



Does nutrition support cause cancer progression ?

Maurizio Bossola
Department of Surgery
Catholic University of Rome

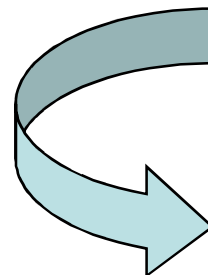
.... Since '70, major concern raised about the possible effect of nutrition, either as parenteral or enteral nutrition, on tumor growth.

Tumor-Host Responses to Various Nutritional Feeding Procedures in Rats¹

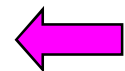
I. L. CAMERON,² W. A. PAVLAT, M. D. STEVENS
AND W. ROGERS

*Departments of Anatomy (I.L.C., W.A.P., M.D.S.) and
Surgery (W.R.), The University of Texas Health Science
Center at San Antonio, 7703 Floyd Curl Drive,
San Antonio, Texas 78284*

J. Nutr. 109: 671-684, 1979.



The importance of nutrition in cancer patients, particularly that nutrition which can be delivered in a carefully controlled manner by enteral or parenteral routes, is receiving considerable attention as an adjunct to therapy (1-7). How does continuous nutritional intake given by the parenteral (iv) or by the intragastric (ig) route affect tumor-host interactions? To



Does nutrition support cause cancer progression ?



- Studies in animals
- Studies in humans



- Studies on tumor proliferation
- Studies on tumor apoptosis



- Studies on TPN
- Studies on specific nutrients



- Studies in Cancer cachexia

STUDIES IN ANIMALS

Cameron et al. (1977). No differences in survival in tumor rats with 1) solid food ad libitum 2) TPN 3) liquid diet ad libitum

Daly et al. (1978). No differences in tumor growth in tumor rats with 1) oral diet ad libitum 2) oral free-protein 3) TPN

**Goodgame et al. (1979). No differences in tumor growth in tumor rats with 1) 1) oral diet 2) TPN 3) dextrose i.v.
4) Amino acids solution**

Popp et al. (1981). TPN stimulate tumor growth in sarcoma bearing rats

Stein et al. (1982). Increase in intratumor essential amino acids content after TPN

Popp et al. (1983). Tumor growth increases with increasing rate of substrate infusion by TPN

Popp et al. (1984). TPN did result in an increase in tumor growth

Hak et al. (1984). TPN had no adverse effect on tumor growth as well as the source of intravenous calories (fat or glucose)

Mendez et al. (1992). Tumor growth was slowed in structured lipid-fed animals

Chance et al. (1996). No differences in tumor growth between TPN with Intralipid or fish oil

