



Memorial Sloan-Kettering  
Cancer Center  
Pain & Palliative Care Service

# Update on cancer cachexia

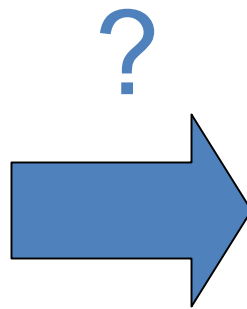
Paul Glare MD  
Chief, Pain & Palliative Care Service  
Dept Medicine  
MSKCC

# Ms RK

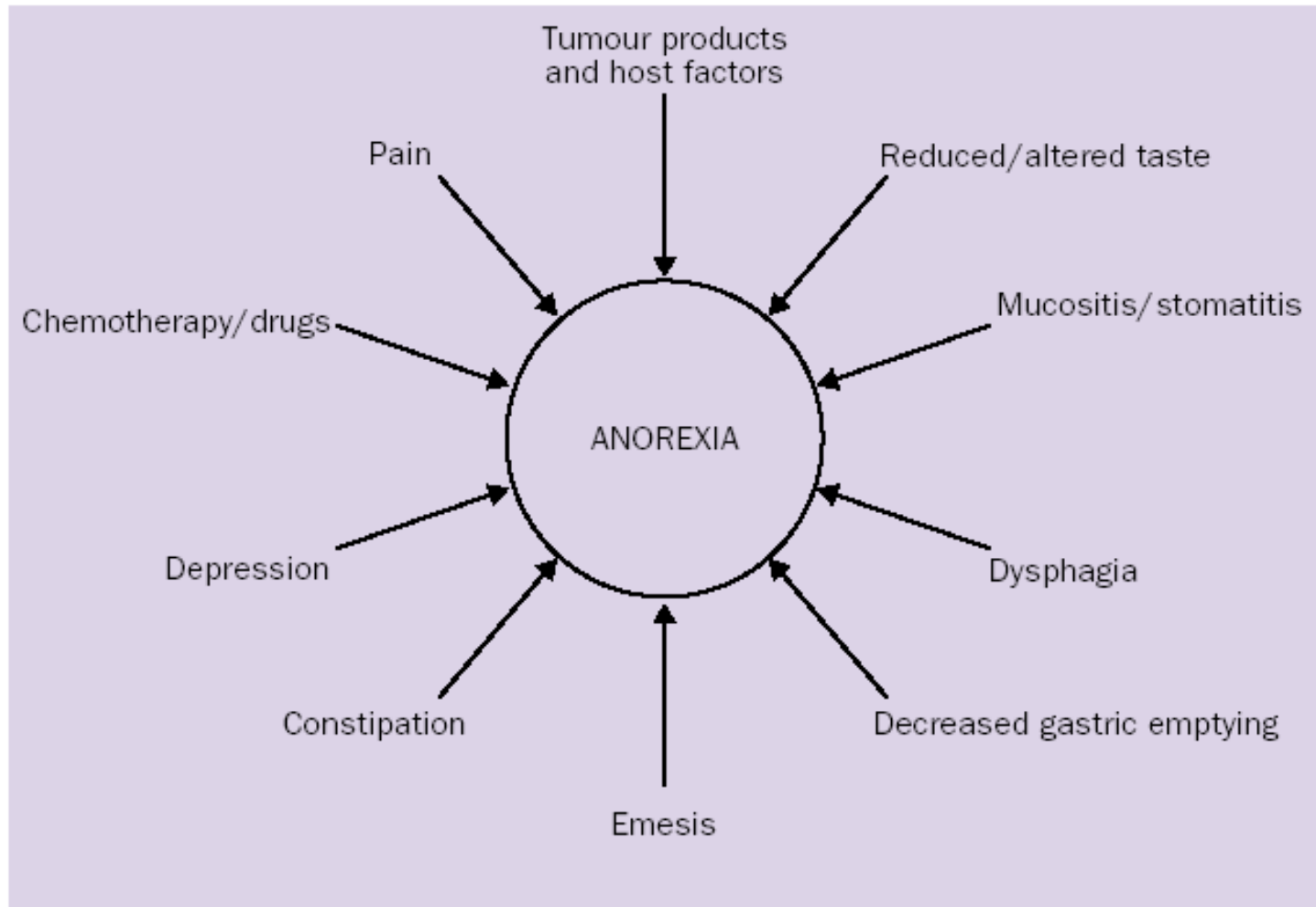
- 43, office manager, single
- Lives in Sydney, Australia; family in NZ
- PH chronic back pain 2° work injury (L4/5 disc bulges) -> depression
- Ex-heavy smoker (30 pack-yr)
- IIIb NSCLC RUL in 11/07
- Rx: inoperable -> concurrent chemoRT till 1/31/08
- Referred to PCS 1/8/08: hospitalized with severe R shoulder pain despite ↑opioids (20mg SC M q4h)
  - dyspnea, nausea, wt loss.
  - otherwise well & self caring

# Progress

- Response to antibiotics: discharged
- 3/08: progress chest CT
  - good response of tumour
  - Ongoing narrowing of large airways
    - Cx recurrent PNA: further hospitalizations
- Fatigue, cough, SOB/OE
- Pall care OPD
  - Pain management
  - Cancer Nutrition Rehabilitation Program
    - Dietitian
    - physiotherapist



