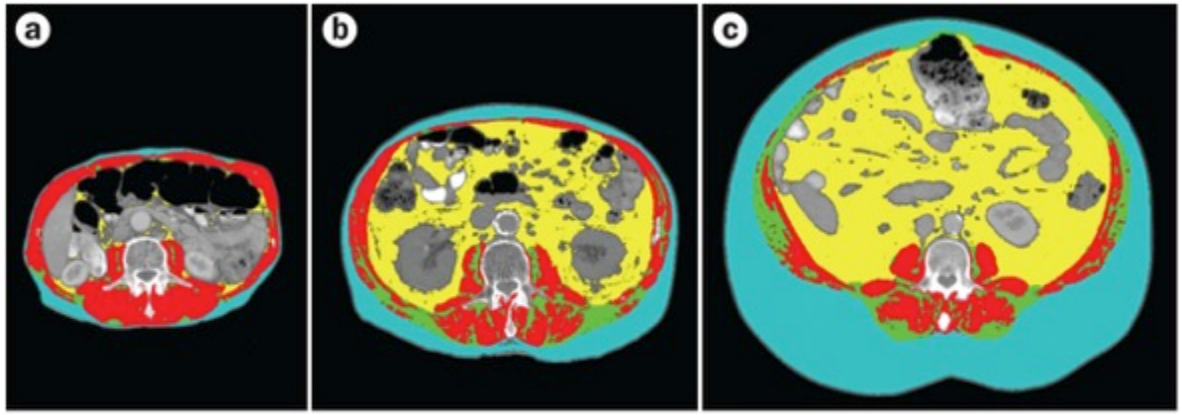
Extensive muscle wasting can be obscured by large fat mass

