

Nutrition and cancer: impact on outcome

**Specific substrate in the
nutrition of the cancer patient**

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Nutrition in cancer: impact on outcome

Specific substrate in the nutrition of cancer patient

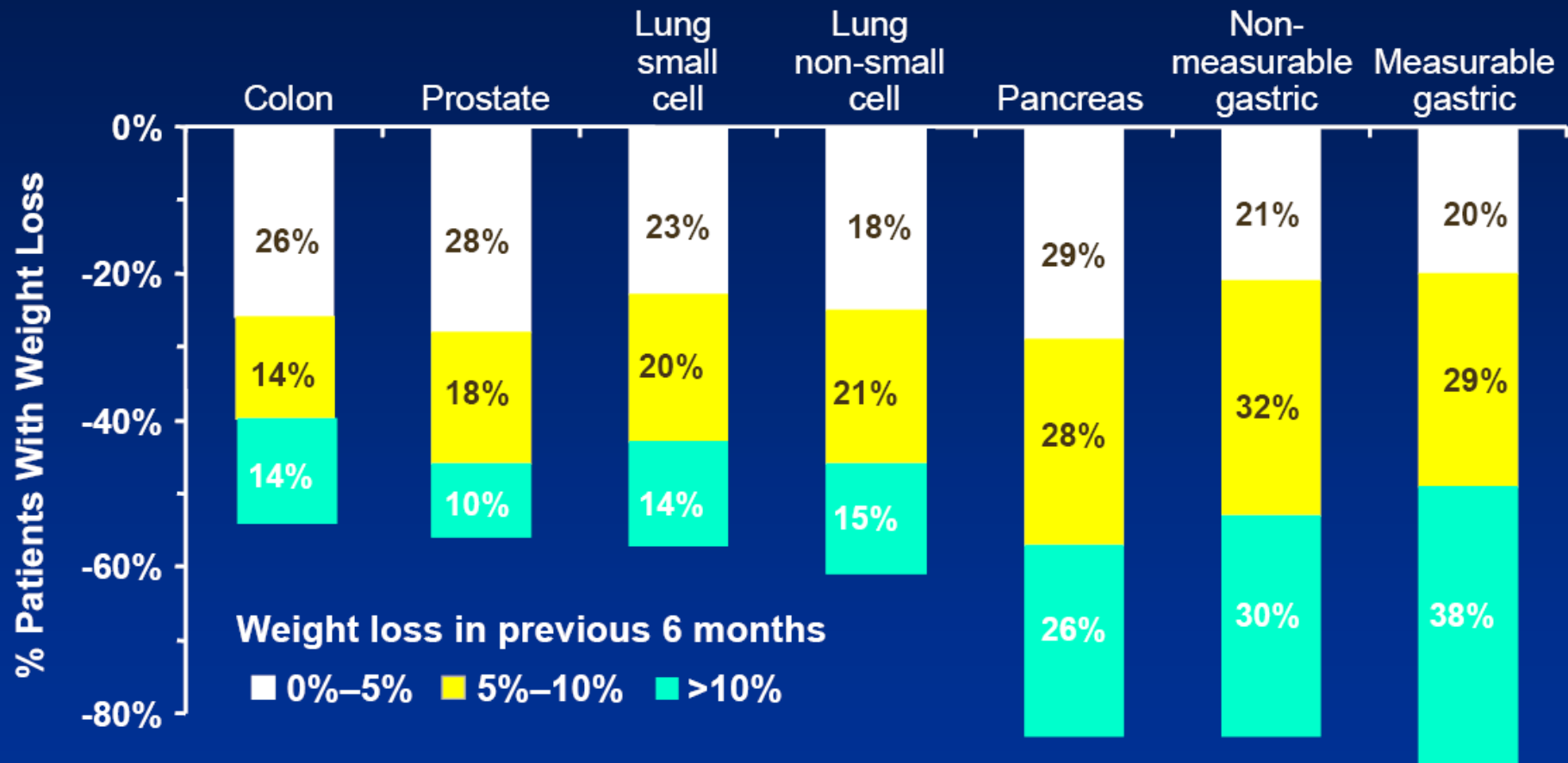
Patient's features	Clinical situation	Nutrition support
<ul style="list-style-type: none">• Age• Type of tumor• Staging• Curability• Multimodal therapy• Patient's willingness• Co-morbidity	<ul style="list-style-type: none">• Perioperative• Chemo/radio• Advanced cancer• Terminal• Weight loosing	<ul style="list-style-type: none">• Diet counseling• ONS• Enteral• Parenteral

