Binary Views
Oncology

Oncology

Anatomy Rules All!

Symptoms? Handmaidens

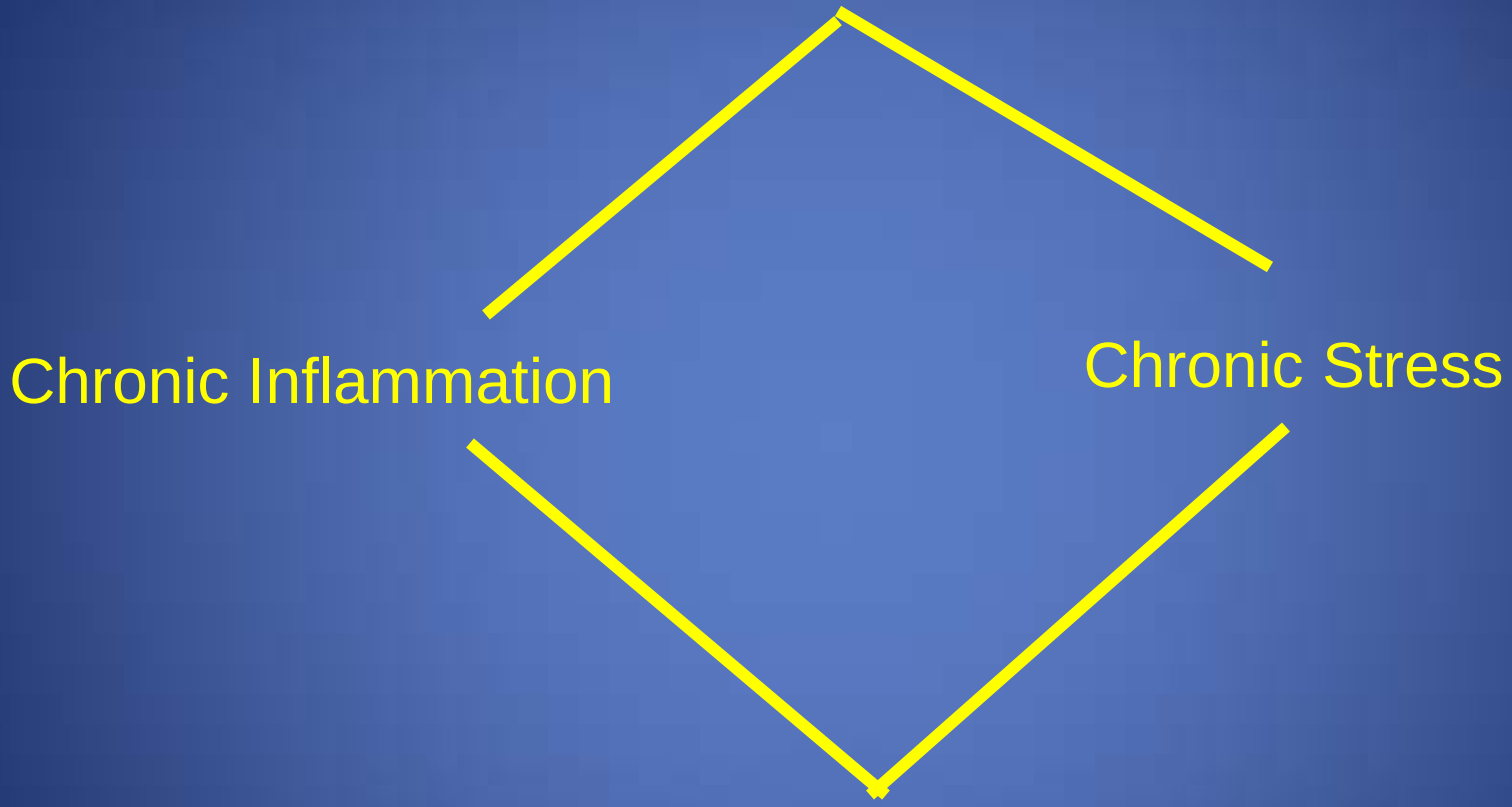
Adopt concept

Biology (Symptoms) key as anatomy

Suffering

Tumour Progress

Factors driving tumor and symptoms



Acute Inflammation

- Innate Immune System
  - Wound healing
  - Tissue repair
  - Angiogenesis
- Adaptive Immune System
  - Specific response to antigen
  - Cytotoxic T cells

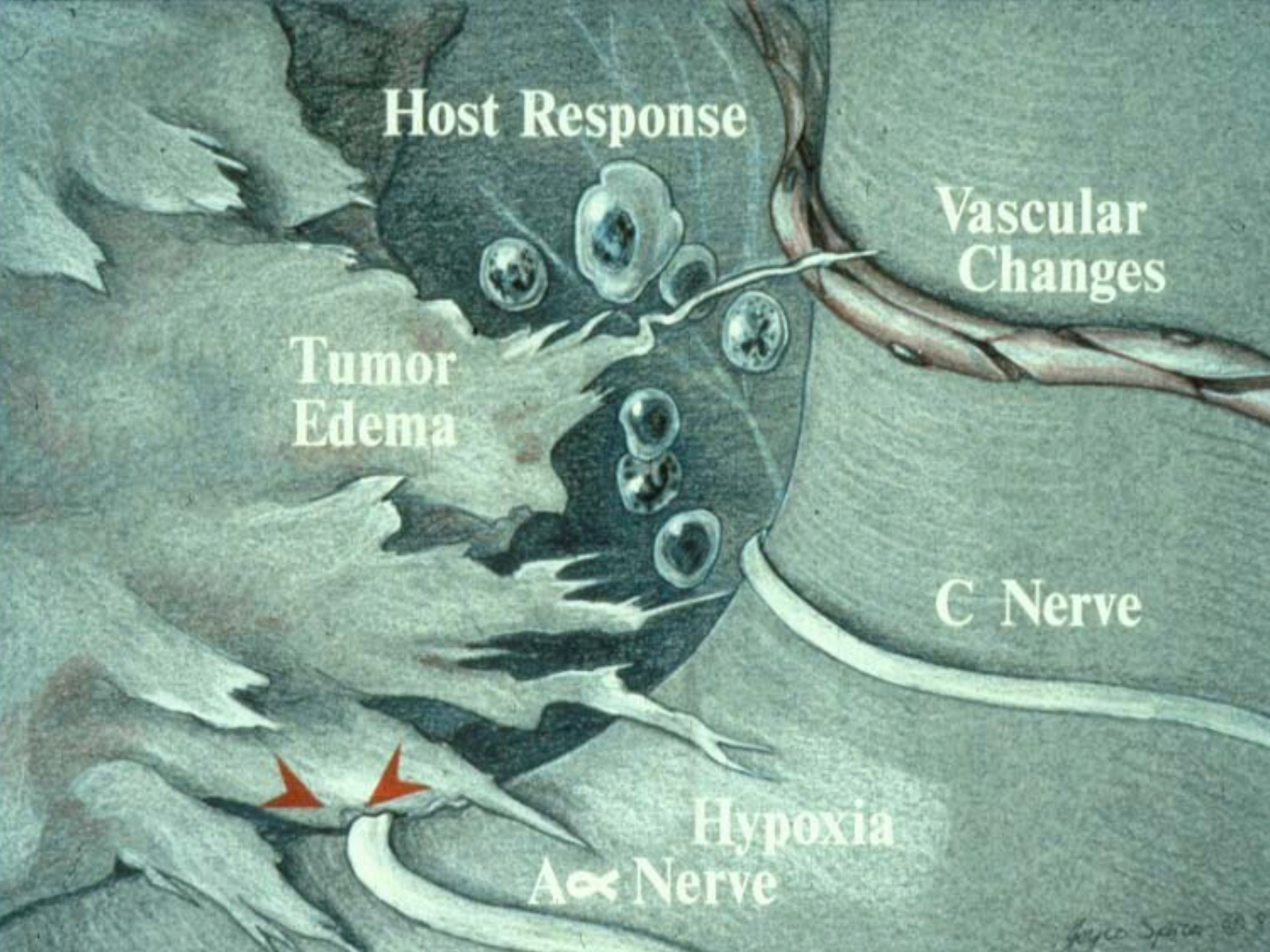
Chronic Inflammation

- Innate ↑

Promote tumour growth and spread

- Adaptive ↓

Reduced NK cell activity


Host Response
Vascular Changes
Tumor Edema
C Nerve
Hypoxia
A∝ Nerve

Advancing Cancers

Infiltrating → **TAM** **TIL**

Growth Factors
Angiogenesis
Proteases – matrix

↓ Tumour Immunity
Th2 ↑ Th1 ↓

We suggest that the inflammatory cells and cytokines found in tumours are more likely to contribute to tumour growth, progression and immunosuppression than they are to mount an effective host anti-tumour response… some types of inflammation may provide 'the fuel that feeds the flames'.

Balkwill, Mantovani. *Lancet*. February 17, 2001

Immune cells regulating tumor growth

Stimulate Cancer Growth	Inhibit Cancer Growth
Innate immune cells	
neutrophils	macrophage (M1)
macrophage (M2)	
myeloid-derived suppressor cells	
Adaptive immune cells	
Th2 $CD4^+$T cell	Cytotoxic $CD8^+$ T cell
$CD4^+$ T regulatory cell	Th1 $CD4^+$ T cell
B lymphocytes	TH17 $CD4^+$ T cell

Adapted – Disis – *JCO* Oct 10 2010

ACS - Cytokines

Not helpful

Int. 1 – B

IL – 8

Helpful?