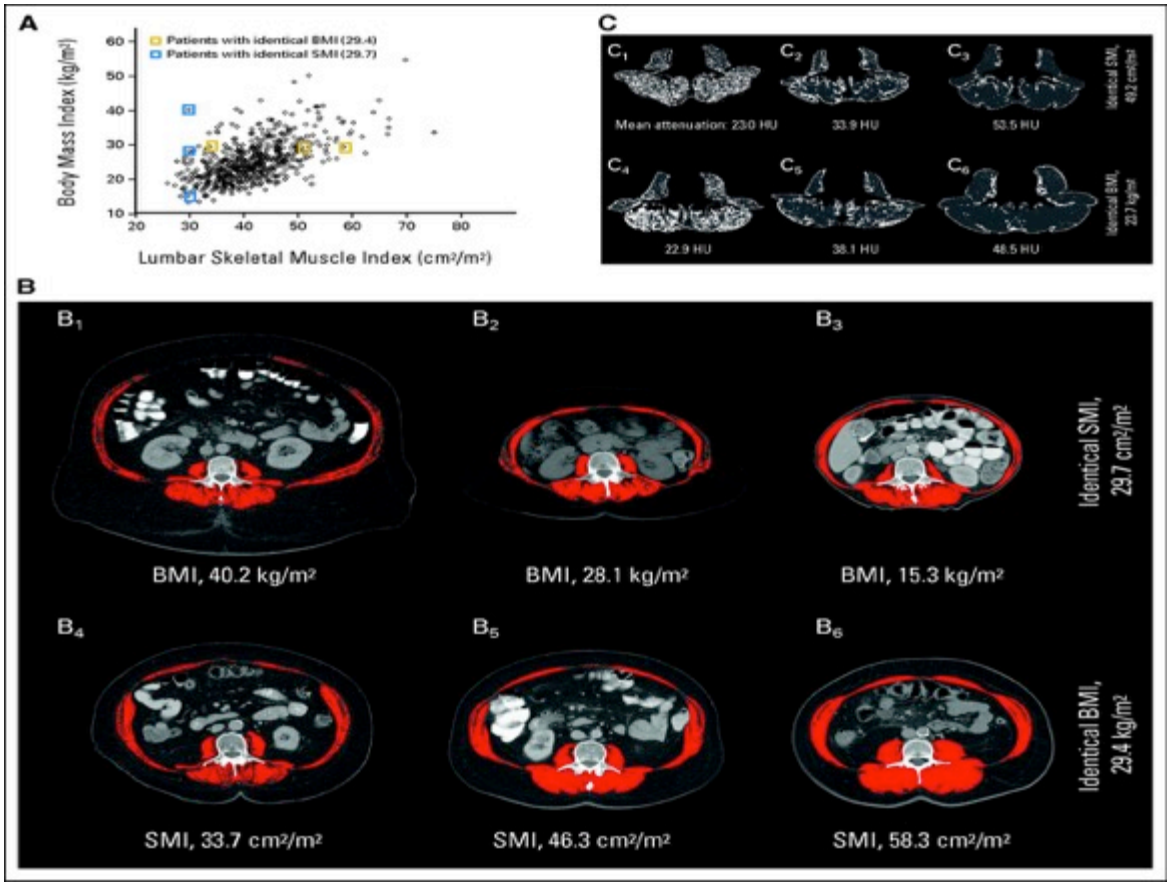


Fearon, K. *et al*. (2012) Understanding the mechanisms and treatment options in cancer cachexia
Nat. Rev. Clin. Oncol.

nature REVIEWS CLINICAL ONCOLOGY

Variation between skeletal muscle index (SMI) and body mass index (BMI)

for females (n = 645)



Martin L et al. JCO 2013;31:1539-1547

Patients with cancer cachexia by the conventional criterion (involuntary weight loss) and by two additional criteria (muscle depletion and low muscle attenuation) share a poor prognosis, regardless of overall body weight

JOURNAL OF CLINICAL ONCOLOGY

The Relationship Between Body Composition and Response to Neoadjuvant Chemotherapy in Women with Operable Breast Cancer

Del Fabbro Oncologist 2012

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- Sarcopenia odds for response 29% lower for each unit higher BMI
- Normal weight (26 pCRs of 44 total) response better in sarcopenia
- How far up or downstream should body composition be evaluated?
- Dosing of chemotherapy better determined by body composition?
- Other methods for evaluating body composition

Ultrasound, Bioimpedance, DEXA,MRI

Body composition and prognosis in 3262 early-stage (I-III)colorectal cancer

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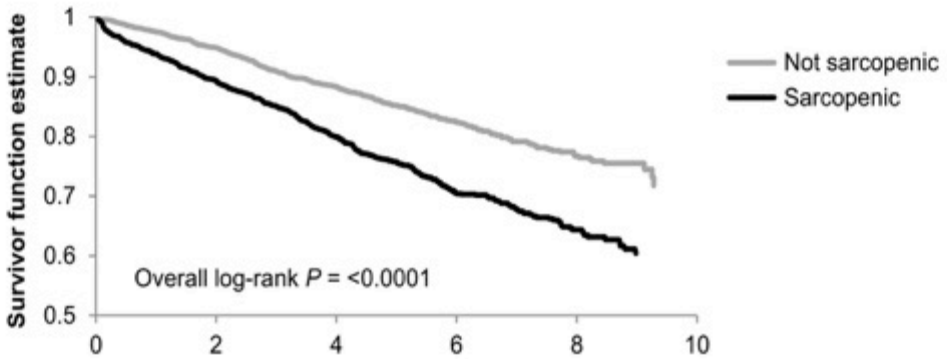
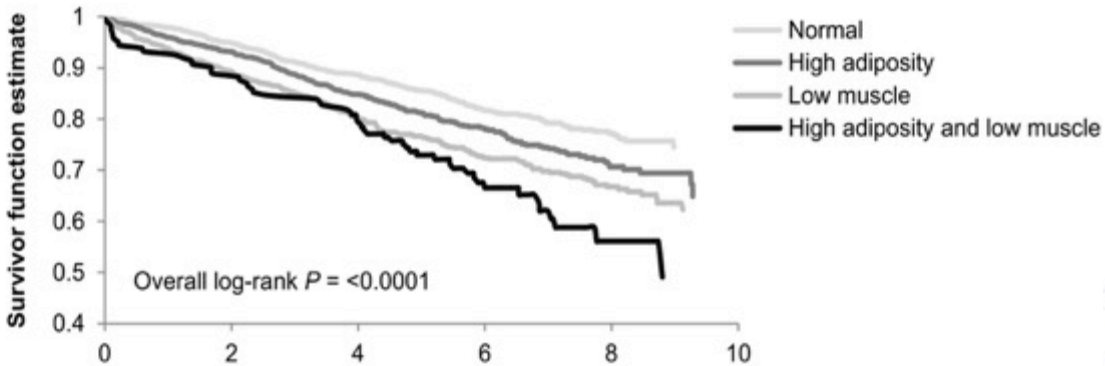
A