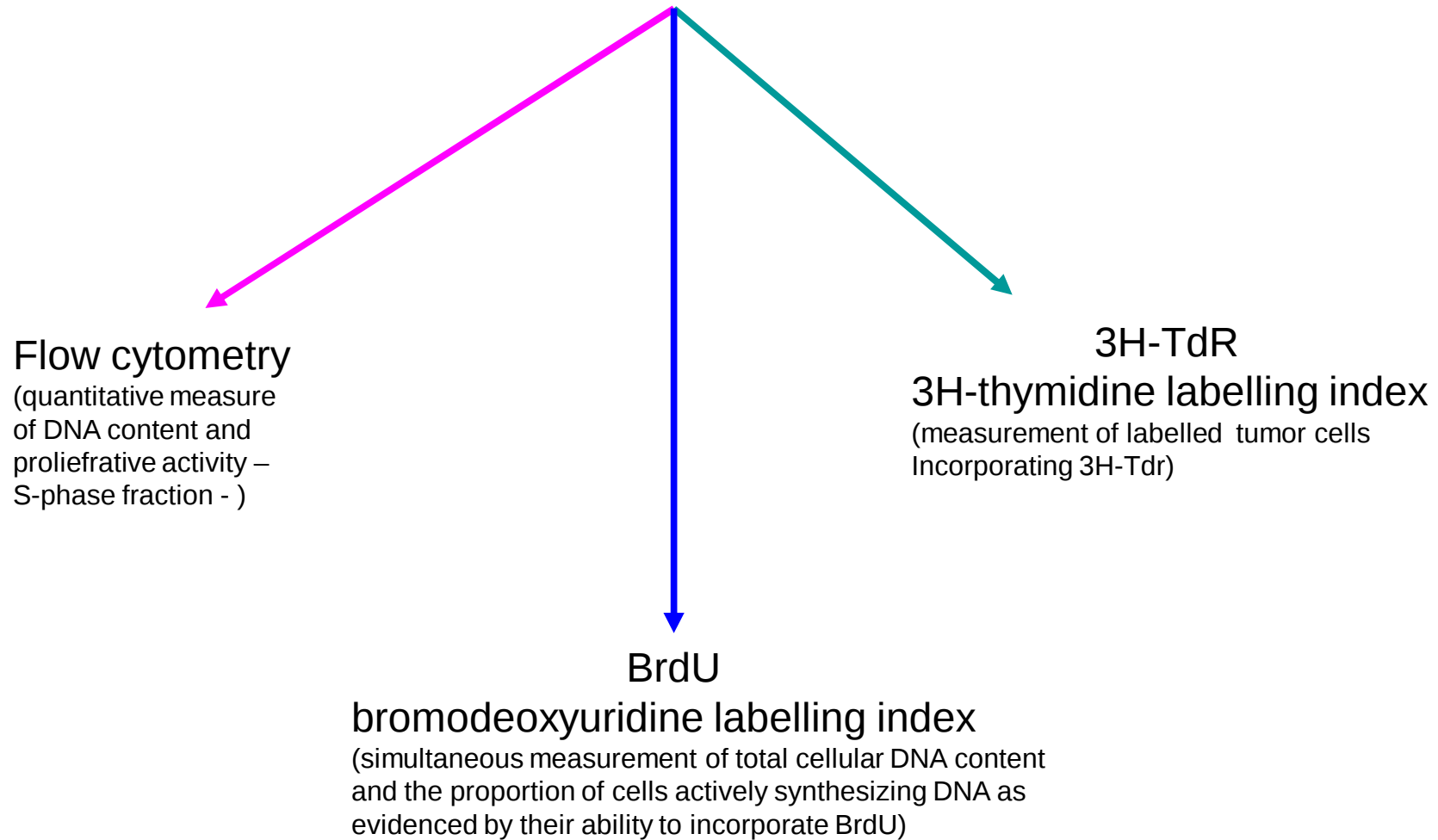
DIFFERENCES BETWEEN EXPERIMENTAL AND HUMAN STUDIES

- the ratio tumor/host exceeds 20% in animals while in human is $\leq 1-2\%$
- tumor doubling time ranges from 2 to 7 days in animals while in human it is one or more months
- the difference in the duration of the tumor life and its relative time under TPN
- tumor immunogenicity

STUDIES IN HUMANS

Author	Number of patients	Diagnosis	Type/duration of nutritional support	Method to assess tumor proliferation	Effect
Mullen et al. (1980)	13	Gastrointestinal cancer	TPN/7-10 days	Protein synthesis	No changes in tumor growth
Ota et al. (1984)	25	Gastrointestinal cancer	TPN/ 11 days	Red blood cells (RBC) polyamine levels	Significant increase in cancer patients in RBC putrescine, spermidine and spermine levels
Baron et al. (1986)	14	Head and neck cancer	TPN / 9 days	Flow cytometry	Increase of percentage of hyperploid with TPN
Franchi et al. (1991)	18	Gastrointestinal cancer		3H-Tdr Labeling Index	After TPN, no increase of proliferating cells
Westin et al. (1991)	9	Head and neck cancer	TPN / 5-7 days	Flow cytometry, ODC activity, Ki-67 activity	After TPN no change in ODC activity, Ki-67 activity, no increase of hyperploid cells at flow cytometry
Dionigi et al. (1991)	33	Gastric cancer	TPN / 18 days	3H-Tdr Labeling Index	After TPN, no increase of proliferating cells
Shaw et al. (1991)	10	Mixed tumors	TPN / 24 hours	Fractional synthetic rate of cancer (14C leucine time specific radioactivity)	No changes after TPN
Frank et al. (1992)	10	Head and neck cancer	TPN / 7 days	BudR and flow cytometry	Increase in the percentage of cells incorporating BudR before and after PN
Bozzetti et al. (1994)	10	Gastric cancer	TPN / 10 days	3H-Tdr Labeling Index	After TPN, no changes in tumor growth
Bozzetti et al. (1999)	20	Gastric cancer	TPN / 10 days	3H-Tdr Labeling Index	After TPN, increase of proliferating cells in 5 cases and no changes in the other 5
Pacelli et al. (2007)	20	Gastric cancer	TPN vs control/ 12 days	BudR and flow cytometry	No changes in the percentage of cells incorporating BudR before and after PN

Tumor proliferation has been assessed by:



Original Communications

Parenteral Nutrition Does Not Stimulate Tumor Proliferation in Malnourished Gastric Cancer Patients

Fabio Pacelli, MD*; Maurizio Bossola, MD*; Laura Teodori, MD†; Maria Luisa Trinca, MD†;
 Antonio Tortorelli, MD*; Fausto Rosa, MD*; and Giovan Battista Doglietto, MD*

From the *Istituto di Clinica Chirurgica, Università Cattolica del Sacro Cuore, Roma, Italy; and the †Divisione di Fisica e Scienze Biomediche, ENEA, CRE, Casaccia, Roma, Italy