# Many causes for anorexia/wt.loss in cancer patients



# Traditional view: starvation

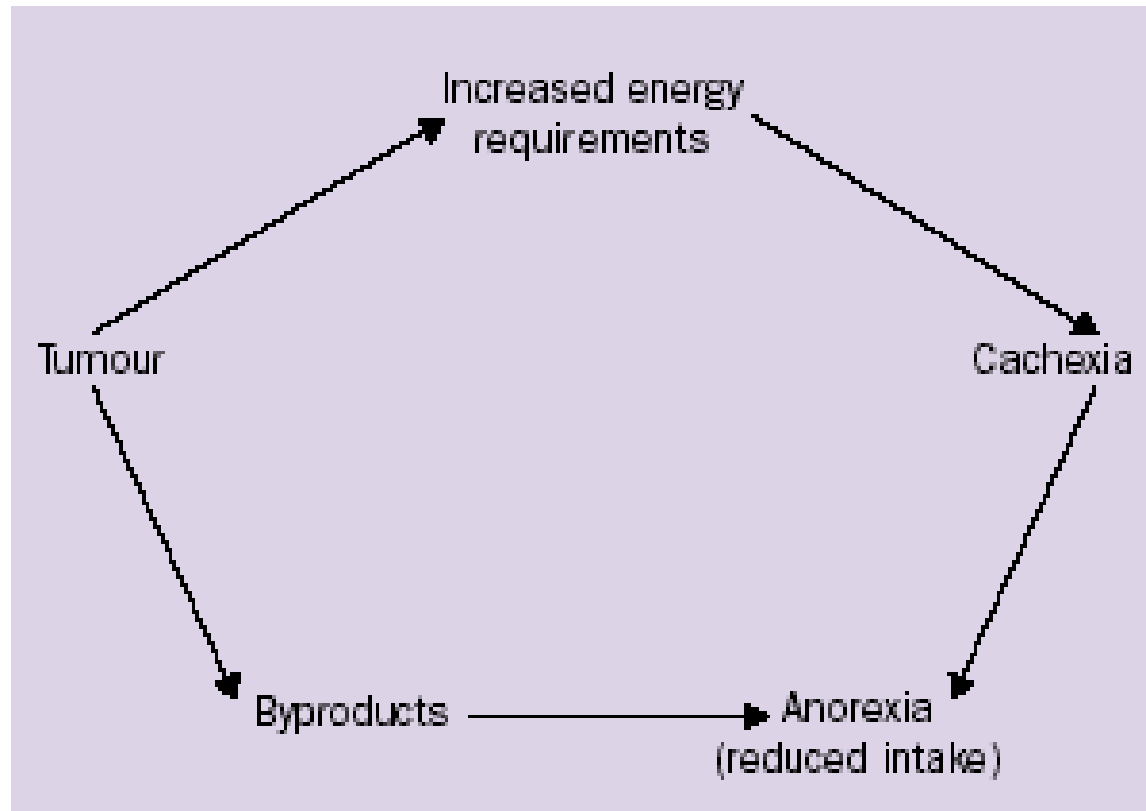
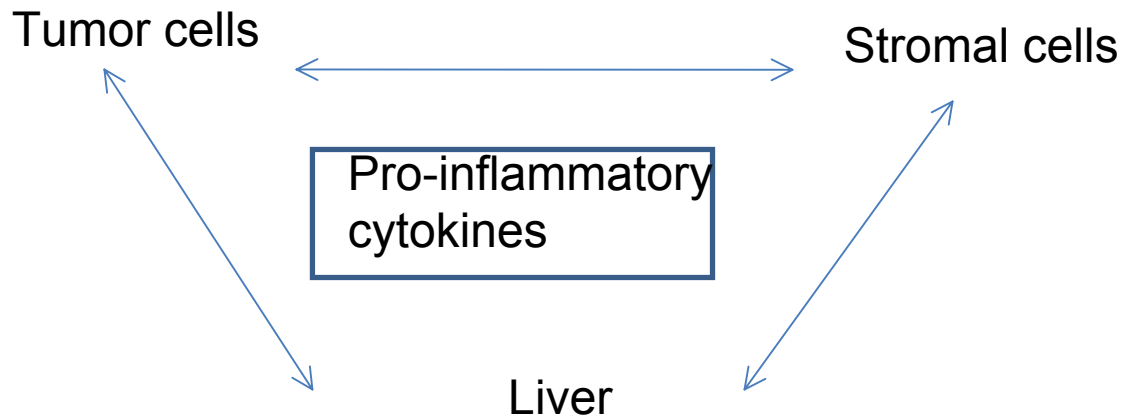


Figure 2. Traditional view of cachexia

# Nutritional alterations: starvation vs. cachexia

Table from Kotler: Ann Intern Med, 2000;133(8):622-634

# Inter-relation of pro-inflammatory cytokines in tumor, stromal & liver cells





# PILOT STUDY OF NUTRITION, INFLAMMATORY MARKERS, QUALITY OF LIFE AND SURVIVAL IN PATIENTS WITH ADVANCED CANCER

P. Glare, S. Adelstein, K. Clark, S. Clarke, J.  
Greaves, J. Read, L. Sharpe

Sydney Cancer Centre, Royal Prince Alfred Hospital,  
University of Sydney

Project funded by NHMRC (Australia) Palliative Care Strategic Research Development Program

# Methods

- Cross sectional survey
- convenience sample: 100 patients referred to hospital-based palliative care team
- Advanced cancer,  $\geq 18$  years, written consent
- Nutritional assessment, quality of life scores
- Systemic Inflammatory markers
- Survival (days) followed up at 6 months

# Study measures

- Nutritional assessment:
  - BMI
  - hand grip strength, Mid-Arm Circumference
  - PG-SGA
  - S. albumin
- Psychosocial:
  - HADS
  - SSQ
  - MQOL
- Systemic inflammation:
  - APR: CRP, B12
  - Pro-inflammatory cytokines, VEGF: BD™ Cytometric Bead Array Flex System modified R2U inflammatory kit
- Survival:
  - Clinical prediction
  - days, truncated at 180

# Sample characteristics

- 61 males, 42 Females
- Median age: 64 years (range 39-88)
- Lung cancer commonest, followed by bowel
- PS: median ECOG = 2
- Prognosis (n=74)  $\geq 3$  months: 69%
- Median actual survival: 8 weeks
  - $\geq 3$  months: 40%
  - <30 days: 30%,  $\geq 6$  months 26%

# Nutrition

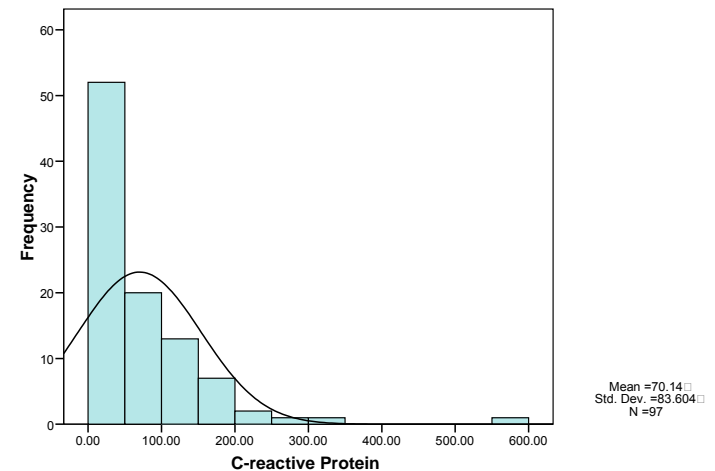
- BMI: Median 23 (13-38)
  - <20: 21; >30: 7
- Food intake: reduced in 85%
- PGSGA: 85% malnourished
  - Severe: 13%
  - Median score: 18 (>9: 80%)
  - Interfering symptoms: 75%
    - anorexia, nausea, constipation (Pain: 28%)

# Inflammatory markers

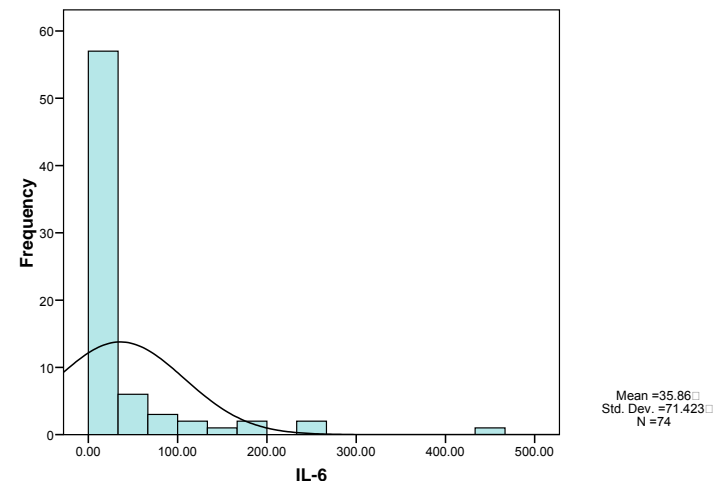
## Acute phase reactants

- CRP
  - Median CRP: 41 mg/L, range 0-562
  - > 10 mg/L: 79%
  - > 100 mg/L: 20%
- CRP highly correlated with IL-6 ( $r^2 = 0.54$ ,  $p < 0.0001$ )
- CRP also correlated with VEGF ( $r^2 = 0.16$ ,  $p = 0.000$ ) but not IL-8.
  - Other cytokines too uncommon to test

