Targeted interventions for nutritional challenges in palliative care

Florian Strasser, MD
Oncology & Palliative Medicine
Cantonal Hospital St.Gallen, Switzerland

Targeted interventions – nutritional challenges PC

Nutritional Challenge

Causes & Goals

Cause – directed Intv.

Goal – directed Intv.

What are the „nutritional challenges“ in Palliative Care?

Loss of weight & appetite → cause suffering
- treat the cause
- alleviate the symptom experience
- support coping with consequences

Cause - directed treatments: no (not yet) predictors of response to (various) interventions

Improve subjective feeling of appetite: so what?

Coping: nihilism or true acceptance – compassion?

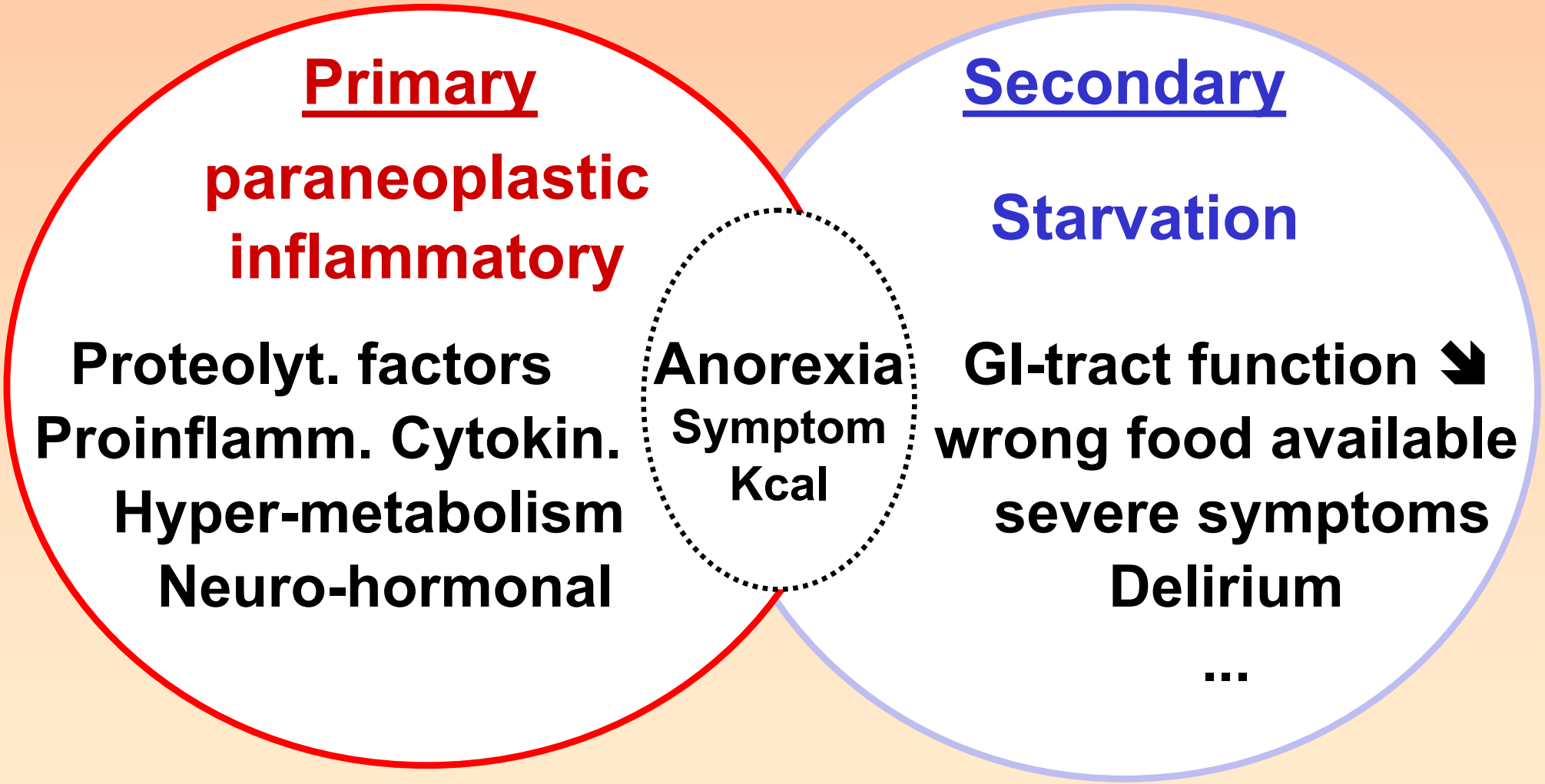
What is a „targeted intervention“ in Palliative Care?

