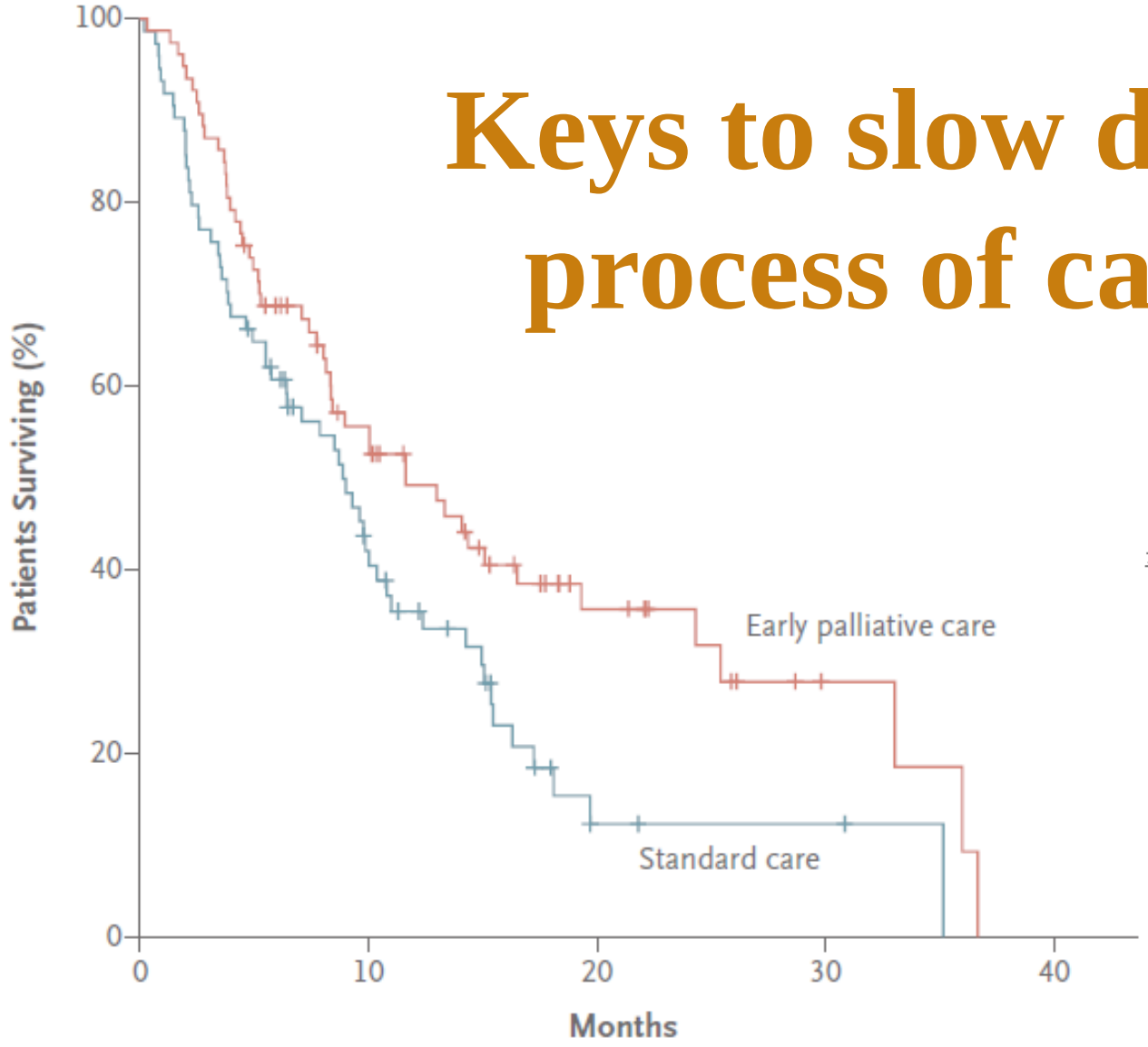
Keys to slow down the process of cachexia



奇美醫院 血液腫瘤科

陳威宇醫師

Cachexia is a family problem needed to be solved

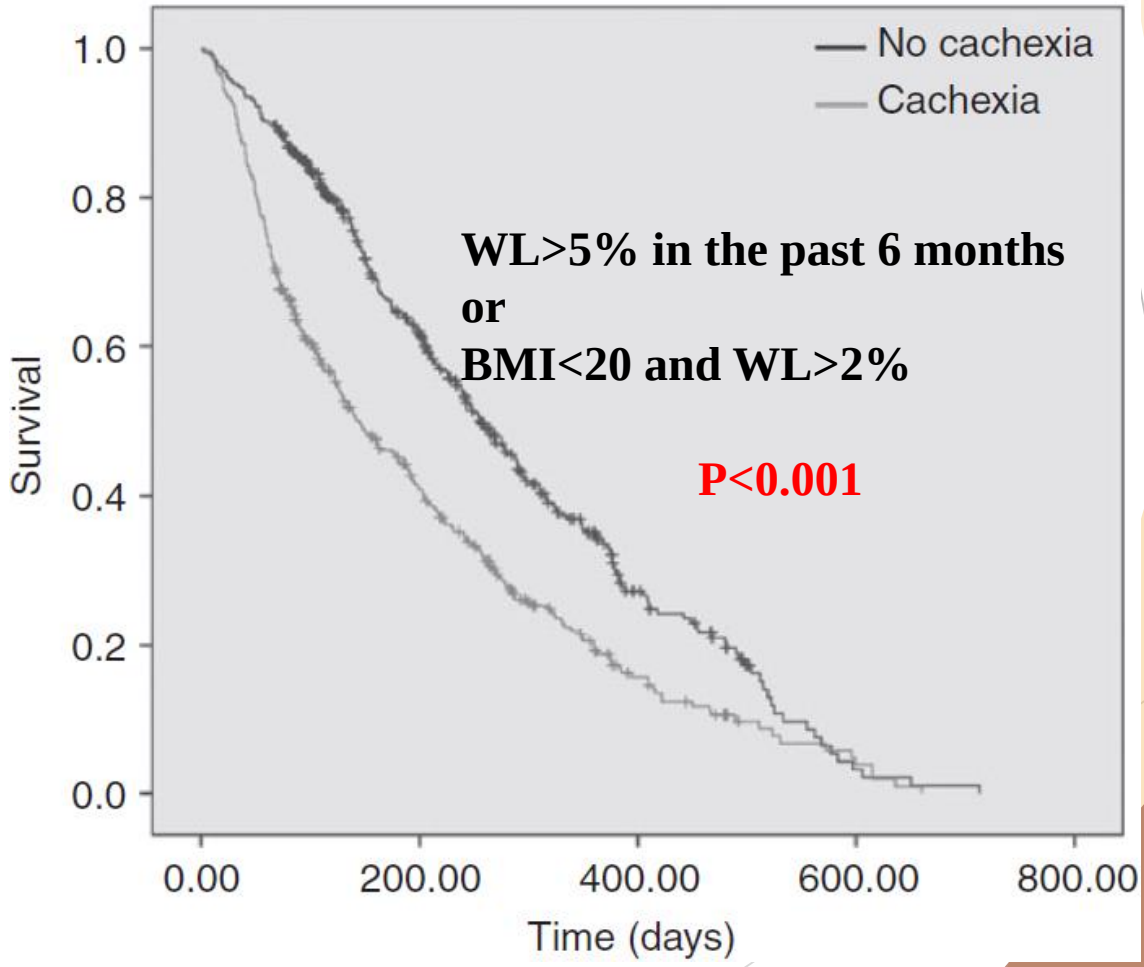
Cancer cachexia reduced survival

No cachexia: 255 days
Cachexia: 142 days

→ **4 months** difference

861 cancer patients;