IL – 12

IL - 15

IL - 24

Both ways:

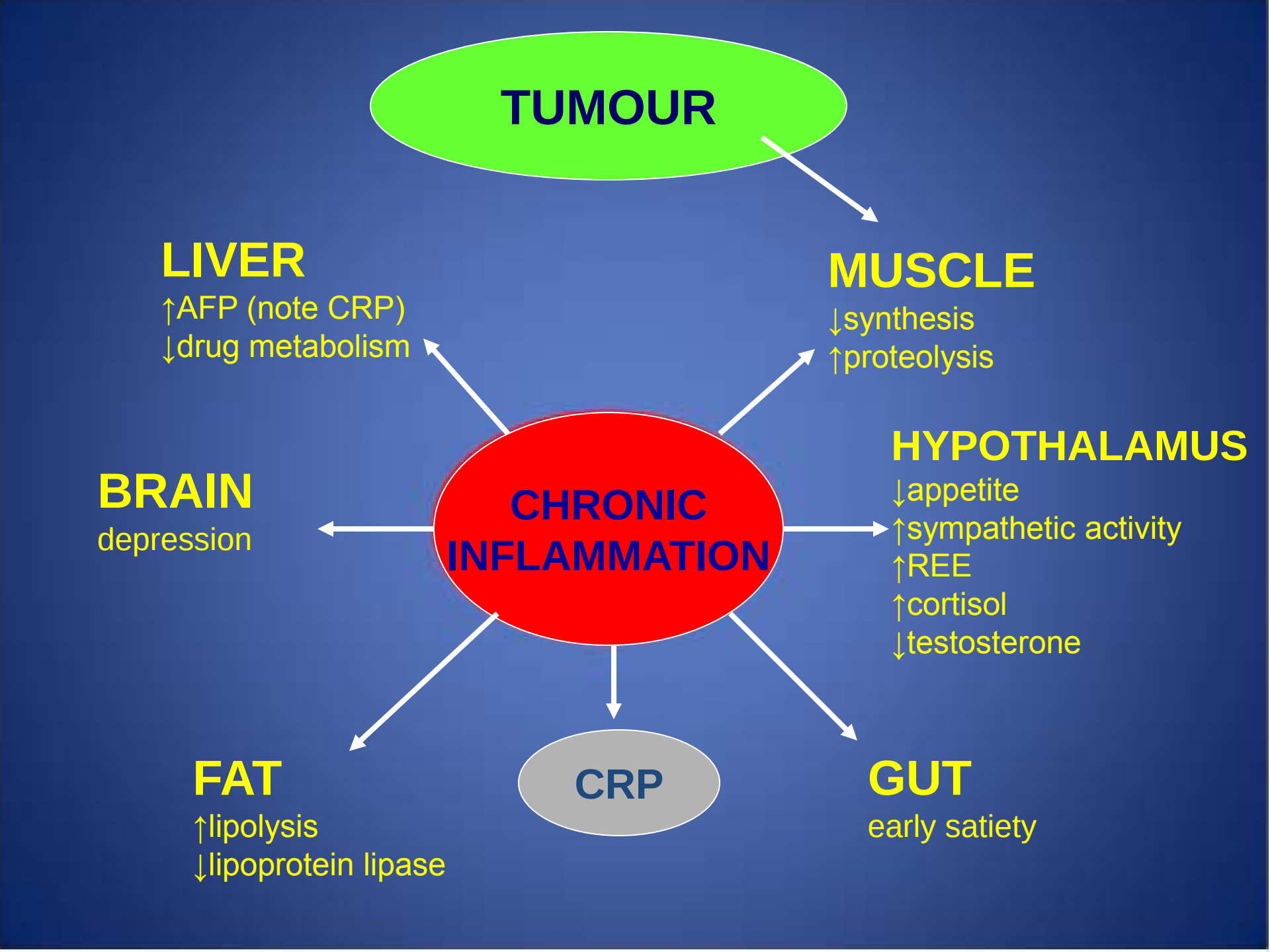
IL-6

IL – 10

IL -17

TNFα

"Taoist – not linear"


TUMOUR
LIVER
↑AFP (note CRP)
↓drug metabolism
MUSCLE
↓synthesis
↑proteolysis
HYPOTHALAMUS
↓appetite
↑sympathetic activity
↑REE
↑cortisol
↓testosterone
BRAIN
depression
CHRONIC INFLAMMATION
CRP
FAT
↑lipolysis
↓lipoprotein lipase
GUT
early satiety

CRP - Prognosis

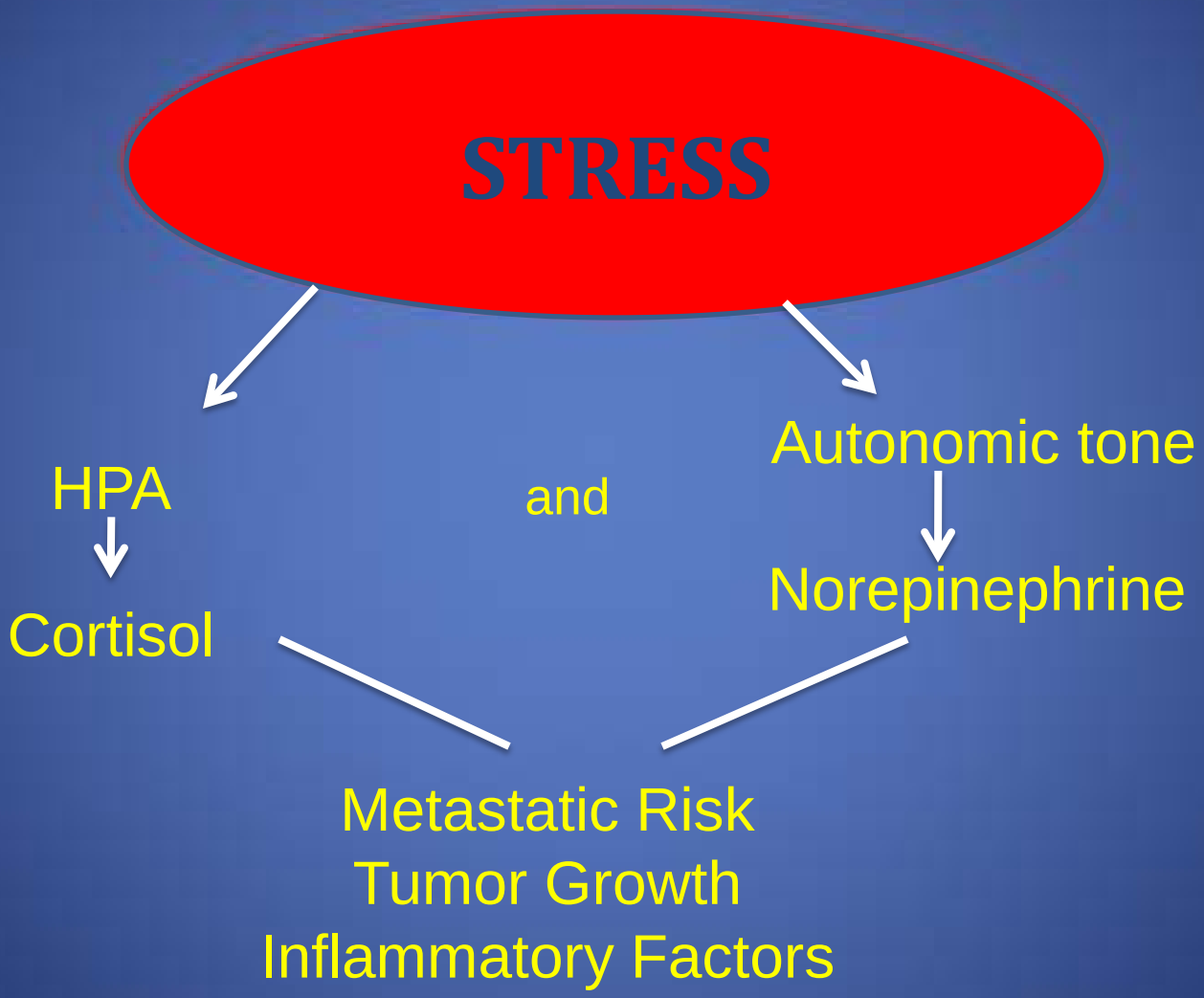
- Ovarian
- Lung
- Melanoma
- Pancreas
- Stomach
- Head and Neck

Resectable Tumours – colorectal, upper GI, renal, bladder

Median survival by CRP Trajectory

	Median survival (months)	95% CI
Normal ⇒ Normal	21.6	11.9-31.6
Normal ⇒ Abnormal	12.3	6.5-18.1
Abnormal ⇒ Normal	10.7	7.6-13.5
Abnormal ⇒ Abnormal	8.3	7.0-9.5
Log Rank (Mantel-Cox)<0.001		

JCO suppl. 2009 abstract 8092



(Modeled on Lutgendorf et al, JCO - 2010; 28-4094)

Inflammation
Immuno-neuroendocrine aberrations

1. ↑ CRF – cortisol
2. ↑ sympathetic activity
   - ↑ Cytokine activity
   - ↑ Pulse –REE
   - Psychosocial stress
3. ↓ testosterone
   - Hypogonadism
     - sex drive
     - activity