Targeted: Cause-directed or Goal-directed

Cause-directed: Primary ACS, Secondary ACS
→ Identify characteristics of ACS (Phenotypes?)
→ Hypothesis-driven tailored intervention

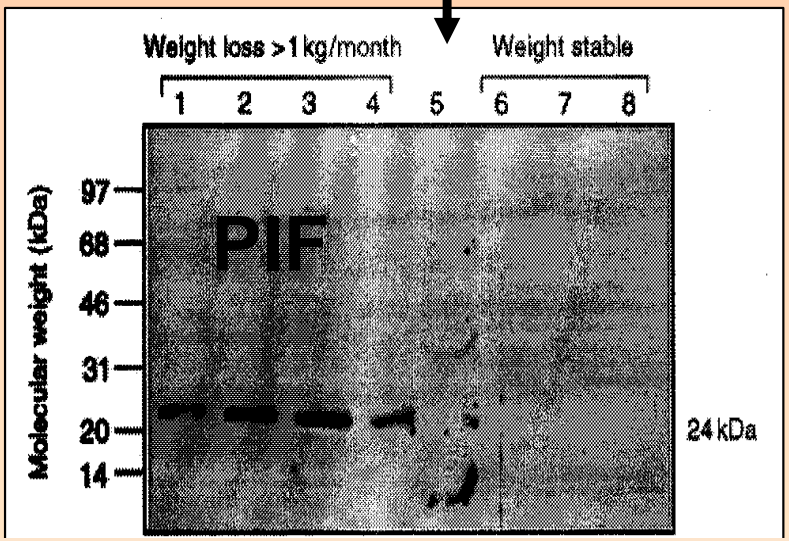
Goal-directed: consequences of ACS
→ Prioritize in the context of patient („Preference“)
→ Estimate likelihood of success („Prognosis“)

Causes of anorexia / cachexia syndromes



Disease-related causes (cancer)

Proteolytic factors
Lipolytic factors



Proinflammatory Cytokines
(IL-6, TNF-a, IFN-y, ..)

Brain
Anorexia
food intake ⇓

Muscle
Cytokine-receptors ⇑
Protein degradation ⇑
Amino-acid uptake ⇓

Gut
Gastric emptying ⇓

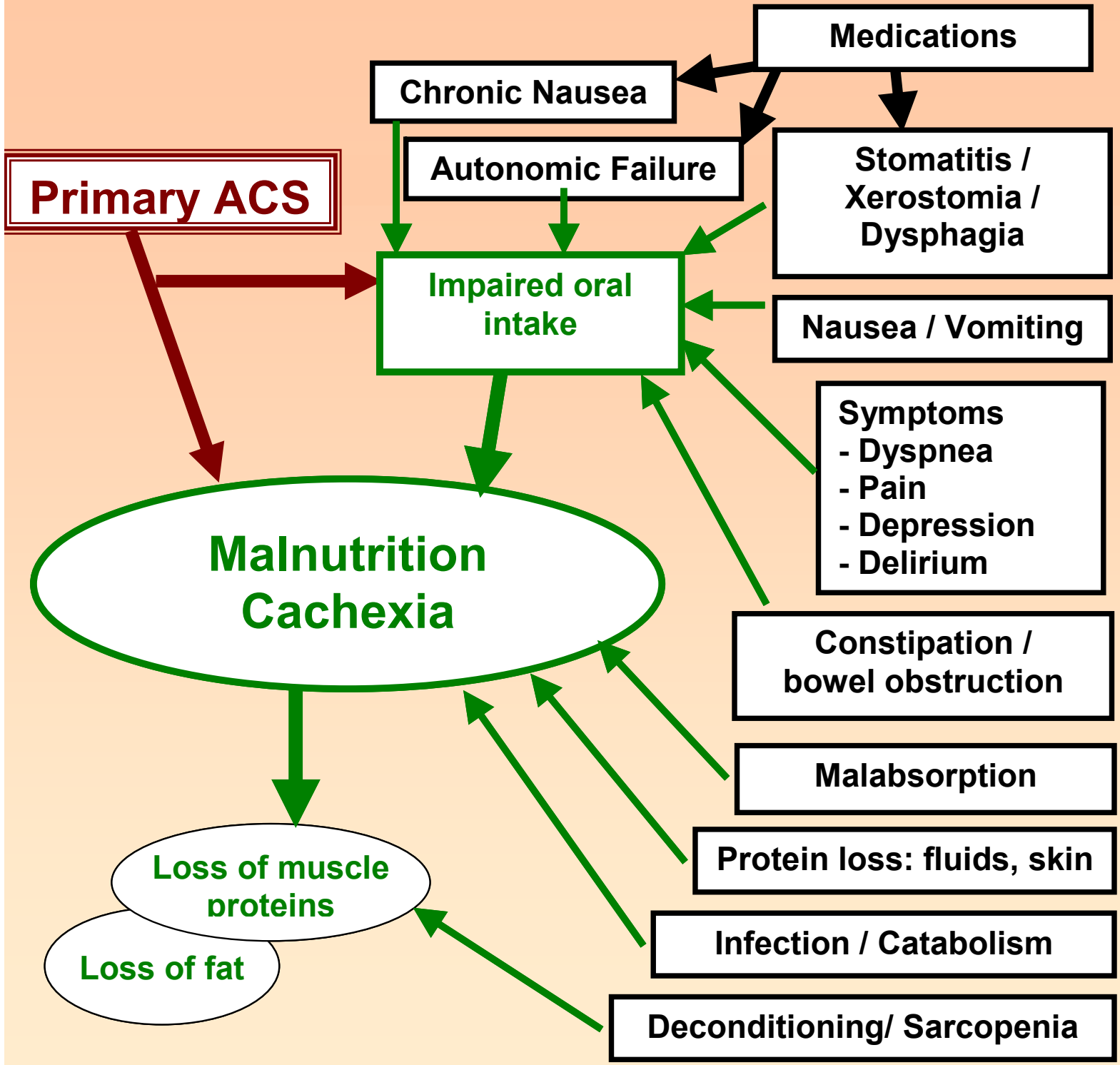
Metabolism
Resting energy expenditure ⇑
Whole body protein & Glucose turnover ⇑
Insulin resistance

Liver
Acute phase proteins ⇑

Metabolic, Neuroendocrine, and Anabolic Abnormalities

Muscle – Liver Axis (Hypermetabolism)	Gut – Brain Axis (Vagus, Hormones)	Brain – Muscle Axis (Anabolic hormon.)