#At risk:						
Not sarcopenic	1,879	1,785	1,645	985	320	0
Sarcopenic	1,383	1,238	1,104	654	236	0

B



#At risk						
Normal	1,251	1,188	1,099	656	226	0
High adiposity	925	864	783	460	151	0
Low muscle	925	827	739	459	162	0
Both	161	144	128	64	17	0

Bette J. Caan et al. Cancer Epidemiol Biomarkers

AACR Cancer Epidemiology, Biomarkers & Prevention

Patient Reported Outcomes
HRQOL, symptoms and prognosis in cancer

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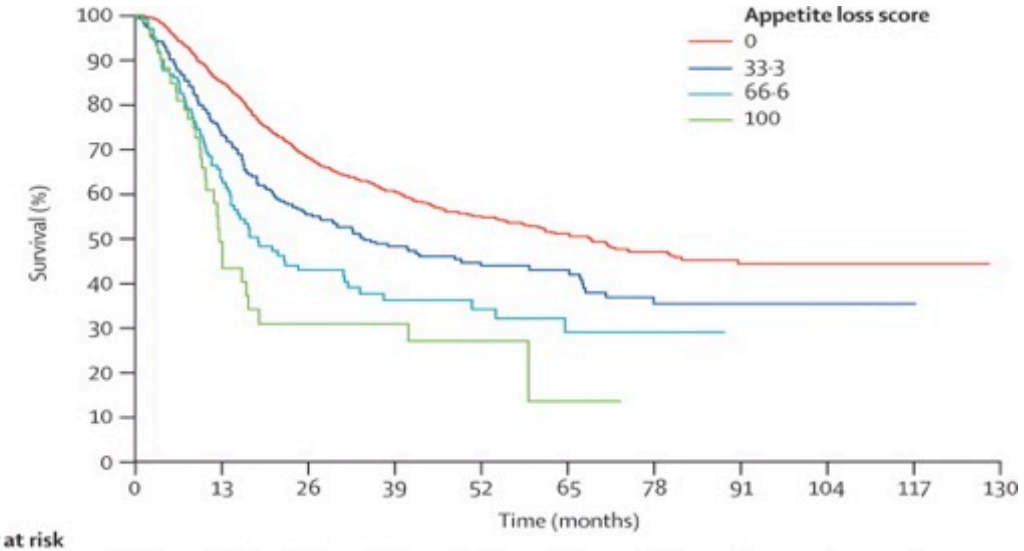
- HRQOL has independent prognostic value for survival

- 104 studies show global quality of life, function domains and symptom scores such as appetite, fatigue and pain were the most important indicators, individually or in combination, for survival *Montezari Health Qual Life out 2009*

Baseline quality of life as prognostic indicator of survival Meta-analysis of individual patient data EORTC clinical trials



Number at risk										
0	1314	984	686	486	310	195	128	46	9	1
33·3	348	205	132	90	60	42	27	12	4	1
66·6	133	65	37	22	17	10	6	0	0	0
100	63	17	9	8	5	1	0	0	0	0

Appetite loss score	Median survival (months; 95% CI)	1-year survival (%; 95% CI)
0	68·86 (58·38–81·12)	86·11 (83·88–87·80)
33·3	35·35 (26·68–59·37)	76·50 (71·38–80·82)
66·6	17·28 (14·39–31·47)	66·19 (56·81–74·00)
100	12·65 (10·64–18·69)	57·94 (42·57–70·63)