Cancer cachexia

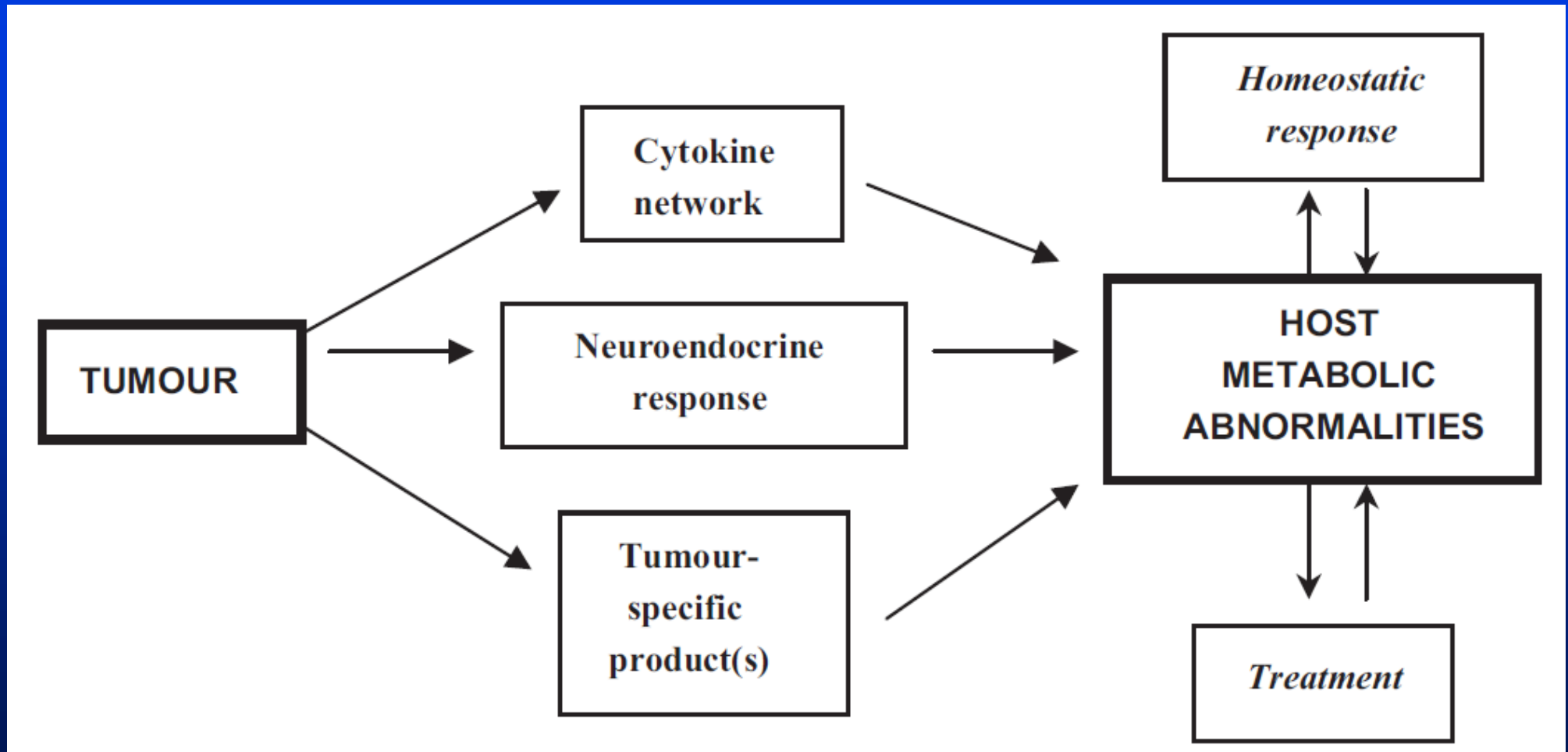
- Chronic wasting syndrome, involving loss of both tissue and lean body mass, which is resistant to conventional nutritional support*
- Occurs in 50% of the patients with cancer
- Weight loss, anorexia, early satiety, weakness, anemia, edema, feelings of weakness and fatigue