Cancer types:
Digestive organs: 28%
Breast cancer: 17%
Respiratory organs: 16%
Male genital organs: 11%
Head: 3%
Others: 26%



Blum, et al Annals of Oncology (2014)

Both malignancy and therapy cancer would cause cachexia

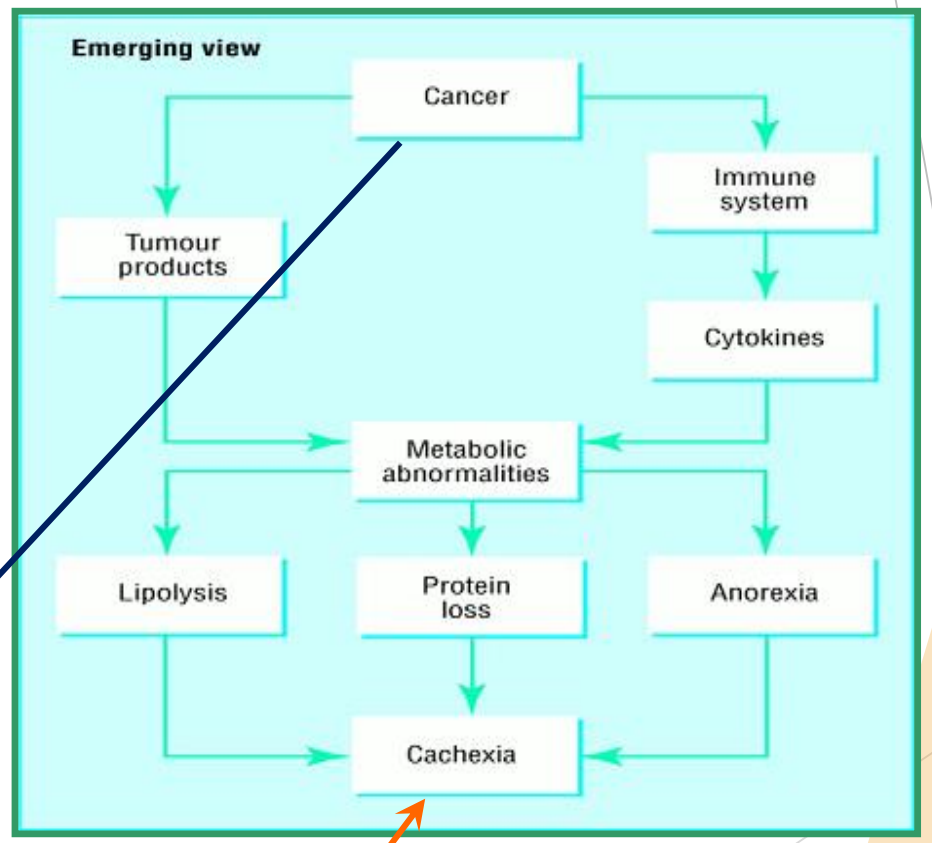
Cause of cancer cachexia

Anorexia of malignancy
- Anorectic factors produced by tumor or host
- Pain
- GI tract obstruction

Anorexia of therapy
- Chemotherapy
- Radiation therapy
- Surgery

Abnormal host intermediary metabolism

JPEN 12:286-298,1988

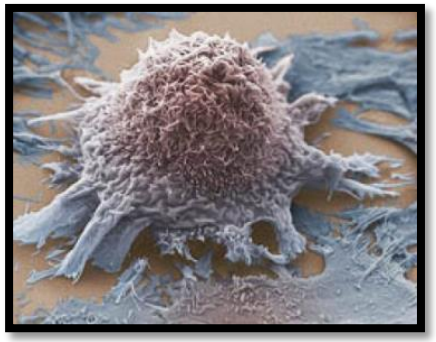


Chronic nausea
Altered taste
Dyspepsia
Pain
Depression

↓Food intake

BMJ. 1997 Nov 8;315(7117):1219-22

Vicious cycle of cancer cachexia

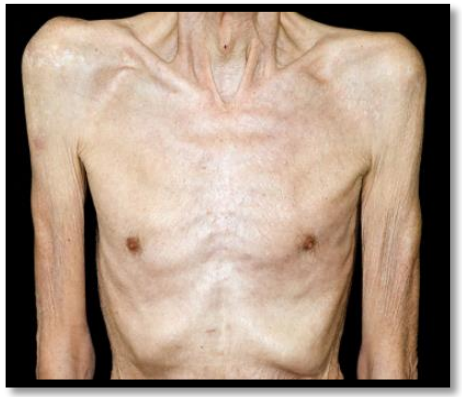


Tumor

Anorexia + Weight loss

Treatment delay

Cancer cachexia



JPEN 12:286-298,1988
Argiles *et al*, *Clinical Nutrition* (2013) 1-6

Definition of cancer cachexia

--an international consensus

One of the definitions matching is cachexia

Panel: Diagnosis of Cancer Cachexia
• Weight loss >5% over past 6 months (in absence of simple starvation)
• BMI <20 and any degree of weight loss >2%
• 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%†

*Defined reference values (sex-specific) and standardised body composition measurements are essential to undertake assessment of skeletal muscle depletion. Although there is a paucity of reference values related to cancer-specific outcomes, a generally accepted rule is an absolute muscularity below the 5th percentile. This can be assessed as follows: mid upper-arm muscle area by anthropometry (men <32 cm^2, women <18 cm^2);31 appendicular skeletal muscle index determined by dual energy x-ray absorptiometry (men <7 · 26 kg/m^2; women <5 · 45 kg/m^2); lumbar skeletal muscle index determined by CT imaging (men <55 cm^2/m^2; women <39 cm^2/m^2);33 whole body fat-free mass index without bone determined by bioelectrical impedance (men <14 · 6 kg/m^2; women <11 · 4 kg/m^2).3
†A direct measure of muscularity is recommended in the presence of fluid retention, a large tum our mass, or obesity (overweight).