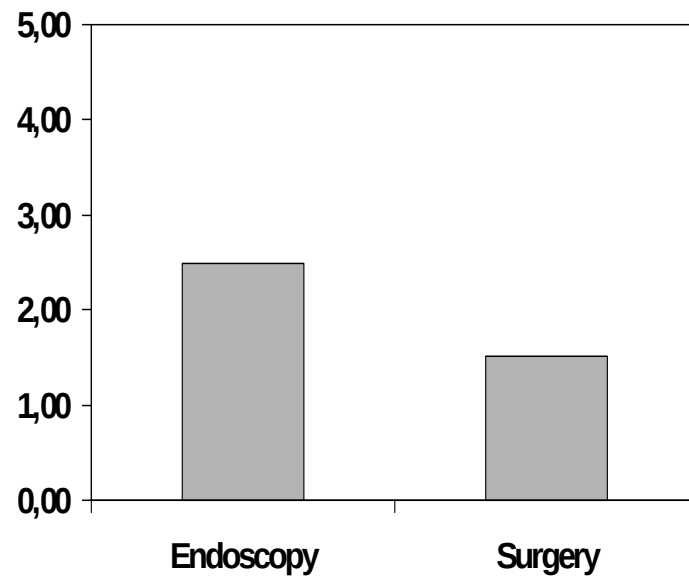
TABLE II
 Patients' characteristics

	Control group (n = 10)	PN group (n = 10)
Sex (M:F)	5:5	5:5
Age, y*	68.7 ± 9.3	70.3 ± 9.5
Weight, kg*	56.2 ± 12.4	55.3 ± 13.9
Weight loss, %*	13 ± 2.1	13.5 ± 2.2
Serum albumin, g/dL*	3.35 ± 0.7	3.32 ± 0.38
Serum transferrin, mg/dL*	203 ± 32.9	213 ± 71.5
Triceps skinfold thickness, cm*	9.7 ± 2.0	9.1 ± 2.1
Midarm muscle circumference, cm*	21.4 ± 2.9	20.8 ± 2.1
Total lymphocytes, n/mL*	1370 ± 266.7	1380 ± 302.7
Tumor site		
Upper third	2	2
Middle third	4	4
Lower third	4	4
Tumor stage†		
I	2	2
II	3	3
III	5	5

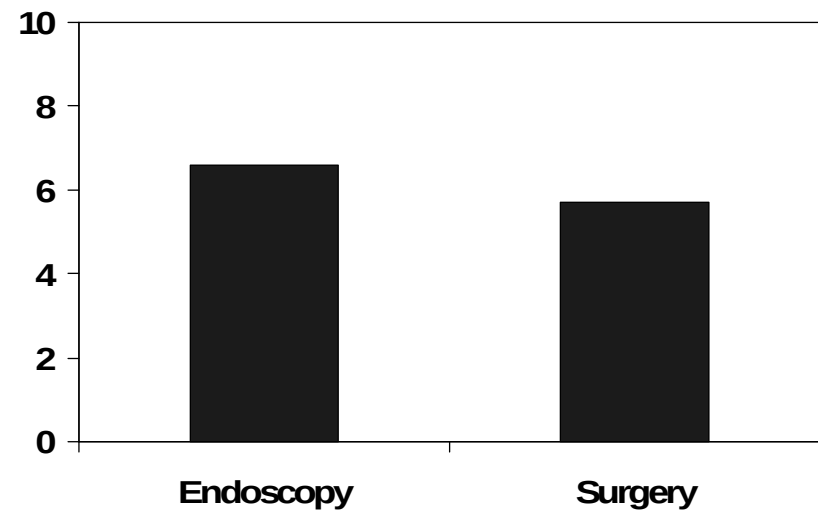
*Data are expressed as mean ± SD.

†According to the American Joint Commission on cancer staging of gastric cancer, 1988.³⁴

**Percentage of cells
incorporating BudR in vitro**



**Percentage of cells in the S-phase
as measured by flow cytometry**



Author	Number of patients	Diagnosis	Type/duration of nutritional support	Method to assess tumor proliferation	Effect
Mullen et al. (1980)	13	Gastrointestinal cancer	TPN/7-10 days	Protein synthesis	No changes in tumor growth
Ota et al. (1984)	25	Gastrointestinal cancer	TPN/ 11 days	Red blood cells (RBC) polyamine levels	Significant increase in cancer patients in RBC putrescine, spermidine and spermine levels
Baron et al. (1986)	14	Head and neck cancer	TPN / 9 days	Flow cytometry	Increase of percentage of hyperploid with TPN
Franchi et al. (1991)	18	Gastrointestinal cancer	TPN/ 8-10 days	3H-Tdr Labeling Index	After TPN, no increase of proliferating cells
Westin et al. (1991)	9	Head and neck cancer	TPN / 5-7 days	Flow cytometry, ODC activity, Ki-67 activity	After TPN no change in ODC activity, Ki-67 activity, no increase of hyperploid cells at flow cytometry
Dionigi et al. (1991)	33	Gastric cancer	TPN / 18 days	3H-Tdr Labeling Index	After TPN, no increase of proliferating cells
Shaw et al. (1991)	10	Mixed tumors	TPN / 24 hours	Fractional synthetic rate of cancer (14C leucine time specific radioactivity)	No changes after TPN
Frank et al. (1992)	10	Head and neck cancer	TPN / 7 days	BudR and flow cytometry	Increase in the percentage of cells incorporating BudR before and after PN
Bozzetti et al. (1994)	10	Gastric cancer	TPN / 10 days	3H-Tdr Labeling Index	After TPN, no changes in tumor growth
Bozzetti et al. (1999)	20	Gastric cancer	TPN / 10 days	3H-Tdr Labeling Index	After TPN, increase of proliferating cells in 5 cases and no changes in the other 5
Pacelli et al. (2007)	20	Gastric cancer	TPN vs control/ 12 days	BudR and flow cytometry	No changes in the percentage of cells incorporating BudR before and after PN