*Skipworth B et al, Clin Nutr 2007, 26, 667-76

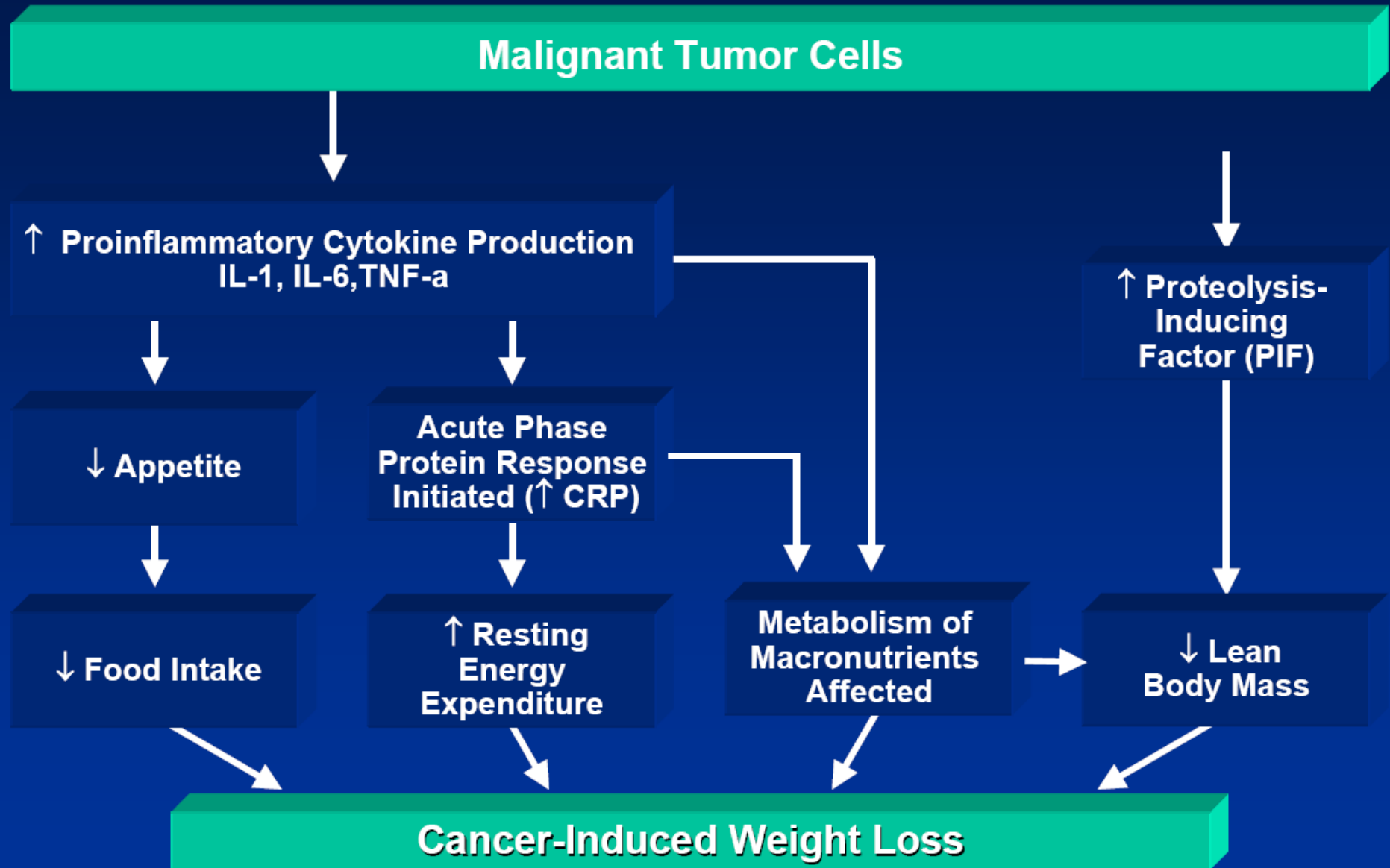
Frequency/Severity of Weight Loss Associated with Cancer