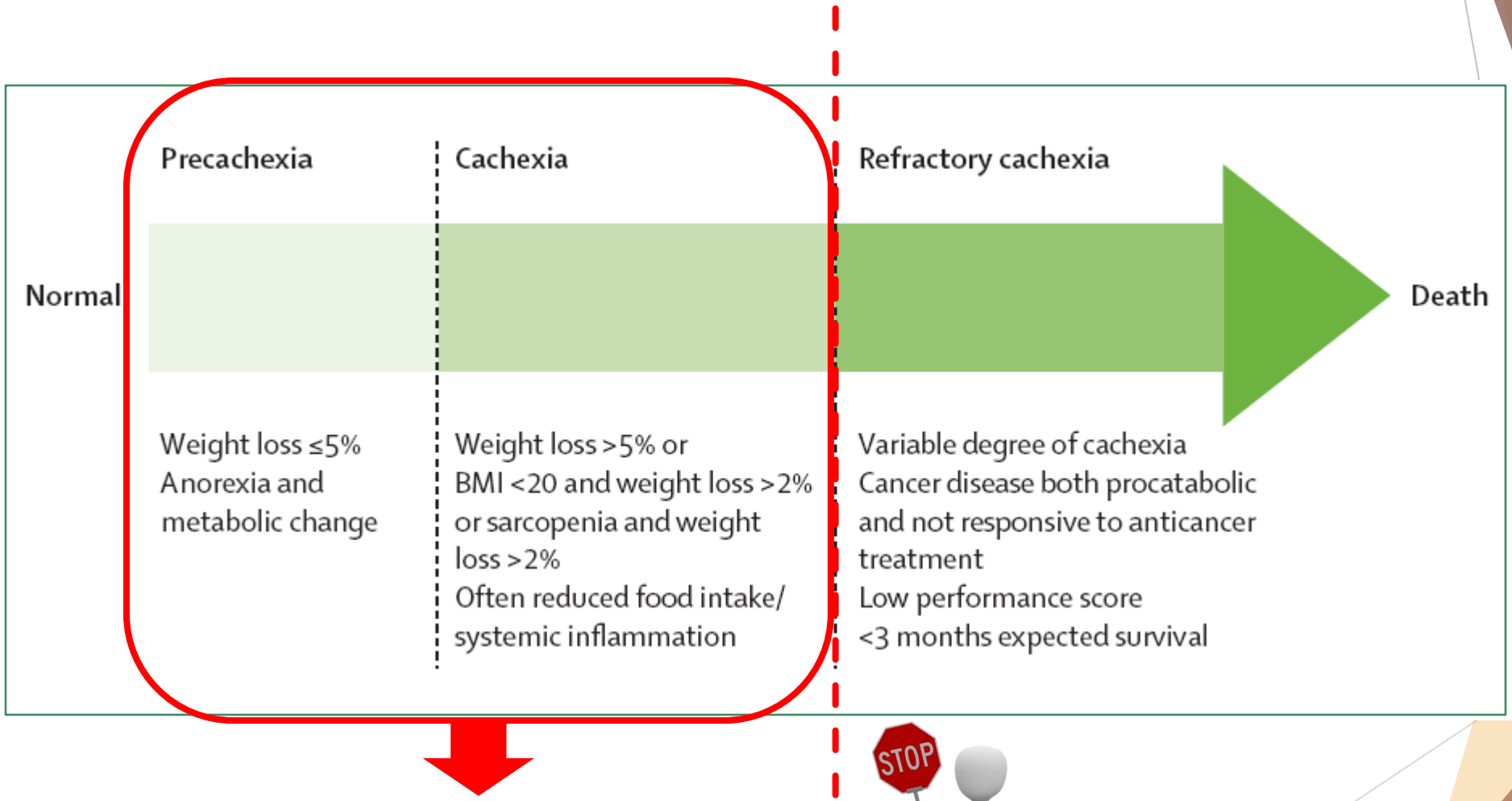
Fearon, K.et al. Lancet Oncol.12, 489-495 (2011)

Six highly prevalent advanced cancer types in cancer cachexia

Ranking	Cancer type	Cachexia (%)
1	**Pancreatic cancer**	88.9%
2	**Gastric cancer**	76.5%
3	**H&N cancer**	53.2%
4	**Esophageal cancer**	52.9%
5	**Lung cancer**	50.0%
6	**Colon rectal cancer**	42.9%

1, Journal of Oncology doi:10.1155/2009/693458
2. Anticancer Res. 2014 Jan;34(1):9-21.
3. Lung Cancer 88 (2017) 304–309
4. Am J Med 1980;69(4):491-97.
5. HEAD & NECK—DOI 10.1002/HED APRIL 2017

Different stages of cachexia



發現惡病質潛在病人，及早治療！
防止病人走入refractory cachexia stage

Fearon, K.et al. Lancet Oncol.12, 489-495 (2011)

NCCN Guideline Recommendation

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Palliative Care

NCCN Guidelines Index
Table of Contents
Discussion

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 solution 1–2 drops SL q4h PRN OR glycopyrrolate, 0.2–0.
Anorexia/ Cachexia (PAL-13)	Life Expectancy: Years; Year to Months • Depression/anorexia: Mirtazapine, 7.5–30 mg PO 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 PO
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 PO OR olanzapine, 5 mg/d PO OR dexamethasone, 4–8 mg/d PO OR consider cannabinoid • Depression: Mirtazapine, 7.5–30 mg PO QHS

1. 先找到病人體重減輕的原因，並進行治療
2. 食慾不振時，建議處方Megestrol acetate

Megest® 麥格斯

- **適應症：**

  - ✓ 癌症患者之惡病體質引起的體重明顯減輕 。
  - ✓ 後天免疫缺乏症候群患者的厭食症，及後天免疫缺乏症候群患者之惡病體質引起的體重明顯減輕。

- **健保給付規範：**

  - ✓ 限用於已排除其他可治療之體重減輕（如全身性感染、影響吸收的腸胃道疾病、內分泌疾病、腎臟或精神病）之具惡病質的後天免疫缺乏症候群患者及癌症患者。
  - ✓ 惡病質之條件包括最近 6 個月以上體重流失>5%，或BMI<20 且體重流失>2%。

- **健保價：$803 /120mL/瓶**
- **建議劑量：10-20cc/day**
- **國際疾病分類碼:**

✧ ICD-10-CM…Cachexia : R64　✧ Abnormal weight loss : R63.4

40mg/mL

63% H&N patients were observed weight loss before CCRT

INFLUENCE OF WEIGHT LOSS ON OUTCOMES IN PATIENTS WITH HEAD AND NECK CANCER UNDERGOING CONCOMITANT CHEMORADIOTHERAPY

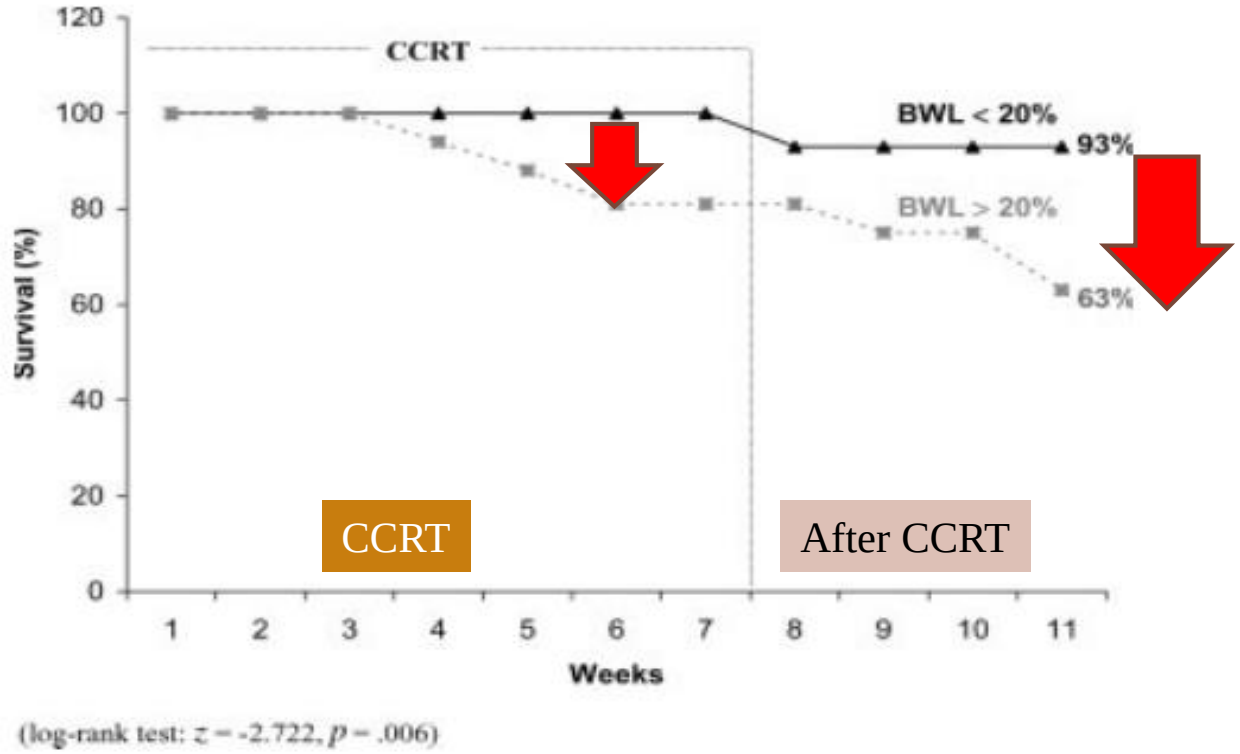
Giorgio Capuano, MD,[1] Alessandra Grosso, MD,[1] Pier Carlo Gentile, MD,[2] Michele Battista, MD,[2] Federico Bianciardi, MD,[2] Annamaria Di Palma, MD,[2] Ida Pavese, MD,[3] Francesco Satta, MD,[3] Michela Tosti, RN,[3] Anna Palladino, RN,[3] Guido Coiro, MD,[3] Mario Di Palma, MD[3]