Histogram of C-reactive Protein

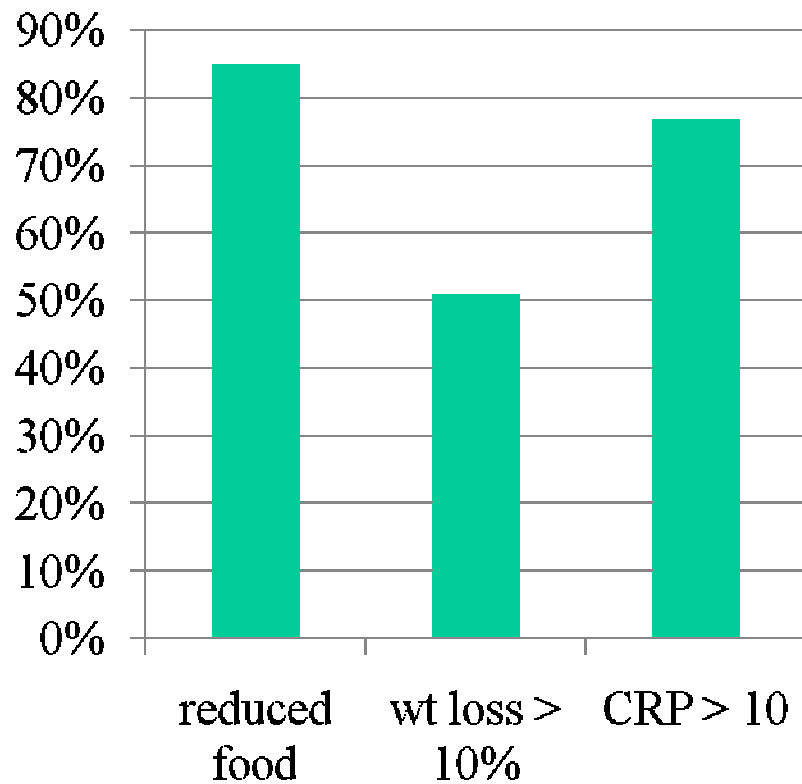


Histogram of IL-6

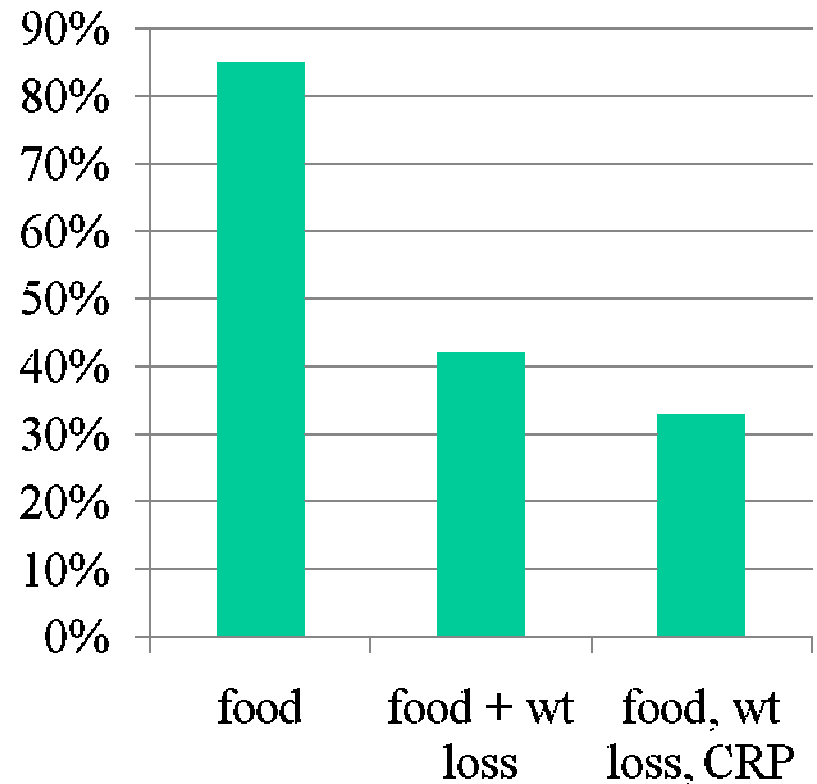


# Prevalence of cachexia?

## Individual factors

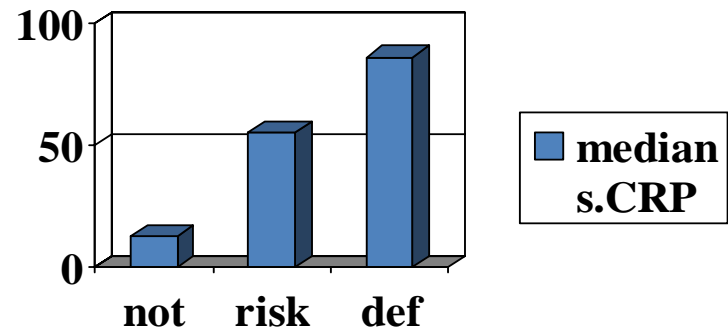


## 3-factor profile of cachexia

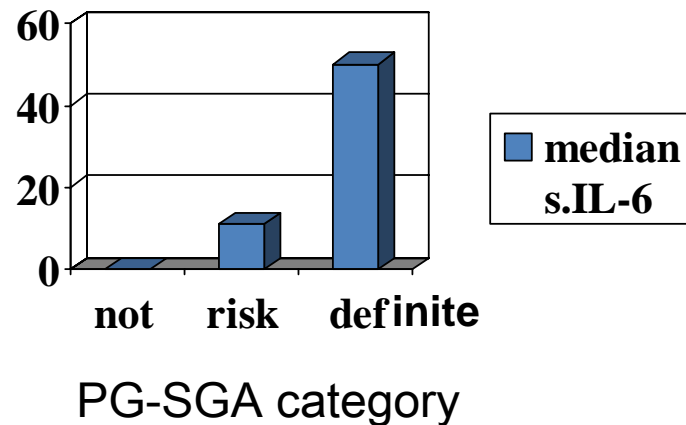


# Associations between Inflammatory markers and nutrition

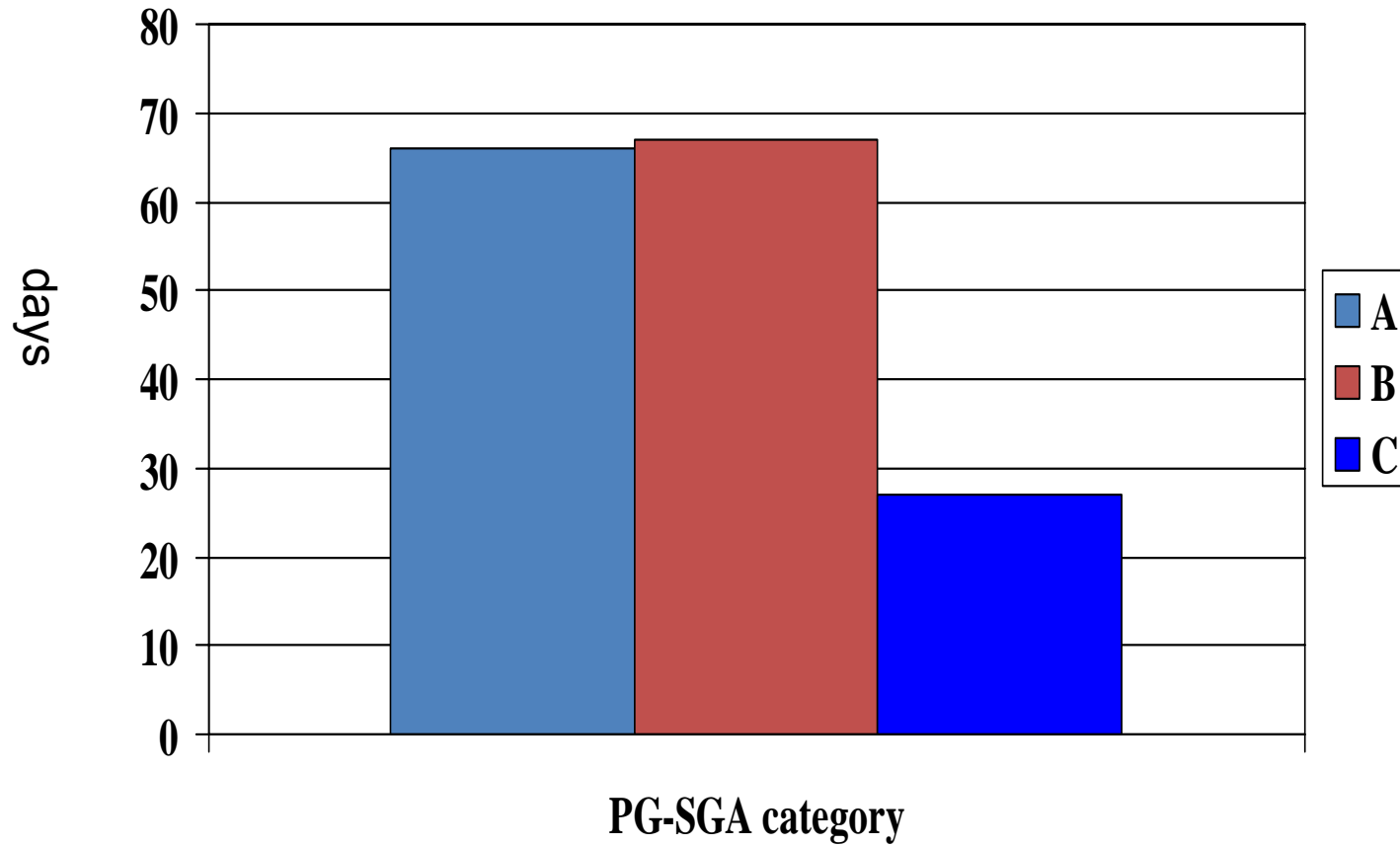