Flow cytometry

1 study:
2 studies:

increase of hyperploid cells
no changes

3H-TdR

4 studies:

no changes

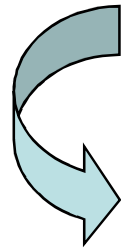
BrdU

2 studies:

no changes

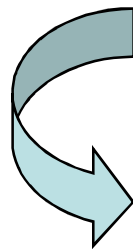
..... and looking at human studies with adequate methods:

- a total of 134 patients studied



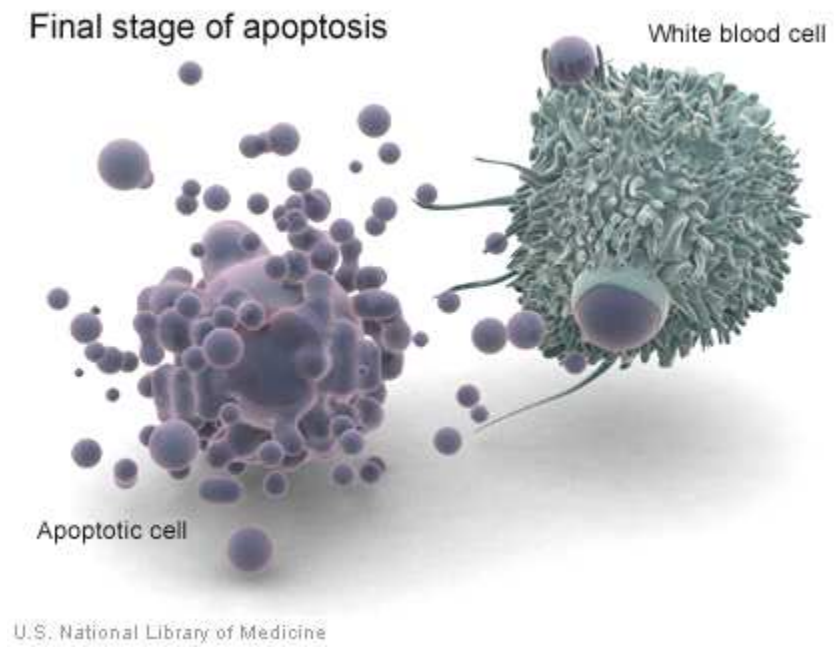
Is it enough?

- Range of duration of TPN: 1 to 18 days



What happens for longer duration of TPN?

.... And what about apoptosis ?





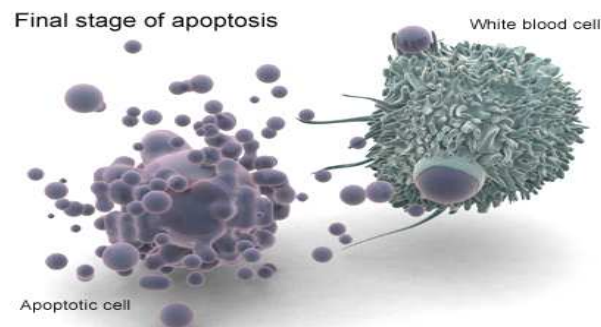
...this is a well-executed study of the effects of parenteral nutrition on cell proliferation and cell cycle kinetics in biopsy specimens of gastric cancer and normal mucosa obtained from patients before and after parenteral nutrition.

The conclusions drawn by the authors are reasonable based on the data they obtained but are too expansive in claiming to show no growth stimulation.

Tumors grow either by increased tumor proliferation or inhibition of apoptosis.

The methods are available to examine both cell proliferation and apoptosis but these authors only studied proliferation and cell cycle kinetics.

Author	Number of patients	Diagnosis	Type/duration of nutritional support	Assessment of apoptosis
Mullen et al. (1980)	13	Gastrointestinal cancer	TPN/ 7-10 days	NO
Ota et al. (1984)	25	Gastrointestinal cancer	TPN/ 11 days	NO
Baron et al. (1986)	14	Head and neck cancer	TPN / 9 days	NO
Franchi et al. (1991)	18	Gastrointestinal cancer	TPN/ 8-10 days	NO
Westin et al. (1991)	9	Head and neck cancer	TPN / 5-7 days	NO
Dionigi et al. (1991)	33	Gastric cancer	TPN / 18 days	NO
Heys et al. (1991)	9	Rectal cancer		NO
Shaw et al. (1991)	10	Mixed tumors	TPN / 24 hours	NO
Frank et al. (1992)	10	Head and neck cancer	TPN / 7 days	NO
Bozzetti et al. (1994)	10	Gastric cancer	TPN / 10 days	NO
Bozzetti et al. (1999)	20	Gastric cancer	TPN / 10 days	NO
Pacelli et al. (2007)	20	Gastric cancer	TPN / 12 days	NO



U.S. National Library of Medicine

The effect of nutrition support
on tumor apoptosis is
UNKNOWN

Targeting Apoptosis with Dietary Bioactive Agents

KEITH R. MARTIN¹

Nutrition and Cancer Laboratory, Department of Nutritional Sciences, The Pennsylvania State University, University Park, Pennsylvania 16802