[1] Clinical Nutrition Unit, Ospedale San Pietro, Fatebenefratelli, Rome, Italy. E-mail: capuano.giorgio@fbfrm.it
[2] Radiotherapy Unit, Ospedale San Pietro, Fatebenefratelli, Rome, Italy
[3] Medical Oncology Unit, Ospedale San Pietro, Fatebenefratelli, Rome, Italy

- From 2003-2006, 40 patients with locally advanced unresectable and nonmetastatic (stage III to IVA) head and neck cancer, who were referred for a CCRT.
- At baseline, involuntarily **weight loss of medium 4% (range 0-25%)** was observed in **63%** of the patients before treatment.
- Nutritional program before, during and after CCRT were conducted.

Head Neck. 2008 Apr;30(4):503-8.

Body weight loss during or after CCRT would negatively influenced patients' survival



- Thirty days after CCRT, twenty-three patients (57.5%) were body weight loss> 20%

Head Neck. 2008 Apr;30(4):503-8.

Megestrol acetate could help slow down body weight loss in H&N ca pts during CCRT

H&N ca pts (n=61)
1. Age 18~75 yrs
2. Weight loss 5% over 6 weeks or 10% over 6 months
3. Treated with CCRT
4. Ingestion of food by mouth or feeding via NG tube

RANDOMIZED

MA 160mg/day, D1-D84 (n=31)

Placebo, D1-D84 (n=30)

During RT (CCRT) and up to 6 weeks **thereafter**

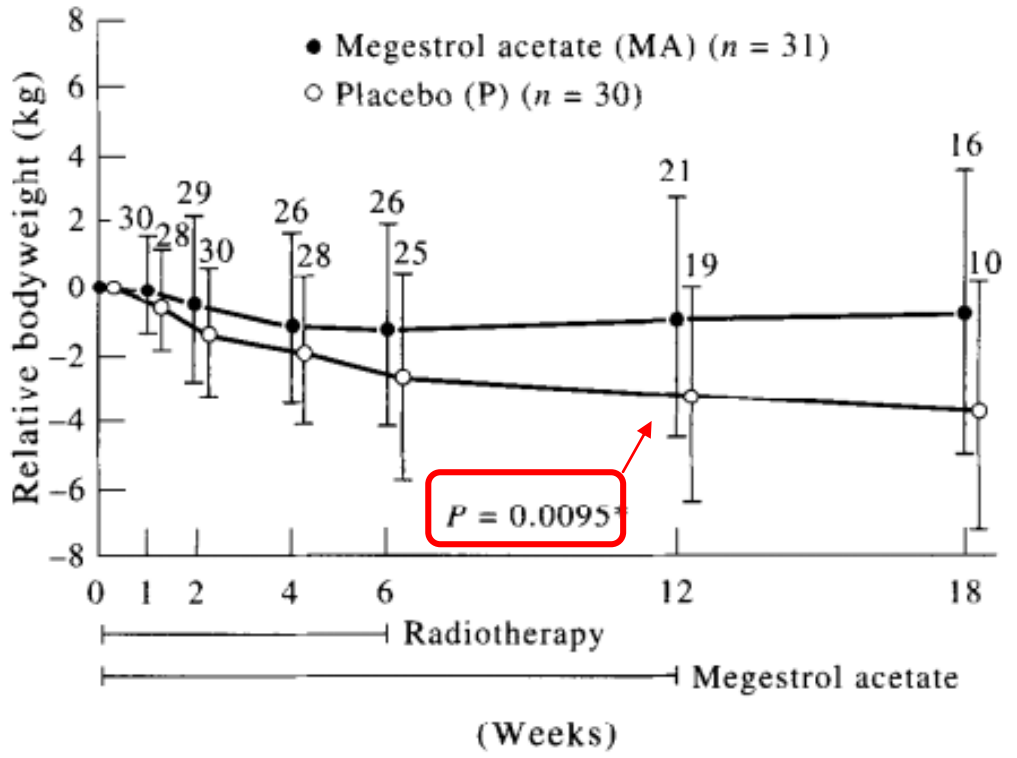


Figure 1. Relative values of body weight in patients of the control group (placebo) and those treated with megestrol acetate. The figures above the bars represent the number of documented patients. For calculation see text (mean + S.D.).

European Journal of Cancer Vol. 33, No. 1, pp. 75-79, 1997

Higher dose & longer period of MA gained more weights

Trial 1

AIDS-associated weight loss (n=236)

RANDOMIZED

1:2:2:2

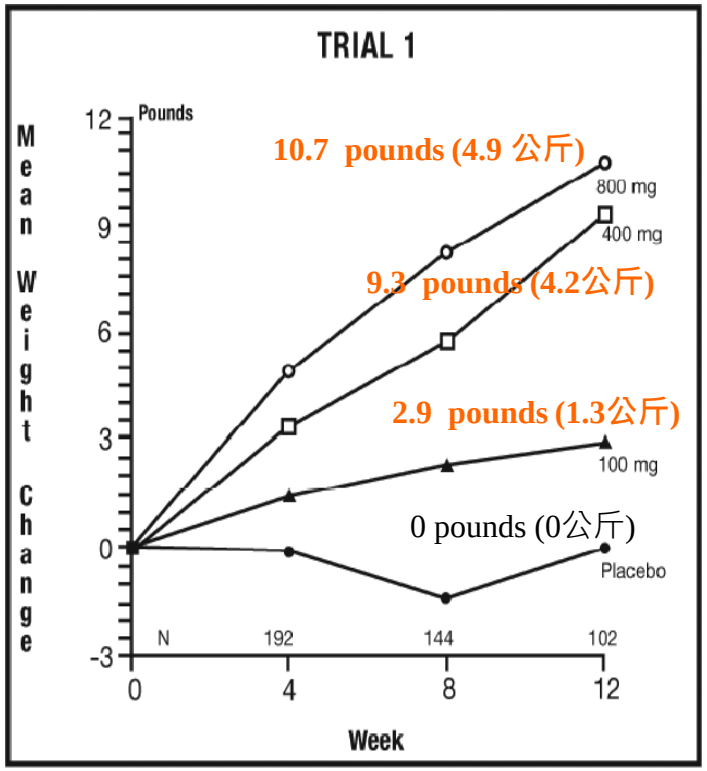
- **Placebo, D1-D84 (n=34)**
- **MA 100mg/day, D1-D84 (n=68)**
- **MA 400mg/day, D1-D84 (n=69)**
- **MA 800mg, D1-D84 (n=65)**