Overall survival curves stratified by QLQ-C30 appetite loss scoreQLQ-C30=the European Organisation for Research and Treatment of Cancer quality-of-life core questionnaire

Chantal Quinten, Corneel Coens, Murielle Mauer, Sylvie Comte, Mirjam AG Sprangers, Charles Cleeland, David Osoba, Kristin Bjordal, Andrew Bottomley

Lancet Oncol Volume 10, Issue 9, 2009, 865–871

Baseline QoL: a prognostic indicator of survival

Meta-analysis: patient data from EORTC clinical trials *Quinten*

2009 Lancet Oncol

- HRQOL parameters of physical functioning, pain and appetite loss $p<0{\cdot}0001$ provided significant prognostic information in addition to
- age
- sex
- distant metastases $p<0{\cdot}0001$

Nutritional Impact Symptoms and treatment

In a Cancer Cachexia Clinic

Del Fabbro ,Hui ,Dalal ,Dev ,Bruera et al. *J Pall Med*. 2011;14:1004-1008.

Nutrition Impact Symptoms	Number Affected (%)	Corresponding Intervention	Number Treated Among Affected (%)
Early satiety	94 (62)	Metoclopramide	74 (79)
Constipation	78 (52)	Laxative	68 (87)
Nausea/vomiting	67 (44)	Antiemetic (metoclopramide)	54 (81)
Depressed mood	63 (42)	Antidepressant (mirtazapine)	51 (81)
Dysgeusia	42 (28)	Zinc supplement	20 (48)
Dysphagia	21 (14)	G I/speech therapy	5 (24)
Dry mouth	14 (9)	Artificial saliva	2 (14)
Mucositis pain	11 (7)	Opioid, topical mouthwash	3 (27)
Dental issues	8 (5)	Dental referral	2 (25)

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Patient ID Information

History (Boxes 1-4 are designed to be completed by the patient.)

1. Weight *(See Worksheet 1)*

In summary of my current and recent weight:

I currently weigh about _____ pounds
I am about _____ feet _____ tall

One month ago I weighed about _____ pounds
Six months ago I weighed about _____ pounds

During the past two weeks my weight has:
☐ decreased (1) ☐ not changed (0) ☐ increased (0)

Box 1

2. Food Intake: As compared to my normal intake, I would rate my food intake during the past month as:

- ☐ unchanged (0)
- ☐ more than usual (0)
- ☐ less than usual (1)

I am now taking:

- ☐ *normal food* but less than normal amount (1)
- ☐ little solid food (2)
- ☐ only liquids (3)
- ☐ only nutritonal supplements (3)
- ☐ very little of anything (4)
- ☐ only tube feedings or only nutrition by vein (0)

Box 2

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply):

- ☐ no problems eating (0)
- ☐ no appetite, just did not feel like eating (3)
- ☐ nausea (1)
- ☐ constipation (1)
- ☐ mouth sores (2)
- ☐ things taste funny or have no taste (1)
- ☐ problems swallowing (2)
- ☐ pain; where? (3)_____
- ☐ other** (1) _____
- ☐ vomiting (3)
- ☐ diarrhea (3)
- ☐ dry mouth (1)
- ☐ smells bother me (1)
- ☐ feel full quickly (1)
- ☐ fatigue (1)

** Examples: depression, money, or dental problems

Box 3

4. Activities and Function: Over the past month, I would generally rate my activity as:

- ☐ normal with no limitations (0)
- ☐ not my normal self, but able to be up and about with fairly normal activities (1)
- ☐ not feeling up to most things, but in bed or chair less than half the day (2)
- ☐ able to do little activity and spend most of the day in bed or chair (3)
- ☐ pretty much bedridden, rarely out of bed (3)