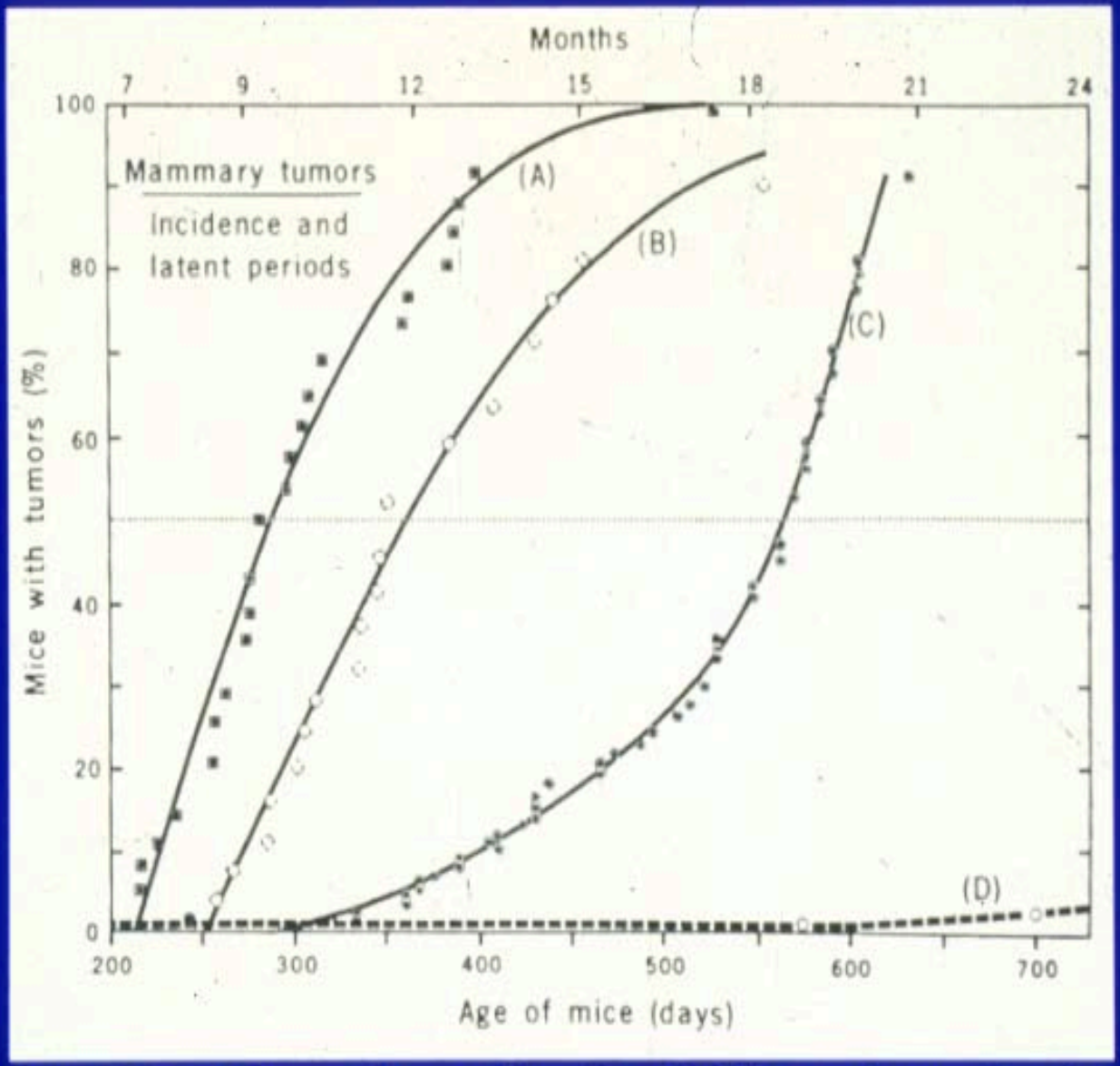
Stress

Mechanisms:

- cancer initiation
- tumor growth
- angiogenesis
- metastases
- reduce apoptosis
- reduce TH_1 AND lymphocytes

Armaiz-Pena et al

Brain behavior and immunity 2009; 23:10-15



Riley Vernon. Mouse Mammary Tumors: Alteration of Incidence as Apparent Function of Stress. *Science* 1975:189:465.

Stress

Animal Data

- Riley……Tumor Growth
- Sloan et al……Metastases

Chronic stress mouse model

30 x ⬆ metastases

Blocked by propranolol

Sloan et al. CancerRes2010;70:1042

Stress

Basic data

Yang et al……Cytokines

Tumor cell lines

Human melanoma

Ben Eliyahu……Survival

Mouse tumor models

Post surgery

Etodolac and Propanolol

Lee et al……Human Ovarian nude mice

Propranolol

Reiche et al……Stress hormone

Switch from Th1 to Th2 immune response

A Human Rodent

1. Elderly
2. Small Tumour Mass
3. Chronic Inflammatory State
4. REE up
5. Both Anorexia and Cachexia
6. Fatigued – low function
7. On chemotherapy/opioids
8. Gender balance

Stress – human correlation

Childhood stress - chronic disease risk

Social deprivation – ovarian cancer (lutgendorf)

_ colorectal cancer (McMillan)

Correlation with immune neuroendocrine change

"Collective evidence points to a prominent role for chronic stress in cancer growth and metastasis"

Moreno-Smith M. et al *Impact of stress on cancer metastasis*.
Future Oncology Dec2010

Stress – human correlation

Breast cancer……..Spiegel
Anderson

GI cancer……Kuchler

Melanoma……..Fawzy

Programs — Cognitive/Behavioural
Mindfulness
Supportive
Exercise – Yoga

Correlations with immuno endocrine change

Biobehavioral influences on cancer progression
Costanzo et al. *Immun-al Clin NA* 2011;109:32

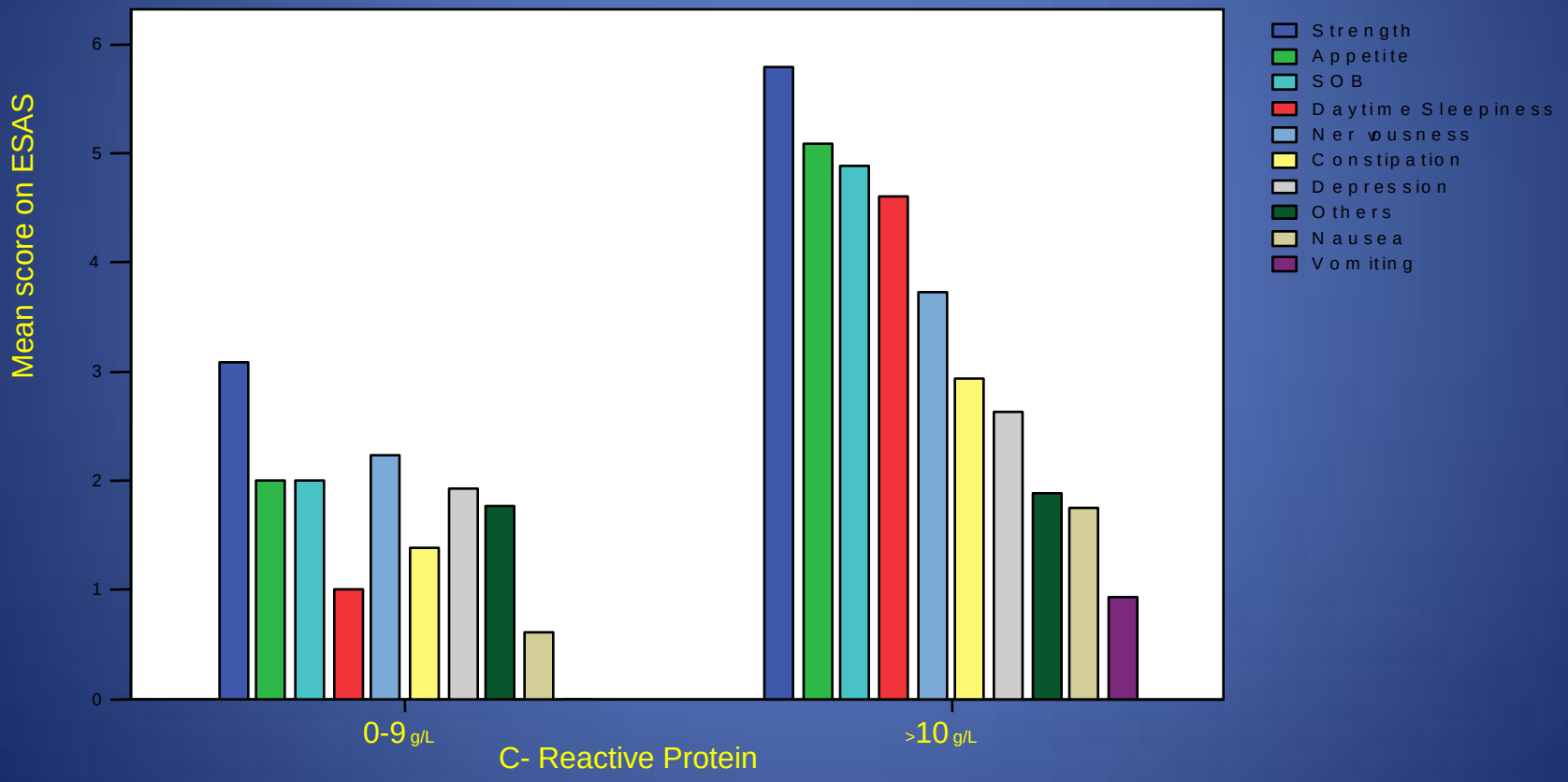
Propranolol - Atenolol

- Effects on β adrenergic blockade

  Breast cancer

- Melhem-Bertrandt A, Chavez-MacGregor M,Lei X et al. Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. *J Clin Oncol* doi: 10.1200/JCO.2010.33.4441.
- Barron TI,Connolly RM, Sharp L et al. Beta blockers and breast cancer mortality: a population-based study. *J Clin Oncol* doi: 10.1200/JCO.2010.33.5422.