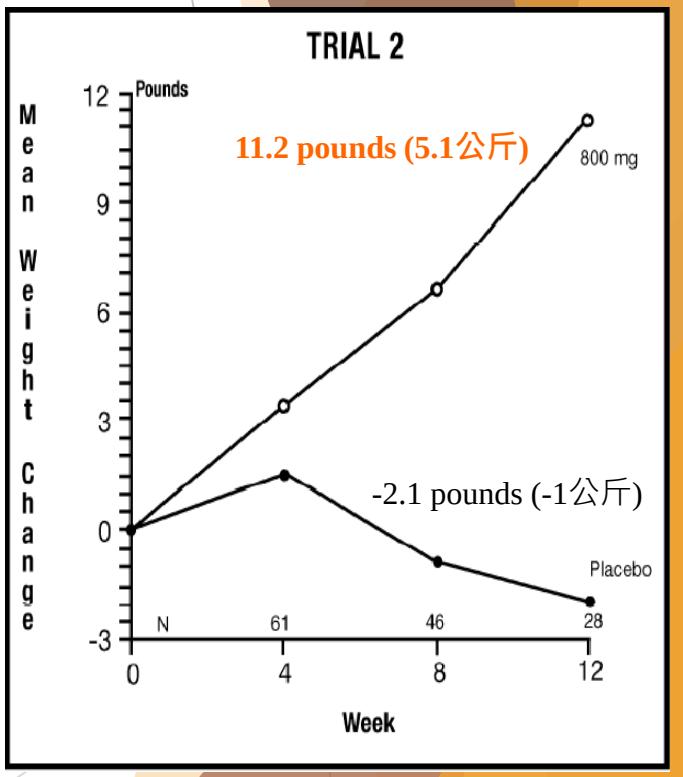
Trial 2

AIDS-associated weight loss (n=87)

RANDOMIZED

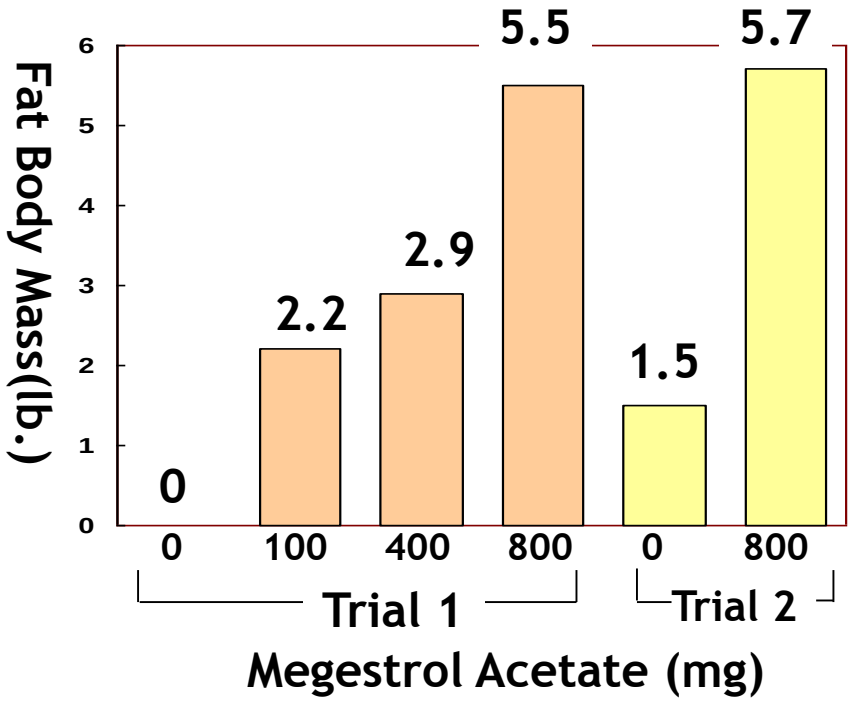
- **Placebo, D1-D84 (n=38)**
- **MA 800mg, D1-D84 (n=49)**

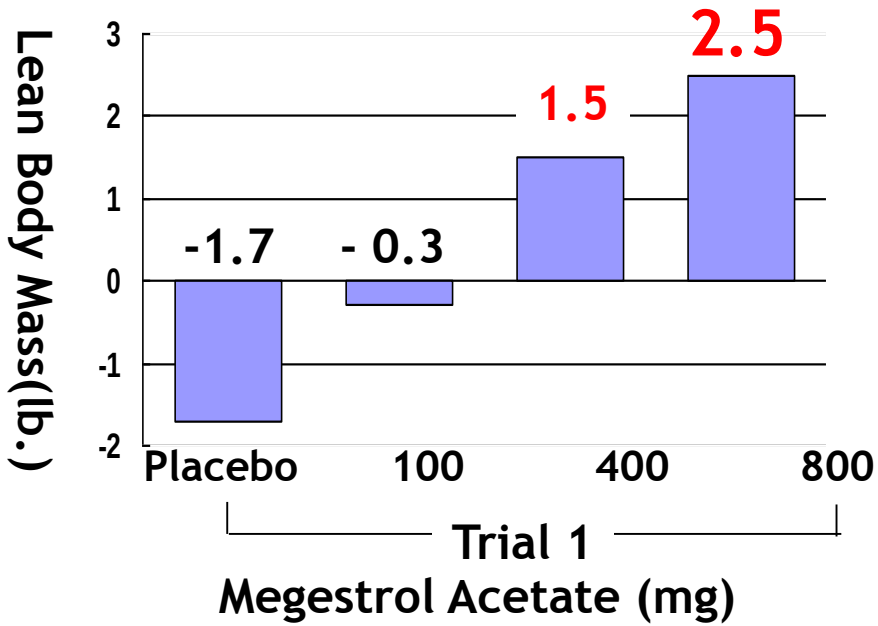




1. *Oncology 1994 ; 51 (suppl I):19-24*
2. *MA: Megestrol acetate*

12-week treatment increased fat body mass & lean body mass, without significant water retention





	0	100	400	800	0	800
Water (liters)	-1.3	-0.3	0	0	-0.1	-0.1

No statistically significant

Oncology 1994 ; 51 (suppl I):19-24

6 weeks treatment of MA improved appetite, 12 weeks treatment gain weights

Megestrol acetate in cachexia and anorexia

Shing-shing Yeh[1]
Michael W Schuster[2]

[1]Northport VAMC, Geriatric division, Northport, NY 11768; [2]Weill Medical College of Cornell University and the New York Presbyterian Hospital, New York, NY 10021, USA

In our experience, most patients had improved appetite by 6 weeks with MA treatment, although the weight gain was not yet significant at that time (Yeh et al 2001, 2000b). A course of treatment with MA for 12 weeks is probably enough to improve the appetite that will result in eventual weight gain. By 6 months, the MA group had significant weight gain. Most of the treated patients gained weight, and there was a trend for this weight gain to be in the form of fat. Increased fat mass has been noted in patients with cancer and AIDS following treatment with MA (Von Roenn et al 1988; Loprinzi et al 1993; Von Roenn 1994; Von Roenn and Knopf 1996). Dulloo and colleagues (Dulloo et al 1997; Dulloo 1998, 1997)

International Journal of Nanomedicine 2006:1(4) 411–416

How would SMI influence mCRC patients who were receiving salvage treatment?