Box 4

Additive Score of the Boxes 1-4 _____ A

Findings and Clinical outcomes

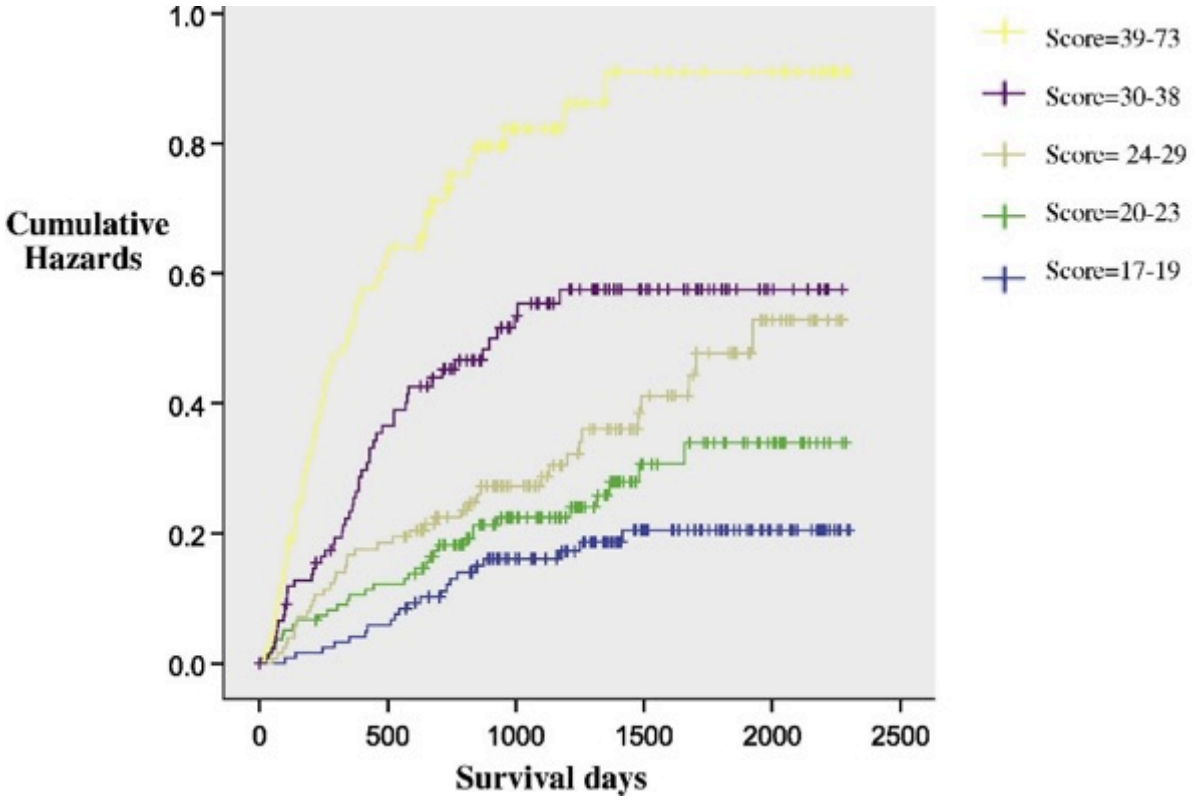
- The median number of NIS = 3
  66% = 2-4 NIS
  20% = 5-8 NIS

- Higher number of NIS associated with
  poor appetite p=0.008
  weight loss p=0.036

- Appetite score improved from 7 to 5 p=0.001

- 34% of patients gained weight

Nutrition impact symptoms in a population cohort of head & neck cancer patients: Multivariate regression analysis of symptoms on oral intake, weight loss and survival



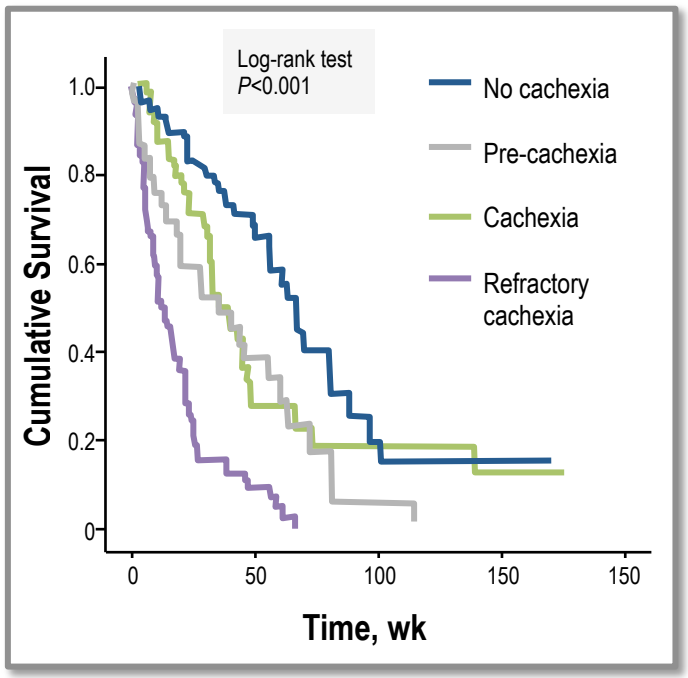
Cumulative hazard plots of survival (days) for total symptom score quintiles.