Correlation Between CRP and Severity of Symptoms Reported by Patients



Sleep - Inflammation

- Acute –
  - Deprivation - ↑ CRP Il-6 Il- 1β
  - Inflammation –

    Poor sleep quality

    Insomnia

    Fatigue

- Bidirectional – vicious circle

- Simpson et al *Nutrition Reviews* Dec 2007

Pain - Inflammation

Animal Studies

↑ Il-6 -- pain models

Il-6 KO -- ↓ pain response

Interference -- opioid response

Human Studies

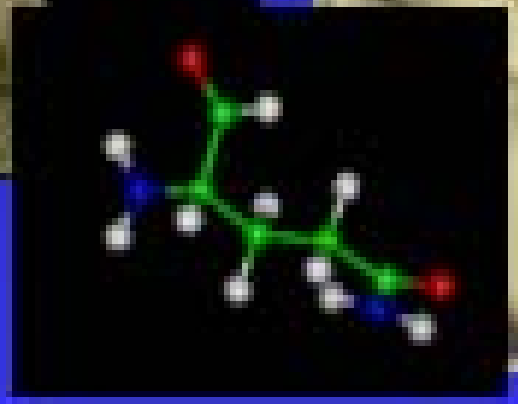
↑ Il-6, TNFα, Il – 1β – Regional CSF (neuropathic pain)

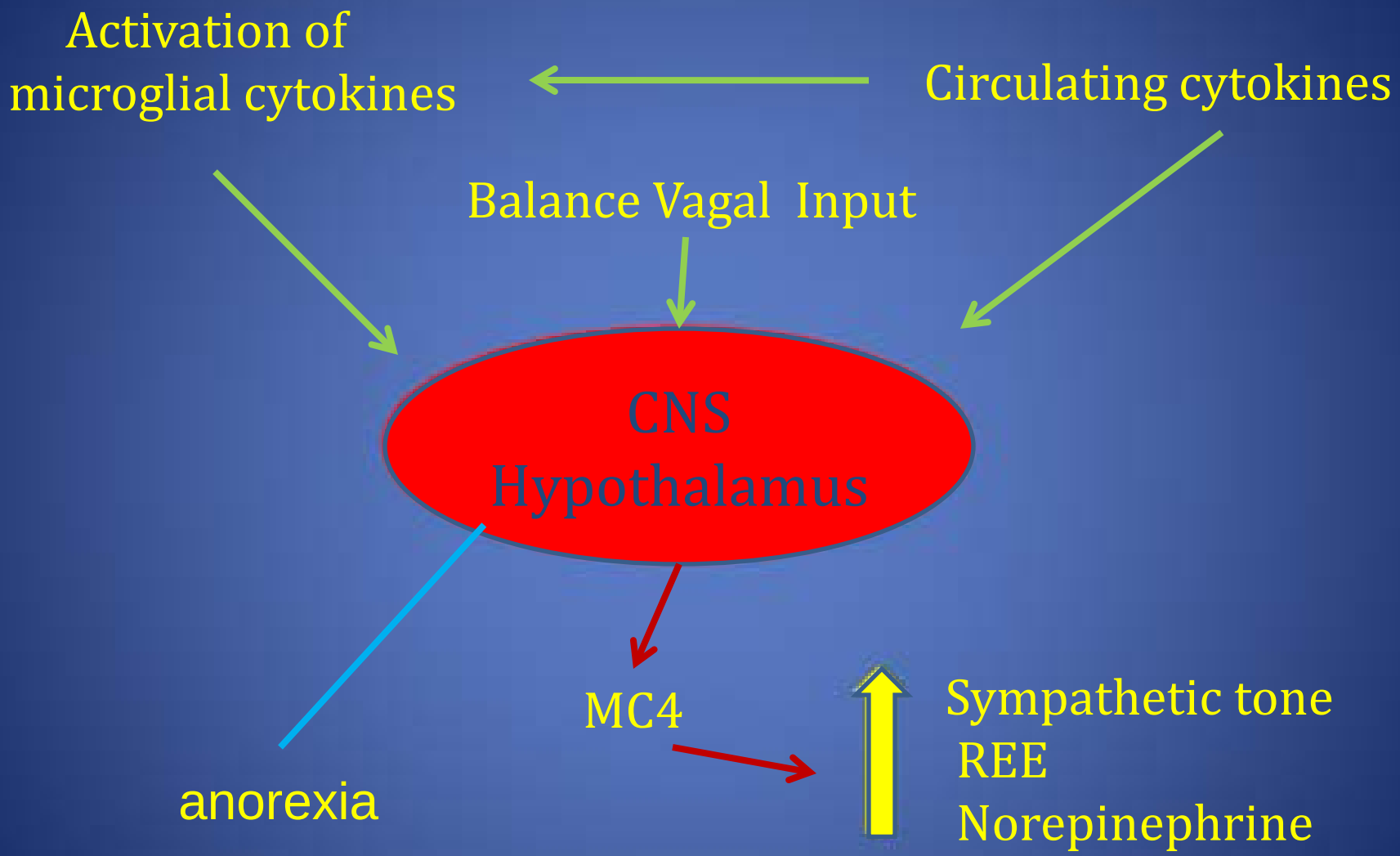
Cancer

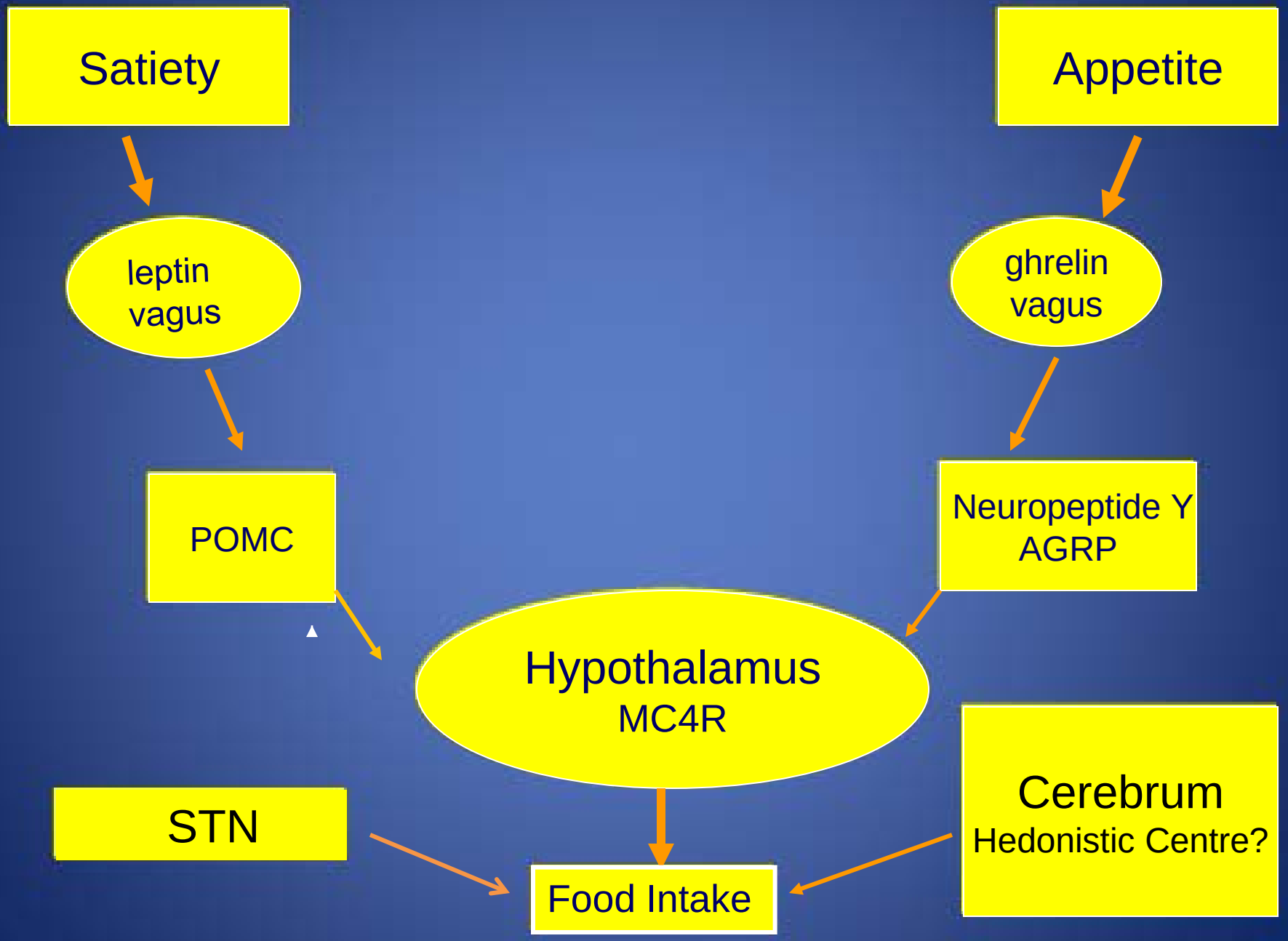
Laird et al:	Trial 1 CRP	Trial 2
	275 patients	174 patients
	0.036	0.032
	0.126 (Pearson)	0.163