Dahele M, Fearon KC. Palliat Med 2004;18:409-17
MacDonald N. J Support Oncol. 2003;1:279-86
Strasser F. Oxford Textbook of Palliative Medicine, 3rd Ed. 2003:520-33



Secondary ACS → Relative impact?

Strasser F, Bruera E
Hemat Onc Clin Nor Am 2002;16:589

Goals: Anorexia / cachexia syndromes and consequences

Weight loss[#*] (unvoluntary, 2% 2 mts or 5% 6 mts)

Loss of appetite[#] (VAS >=3/10 or „a problem“)

Nutritional intake↘[#*] (<20 kcal/kg or <75% normal)

Body composition ↘ (BMI*, fat, muscle, nutrients)

Function ↘ (mobility, self care, domestic life)

Quality of life ↘ (fatigue, dyspnea, ...; wounds, ...)

Psycho-social-existential distress (pat., family)

[#] **Anorexia/Cachexia**

(Loprinzi C et al.)

*** Malnutrition**

Kondrup J et al. Clin Nutr 2003;22:415-21

Time and likelihood to reach goal

	Time to „response“		
	days	wks	mts
Weight loss - survival			
Loss of appetite			
Nutritional intake			
Body composition			
- Edema			
Function physical			
Quality of life			
- Fatigue (physical)			
Eating-related Distress			

Poor evidence to support this slide ...

Goals and priorities

What is the Goal?	Pain	Anorexia
Symptom - Intensity	Sympt-Ass	Sympt-Ass
Causing Factors better	Pain Syndromes	Primary Syndromes
Perpetuating Fct.	Risk factors	Secondary
Function and Quality of life	Physical, social, role, .	Physical, Fatigue, ..
Distress of patient and family	Re-priorization	Eating-relat. distress

Targeted interventions – nutritional challenges PC

Nutritional Challenge

Causes & Goals

Cause – directed Intv.

Goal – directed Intv.

Cause – directed interventions for Anorexia/Cachexia

Anti-neoplastic interventions

→ may contribute to stabilization of weight loss and anorexia (several data: pancreatic ca., NSCLC, CRC,..)

(or do they cause muscle wasting? [taxans])

(is neuromuscular dysfunction contributing to muscle loss?)

Non-cancer

Disease-modifying treatments: AIDS, CHF, ..

Italic: „neg“
Red: Combos

Pharmacological approaches P-ACS

Progestins (Megestrol acetate, MPA)

Corticosteroids

(? Prokinetic agents (domperidone, metoclopramide))

Cannabinoids, synthetic Cannabinoids

Ω-3-fatty acids (Eicosapentaneoic acid [EPA])

Thalidomide

Anti-TNF (infliximab, enbrel); anti-IL6, etc.

Anti-oxidants, COX-II inhibitors

Ghrelin, GH-secretagogues small molecules

Anabolics (clenbuterol, **oxandrolone**, ***fluoxymester***.)

Condit. essent. Nutr. (BCAA, Arg., Glutamine, Zinc, Carnitine,…)

ATP / ACE-Inhibitors / Allopurinol /B2-mimetics

Melatonin / rezeptor-antagonists

Erythropoietin

Interleukin – 15, gene-therapy (IGF-1)

Cause – directed interventions for P-ACS

Italic: „neg“
Red: Combos

Pharmacological approaches P-ACS

Progestins (Megestrol acetate, MPA)
Corticosteroids
(? Prokinetic agents (domperidone, metoclopramide))

Cannabinoids, synthetic Cannabinoids
Ω-3-fatty acids (Eicosapentaneoic acid [EPA])
Thalidomide
Anti-TNF (infliximab, enbrel); anti-IL6, etc.
Anti-oxidants, COX-II inhibitors
Ghrelin, GH-secretagogues small molecules
Anabolics (clenbuterol, **oxandrolone**, ***fluoxymester***.)
Condit. essent. Nutr. (BCAA, Arg., Glutamine, Zinc, Carnitine,…)
ATP / ACE-Inhibitors / Allopurinol /B2-mimetics
Melatonin / rezeptor-antagonists
Erythropoietin
Interleukin – 15, gene-therapy (IGF-1)

Trials restricting pro-actively interventions to patients presenting with distinct genomic or biological alterations

→ Very rarely done

Is a (puristic) single-target approach a reasonable gold standard?

Innovative - clinical reality – trials

Inter-individual variability

EPA: individual differences in tolerability of supplements, blood level ←→ effects

Fearon Gut 2003

IL-1R polymorphism predict reponse to anti-inflamm. Drugs?

Graziano F et al., JCO 2005;23:2339

Ghrelin: dose variability for maximal effect?

Hypothesis to be tested

MC4-R antagonists: MC4-R polymorphism?

Marks DL et al., Endocrinology 2003

TLR-polymorphism P5.75

DGC (dystrophin glycoprotein complex) D16, P3.35

Etc., etc.