Arazm Farhangfar, Marcin Makarewicz, Sunita Ghosh, Naresh Jha, Rufus Scrimger, Leah Gramlich, Vickie Baracos
Oral Oncology, Volume 50, Issue 9, 2014, 877–883

Using Multiple Domains

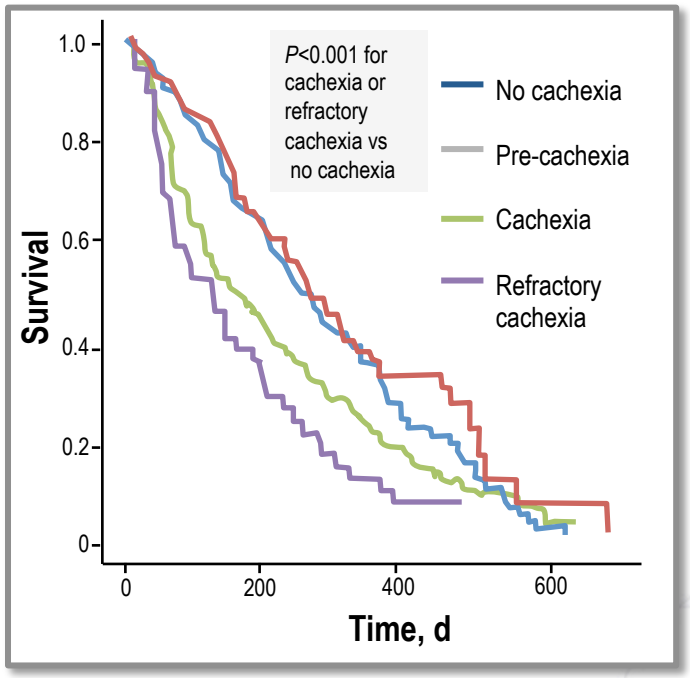
Weight loss, BMI, appetite, imaging, lab data for Cancer Cachexia stages

Consensus criteria for weight and BMI, plus biochemical markers and patient characteristics : Lung and GI cancer



- N=207
- Metastases, 66%[1]