Host-tumour interaction



Pathogenesis of Cancer Cachexia



Cancer cachexia

Resulting metabolic derangements

Insulin
resistance

Increased
lipolysis

Normal or
increased
lipid oxidation

Increased
protein
turnover

Increased
production
of APPR

Cancer cachexia

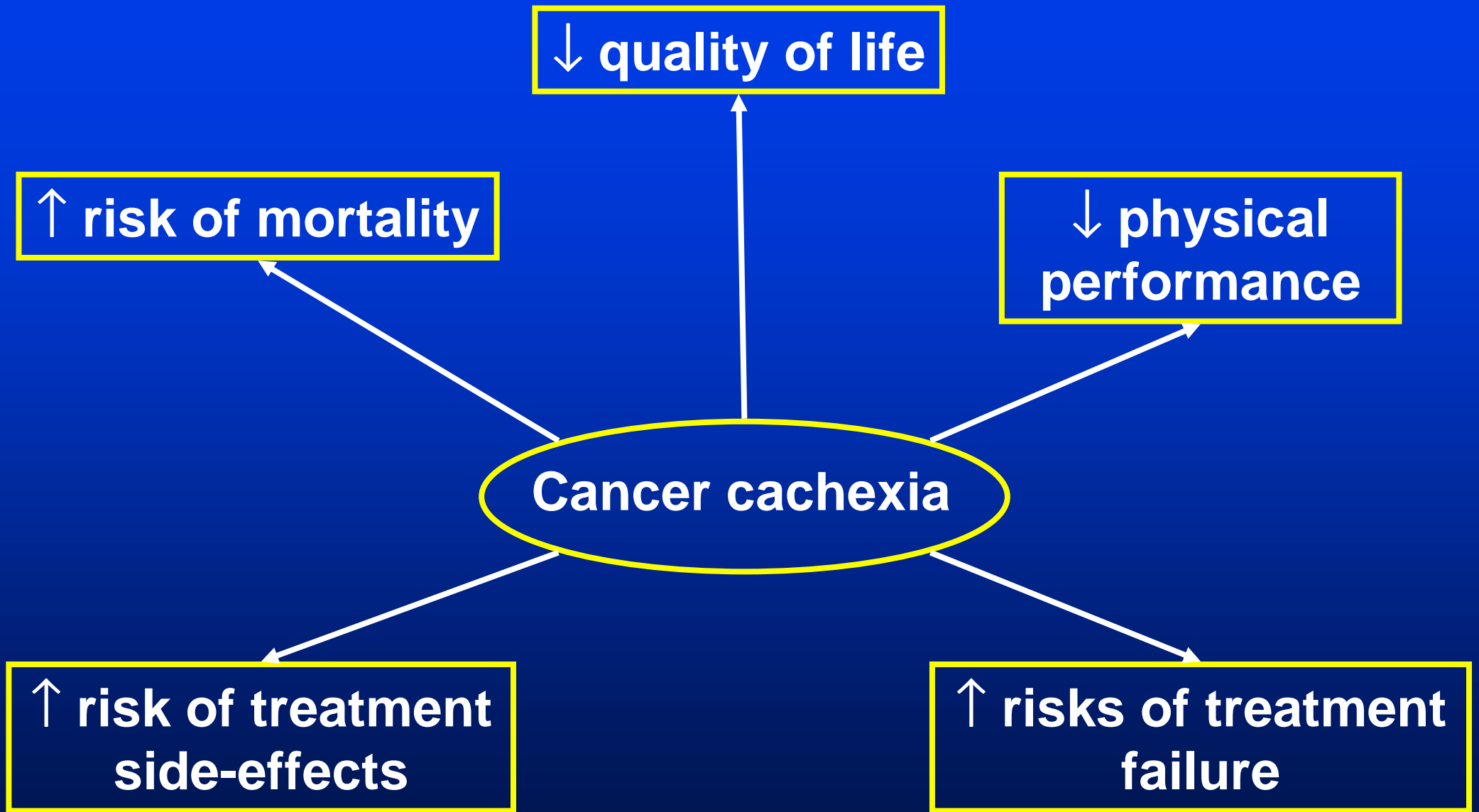
Lipid metabolism

- **↑ lipid metabolism**
 - ↓ glycerol and FA release → oxidation
 - ↓ neoglucogenesis
- **↑ hyperlipidemia**
 - ↓ lipoprotein-lipase activity (TNF/INF- γ)
 - ↑ hepatic lipogenesis (VLDL) (IL-1, IL-6, IFN- γ)

Cancer cachexia

Beyond the host-tumour interaction

- Patient demographics
 - age (+ sarcopenia)
(= degenerative loss of skeletal muscle)
 - physical activity (REE \leftrightarrow TEE)
- Kinetics of protein metabolism



Cancer patients

Can we do better in using **specific substrates** in comparison with conventional nutrition for avoiding cancer cachexia?

Cancer cachexia

Kinetics of protein metabolism in cancer patient

- In fasted cancer patient, whole-body protein metabolism is markedly increased
- Repeated half-hourly oral supplement feeding reduce-whole-body protein breakdown

but...

no clinically applied feeding protocol has been completely successful at reversing cancer-associated weight loss

Cancer cachexia

Kinetics of protein metabolism

- 2.6 g of muscle protein must be catabolised to produce 1 g of fibrinogen

→ key role of Acute Phase Protein Response

Do cancer patients require a distinct nutrient composition? (parenteral nutrition)

- Probably yes (c)
- The **vast majority** of ambulatory or hospitalized cancer patients requiring PN for only a short period of time (surgical patients, patients requiring a bowel rest for severe GI adverse effects from chemotherapy or radiation, etc.) do **not need any specific formulation**

*Guidelines on PN in non-surgical oncology
Bozzetti F, Arends J et al, in press*

Do cancer patients require a distinct nutrient composition? (PN)

However, a special attention should be paid to patients with frank cachexia requiring PN for several weeks because of the well-known abnormalities in the energy substrate metabolism in these conditions

There is some suggestion for using a **high percentage of lipid** in the admixture (~ 50% of non-protein energy requirement), on the basis of the pathophysiological and clinical considerations

*Guidelines on PN in non-surgical oncology
Bozzetti F, Arends J et al, in press*

Rationale for using “High percentage of lipid” in cancer patients

- Fat is efficiently mobilized and utilized as a fuel source in cancer patients

Waterhouse C et al, Cancer Res 1971; Shaw J et al, Ann Surg 1978

- Fat oxidation rate is significantly increased in weight-losing cancer patients

Hansell D et al, Ann surg 1986

- Clinical studies (few)

- Intralipid infusion significantly decreased net protein catabolism

Shaw J et al, JPEN 1988

- lipid utilization (clearance was significantly increased in cancer patients, especially in weight-losing patients)

Kober J et al, Eur J Clin Nutr 1999

Rationale for using “high percentage of lipid in cancer patients”

- A glucose-based PN may cause a positive balance of water and sodium
- Administration of glucose might precipitate peritoneal effusion in patients with carcinomatosis

Use of lipid in cancer patient Recommendations

A 1 to 1 fat to glucose energy ratio might be a sensible approach in cancer patients and higher ratios might be tried when pleural or peritoneal effusions are present

*Guidelines on PN in non-surgical oncology
Bozzetti F, Arends J et al, in press*

Is supplementation with special
substrates or modulators
beneficial in cancer patients?