- CRP: inversely related to nutritional status



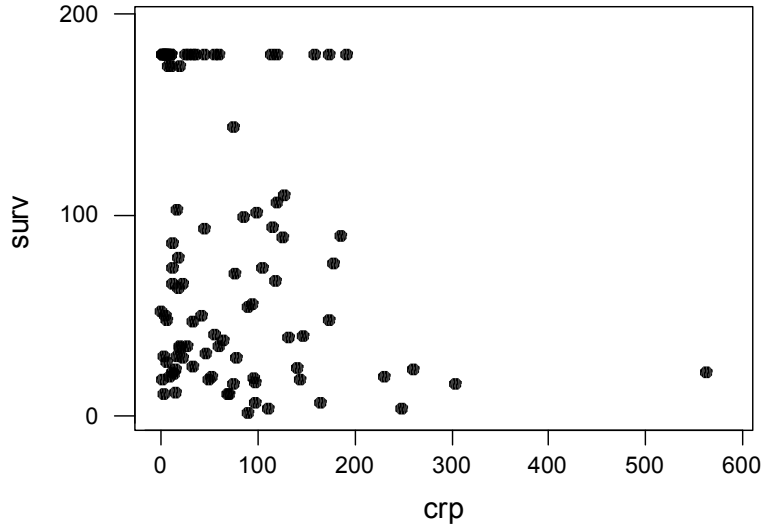
- IL-6: level inversely related to nutritional status



# Nutrition and survival

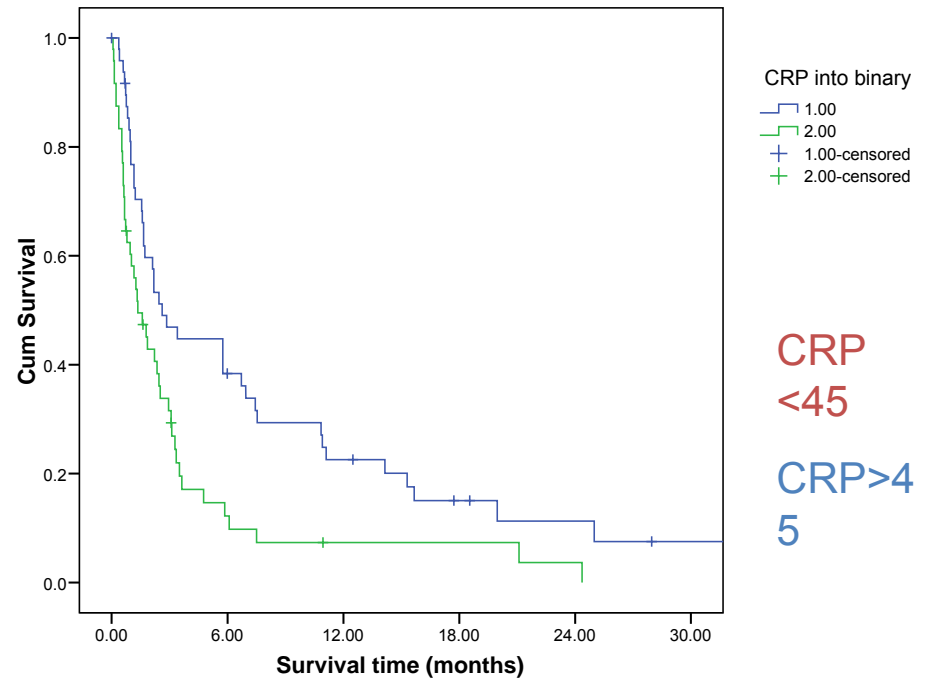


# Cytokines/CRP & survival



$r^2 = -0.241, p = 0.018$

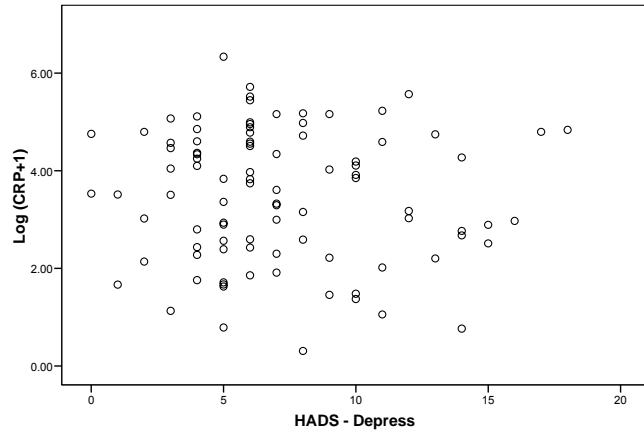
Survival Functions (CRP into binary)