EPA: only of potential benefit in patient subgroup able to eat

N-3 FA enriched

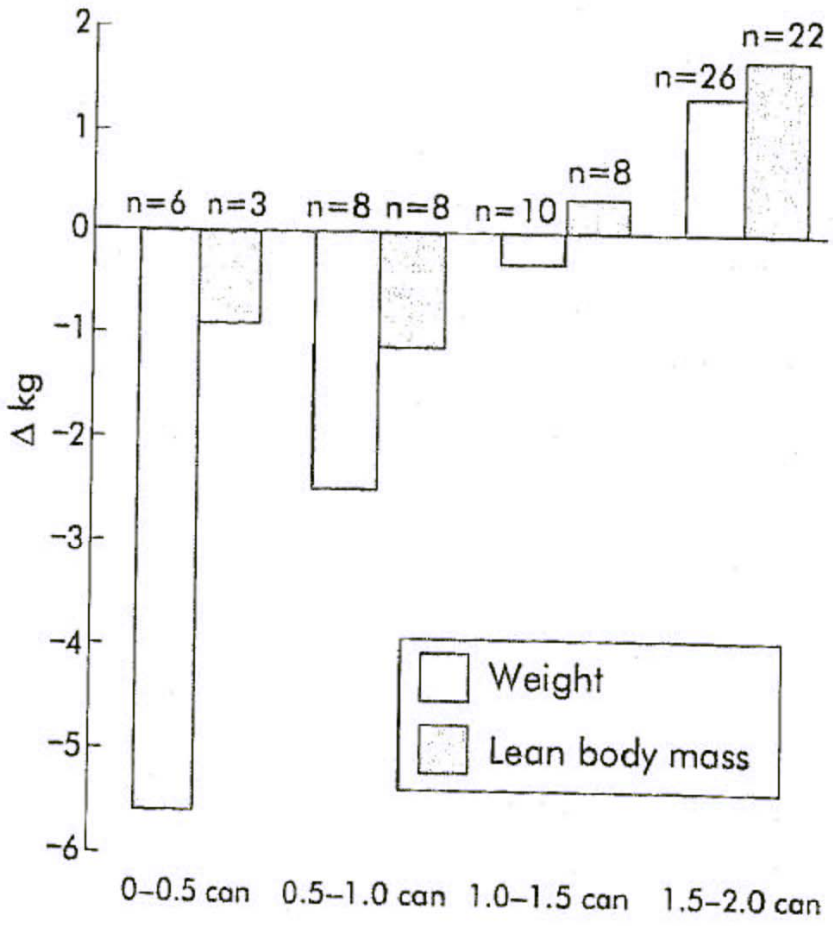


Figure 5 Effect of intake of protein and calorie dense oral supplement with n-3 fatty acids on change in weight and lean body mass at eight weeks in patients with pancreatic cancer cachexia.

Effect on weight and lean body mass correlates with dose (# drinks / day)

→only patients with good appetite may increase LBM (lean body mass)

Fearon K et al. Gut 2003;52:1479-84

EPA-enriched Nutrit. Suppl. (E) vs Control (C)