Table 1. Modulation of Apoptosis by Dietary Bioactive Agents

Organosulfur compounds		
Diallyl sulfide (DAS)	Allium vegetables, garlic compounds	Upregulate Bax; downregulate Bcl-2
Diallyl disulfide (DADS)	Allium vegetables, garlic compounds	Upregulate p53 and Bax; activate caspase 3; downregulate Bcl-2
Ajoene	Allium vegetables, garlic compounds	Activate caspase 3; downregulate Bcl-2; JNK, p38, ERK activation
Allicin	Allium vegetables, garlic compounds	Activate caspases 3, 8, 9; cleave PARP
S-allyl cysteine (SAC)	Allium vegetables, garlic compounds	Downregulate Bcl-2
S-allylmercaptocysteine (SAMC)	Allium vegetables, garlic compounds	Increase caspase 3 activity; JNK activation
Polyphenols		
Epigallocatechin gallate (EGCG)	Green tea, chocolate	Activate Fas; inhibit NF- κ B; caspase activation; alter membrane function
Catechin	Teas	Inhibit p38, PI3K, and AP-1 activation
Genistein	Soybeans	Inhibit NF- κ B; activate caspases; induce Bax
Resveratrol	Red grapes, peanuts, berries	Caspase activation; inhibit NF- κ B; induce FasL
Curcumin	Turmeric, curry, mustard	Inhibit NF- κ B and AP-1; caspase activation; disrupt MTP; induce Bax
Ellagic acid	Strawberries, walnuts, pecans	Increase caspase 3 activation; upregulate p53; activate MAPK, JNK, p38
Capsaicin	Chili peppers	Disrupt MTP; cyto <i>c</i> release; inhibit Bcl-2; induce Bax; caspase activation
Isothiocyanate		
Sulforaphane	Cruciferous vegetables, broccoli	Activate ERK; inhibit NF- κ B; activate caspase 3; downregulate Bcl-2
Phenethyl isothiocyanate (PEITC)	Radish, cabbage	Inhibit NF- κ B; activate caspase 3; cleave BID; inhibit PKC; activate p53
Allyl isothiocyanate (AITC)	Mustard	Activate caspase 8 and JNK; cleave BID; downregulate Bcl-2 & Bcl-xL
Benzyl isothiocyanate (BEITC)	Garden cress	Increase Bax/Bcl-2 ratio; activate caspase 3, JNK, p38; cyto <i>c</i> release
Glucosinolate		
Indole-3-carbinol	Cruciferous vegetables	Inhibit NF- κ B, PI3K, Akt, Bcl-2, and Bcl-xL; activate caspases; induce Bax;
3,3'-Diindolylmethane	Cruciferous vegetables	induce cyto <i>c</i> release; increase TRAIL receptor, downregulate BAD
Carotenoids		
Beta carotene	Orange-yellow vegetables	Alter membrane function
Lycopene	Tomato	Induce cyto <i>c</i> release; alter MMP;
Lutein	Dark green vegetables	Induce p53; upregulate Bax; downregulate Bcl-2
Mineral		
Selenium	Cereal grains, meat, fish	Inhibit NF- κ B; induce p53; inhibit PKC; alter redox status; modulate JNK

...and what about survival ?

The effect of total parenteral nutrition on the survival of terminally ill ovarian cancer patients[☆]

Laurent Brard^{a,*}, Sherry Weitzen^b, Suzanne L. Strubel-Lagan^a, Narasimha Swamy^b, Mary E. Gordinier^c, Richard G. Moore^a, Cornelius O. Granai^a

^a Program in Women's Oncology, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Women and Infants' Hospital, Brown University, 101 Dudley Street, Providence, RI 02903, USA

^b Division of Research, Department of Obstetrics and Gynecology, Women and Infants' Hospital, Brown University, Providence, RI 02903, USA

^c James Graham Brown Cancer Center, University of Louisville, Louisville, KY 40202, USA

Received 12 October 2005

Available online 27 March 2006

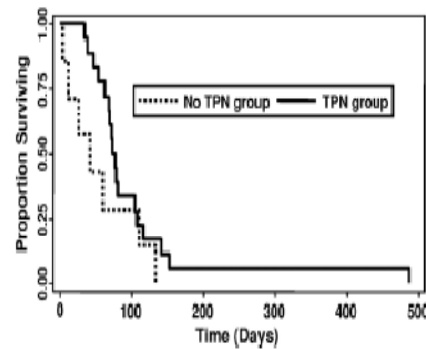


Fig. 2. Survival in days from TIO to death among those receiving chemotherapy, comparing TPN and non-TPN recipients (P value for test of equality of survival curves = 0.1754).

4 weeks advantage

Palliative Nutritional Intervention in Addition to Cyclooxygenase and Erythropoietin Treatment for Patients with Malignant Disease: Effects on Survival, Metabolism, and Function

A Randomized Prospective Study

Kent Lundholm, M.D., Ph.D.¹

Peter Daneryd, M.D.¹

Ingvar Bosaeus, M.D., Ph.D.²

Ulla Körner²

Elisabet Lindholm¹

BACKGROUND. The role of nutrition in the palliative treatment of patients with malignancy-related cachexia is unclear. The goal of the current study was to determine whether specialized, nutrition-focused patient care could improve integrated whole-body metabolism and functional outcome in unselected weight-losing patients with malignant disease who were receiving systemic antiinflammatory (cyclooxygenase [COX]-inhibitory) treatment along with erythropoietin (EPO) support.