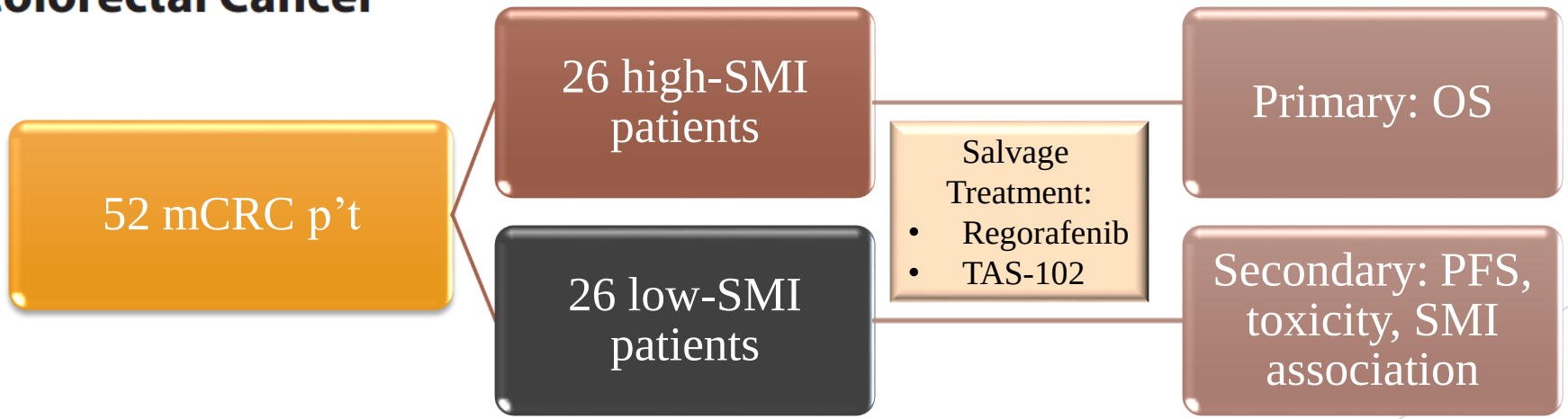
Original Paper

Digestion

Digestion 2019;99:79–85
DOI: 10.1159/000494417

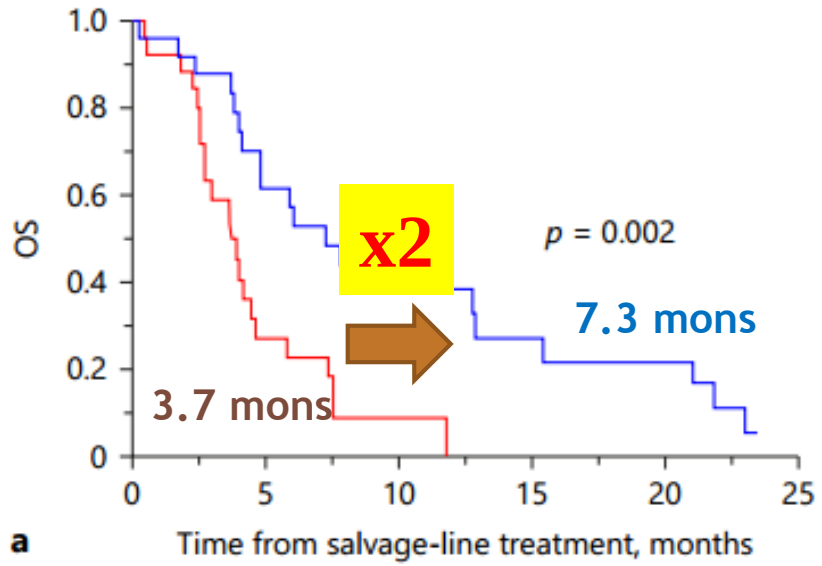
Published online: December 14, 2018

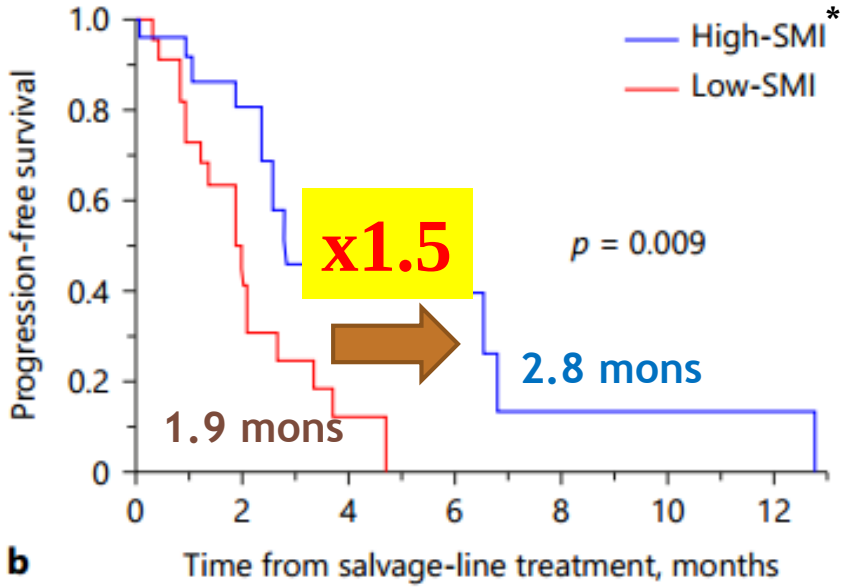
Low Skeletal Muscle Mass before Salvage-Line Chemotherapy Is a Poor Prognostic Factor in Patients with Refractory Metastatic Colorectal Cancer



Digestion 2019;99:79–85

PFS and OS were significantly shorter in low SMI group

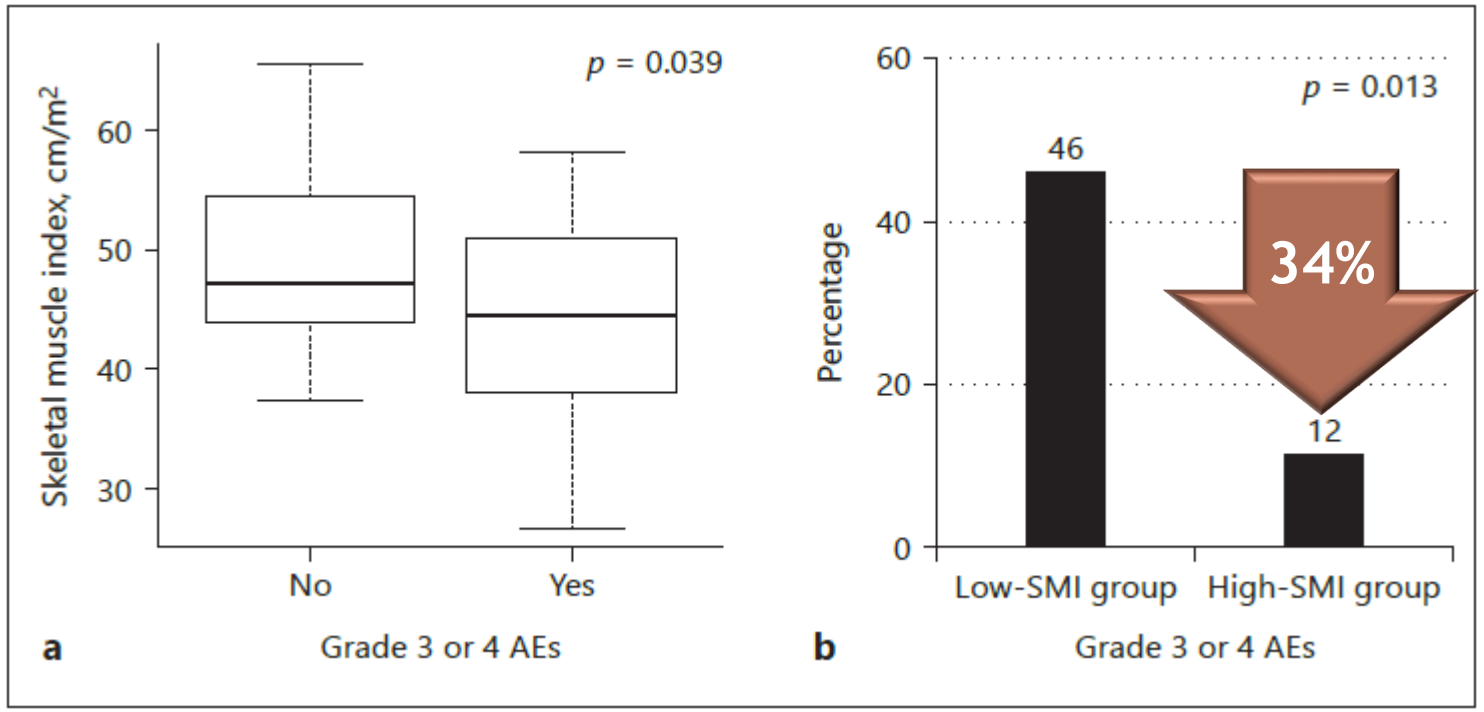




Digestion 2019;99:79–85

*: SMI, Skeletal Muscle Index

Higher percentage of Gr.3 or 4 adverse effects in low-SMI group



Digestion 2019;99:79–85

Table 2. Univariate and multivariate analyses of prognostic factors for overall survival