*Pain*2011;152:460-463

Cancer Cachexia - Anorexia




Activation of microglial cytokines
Circulating cytokines
Balance Vagal Input
CNS Hypothalamus
anorexia
MC4
Sympathetic tone
REE
Norepinephrine


Satiety
Appetite
leptin
vagus
ghrelin
vagus
POMC
Neuropeptide Y
AGRP
Hypothalamus
MC4R
STN
Cerebrum
Hedonistic Centre?
Food Intake

Metabolic changes in tumor related weight loss

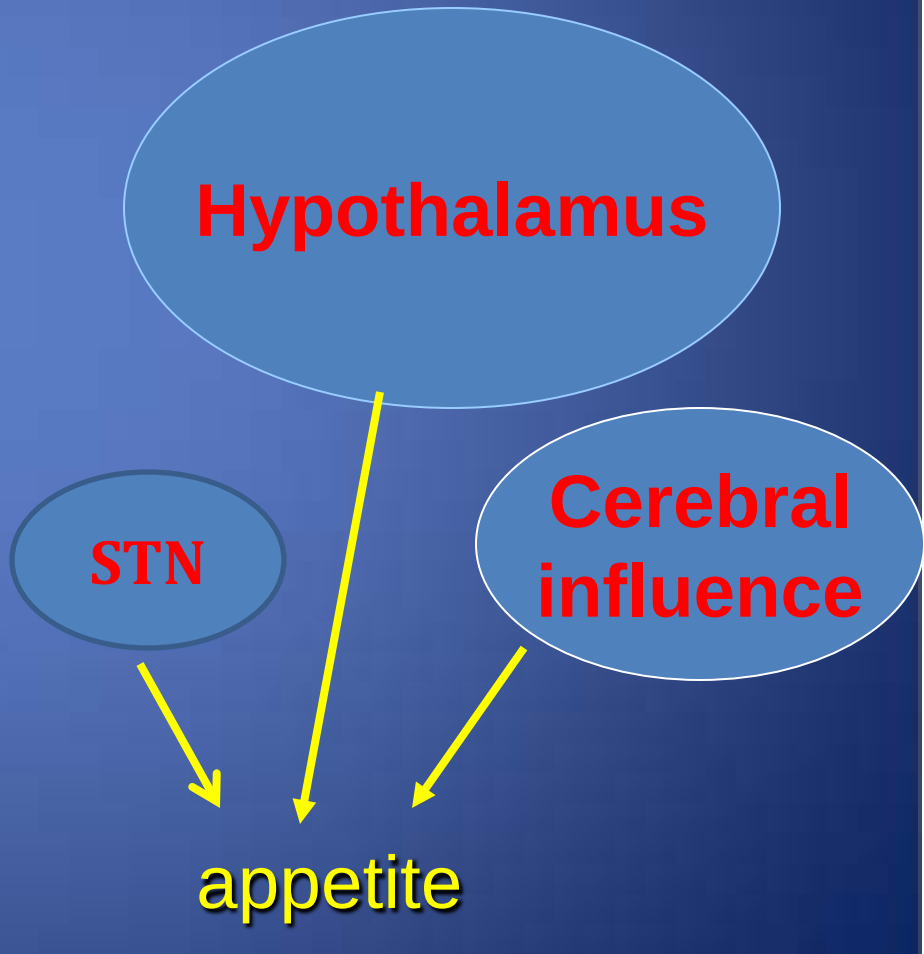
- insulin resistance
- diminished lipogenesis
- increased lipolysis
- increased protein synthesis – liver
- ↓ muscle synthesis ↑ proteolysis
  acute phase protein response – CRP
- ↑ inflammatory cytokines
- Il-1β, Il-6, other Th_2 cytokines)
- ↑ REE

Anorexia-cachexia

PERIPHERAL

- Inflammation
  - cytokines, eicosanoids
- Muscle loss
- Hypercatabolism
  - dysautonomia
- Hypogonadism
- Oxidative Stress
- Activin?
- Genetic Predisposition
- Tumor Factors

CENTRAL



Chronic Inflammation - Cancer

- Immune response often facilitates tumor progress
- Tumor cells produce inflammatory chemical mediators assisting growth
- Inflammatory mediators enhance many cancer symptoms
- Early evidence – anti-inflammatory agents may modify the course of cancer
- Will anti-inflammatory (palliative) therapies improve life quality and quantity?
- Relief of cachexia -  survival?

Palliative Care-improve outcomes?

- Quality of life --- Seven studies
  - Yes – 5/7
- Symptoms --- Fifteen studies
  - "overall the results of these 15 studies provide little evidence to support the efficacy of palliative care interventions in alleviating physical symptoms" –

– El-Jawahri et al. *Suppor Oncol* May/June 2011

WHO Definition Palliative Care - 2002

"Palliative care is an approach which improves the quality of life of patients facing the problems associated with life-threatening illness, through prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."

The McGill Cancer Nutrition-Rehabilitation Program

www.mcgill.ca/cnr

CNR Interdisciplinary Team MUHC-RVH

PHYSICIAN
ONCOLOGISTS
Medical Intervention

PHYSIOTHERAPIST
Functional Evaluation
and Rehabilitation

PATIENT
AND
FAMILY

DIETITIAN
Nutritional Evaluation
and Recommendations

NURSING, PSYCHOLOGIST,
OCCUPATIONAL THERAPIST,
SOCIAL WORKER

[redacted]

Slide courtesy Nelda Swinton

Conceptual model of cancer trajectory

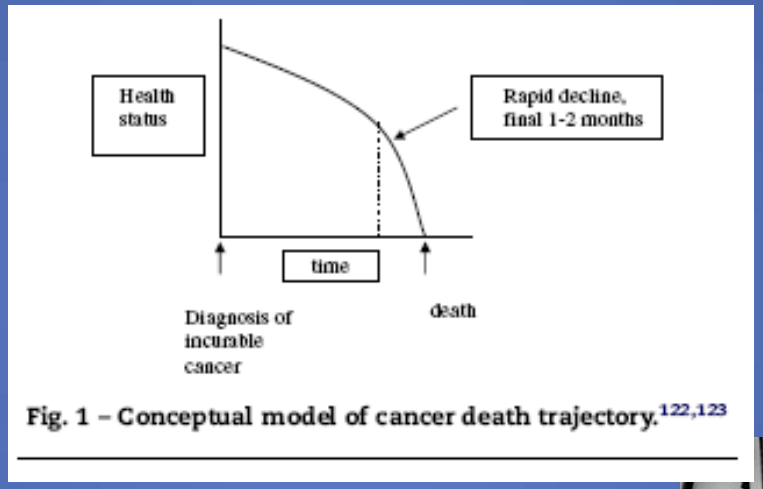


Fig. 1 – Conceptual model of cancer death trajectory.[122,123]

Barb Tarbox 1961 - 2003

Workup

- Questionnaires
  - ESAS
  - Distress
  - PG-SGA
  - CHAMPS
- CRP
- WBC
- Testosterone - bioavailable
- Thyroid