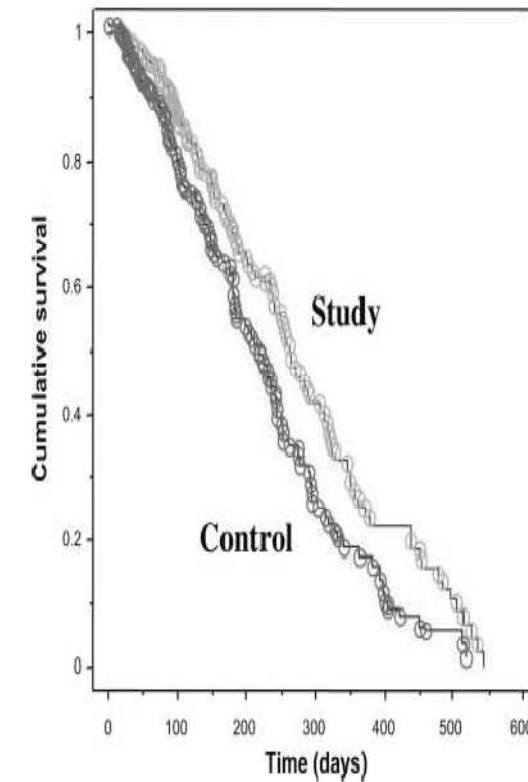


FIGURE 1. Survival data for the study (nutritional support) and control groups over the course of follow-up ('as-treated' analysis; $P < 0.001$).

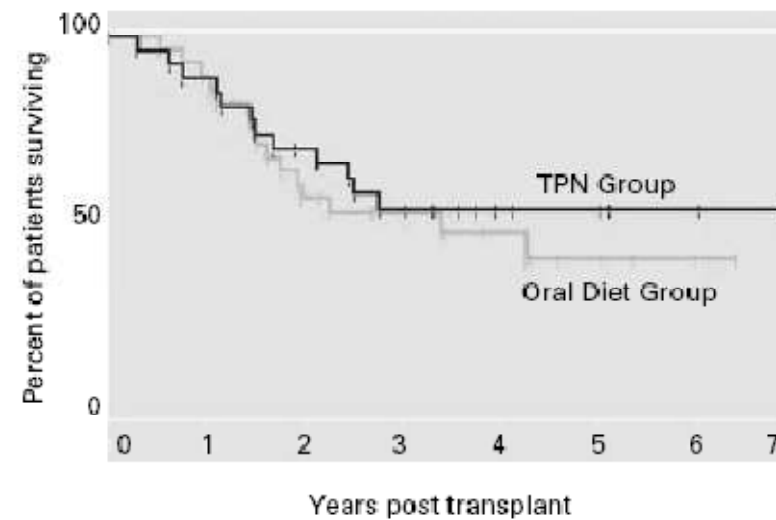


Parenteral Nutrition

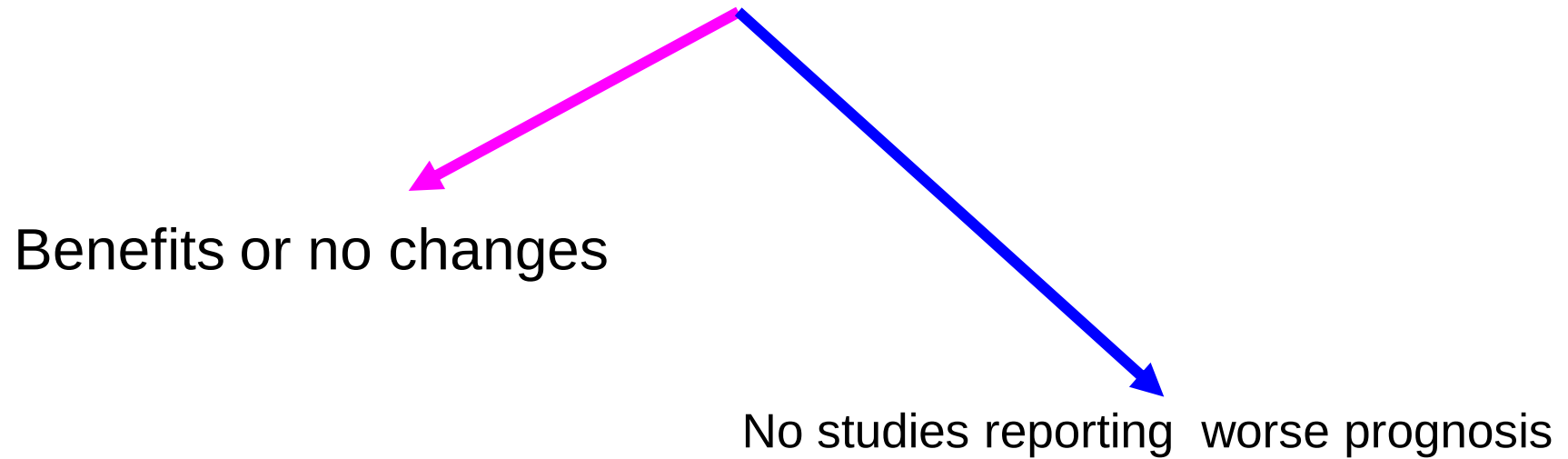
Total parenteral nutrition vs oral diet in autologous hematopoietic cell transplant recipients