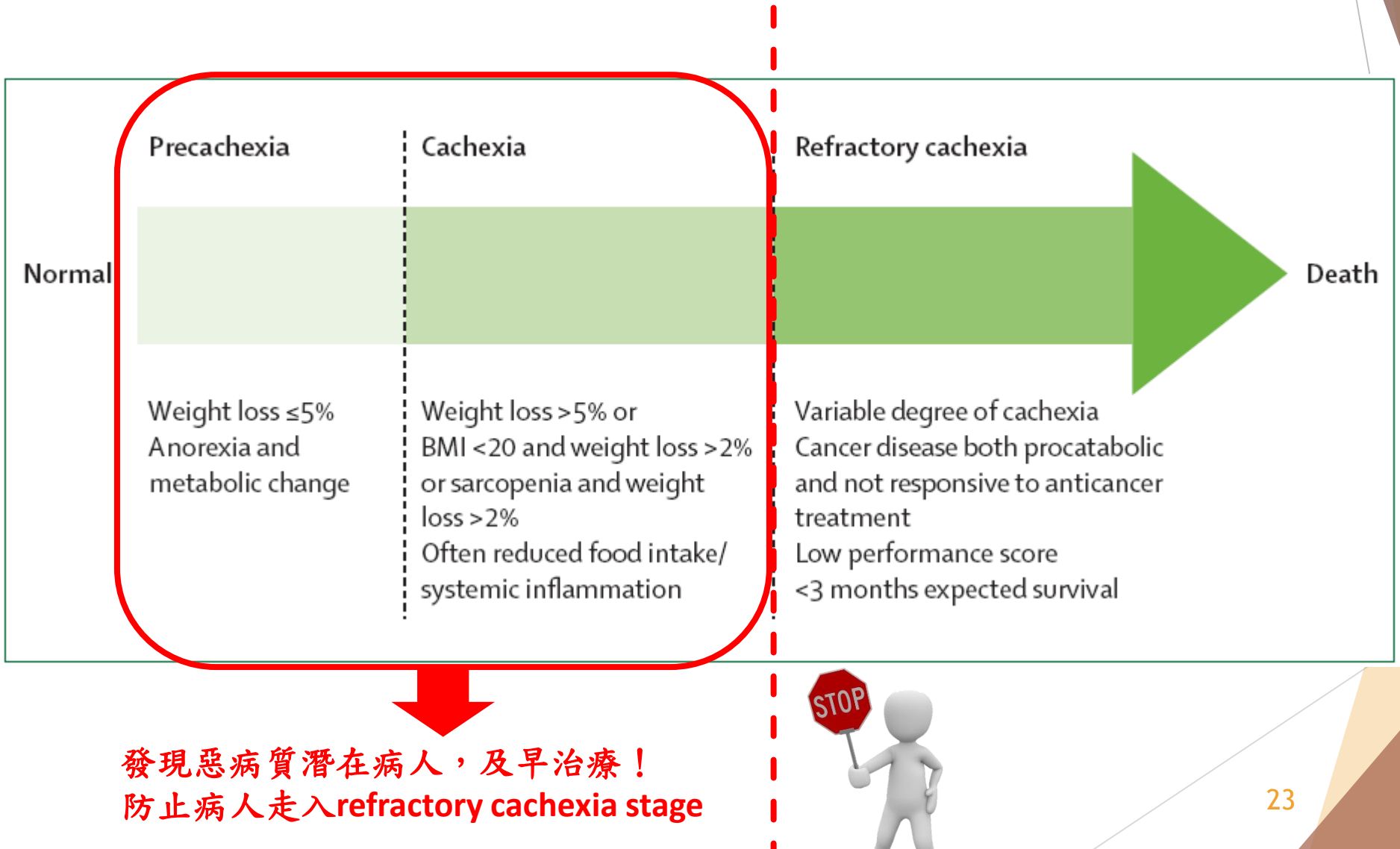
Variables	Univariable			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Gender						
Male	1					
Female	0.919	0.479–1.710	0.791			
Age, years						
<70	1					
≥70	1.304	0.602–2.594	0.481			
Performance status						
EOCG 0–1	1			1		
EOCG 2	6.398	1.739–19.367	**0.008**	5.598	1.525–16.907	**0.013**
Tumor site						
Right	1					
Left	0.710	0.316–1.898	0.463			
Time to metastasis						
Synchronous	1					
Metachronous	1.046	0.518–2.012	0.895			
Primary tumor resection						
Yes	1					
No	1.087	0.518–2.119	0.816			
KRAS status						
Wild type	1					
Mutant	1.298	0.682–2.460	0.423			
Salvage univariate-line treatment						
Regorafenib	1					
TAS-102	0.993	0.538–1.938	0.983			
Overwight/obesity (BMI)						
Yes	1			1		
No	2.905	1.291–7.785	**0.008**	2.156	0.098–5.973	0.084
Skeletal muscle index						
High	1			1		
Low	2.872	1.458–5.851	**0.002**	2.381	1.189–4.944	**0.014**

BMI, kg/m^2, median (range)
Underweight (<18.5)
Normal (18.5–24.9)
Overweight/obesity (>25)

Digestion 2019;99:79–85

Take Home Message

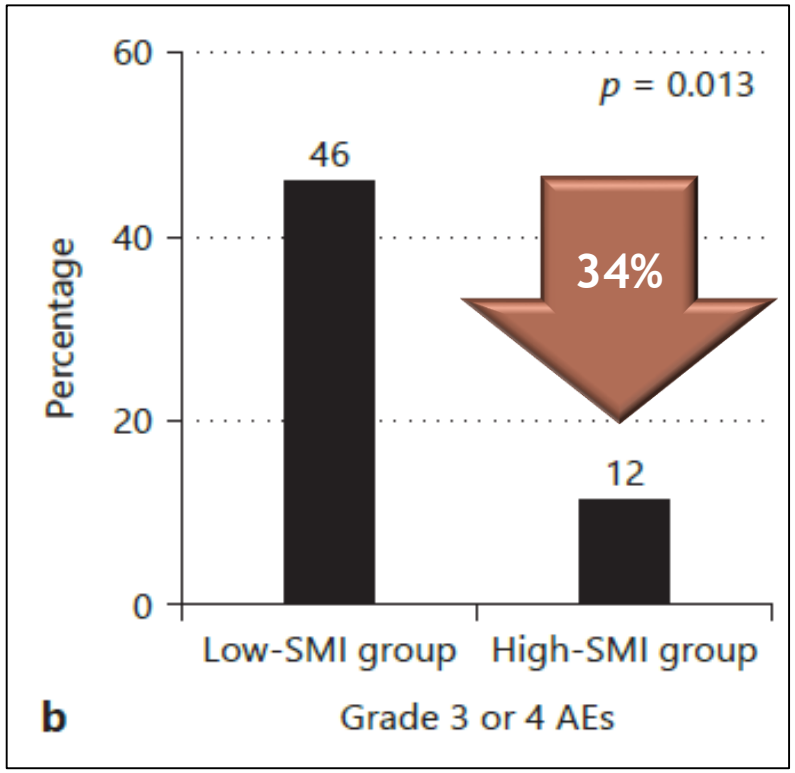
及早治療帶給病人更多幫助!