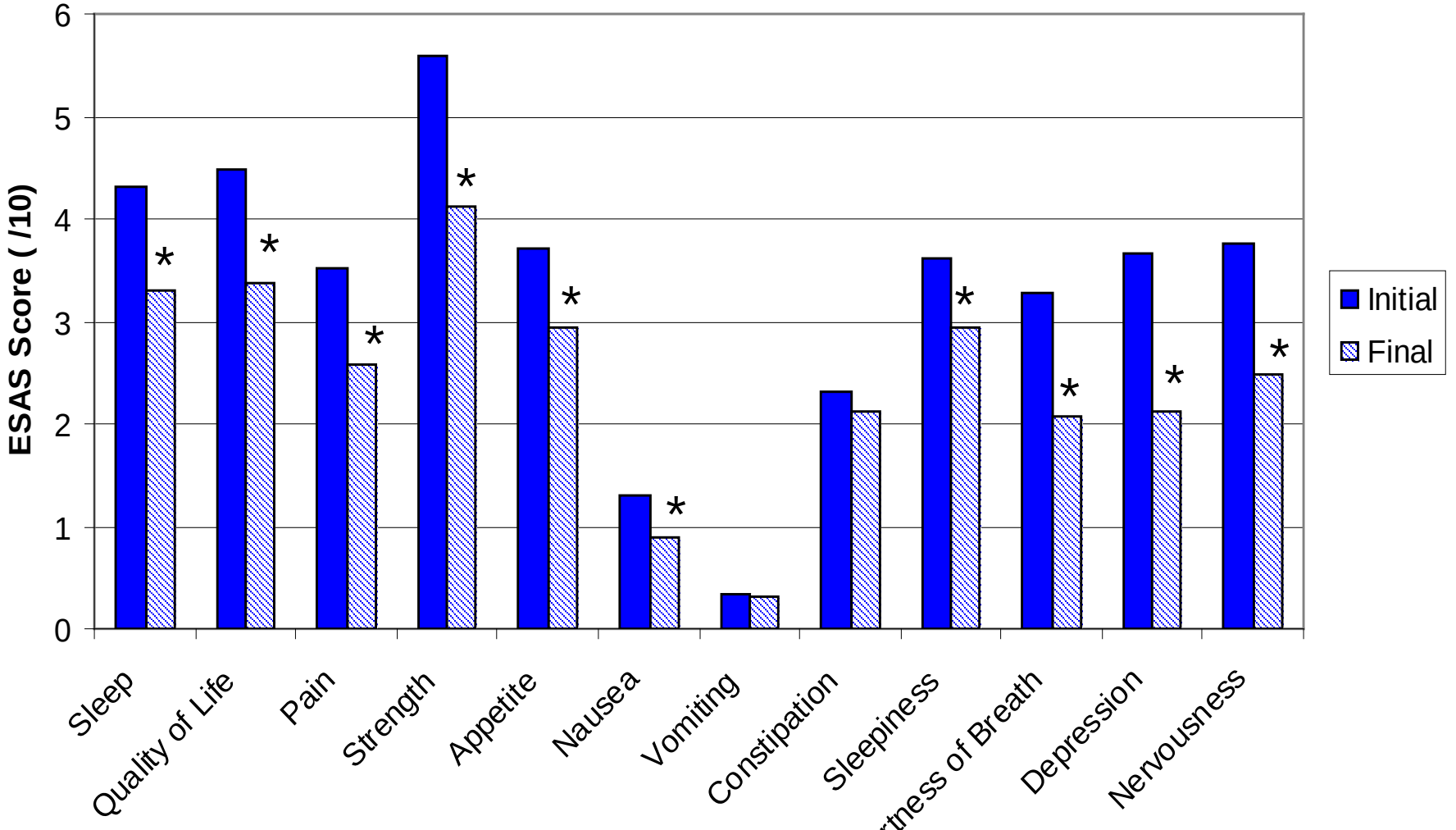
Rehab Tests

- Tests (endurance, strength, ROM, balance)
  - 6MW, Gait, Balance
  - CHAMPS (general activities – all types)- fatigue
  - Sit to stand
  - Gait speed
  - Review safety

Program

- 8 – 10 weeks with clear initial and end evaluation
- Nutritional counselling
- Basic intervention= physio 1-2 times /week
- 1 visit / 2 weeks other team members
- Caregiver information
- Weekly psycho-education groups – meet once /week x 9 rotating sessions

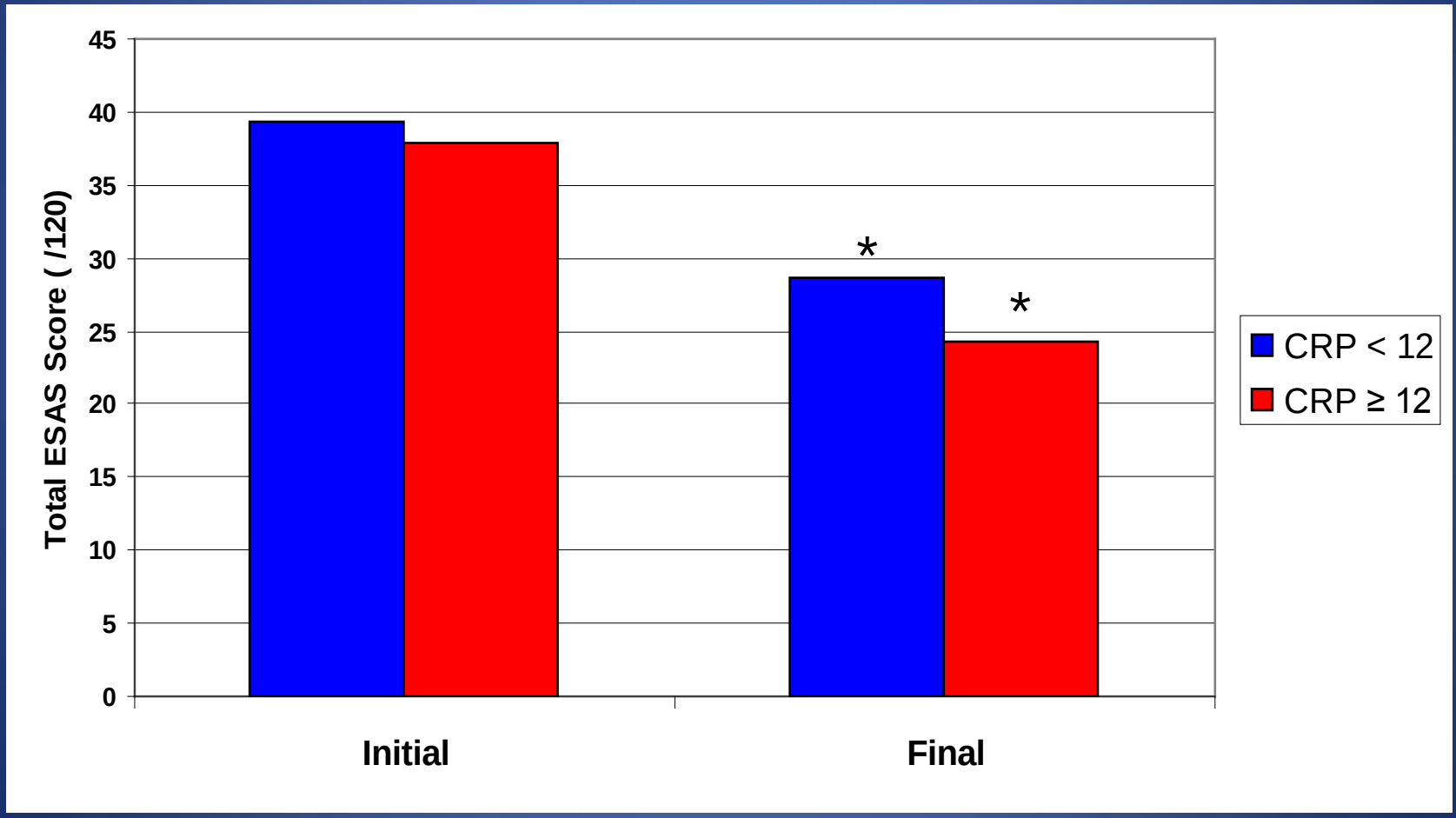
Changes in ESAS Scores after 8-week CNR program for Patients with Advanced Cancer presenting with CRP < 12 at Initial CNR Evaluation (N = 95)



Note: Higher scores indicate worse symptoms

*** *p* < 0.05 vs. Initial**

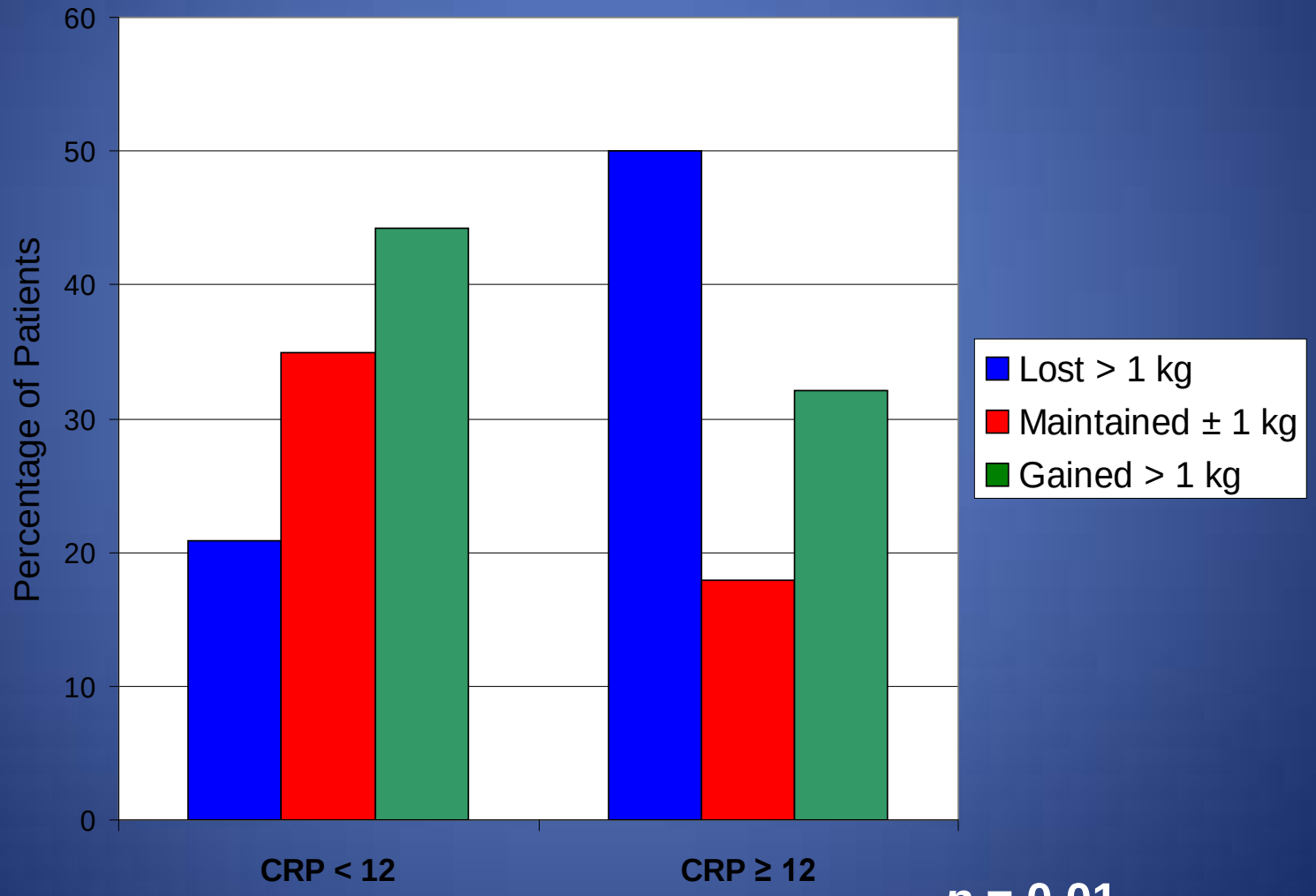
Initial and Final Total ESAS Scores for Patients with Advanced Cancer presenting with CRP < 12 or CRP ≥ 12 at Initial CNR Evaluation (N = 103)