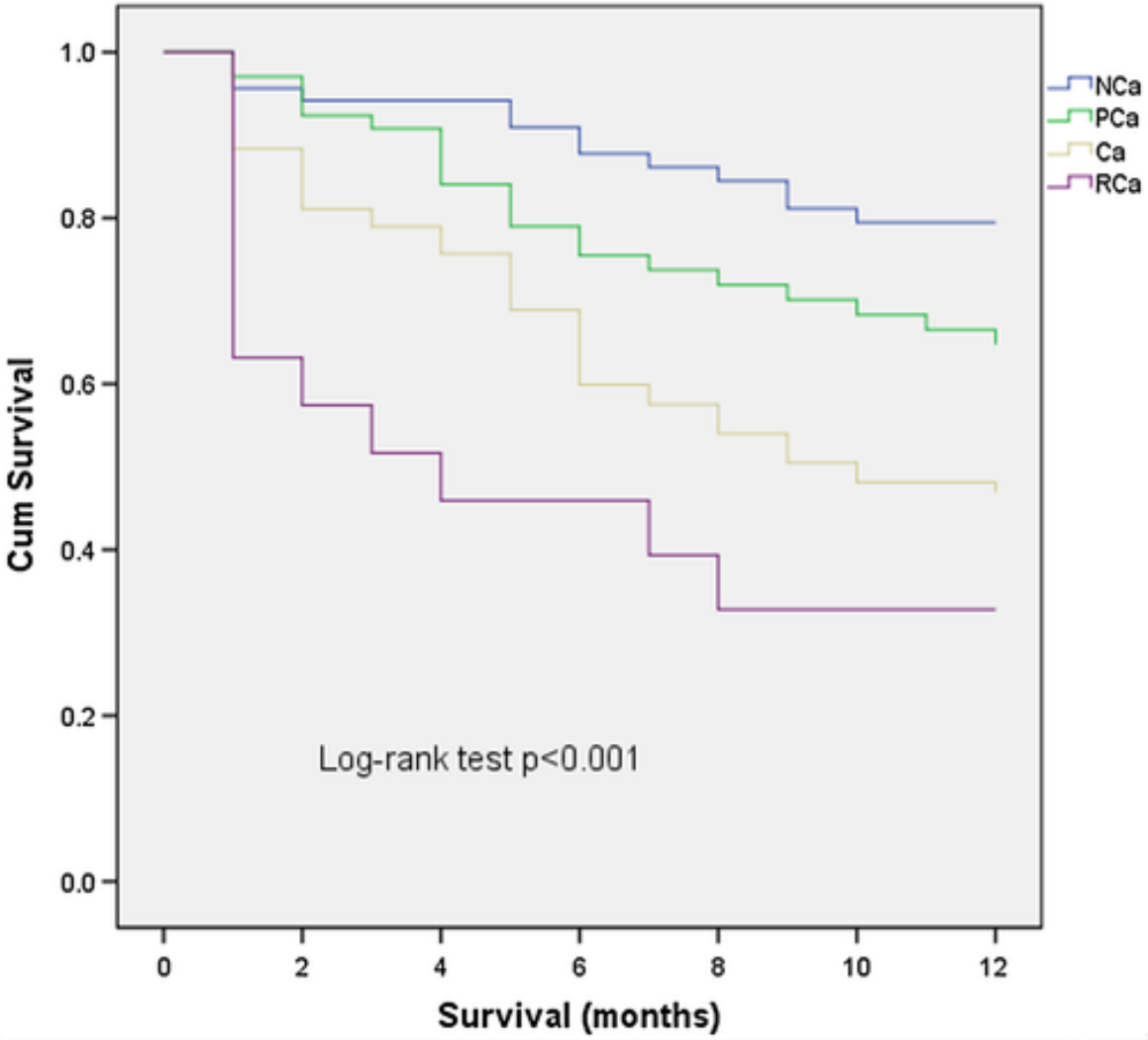
Consensus criteria for weight and BMI multiple cancer types



- N=861
- Metastases, 85%[2]

1. Vigano A, et al. *Crit Rev Oncog*. 2012;17:293-303; 2.. Blum D, et al. *Ann Oncol*. 2014;25:1635-1642 3.Argiles ,CASCO JCSM 2011

Development and validation of a clinically applicable score to classify cachexia stages in advanced cancer patients