S Roberts¹, J Miller², L Pineiro¹ and L Jennings¹

¹Baylor University Medical Center, Dallas, TX, USA; and ²Meredith Corporation, Des Moines, Iowa, USA



Effect of nutrition support on cancer survival



SPECIFIC NUTRIENTS

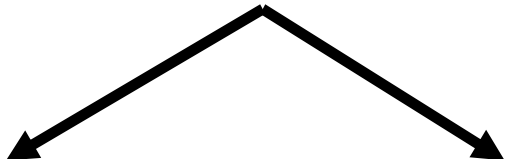


Arginine

- is a key component of immunonutrition
- is a strong stimulator of immune function and, in particular, of macrophage phagocytic activity, natural killer cells activity, and lymphokine activated killer cells activity.
- has been shown to have both stimulating and inhibiting effects on tumor growth, either in vitro and in vivo.

Ω 3-fatty acids

studies in vitro or in animals



Decrease of
tumor proliferation

Induction of
tumor apoptosis

WHAT HAPPENS WITH Ω 3-FATTY ACIDS ENRICHED LIPID EMULSIONS
IN HUMANS ?

CANCER CACHEXIA

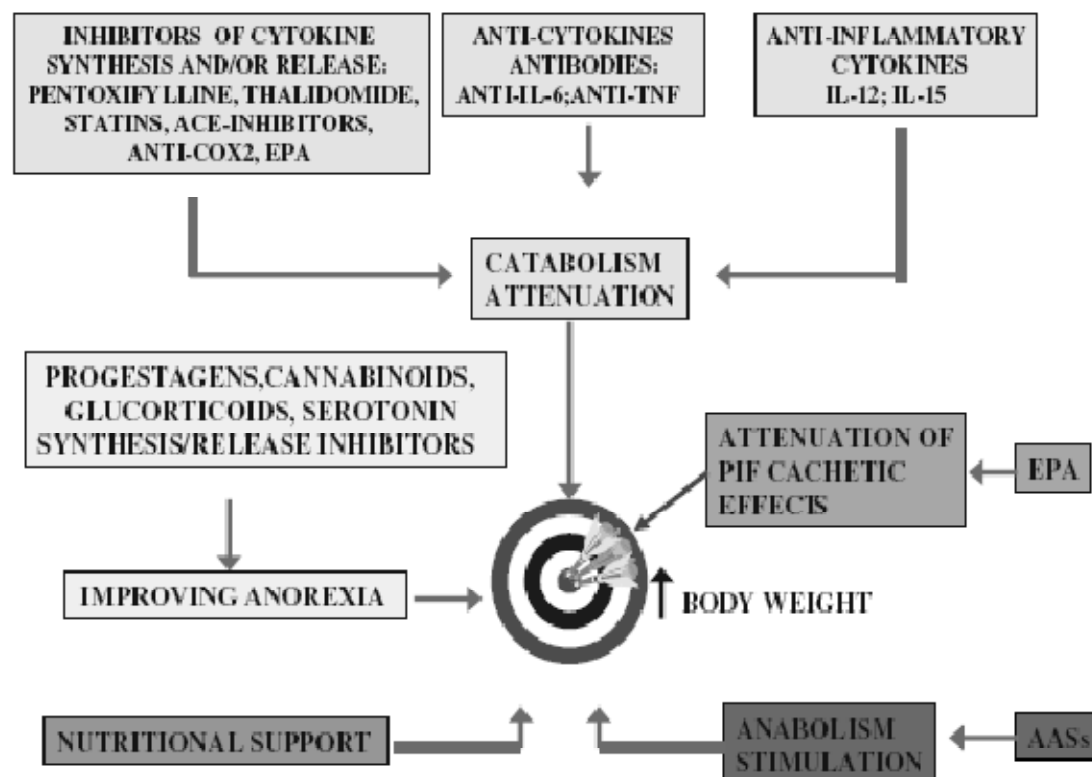
TABLE 1. *Approved therapies for cancer cachexia: results of clinical trials*