Preliminary data suggest a potential
positive role of **insulin**

*Guidelines on PN in non-surgical oncology
Bozzetti F, Arends J et al, in press
Lundholm et al, Clin Cancer Res 2007*

Insulin treatment in cancer cachexia effects on survival, metabolism and physical functioning

- n = 138 patients with advanced cancer
- Palliative treatment + prevention anemia + specialized nutrition support:
 - control
 - insulin (0.11 ± 0.05 U/kg/d)
- Results (1): Insulin Group:
 - stimulated CHO intake
 - decrease serum free-fat fatty acids
 - increased whole body fat
 - fat-free lean tissue mass was unaffected

Guidelines on PN in non-surgical oncology

Bozzetti F, Arends J et al, in press; Lundholm et al, Clin Cancer Res 2007

Insulin treatment in cancer cachexia effects on survival, metabolism and physical functioning

- n = 138 patients with advanced cancer
- Palliative treatment + prevention anemia + specialized nutrition support:
 - control
 - insulin (0.11 ± 0.05 U/kg/d)
- Results (2): Insulin Group:
 - improved metabolic efficiency during exercise
 - did not increase maximum exercise capacity or spontaneous physical activity
 - tumors markers (CEA, CA-125, CA 19-9) not influence by insulin
 - improved survival of insulin-treated group ($p < 0.03$)

Guidelines on PN in non-surgical oncology

Bozzetti F, Arends J et al, in press; Lundholm et al, Clin Cancer Res 2007

**Is supplementation with special
substrates or modulators
beneficial in cancer patients?
w3 fatty acid?**

**“No benefit from the oral administration of
EPA in patients with consolidated
cachexia”**

based on 5 RCTs including 759 patients

Guidelines on PN in non-surgical oncology

Bozzetti F, Arends J et al, in press; Lundholm et al, Clin Cancer Res 2007

Is supplementation with special substrates or modulators beneficial in cancer patients?
w3 fatty acid?

**COCHRANE Review: no benefit
but**

- In 2 studies: reduced dosage of the administered EPA over the advised prescription**
- In 3 RCTs: short-term duration**

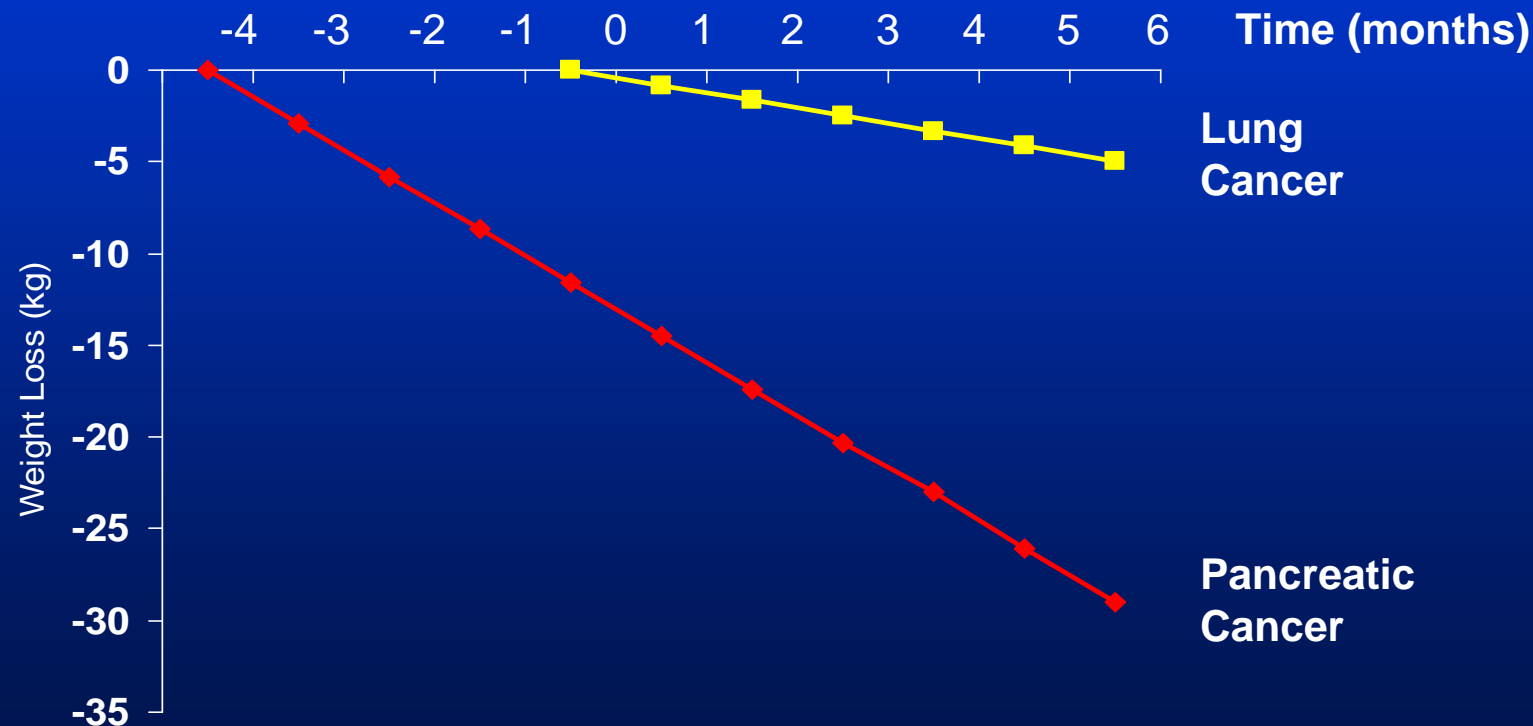
The COCHRANE review underscores the need of further RCTs addressing issue of preventing rather than treating cachexia