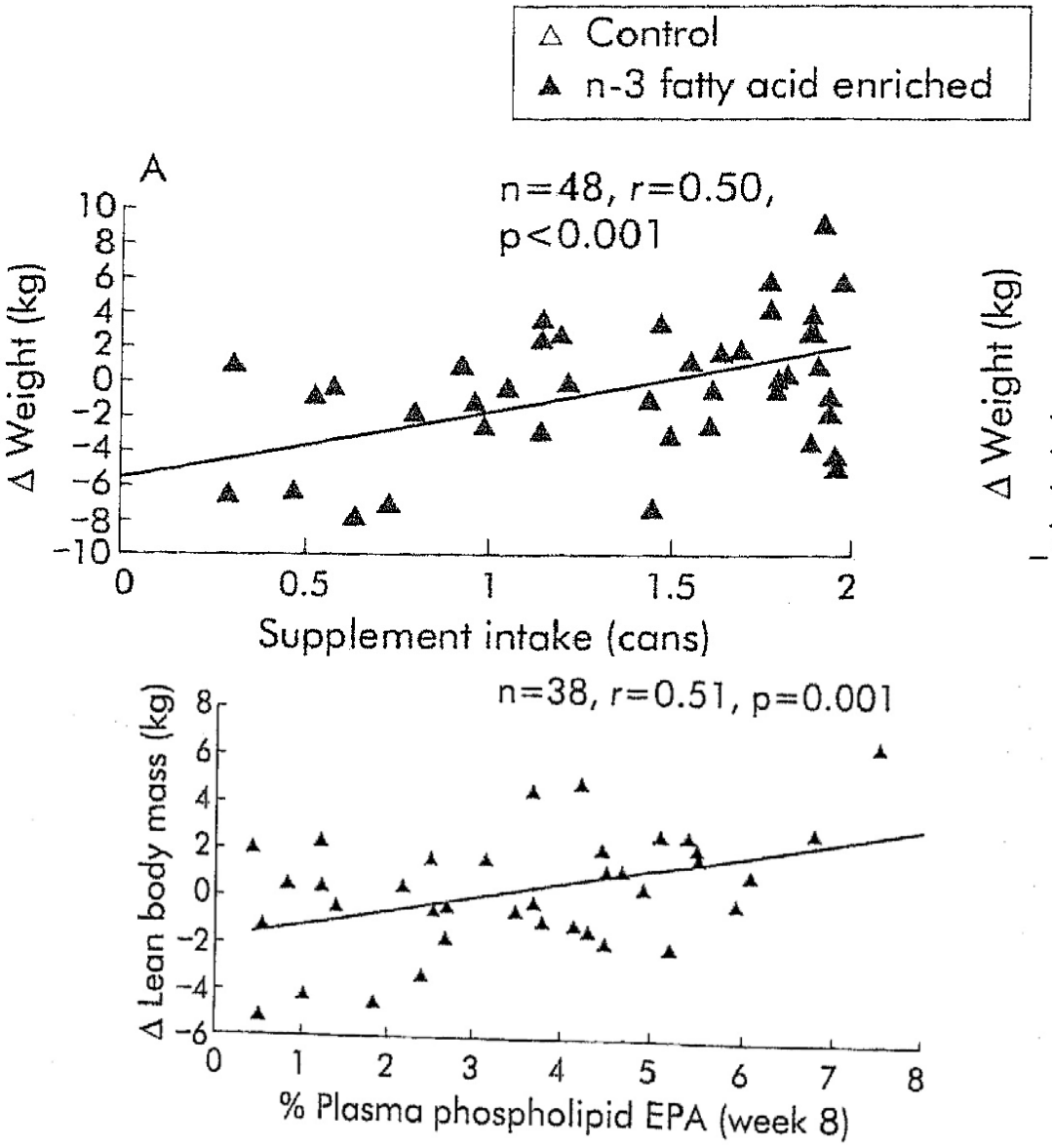


Figure 6 Relationship between plasma phospholipid eicosapentaenoic acid (EPA) levels and change in lean body mass at eight weeks in patients consuming the protein and calorie dense oral supplement with n-3 fatty acids.

Correlation Weight and LBM with

- **Nr. n-3-FA-Drinks**
- **EPA-Blood-levels**
- **Nr. n-3-FA-Drinks**

Fearon K et al. Gut 2003;52:1479-84

Kantonsspital St.Gallen

Innovative - clinical reality – trials

Combinations of treatments

<u>Combination of various mechanisms</u>

Some studies done:

- combination of drugs, not mechanisms

- Various psychosocial aspects of counselling

In future targeted-combinations?

Orexigenic & Muscle & Antiinflammatory

...

Combination-therapies
Progestine & EPA-enriched Supplements

Patients and Methods

Four hundred twenty-one assessable patients with cancer-associated wasting were randomly assigned to an EPA supplement 1.09 g administered bid plus placebo; MA liquid suspension 600 mg/d plus an isocaloric, isonitrogenous supplement administered twice a day; or both. Eligible patients reported a 5-lb, 2-month weight loss and/or intake of less than 20 calories/kg/d.

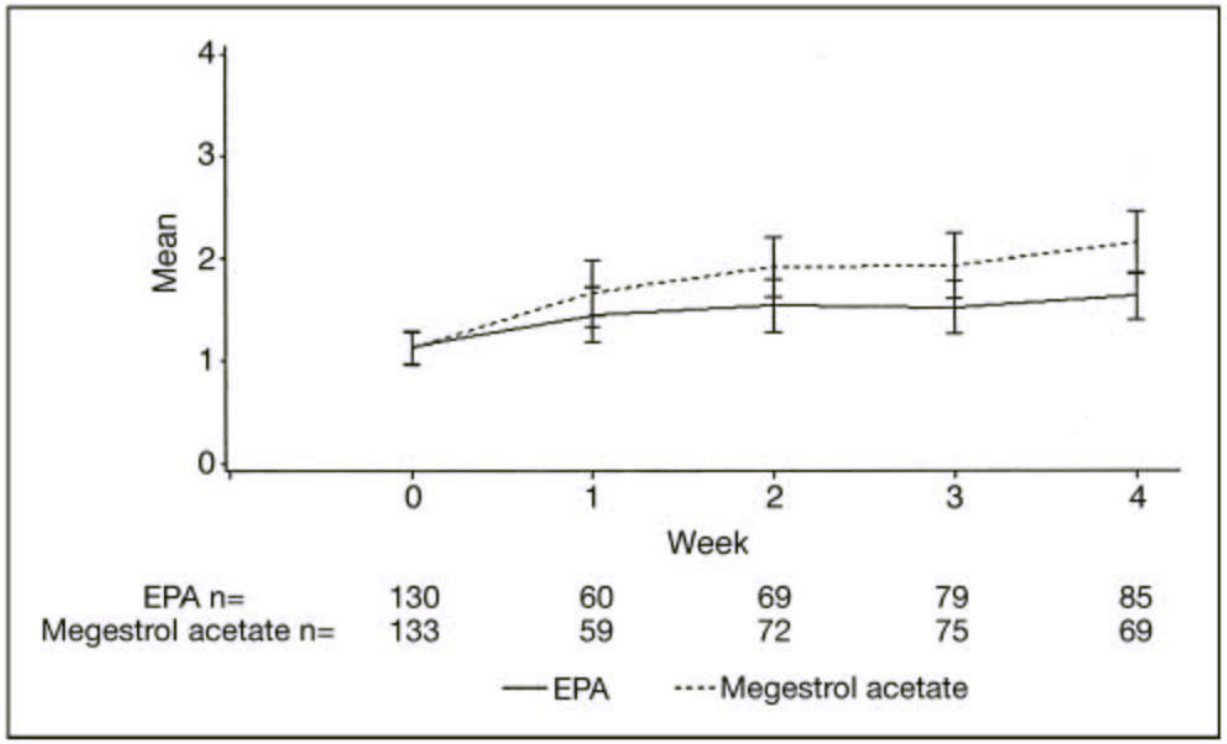


Fig 1. Serial assessment of appetite with the Functional Assessment of Anorexia/Cachexia Therapy suggested that single-agent megestrol acetate provided better appetite stimulation compared with the eicosapentaenoic acid (EPA) supplement. Graph shows mean scores with 95% CIs.