Note: Higher scores indicate worse symptoms

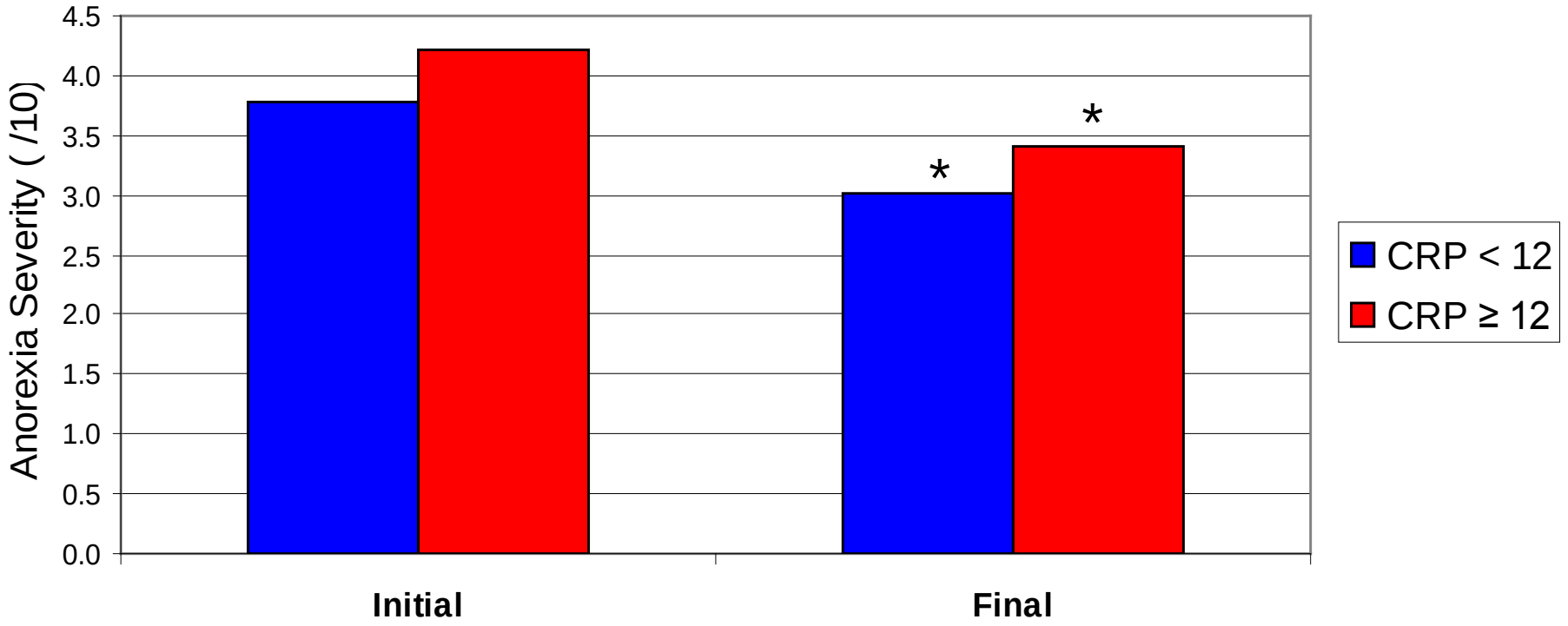
* $p < 0.05$ vs. Initial

Percentage of Patients with Advanced Cancer who Lost, Maintained or Gained Weight during the CNR program by Inflammatory Status (N = 114)



$p = 0.01$

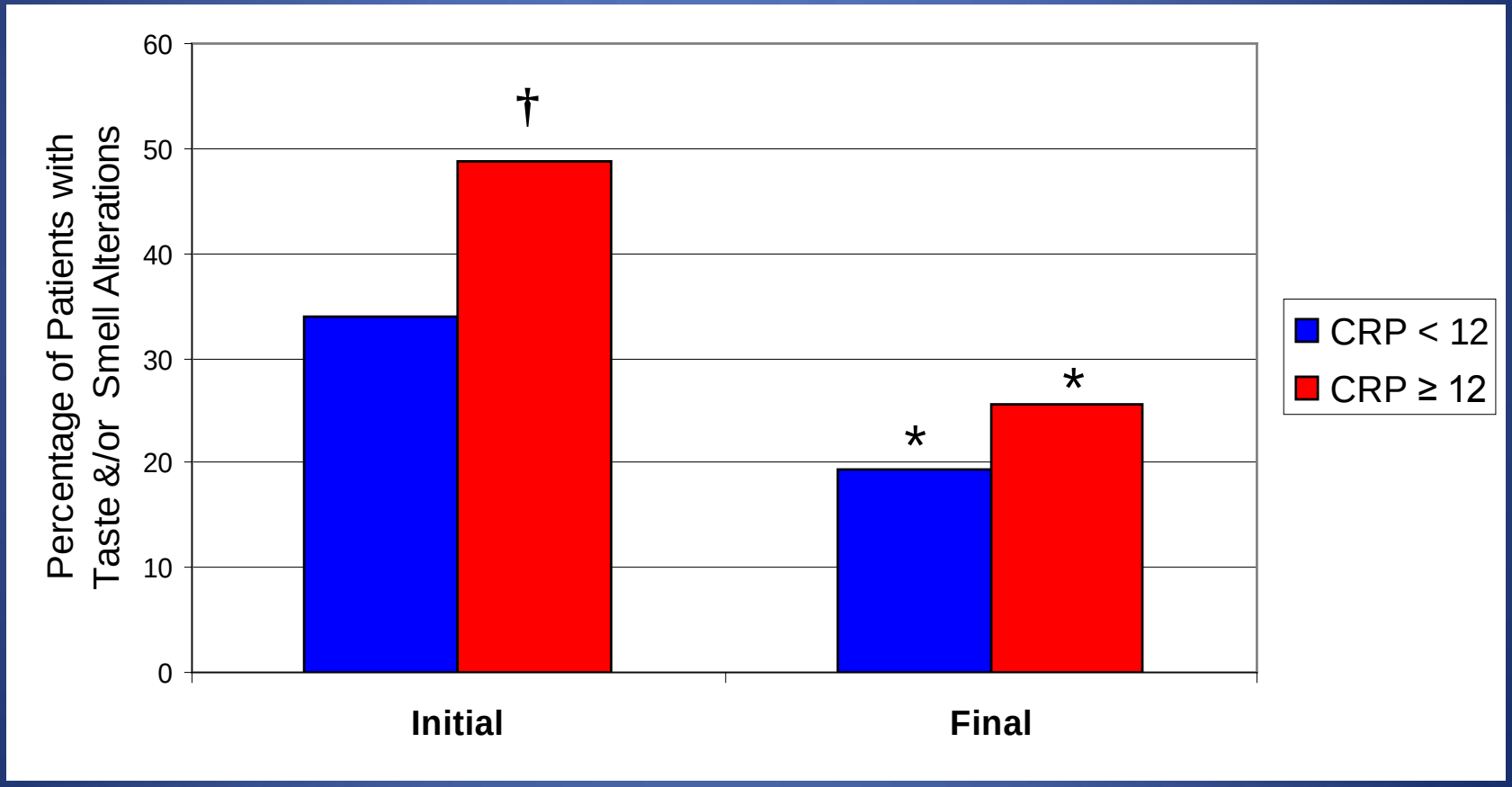
Initial and Final ESAS Anorexia Scores for Patients with Advanced Cancer presenting with CRP < 12 or CRP ≥ 12 at Initial CNR Evaluations (N = 117)



Note: Higher scores indicate worse symptoms

* $p < 0.05$ vs. Initial

Percentage of Patients with Advanced Cancer with Taste &/or Smell Alterations at Initial and Final CNR Evaluations (N = 103)



* $p < 0.05$ vs. Initial; † $p < 0.05$ vs. CRP < 12

Evaluation

- High patient satisfaction
- Advanced cancer patients can exercise
- CRP status determines completion of an exercise program
- Measured improvements in appetite, weight and function

Multimodal program

Is our program anti-inflammatory?