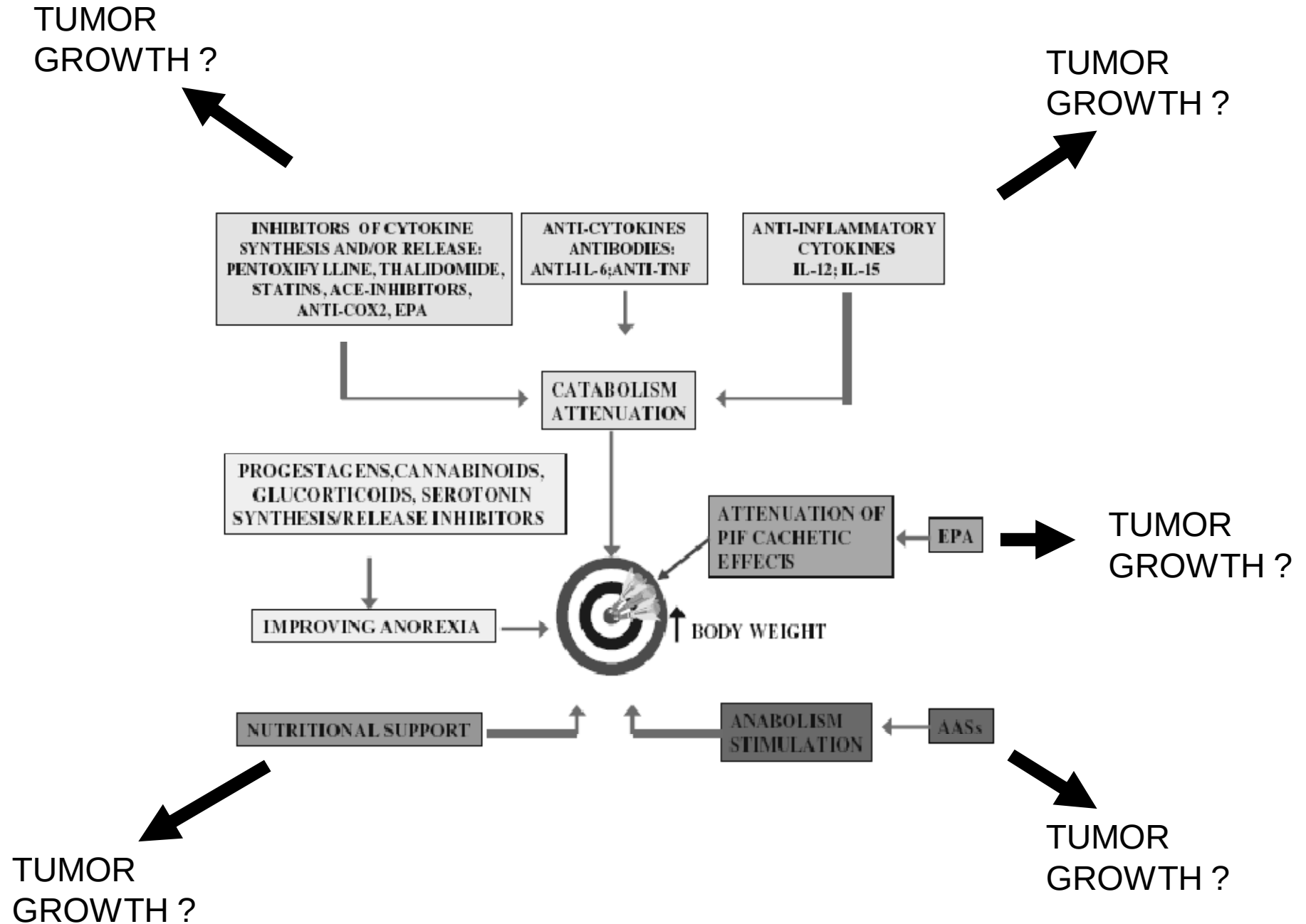
Author (year)	No. of patients	DIAGNOSIS	Type of intervention	Duration	Effect
Lopez et al. (2004) ^{30*}	3887	Cancer	Megestrol acetate	Various	Improvement in appetite and weight gain
Jatoi et al. (2002) ³³	469	Cancer	Dronabinol	~10 weeks	Dronabinol less effective than megestrol in treatment of anorexia
Wigmore et al. (2000) ⁴⁷	26	Pancreatic cancer	Eicosapentaenoic acid-enriched oral supplements	12 weeks	Prevention of weight loss
Fearon et al. (2003) ⁴⁸	200	Pancreatic cancer	Eicosapentaenoic acid enriched oral supplements	8 weeks	No nutritional advantage with respect to oral supplement alone
Moses et al. (2004) ⁴⁹	24	Pancreatic cancer	Eicosapentaenoic acid-enriched oral supplements	8 weeks	Increase in physical activity
Jatoi et al. (2004) ⁵⁰	400	Lung and gastrointestinal cancer	Eicosapentaenoic acid-enriched oral supplements	4 weeks	Less effective than megestrol acetate in weight gain

* Systematic review.

Skeletal Muscle in Cancer Cachexia: The Ideal Target of Drug Therapy

Maurizio Bossola*, Fabio Paccelli, Antonio Tortorelli, Fausto Rosa and Giovan Battista Doglietto





Summary

- There is evidence that parenteral and enteral nutrition support do not stimulate tumor proliferation
- Such evidences derive from short term studies (2-15 days) and from a limited number of patients studied
- There are not data on tumor apoptosis
- The data on survival seem to show a benefit of nutrition support or, at least, no deterioration of prognosis
- The effect of specific nutrients on tumor growth needs to be further elucidated
- The effect of the future drugs/nutrition association on tumor growth in cancer cachexia is completely unknown

Thank you for your attention