No improvement of appetite or weight more than megestat alone or combination

Jatoi A et al. J Clin Oncol 2004;22:2469-76

Kantonsspital St.Gallen

Combination-therapies
Progestine & d-9-THC (Cannabinoid)

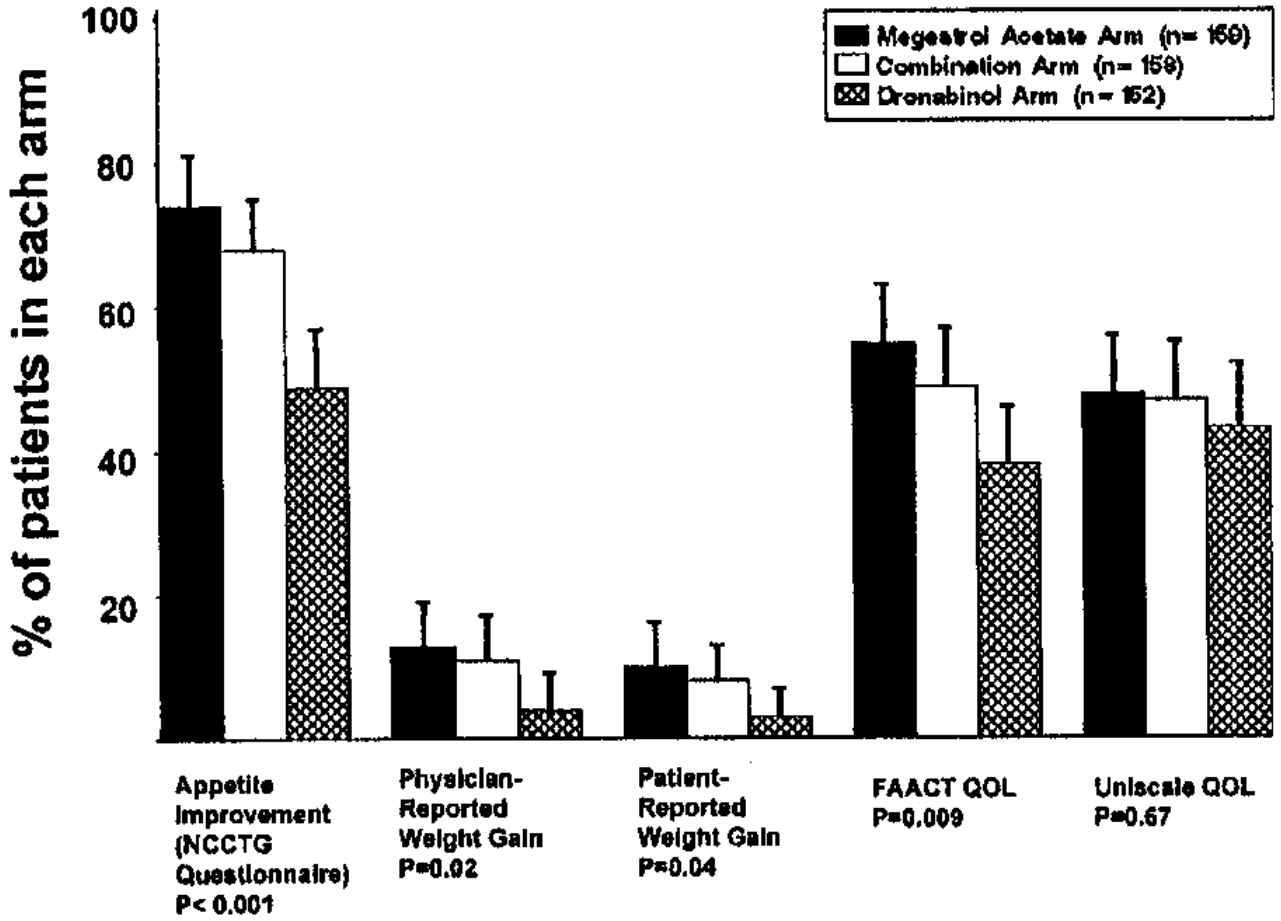


Fig 1. Megestrol acetate improved (1) appetite, (2) physician-reported weight, (3) patient-reported weight, and (4) FAACT QOL score (Fisher's exact test, $P < .001$, .02, .04, and .009, respectively). The UNISCALE found no significant differences in QOL. Bars represent 95% confidence intervals.