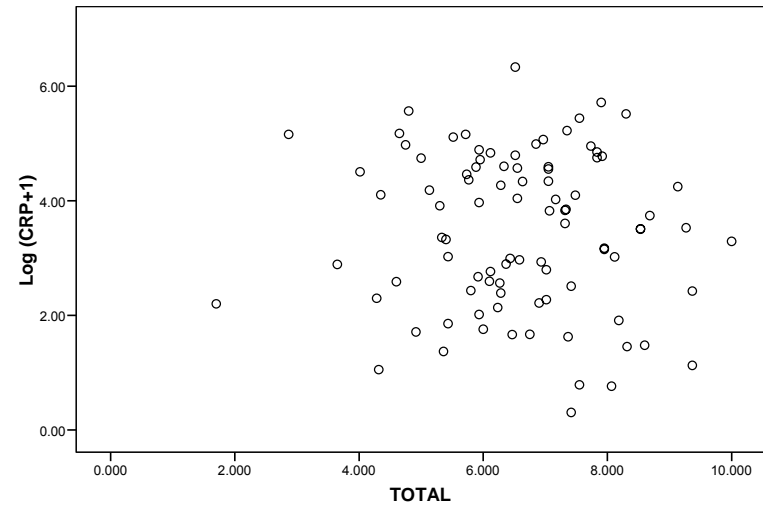
LRT 8.35,  $p = 0.004$ , HR 1.89 (1.22-2.92)

# CRP & psychosocial domains: no associations

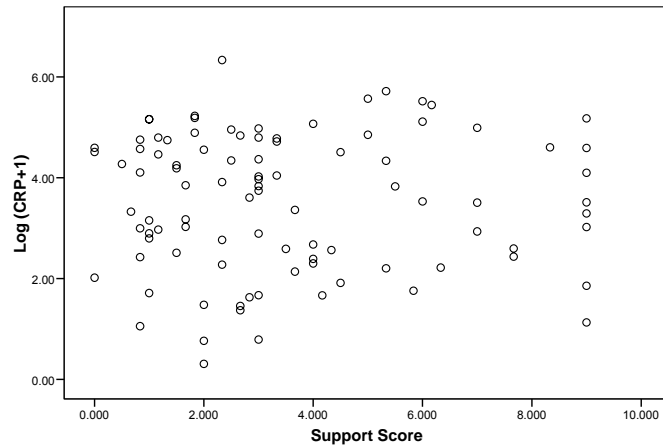
Log C-reactive Protein vs HADS (Depression)



Log C-reactive Protein vs Total MG QoL

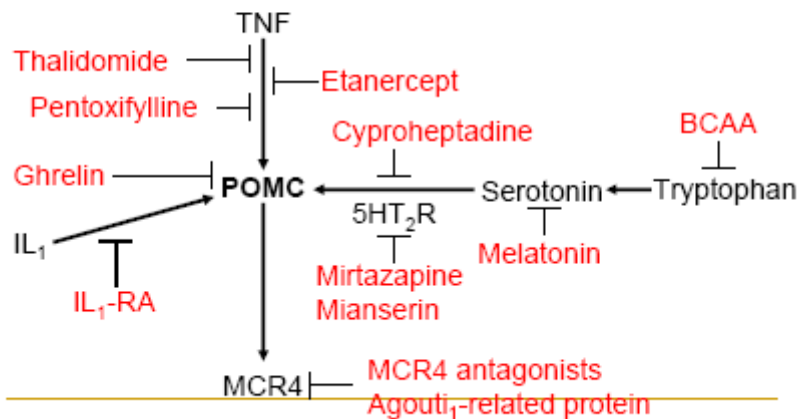


Log C-reactive Protein vs Support Score

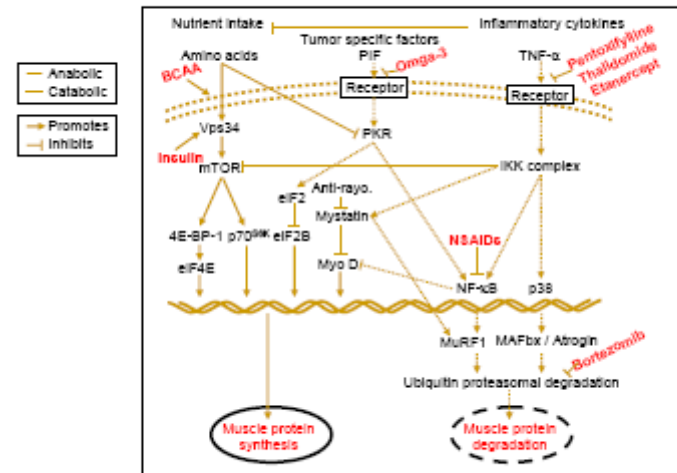


# Therapy: Pharmacological options

## Anorexia-Cachexia Pathway and Appetite Active Agents



## Key Signaling Pathways



Amino acids stimulate muscle protein synthesis through the mTOR pathway. Inflammatory cytokines and tumor specific factors inhibit muscle protein synthesis and promote muscle protein degradation.

Courtesy of Mel Davis, Cleveland Clinic

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## Multi-drug trials

- Fish oil (eicosapentaenoic/docosahexanoic acid) 4.9 g/day / 3.2 g/day
- Melatonin 18 mg qhs
- After 4 weeks- FO + melatonin
- Results: weight stabilization or gain
  - FO 38%
  - melatonin 27%
  - combination 63%

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**Persson C et al, Nutrition. 2005 Feb;21(2):170-8**  
***Slide: Courtesy Mel Davis, CCF***

Patients no longer receiving std anti cancer Rx

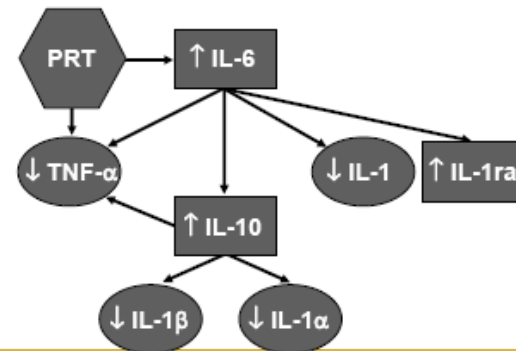
Some weight stabilization but no changes in biochemistry or cytokines

# “Strengthen muscles as well as feed them”

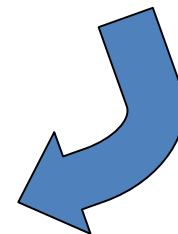
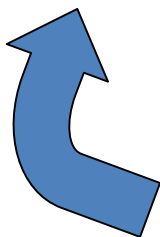
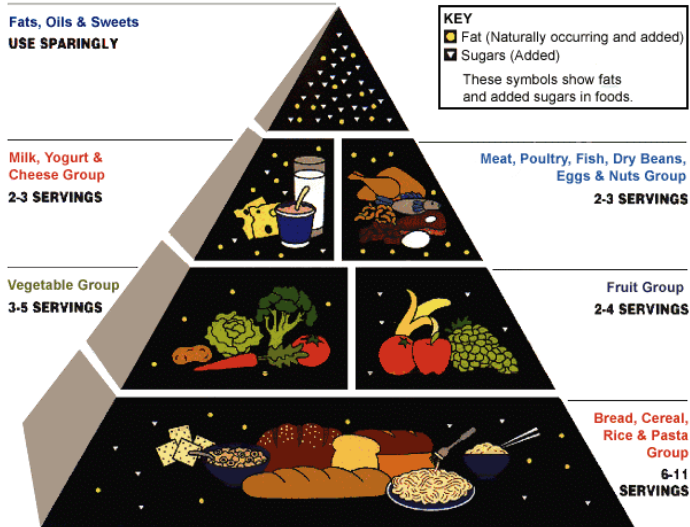
## Physical Exercise