Zhou T.J Cachexia Sarcopenia Muscle. 2018

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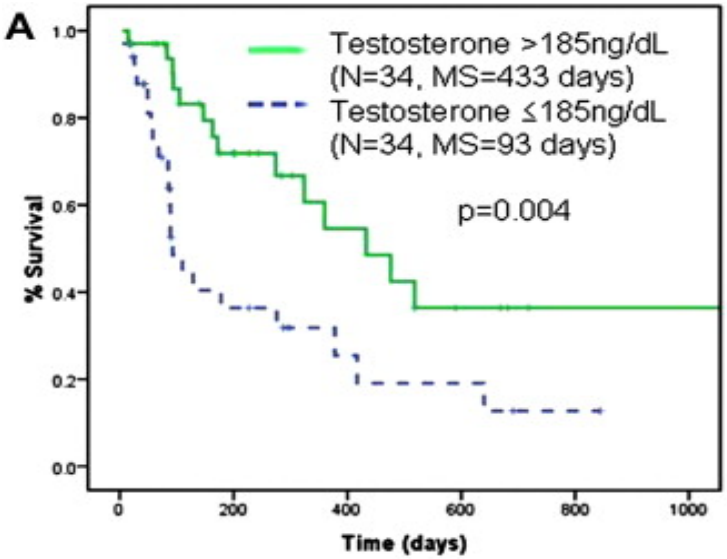
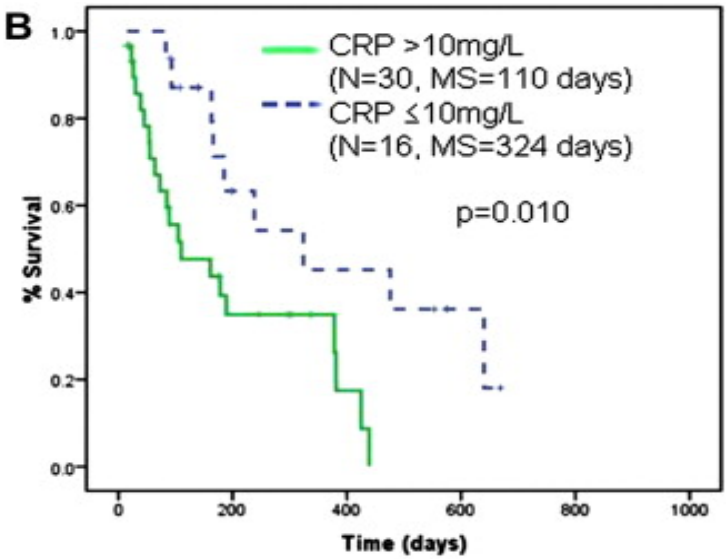
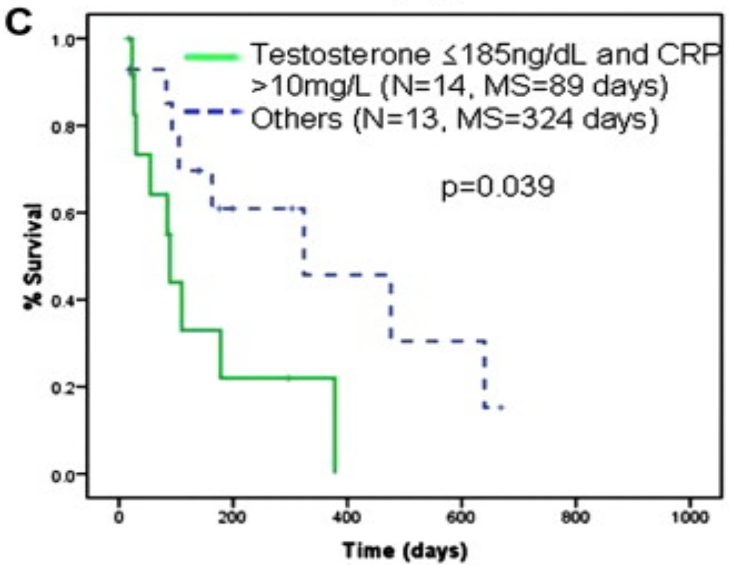
Other markers or domains in cachexia







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Survival analyses (Kaplan-Meier) with comparisons of curves . Survival of male patients with testosterone levels ≤185 ng/dL (blue) was decreased.

Associations Among Hypogonadism, C-Reactive Protein, and Survival in Male Cancer Patients with Cachexia

Egidio Del Fabbro, David Hui, Zohra I. Nooruddin, Shalini Dalal, Rony Dev, Gina Freer, Lynn Roberts, J. Lynn Palmer, Eduardo Bruera

www.mascc.org/meeting
Journal of Pain and Symptom Management, Volume 39, Issue 6, 2010, 1016–1024

Summary

- Consensus Cancer Cachexia definition updated
- Core criterion =weight loss

  Weight loss criteria modified by initial BMI
- Validated by large study resulting in grading system 0-4
- Additional domains may enhance the system
- Importance of appetite and NIS
- Body composition throughout trajectory
- Identify patients in clinical practice,

  prognosticate, design and inclusion of subjects in clinical trials


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