D-9-THC = Dronabinol
2.5 mg 2x /day
Megestrol-Acetat
800mg/d
Placebo for both
N=469

D-9-THC worse than Progestine

D-9-THC no improvement in combination

Jatoi A et al. JCO 2002; 20:567-73

Kantonsspital St.Gallen

A (not so called) combination intervention

Nutritional counselling

EBer **Table 4.** Median QoL Dimensions Scores **Suppl** **Free**

Items	Group 1			Group 2			Group 3		
	Onset	End	3 Months	Onset	End	3 Months	Onset	End	3 Months
Function scales									
Global QoL	48	75*	82†‡	46	70*	62†	47	35*	30†
Physical function	49	74*	79†	48	65*	60†	45	25*	22†
Role function	50	78*	80†	52	65*	58	48	20*	19†
Emotional function	55	79*	83†	50	48	50	51	38*	28†‡
Social function	52	82*	85†	51	48	51	49	30*	26†
Cognitive function	64	73*	70†	62	62	54	62	55*	46†‡
Symptoms, scales									
Fatigue	30	55*	26‡	31	75*	78†	29	78*	79†
Pain	25	63*	15†‡	22	74*	30†‡	23	78*	73†
Nausea and vomiting	15	50*	10‡	14	71*	37†‡	12	72*	68†
Symptoms, single items									
Dyspnea	5	8	8	6	7	13	5	6	15
Sleep disturbance	30	40*	29‡	28	55*	75†‡	32	60*	78†‡
Appetite	45	57*	48‡	40	59*	72†‡	42	65*	75†‡
Constipation	12	10	10	11	9	8	9	8	8
Diarrhea	38	45	39	35	81*	72†‡	33	92*	78†‡
Finance	14	14	14	11	11	11	12	12	12

NOTE. Higher scores on function scales indicate better functioning; higher scores on symptom scales or single items denote increased symptomatology or worse financial impairment. (———) Highlights overall significant improvement; (– – –) highlights overall significant deterioration; (· · ·) highlights overall nonsignificant deterioration.

Abbreviations: QoL, quality of life; RT, radiation therapy.

*Significant differences between baseline end of RT.

†Significant differences between baseline and at 3 months.

‡Significant differences between end of RT and at 3 months.

Ravasco P et al. J Clin Oncol 2005; 23(7)

Goal-directed increase of kalories etc?

Advanced cancer pts, „gut works“: No TPN

In pts having catabolic metabolism (active cancer), “artificial” increase of kaloric (nutritional) intake is inefficient, and causes adverse effects.

Many studies confirm in-effectivity of TPN:

- **adjunctive to chemotherapy or radiotherapy**
- **Cachectic pts with “intact” bowel function**

VA TPN Clin Study Group NEJM 1991:325:525
Bozzetti F, et al. Nutrition 12(3):163-7,1996
Klein S, et al. Am J Clin Nutrition 66,683-706, 1997
Torelli GF et al. Nutrition 15(9):665-7,1999
Winter SM. Am J Med 109(9):723-6, 2000

Revival of TPN when catabolism controlled?

TPN indicated: no oral intake (starvation)

- ► GI- dysfunction or treatment toxicity
- ► Duration expected: >= (5-) 7 (-10) days
- ► Prognosis > 40-60 days*

TPN pre-operative:

- ► Pts. with Cachexia
- ► Pts. with GI-tract malignancies (and others?)

*Nitrogen loss critical to survival 33-37%, 8-10 wks
Bozzetti F Nutrition 2001;17:67

Am Soc PE Nutr. JPEN 2002;26:SA1-138
Klein S et al. Cancer 1986;58:1378

Kantonsspital St.Gallen

Example: TPN if starvation

52 Pat., incurable, advanced cancer, 1979-99, Mayo
Retrospective review of Home-TPN

Indication: **Bowel obstruction** (n=20)
Shortbowel-Syndr., Malabsorption (n=16)
Fistula (n=11)
Dysmotility (n=3)
Nausea/vomiting, mucositis (n=2, n=1)
Anorexia (n=2)

Overall survival: 5 months (1-154)
Complications: 18 Infections, 4 Thrombosis, ..

Hoda D et al. (Mayo-Group), Cancer 2005;103:863

Kantonsspital St.Gallen

Goal-directed relieve of Eating-related Distress
A role for psycho-social-existential counseling?

Appetite	Fluctuating, unpredictable, disgust
Inability to eat	Predictable but dread of starving
Loss of weight	Difficult to control, unpredictable
	Eating ←→ Weight not linked
Insecurity	What is healthy? Adaption, learning
Partnership	Pressure, caring by food, innovative
Social contacts	Limitations practical, „normal“
Professionals	Not helpful advice, foresight
Weak/Death	Fight a loosing battle → ready to die

Strasser F et al. Eur Assoc. Pall Care, 2004

I) Distress of patients related to eating and weight loss

1. Not able to eat

A) Loss of appetite:
- Rapid and unpredictable changes of intensity
- Sudden blocks
- Aversions and unexpected food preferences
- Multi-dimensional suffering impairs appetite

B) Ability to eat
- Changed consistencies of food
- Food gets stuck
- Fear of choking

C) Combination of loss of appetite and inability to eat

2. Loss of weight
- Unpredictable, not related to eating
- Point of no return

3. Existential distress
- Weight loss as a sign of uncontrolled tumour
- Weight loss leading to death
- Patients force themselves and fight for survival

II) Distress of partners related to eating and weight loss

A) Change of cooking habits
- Daily changing needs, unpredictable if successful
- Partners feel sorry for food which is not tasty food
- Feelings of insufficiency
- Obliged to eat food left by patient
- Food prepared may be an unhealthy diet for partner