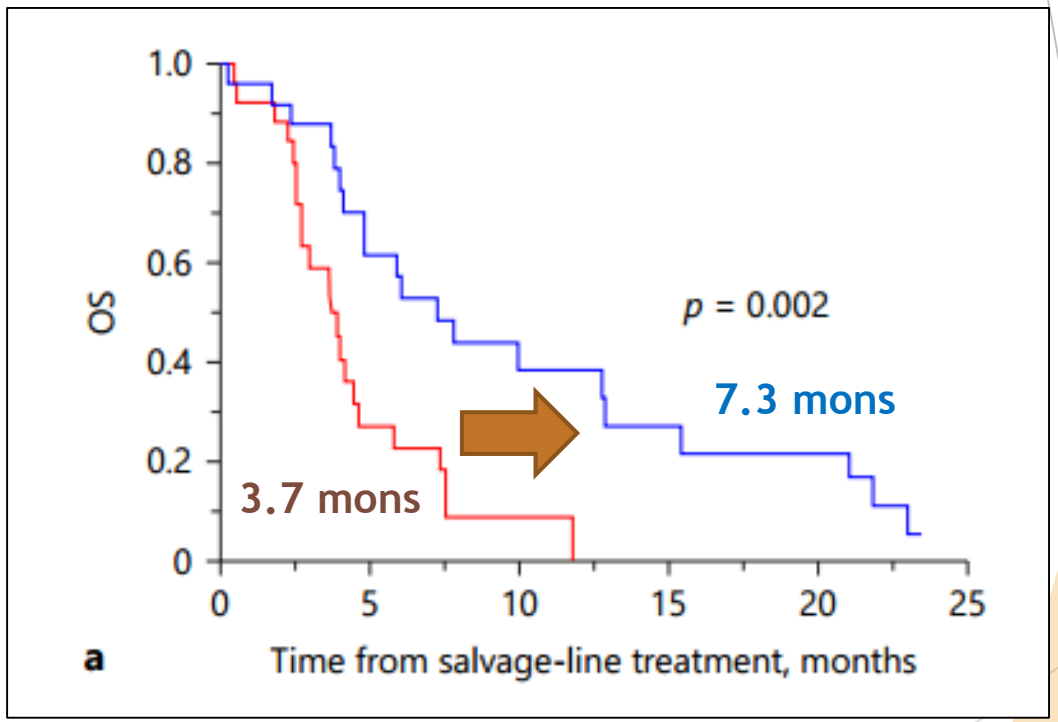


發現惡病質潛在病人，及早治療！
防止病人走入refractory cachexia stage

Fearon, K.et al. Lancet Oncol.12, 489-495 (2011)

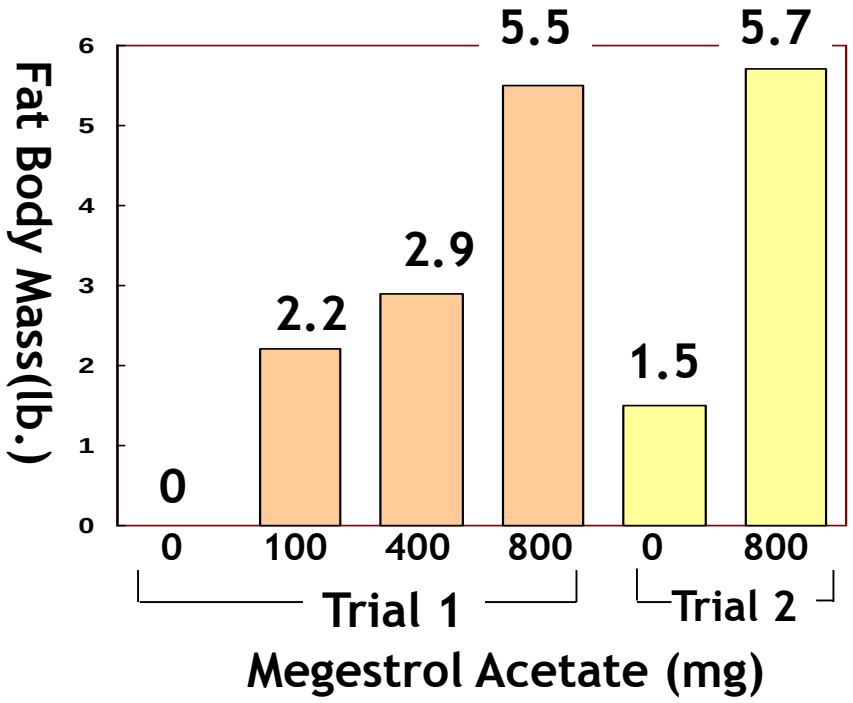
肌肉多，耐受好，存活長!

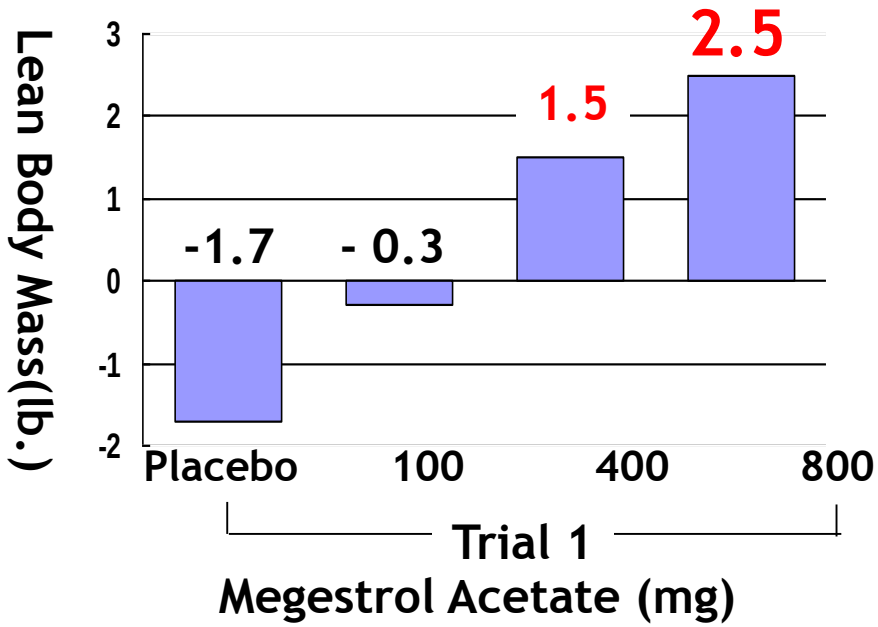




Digestion 2019;99:79–85

Megestrol “足量”治療很重要!





	0	100	400	800	0	800
Water (liters)	-1.3	-0.3	0	0	-0.1	-0.1

No statistically significant

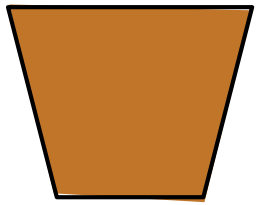
Oncology 1994 ; 51 (suppl I):19-24

足量: 10-20cc/day，至少喝滿3個月!

健保

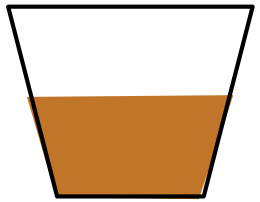
Weight loss >10%

20 cc/day



Weight loss 5~9%

10 cc/day



3 mons ↑

1. 2018 NCCN Guidelines Megestrol acetate 400~800 mg/day
2. Annuals of Internal Medicine 1994; Volume 121, Number 6
3. Am J Med. 1980 Oct;69(4):491-7.
4. J Natl Cancer Inst 82:1127-1132,1990