N3 fatty acids, cancer, cachexia: a systematic review of the literature

- Seventeen studies (8 of high quality)
- Panel of experts:
 - oral supplements with omega-3 benefit patients with advanced cancer and weight loss
 - advantages observed were: increased weight and appetite, improved QoL; reduced post-surgical morbidity
 - it is recommended to administer > 1.5 g/day
 - better tolerance is obtained administering low-fat formula for a period of at least 8 weeks

Why study pancreatic cancer patients?

- Dramatic weight loss
- Smaller sample size
- Shorter study duration



Wigmore SJ. British J Cancer 1997;75:106

Staal-van den Brekel AJ. Cancer Research 1994;54:6430

Study inclusion criteria

- Male or nonpregnant, nonlactating female > 18 years
- Advanced adenocarcinoma of the pancreas
- Weight loss > 5% in 6-months
- Karnofsky score > 60
- Expected survival > 2 months
- Agree to stop all other nutritional supplements

Study supplement comparison

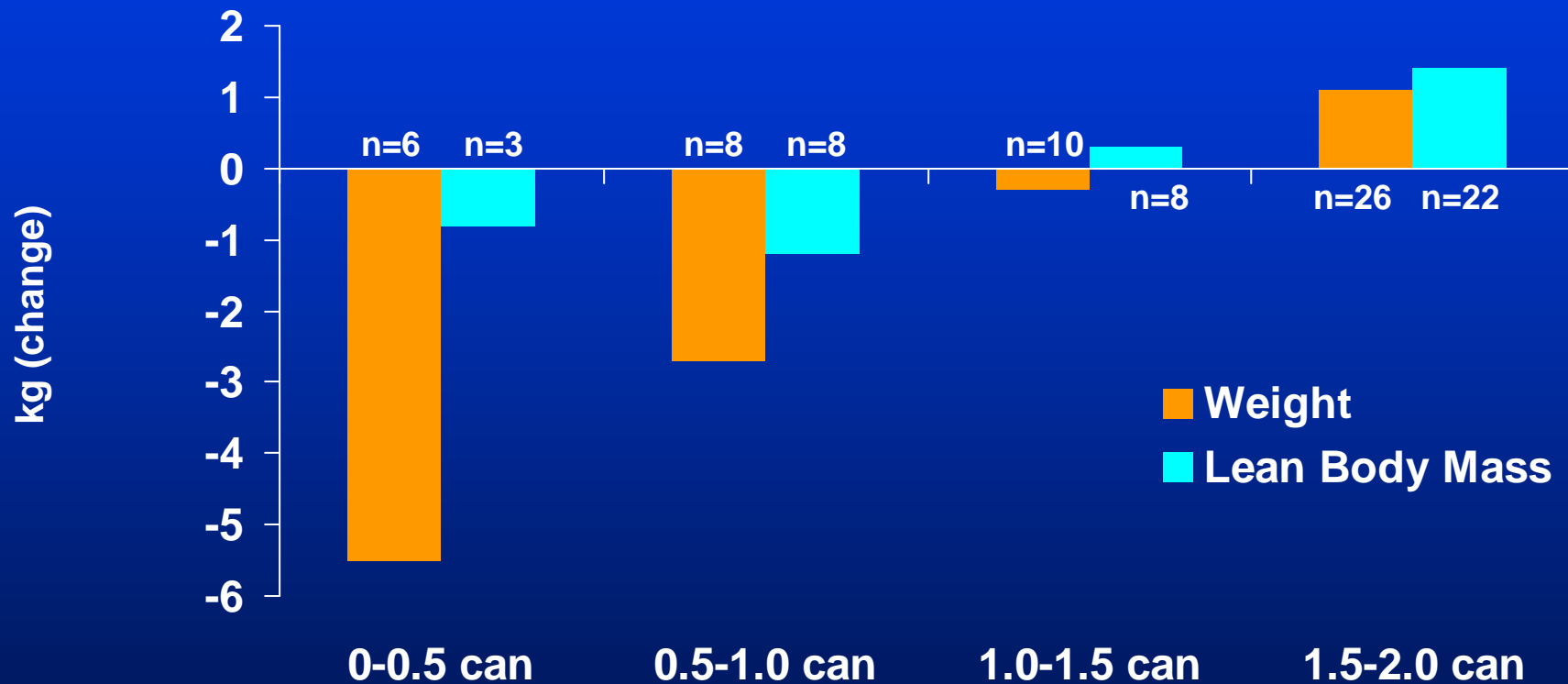
Experimental/Control

- 300 kcal per serving
- Protein – 16 g
- Carbohydrate – 50 g
- Fiber – 5 g (2.6 g FOS)
- Fat – 6 g

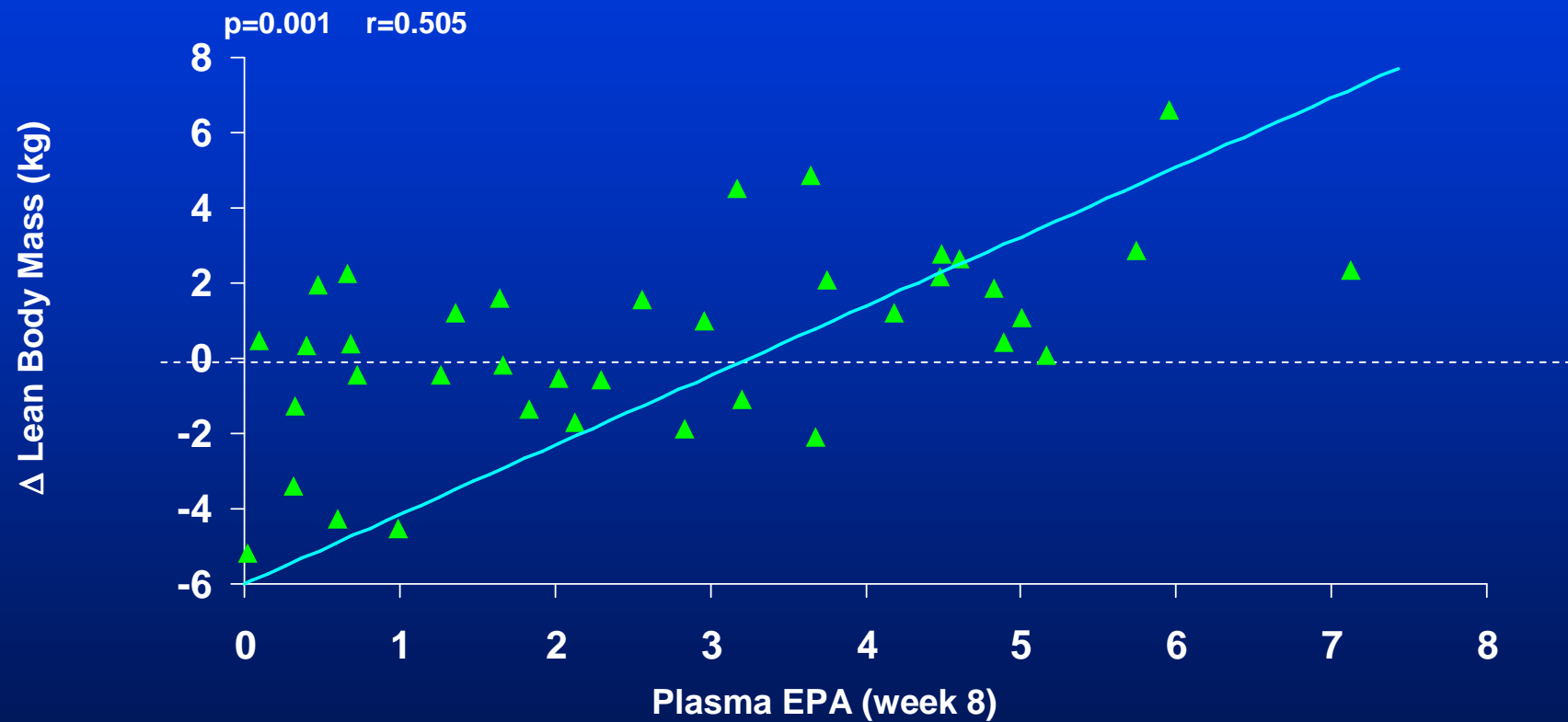
Experimental Product

- EPA – 1.09 g
- DHA – 0.46 g
- Enhanced antioxidants
(vitamins A, C, E and Se)

Effect of ProSure on Change in Weight and Lean Body Mass at 8 Weeks



Plasma EPA vs. Lean Body Mass



Fearon KCH. 2001. Eur J Cancer. 37:27S

Specific “substrates” in pre(peri) operative period?