- Increases total energy expenditures
- Reduces local muscle cytokines
- Increases muscle anti-apoptotic and anabolic factors
- Improves cytochrome C oxidase
- Reduces central activation failure

## Anti-Inflammatory Effects of Progressive Resistance Training



Slide courtesy of Mel Davis



# Multidisciplinary team



## PROGRAMS

- Adolescent and Young Adult Onc
- Cancer Epi
- Cancer Genetics
- Cancer Nutrition-Rehabilitation ▶
- Cancer Prevention
- Clinical Research
  - *Clinical Research Unit*
- *Cooperative Research Groups*
- Community Onc
- Head & Neck
- Hematology/Onc
- Medical Oncology
- Nursing Oncology
- Palliative Care
- Pediatric Oncology
- Psychosocial Onc
- Radiation Onc
  - *Med Phys Unit*
- Surgical Oncology
- Whole Person Care

## Programs

### Cancer Nutrition-Rehabilitation



The [Cancer Nutrition-Rehabilitation Program](#)—introduced in 2002—provides treatment for cancer patients suffering from loss of appetite, weight and function, and increased fatigue, as a result of their illness. This Program was created to enable patients with advancing cancer to maintain dignity, function, and a high quality of life, throughout the course of their illness.

The mission of Cancer Nutrition-Rehabilitation encompasses the three key areas of clinical care, research and education:

- To develop and administer nutritional and rehabilitation programs for cancer patients suffering from poor appetite, malnutrition, weight loss, fatigue and loss of function;
- To conduct research aimed at understanding the underlying biological reasons for the above symptoms in some cancer patients;
- To educate patients, family caregivers and health professionals in new ways to manage the above symptoms.

The following goals reflect this mission:



# Cancer nutrition and rehabilitation—its time has come!

*M.R. Chasen MBCChB MPhD(Pall Med)\* and  
A.P. Dippenaar†*

## ABSTRACT

Cancer is a systemic disease that can affect nearly every organ in the body, resulting in a progressive loss of organ function. That loss of function may be initially slow, having minimal effect, or it may be rapid, resulting in more dramatic changes.

The usual medical management of patients with cancer has focused more specifically on the administration of cytotoxic treatments. These treatments can potentially eradicate or minimize the tumour, but they may also have toxic side effects that in turn can also affect the patient.

Cancer rehabilitation is a process that assists the individual with a cancer diagnosis to obtain optimal physical, social, psychological, and vocational functioning within the limits created by the disease and its treatment. The McGill Cancer Nutrition and Rehabilitation (CNR) program developed as a result of the ever-increasing demand for a focus on addressing individual cancer patients and their needs, as well as on achieving optimal tumour-related outcomes. Using an interdisciplinary approach, the CNR's global objective is to empower individuals who are experiencing loss of function, fatigue, malnutrition, psychological distress, and other symptoms as a result of cancer or its treatment to improve their own quality of life. All team members—experts in their respective fields—assess all patients. At a subsequent team discussion and planning meeting, a specific 8-week program is designed for each patient. The hoped-for outcome for the CNR program is primarily to empower patients to “take control” or to enable them to improve their own quality of life. This article reviews the philosophy of the CNR's approach and the roles played by the various members of the team.

## KEY WORDS

Rehabilitation

## 1. INTRODUCTION

Cancer may develop in almost any area or system within the body<sup>1</sup>. The neoplasm not only directly affects

the region in which it arises; it can metastasize to distant sites, causing a variety of complications at those sites. Disruption of metabolism and endocrinology may directly or indirectly influence any number of bodily systems<sup>1,2</sup>. The many complications that the cancer causes can affect a patient's quality of life in many domains—physical, social, psychological, and work-related.

The medical management of patients with cancer has usually focused on the administration of cytotoxic treatments to potentially eradicate or minimize the tumour burden. These treatments may be extremely toxic to the body. Various treatment modalities are often a cause of altered functioning, affecting daily occupational routines<sup>1</sup>. Co-administered medications, used to control symptoms or to treat adverse events associated with treatment modalities, can produce their own adverse events.

The primary aim of treatment has been to cure patients of their disease. However, the American Society of Clinical Oncology has emphasized to its members the importance of recognizing the point in the illness trajectory when treatments should focus more on symptom management and psychosocial support for the patient whose tumour is not curable. That approach takes into account the cultural, religious, and social belief systems that can also influence the patient's perspective on his or her disease and on the illness experience<sup>1,3,4</sup>.

## 2. CANCER REHABILITATION

Cancer rehabilitation is a process that assists the individual with a cancer diagnosis in obtaining optimal physical, social, psychological, and vocational functioning within the limits created by the disease and its treatment. An imperative in accomplishing these goals is a coordinated multidisciplinary team approach that addresses the potential rehabilitation needs of the individual from the time of the cancer diagnosis onward.

Historically, the concept of cancer rehabilitation stems from an integral component of *The [U.S.] National Cancer Act of 1971*. That legislation declared cancer rehabilitation to be an objective, and it directed funds toward the development of training programs and

- Dietitian
- Physiotherapist
- Psychologist
- Nurse
- Doctor



# Cancer Nutrition Rehabilitation Program

Paul Glare, MD

Wendy Jongs, RD

Bill Zafiropoulos, PT

# Role of Physician

- Appropriate for CNRP (vs. palliative care): prognosis
- Orexigenic drugs: Megestrol
  - *Novel agents: clinical trials*
- Other symptoms interfering with eating
- safe for physical therapy
  - Cancer complications
  - Comorbidities

# Role of Nutritionist

- Make an appropriate nutritional assessment
- Provide individually tailored nutritional advice
- Recommendations to help meet nutritional needs
- Monitor and evaluate the outcomes
- Liaise with the team regarding nutrition impact symptoms
- Provide appropriate information regarding complementary and alternative therapies

# Role of Physical Therapist

- Goals:
  - Reduce symptoms disability and handicap
  - Physical training endurance and strengthening
  - Improve functional independence
  - Individually tailored and designed programs
- A comprehensive assessment is performed
- Patients are reassessed at regular intervals
  - 2 month Program: strengthening plus endurance
  - Home based vs gym based

NUTRITION and REHABILITATION CLINIC  
Gloucester House 5

FIRST VISIT

Name: ~~XXXXXXXXXX~~ Date: 29/10/07.  
MRN: 1634433. DOB: 23/9/1935  
Referred by: Paul GLARE.

<b>Diagnosis:</b> <input checked="" type="checkbox"/> NSCLC <input type="checkbox"/> Colo-rectal <input type="checkbox"/> Breast <input type="checkbox"/> SCLC <input type="checkbox"/> Pancreatic <input type="checkbox"/> Ovarian <input type="checkbox"/> Head and Neck <input type="checkbox"/> Gastric <input type="checkbox"/> Other: _____		
Date of diagnosis: Treatment: chemotherapy trial		
<b>Stage:</b> <input type="checkbox"/> 1A/1B <input type="checkbox"/> 3B <input type="checkbox"/> EXT <input type="checkbox"/> 2A/2B <input type="checkbox"/> 3B+ <input type="checkbox"/> Other: _____ <input type="checkbox"/> 3A <input checked="" type="checkbox"/> 4		
<b>Metastasis:</b> <input type="checkbox"/> Liver <input type="checkbox"/> Bone <input checked="" type="checkbox"/> Adrenal <input type="checkbox"/> Brain <input type="checkbox"/> Lung <input type="checkbox"/> Other: pancreas		
Past medical history: <del>Not of note</del> cardiac		
Family history:	Social history: Lives with daughter	
Medications: Tramadol/Painmax Celebrex Acalat Lipitor Zactima vs. Tarceva.	CRP: 290.1 (Pre)Alb: 33L } valid 07-	
Current wt: 61.6kg      Ht: 164cm Current BMI: 22.9 Weight loss: 8.8% (6/112).	6 minute walk test: initial Ax performed pt to attend rehab gym program.	
Body Composition: TSF MAMC	Hand grip: %body fat: eaten fluids time	

HEHP, fish oils.