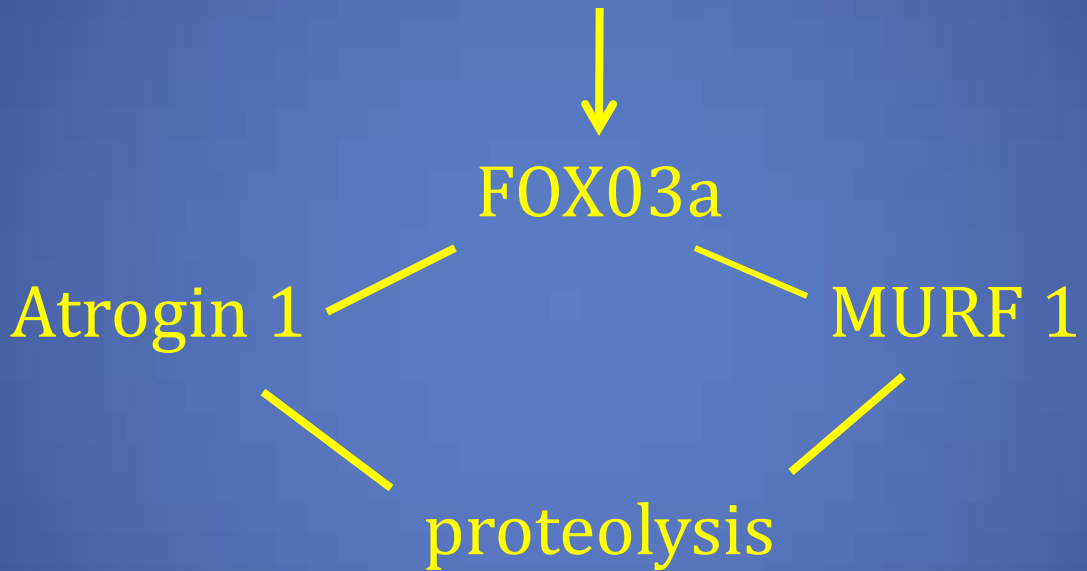
1. Dietary advice – yes
2. Exercise – yes
3. Psychosocial component – yes
4. Drugs – not really

Note – no overall change in CRP status

Activin RIIB

Colon 26 Ca model

Activin RIIB



NO reduction cytokines

Reduction tumor growth

BUT ↑ muscle mass ↑ survival

Zhou et al. *Cell* 2010;*142:531*

Drugs - Cachexia

- Re-examine Omega 3's/NSAIDs
- Selective androgen receptor modifiers (SARMS)
- β agonists – formoterol
- B agonists – propanolol
- Cytokine inhibitors – anti Il-6
- Activin – myostatin

  reversal

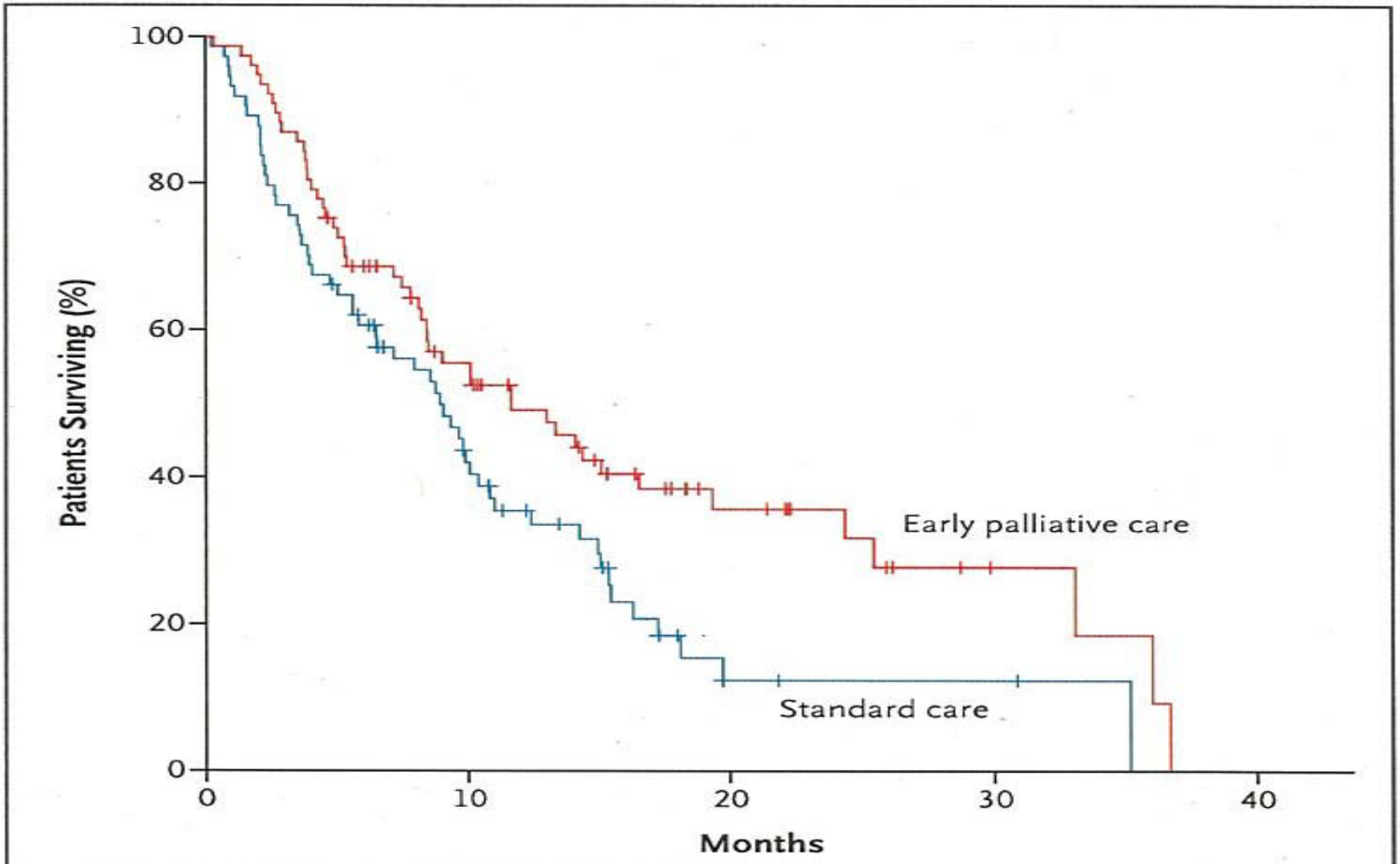


Figure 3. Kaplan–Meier Estimates of Survival According to Study Group.

Temel et al, N Engl J Med 2010; 363:733-742

Palliative Care – what we do

1. Identify – manage psychosocial issues
2. Emphasis on caregiver support
3. Relief of physical causes of suffering
4. Focus on Nutrition
5. Focus on muscle function and rehabilitation

Hypothesis –

Palliative Care interventions may impact on patient survival as well as Q/L

Animal data is sufficient to support this hypothesis. Human data is very modest but compelling.

Palliative Care – what we do

1. Identify – manage psychosocial issues
2. Emphasis on caregiver support
3. Relief of physical causes of suffering
4. Focus on Nutrition
5. Focus on muscle function and rehabilitation

If true the importance to cancer patients is major and must lead to prioritizing integrated palliative care/chemo-bio trials.

A substantive change in both oncology thinking and trial structure is required. We must study whole care packages not simply drugs.

Ethical Issues – Trial Research

- Priorities
  - Set for patient interest?
    - Drug costs
    - Low probability trials
    - ‘me too’ trials
- Patient’s best interest
  - Business interests
    - Price per patient
    - Locale
    - Investigator CI

You are not eligible if you are taking part in another trial

Fastidious vs Pragmatic trials

Fastidious vs Pragmatic Trials

- Fastidious Trials – 'using homogeneous groups, reducing or eliminating ambiguity'

- Pragmatic Trials – 'would incorporate heterogeneity, ambiguity, and other messy aspects of clinical practice'

Feinstein – *Ann Int Med 1983*

Ideal Trial - I

- Pragmatic – reflecting practice
- Reflect multifactorial nature
- Wide application
- Newly diagnosed patients

Ideal Trial - II

- Patients – 1st Line
  - True 'Best Supportive Care'
  - Symptom Control
  - Nutrition and Exercise
  - Palliative care involvement
- Chemobiotherapy vs chemobiotherapy
  - SARMS
  - anti-inflammatory agent
  - anti-myostatins
- Stratify by CRP

MENAC Trial - EAPC Research Network

Stratifyadvanced lung, pancreas, colorectal

Standard Palliative Care

Nutrition – counseling – HMB&EPA
Exercise
Drug - Celecoxib

Stratify – Weight Loss – CRP - Chemotherapy

Courtesy Stein Kaasa

Improving Symptom Research

1. Change in mind set. Symptoms reflect tumour activity and are probably as important as partial anatomic change in tumour mass.
2. Change trial priority.
   - Curative trials
   - Pragmatic trials – care package
   - Fastidious trials – limited studies on drugs with limited inclusion/exclusion clauses
   - ‘Me too’ trials

Proposals

1. Engage Binary Vision
2. Collaborative Group
   - international
3. Funding
   - public
   - probonum ? – industry, philanthropic
4. End Points
   - quality of life
   - Function
   - survival

Upon this gifted age, in its dark hour,
Rains from the sky a meteoric shower
Of facts…they lie unquestioned, uncombined.
Wisdom enough to leech us of our ill
Is daily spun, but there exists no loom
To weave it into fabric

Edna St Vincent Millay