B) Fear of loss
- Intuitive deduction from observation, fighting the unspoken

C) Cooking as expression of love

III) Couple strategies

1. Innovative learning

A) Trying out and testing
- Changing meal composition, mealtimes

B) Searching for advice
- Available advice is tried out
- Unsolicited advice
- Professional advice not helpful, too late
- Professionals not interested
- Trying to understand in order to relieve pressure
- Recognizing goals which are unachievable

2. Pressure
- Patients force themselves, check scale
- Partners share personal distress and worries to force patients to eat
- While gone, partner distribute food in the home for patients to find
- Couples experience violent thoughts and actions

3. Acceptance
- *Switching off reasonable mind*, gritting one's teeth
- Expressing limitations to the partner
- Focusing on the meaning of other facets of daily life

Identified elements of ERD → Assessment instrument under developpment

Pilot study: description of ERD-interventions made in a nutrition – fatigue clinic by a psychooncological nurse

Kantonsspital St.Gallen

Targeted interventions – nutritional challenges PC

Nutritional Challenge

Causes & Goals

Cause – directed Intv.

Goal – directed Intv.

What Clinical Trials are done in Cancer Cachexia?

Search of registries and grant databases
[http://www.controlled-trials.com/isrctn/]
[http://www.cancer.gov/search/clinical_trials/]
[http://www.cancerbacup.org.uk/Trials/Search]
[http://crisp.cit.nih.gov/] [http://www.snf.ch]

Abstracts of cachexia or oncology meetings
ASCO – ECCO/ESMO
Cachexia conferences

Personally communicated information

Clinical Trials in Cancer Cachexia

Types of interventions

	Pharm	Nutr	Psych	Comb	Target	Prev	Edu
Enbrel vs Pl NCT00127387	X						
Etanerc vs Pl NCCTG-N00C1	X						
Cyproh & MA NCT00066248	X						
Ghrelin vs Pl ISRCTN26185223	X						
EPA vs ctrl NCRN 1435	X						

→ Few trials registered

New drugs	X				X	(X)	
Nutritional Intervent.		X					

Roma 2005: Nutritional counselling, Integrated nutritional intervention, BCAA, Appetite stimulants, Orexigenic peptides, Ghrelin and ghrelin analogues, GH, IGF-1, Anabolic steroids, EPA, Gene therapy, Skeletal muscle stem cell therapy, Myocyte rejuvenation, **Etc**.

Scotish-UK	X	X			X		
Italy-North	X				X		
Mayo-NCCTG	X				X		
Switzerl.	X	X			X	(X)	

Clinical Trials in Cancer Cachexia

Populations studied

	Any tumour	Selected	no ACS	early	late	PS
Enbrel vs Pl NCT00127387	bone mets	Lu/Pr	X	-	-	<3
Etanerc vs Pl NCCTG-N00C1	Any			wl 2% 2mts		nr
Cyproh & MA NCT00066248	Any (kids 2-20)		X			nr
Ghrelin vs Pl ISRCTN26185223	Any				X	any
EPA vs ctrl NCRN 1435	Any			h/o ong wl		nr
New drugs	various and selected			weight loss?		
Nutrit. Intervent.	various and selected		X	X		

Roma 2005: Nutritional counselling, Integrated nutritional intervention, BCAA, Appetite stimulants, Orexigenic peptides, Ghrelin and ghrelin analogues, GH, IGF-1, Anabolic steroids, EPA, Gene therapy, Skeletal muscle stem cell therapy, Myocyte rejuvenation, **Etc**.

Scotish-UK	X	X	X
Italy-North	X		X
Mayo-NCCTG	X		X
Switzerl.	X		X

Clinical Trials in Cancer Cachexia

Endpoints

	BodyCom	Function	QoL	Family	NutrInt
Enbrel vs Pl NCT00127387	NR („combat fatigue and cachexia“)				
Etanerc vs Pl NCCTG-N00C1			„QoL“		
Cyproh & MA NCT00066248	„how well improve appetite & prevent cachexia“				
Ghrelin vs Pl ISRCTN26185223	X	subj.	XXX	-	XX
EPA vs ctrl NCRN 1435	X (wl)				

New drugs	various and selected			weight loss?
Nutrit. Intervent.	various and selected	X		X

Roma 2005: Nutritional counselling, Integrated nutritional intervention, BCAA, Appetite stimulants, Orexigenic peptides, Ghrelin and ghrelin analogues, GH, IGF-1, Anabolic steroids, EPA, Gene therapy, Skeletal muscle stem cell therapy, Myocyte rejuvenation, **Etc**.

Scotish-UK	X	obj/subj	X	-	X
Italy-North	X	obj/subj	X	-	?
Mayo-NCCTG	X	subj	X	-	?
Switzerl.	X	obj/subj	XX	X	X

Clinical Trials in Cancer Cachexia

Types of interventions

A decade ago: nutritional and single-agent pharmacological interventions → few approved tx

Increasingly: combination treatments of approved and experimental compounds

Many promising compounds: phase I/II and III stage

Few phase III results: reported but not confirmed (ATP, Thalidomide), not yet reported (oxandrolone)

Few groups: effects of nutritional counselling, psychosocial aspects of cachexia and anorexia

Targeted interventions – nutritional challenges PC

Nutritional Challenge

Causes & Goals

Cause – directed Intv.

Goal – directed Intv.

Thanks

Contact

Florian.strasser@kssg.ch

Fstrasser@bluewin.ch