PG SA - 9  
SGA - B

NUTRITION AND REHABILITATION CLINIC

Gloucester House Level 5

Date: 29/10/07

Palliative Consultant *SCALE*  
 Pain well controlled by Oxycodone.  
 Fit for physiotherapy  
*PLG*

Clinical Nurse Consultant

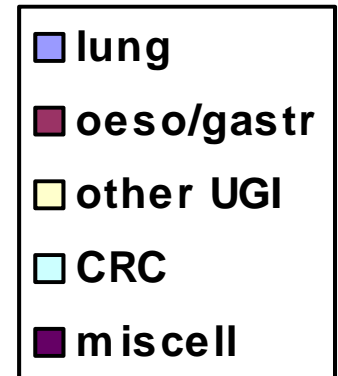
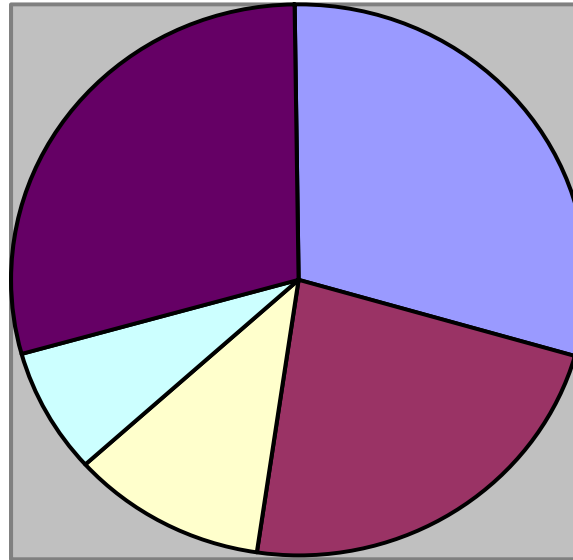
Dietitian 29/10/07.  
 EFR = 88 7400 - 853067      ↑ intake recently  
 Est prot = 74-92g.      HEHP additions  
 (P) cond. HEHP.  
 ↑ HEHP fluids, fuko  
 esp. clc.

29/10/07. Initial Ax performed.  
 Physiotherapist  
 bmwt: Pt to attend regular gym  
 program rehab x1/wk daughter to  
 transport patient.  
*PLG* (29/10/07) pt

Psycho-oncology

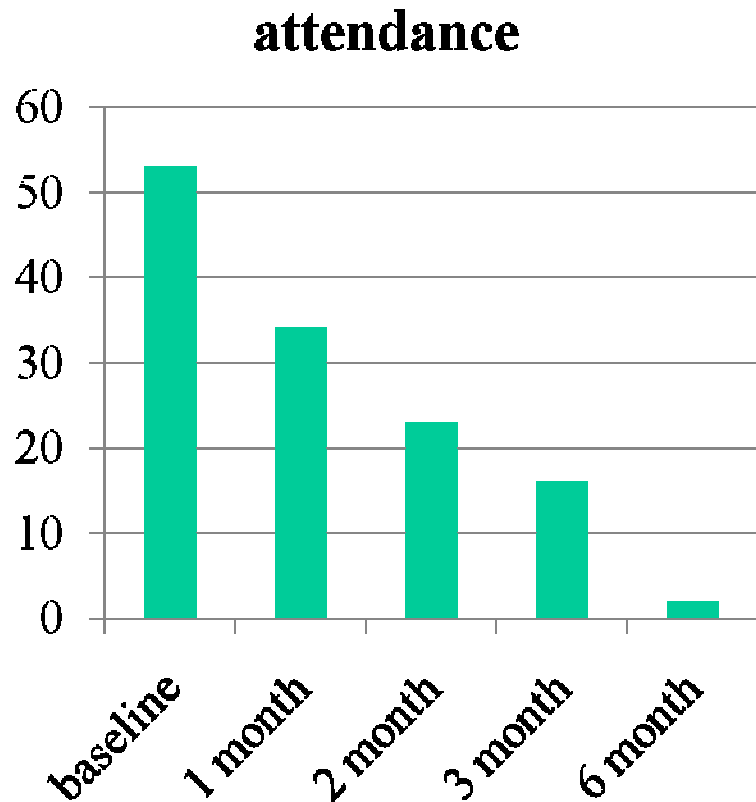
# Activity (10/07-5/08): 52 patients

- 35 m, 27f
- 62.5 yrs (24-85)
- All stage III/IV cancer
  - 80% on Rx (2/3 chemo)
- KPS 70 (all 50+)
  - 6MWT: 444 m;
  - HGS 75% predicted
- wt loss: 12%;
  - BMI 21;
  - Malnourished 85%
- CRP >10: 76%
- albumin <35: 28%