“In cancer patients undergoing upper major abdominal surgery preoperative EN preferably with immune modulating substrates (arginine, w-3 fatty acids and nucleotides) is recommended for 5-7 days independently of their nutritional risk” (A)

Preoperative oral supplementation

- Prospective study
- 350 patients, GI cancer, weight loss < 10%
- Diet:
 1. oral supplementation* 5 days before surgery
 2. idem + postop. feeding
 3. no artificial nutrition

*1 L/day Impact[®] 12.5 g arginine, 3.3 g w-3, 1.2 g RNA

Preoperative oral supplementation

	Conventional	Preop	Periop
• Death	1	1	2
• Infectious complications	31	14*	16*
• Non infectious	36	30	28
• Length of hospital stay	14±7	11.6±4*	12.2±4*

Gianotti et al. Gastroenterology 2002, 122, 1763

Perioperative nutrition in malnourished surgical patients

- Prospective, randomized study
- 196 malnourished patients (weight loss > 10%)
- Diet: 1. postop standard enteral feeding
2. preop enriched diet (7 days) + postop standard feeding
3. preop enriched diet (7 days) + postop enriched formula

	1	2	3	
postop complications	24	14*	9*	(p=0.02)
length of stay (days)	15.3	13.2	12.0	(p<0.001)
(arginine, w-3, RNA; ± 910 ml/d)				

Braga. Arch Surg 2002, 137, 174

Enteral nutrition in postoperative period – Which substrates?

In most patients a standard whole protein formula is appropriate (C)

With special regard to patients with obvious severe nutritional risk, those undergoing major cancer surgery of the neck and of the abdomen as well as after severe trauma benefit from the use of immune modulating formulae (enriched with arginine, w-3, nucleotides) (A)

Specific substrates in the nutrition of the cancer patient

Enteral nutrition – Do cancer patients require a distinct nutrient composition?

Standard formulae are recommended for enteral nutrition of cancer patients (C)

“There are no data – other than in perioperative nutrition – available on the effects of formulae enriched in glutamine or other immune modulating substances on the nutritional status of cancer patients

If patients experience a feeling of early satiety and refuse the full volume of the prescribed EN, the high-energy and high-protein form may be preferable (IV)

Arends J et al, Guidelines non-surgical oncology, Clin Nutr 2006

Specific substrate in the nutrition of cancer patient

Pro – Pre - Synbiotics

- Perioperative period:

- for formulae containing symbiotics with fibre and Lactobacillus, a significantly lower incidence of infections was shown after major abdominal surgery (gastric/pancreas) (1b)

Rayes N et al, Nutrition 2002

- Organ transplantation:

- compared to standard formulae, combined with selective decontamination of the small intestine, the use of a high fiber formula with probiotic bacteria (lactobacillus plantarium) has been shown to reduce significantly the rate of infections (1b)

Rayes N et al, Transplantation 2002

Specific substrates in the nutrition of the cancer patient

Hemotopoietic stem cell transplantation (HSCT)

Is enteral delivery of glutamine or EPA useful?

None of the 4 trials investigating oral glutamine could prove any major advantages

(Anderson et al, 1998; Schloerb et al, 1999; Coghlin D et al, 2000; Jebb, 1995)

Enteral administration of glutamine or EPA is not recommended in HSCT (C)

(Arends J, Clin Nutr 2006)

Is parenteral delivery of glutamine useful?

Yes (Grade B)

(Brown S et al, 1998; Goringe A et al, 1998; Mercadal, 2007; Gomez C, 2007)

Bozzetti, Guidelines on PN, in press

Does Parenteral Nutrition “feed” the tumour?

Probably yes, but without known deleterious effects on the outcome and thus this consideration should have no influence on the decision to feed a cancer patient when PN is clinically recommended

Specific substrates in the nutrition of the cancer patients

Take-Home messages (1)

Peri-operative period

- **Immune modulating substrates** (arginine, w-3 fatty acids, nucleotide) are recommended in the perioperative period
- There are only a few data for the benefit of pro/symbiotics formulae in the perioperative period

Specific substrates in the nutrition of the cancer patients

Take-Home messages (2)

Cancer cachexia

- In patients with frank cachexia, a high percentage of lipid is recommended (glucose: lipid 1:1)
- There is no strong evidence for the use of oral **EPA** enriched formulae in cancer cachexia
- **High energy** and **high-protein** formulae may facilitate tolerance
- Subcutaneous insulin could be beneficial in weight-losing cancer

Specific substrates in the nutrition of the cancer patients

Take-Home messages (3)

Hemotopoietic stem cell transplantation

While the use of **glutamine-enriched** formulae in HSCT is not recommended, parenteral glutamine might be beneficial

Specific substrates in the nutrition of the cancer patients

Take-Home messages (4)

Except in some situations, the majority of cancer patients do not need any specific formulation