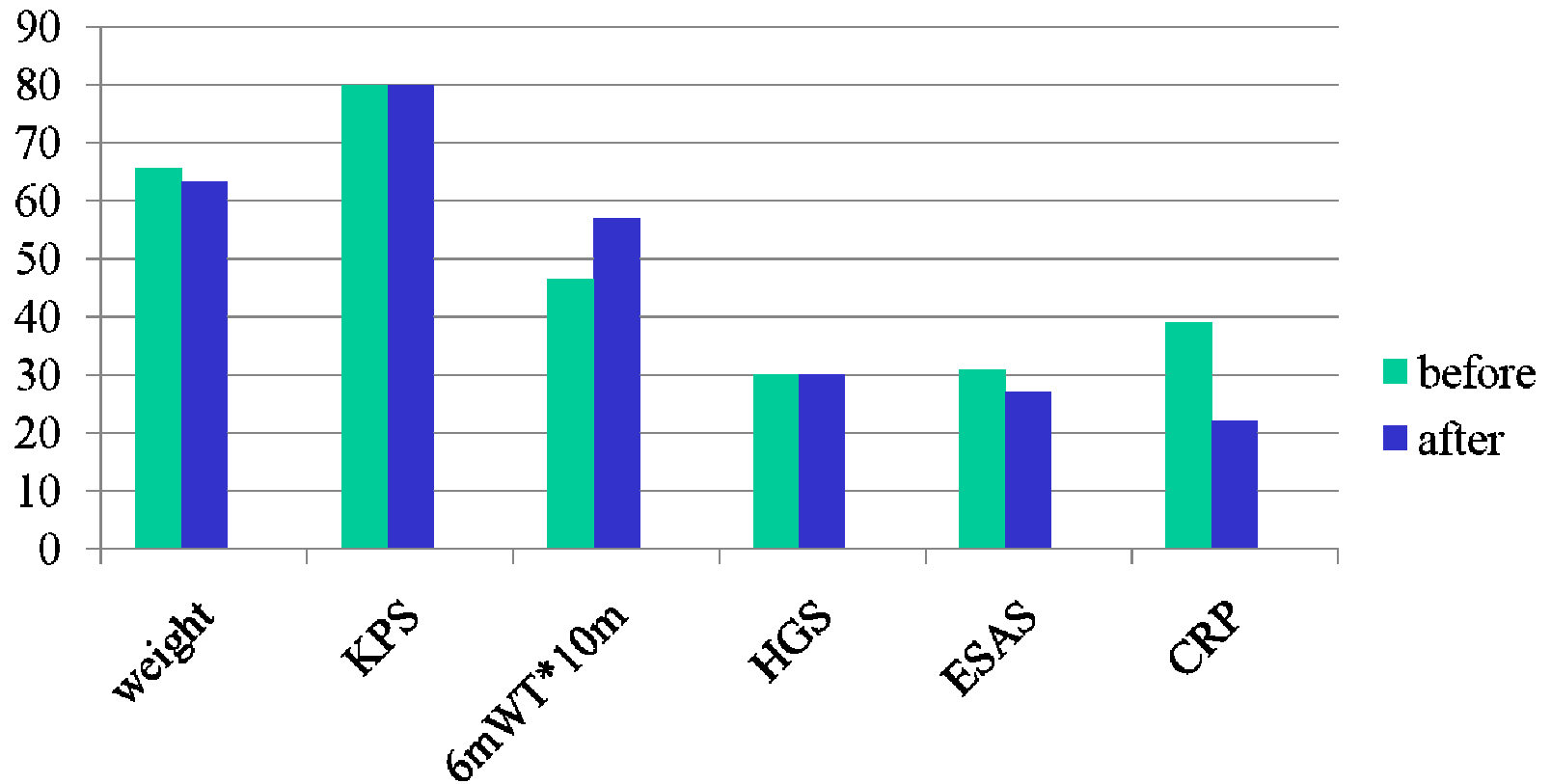
# Adherence

Attendance at follow-up assessments: 1, 2, 3, 6 mo.



- Predictors: sig
  - 6mWT > 1/4 mile
  - On chemotherapy
- Predictors: trend
  - Male
  - KPS  $\geq$  80%
  - Weight loss  $\leq$  10%
  - PGSGA scores  $\leq$  18
  - serum albumin  $\geq$  35
  - serum C-reactive  $\leq$  30
  - GPS 0 -1
  - ESAS score  $\leq$  30

# 2 month outcomes, n=25



# RK: nutritional issues

- BMI : 23.3kg/m<sup>2</sup>
- Weight loss: 5.2kg over 6 months (7.2%)
- PG-SGA 8 (SGA A) → 15 (SGA B) on therapy
- Taking mixture of herbal supplements, juices
- Avoiding dairy, meat/poultry and soy products
  - ? Adequate dietary protein, iron and zinc
- CRP 32 (PNA): ?Eicosapentanoic acid

# RK: nutritional intervention

- Pre treatment goal:
  - Adequacy of diet esp. protein and calories
  - Appropriate information re: food beliefs
    - o ‘Nutritional cook’, agreed to soy, organic chicken
- During treatment:
  - Regular monitoring of weight and adequate intake
  - Nutritional supplementation and protein fortifier
- Post treatment:
  - Maintain healthy body weight
  - Healthy eating to reduce reoccurrence

# RK – Physical Therapy Assessment

- Walking on flat 200 – 300 yards, limited by SOBOE and fatigue
- 2 flights of stairs limited by SOBOE
- LBP disc lesions (L4-L5 and L5-S1)
- Referred R shoulder and R chest pain
- 2 admissions to hospital with RUL collapse/PNA

# Physiotherapy Mx

- Treadmill 15 mins Mod Borg = 3 - 4
- Cycle Ergometry 15 mins 35 – 50 W
- Quads Ext 3 X 10 7.5 – 13 kgs
- Leg Press 3 X 10 15 – 30 kgs
- Lat Pull down 3 X 10 13.5 – 18 kgs
- Pec Dec 3 X 10 5 – 10 kgs
- Abs floor and ball 3 X 10
- ACBT huff and coughing
- Breathing control
- Dyspnoea management strategies
- Home Exercise Program

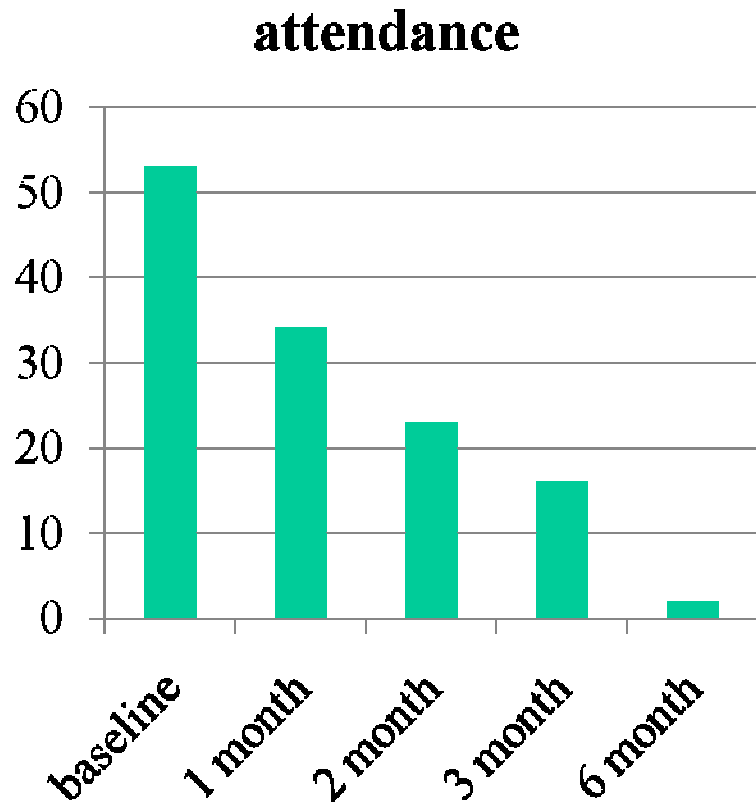
# RK: outcome

	1/30/08	3/19/08	4/14/08	5/19/08
Pain	Duragesic 50 ugh/h	p.r.n Oxynorm	nil	Occas LBP
Other symps	Nausea (chemo) Cough, SOB, fatigue	cough (=pain) fatigue	Cough, SOBOE Fatigue	Much better
PS	60%	70%	80%	80-90%
Weight	61.2 kg (-12%)	61.4 kg	61.8 kg	64.6 kg
CRP	32	200	19.9	
6mWT	100 m		800 m/d	Km/d

# Summary/conclusions

- Weight loss is common in advanced patients
- Multifactorial but cytokines play an important role
- Early intervention important
  - Everyone: weigh/CRP
- Multimodal approach: diet-exercise-symp-s-drugs
  - Ideally done as a MDT
  - Identifying suitable candidates
  - Our patient RK responded well
  - Fitting in around treatments: challenging
- Need outcome data: in homogeneous populations

# What role in palliative care/hospice?



- Predictors: sig
  - 6mWT > ¼ mile
  - On chemotherapy
- Predictors: trend
  - ESAS score  $\leq 30$
  - KPS  $\geq 80\%$
  - Weight loss  $\leq 10\%$
  - Male
  - serum C-reactive  $\leq 30$
  - GPS 0 -1
  - PGSGA scores  $\leq 18$
  - serum albumin  $\geq 35$