Is enteral nutrition a primary therapy in cancer patients?

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Abstract
At present, there is limited evidence for the role of enteral nutrition as a primary therapy in cancer patients. Cachexia commonly occurs in patients with advanced cancer. A consensus view from a large number of studies suggests that cachexia cannot be fully reversed by vigorous enteral nutritional support. A review is included of the available data on the effects of enteral nutritional support on the common indices of nutritional state and on the final outcome of patients receiving enteral nutrition in conjunction with radiotherapy or chemotherapy, or both. The ‘nutritional’ effects are probably limited because the duration of the nutritional support in most studies consists of a few weeks while malnutrition in the cancer patients often occurs over many months.

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TABLE I The effect of enteral nutrition on body weight, body fat, indices of muscular mass, and lean body mass

Tumour site	Regimen per kg per day		Duration (days)	Results*	Authors
	kcal	N ²			
Body weight					
Oesophagus	63	0.35	21	+	Lim <i>et al</i> ⁴
Oesophagus	44	0.14	14	=	Burt <i>et al</i> ^{5,6}
Oesophagus	37	0.33	35	=	Cozzaglio <i>et al</i> ^{7,†}
Head-neck	34	0.20	49	=	Balzola <i>et al</i> ^{8,†}
Head-neck	49	0.30	49	+	Balzola <i>et al</i> ^{8,†}
Head-neck	39	0.24	28	=	Daly <i>et al</i> ^{9,†}
Gastrointestinal	44	0.20	15	=	Braga <i>et al</i> ¹⁰
Heterogeneous	35	0.21	14	+	Bennegard <i>et al</i> ¹¹
Heterogeneous	43	0.28	28	+	Cristallo <i>et al</i> ¹²
Heterogeneous	42	0.38	18	+	Ravera <i>et al</i> ¹³
Heterogeneous	58	0.19	14	+	James <i>et al</i> ¹⁴
Body fat (triceps skinfold)					
Gastrointestinal	44	0.20	15	=	Braga <i>et al</i> ¹⁰
Heterogeneous	35	0.21	14	=	Bennegard <i>et al</i> ¹¹
Heterogeneous	43	0.28	28	+	Cristallo <i>et al</i> ¹²
Heterogeneous	42	0.38	18	+	Ravera <i>et al</i> ¹³
Heterogeneous	58	0.19	14	+ TBF	James <i>et al</i> ¹⁴
Indices of muscular mass					
Arm muscle circumference					
Head-neck	38	0.24	28	=	Daly <i>et al</i> ⁹
Gastrointestinal	44	0.20	15	=	Braga <i>et al</i> ¹⁰
Heterogeneous	43	0.28	28	+	Cristallo <i>et al</i> ¹²
Heterogeneous	42	0.38	18	=	Ravera <i>et al</i> ¹³
Urinary creatinine					
Heterogeneous	35	0.21	14	=	Bennegard <i>et al</i> ¹¹
Heterogeneous	42	0.38	18	=	Ravera <i>et al</i> ¹³
Urinary 3-methylhistidine					
Oesophagus	44	0.14	14	=	Burt <i>et al</i> ⁶
3-Methylhistidine efflux (from the leg)					
Heterogeneous	37	0.17	14	–	Lundholm <i>et al</i> ¹⁵
Tyrosine efflux					
Heterogeneous	37	0.17	14	=	Lundholm <i>et al</i> ¹⁵
AA and BCAA efflux					
Heterogeneous	40	0.24	14	=	Bennegard <i>et al</i> ¹⁶
Lean body mass					
Nitrogen balance					
Oesophagus	77	0.41	7–21	pos	Haffeejee and Angorn ¹⁷
Oesophagus	44	0.14	14	=	Burt <i>et al</i> ⁵
Heterogeneous	35	0.21	14	pos	Bennegard <i>et al</i> ¹¹
Heterogeneous	42	0.38	18	pos	Ravera <i>et al</i> ¹³
Total body nitrogen					
Heterogeneous	58	0.19	14	=?	James <i>et al</i> ¹⁴
Whole body potassium					
Oesophagus	44	0.14	14	=	Burt <i>et al</i> ⁵
Heterogeneous	35	0.21	14	+	Bennegard <i>et al</i> ¹¹
Heterogeneous	58	0.19	14	+	James <i>et al</i> ¹⁴

*+, increase; –, decrease; =, no change; pos, positive; TBF, total body fat; †radiotherapy; ‡radiotherapy plus chemotherapy; AA=amino acids; BCAA=branched chain amino acids.

There is some evidence that enteral nutrition is probably not successful as a primary therapy in many patients with the cancer cachexia syndrome. The suggestion derives from metabolic balance studies done in humans.

The techniques used to undertake such studies are based on the assumption that certain elements are found in comparatively fixed proportions in normal lean body mass. If an organism retains these elements in these ratios, it may be right to assume that normal lean body mass is being formed; conversely significant deviation from these ratios, as occurs in cancer patients, means that normal lean body mass is not being repleted and that the elements retained are being used for other purposes.

In certain circumstances, however, enteral nutrition may be useful in cancer patients whose weight loss is exacerbated by such complications as fistulas, short bowel obstruction, and vomiting or malabsorption induced by the tumour itself or the treatment. There may also be patients who, at different times in the course of their disease, may gain transient benefit from nutritional support.

In this paper we will discuss the effects of enteral nutrition on the nutritional state of cancer patients and its role in conjunction with other treatments. Finally, the possible effect of enteral nutrition on tumour growth in humans is discussed.

Enteral nutrition and nutritional state

Although the first controversial papers on naso-gastric feeding with milk based formulas date back to the 1950s,^{1–3} substantial experience has been gained in the past decade (Table I).

Enteral nutrition can increase body weight (even during chemotherapy¹⁸) mainly as a result of accumulation of body fat, whereas indices of muscle mass (arm muscle circumference, urinary excretion of creatinine and 3-methylhistidine) as well as amino acid efflux from the leg are only slightly affected by the nutritional support.

Studies on nitrogen balance and whole body potassium point to an increase in lean body mass, whereas no substantial data exist on total body nitrogen. Total protein, transferrin, cholinesterase, thyroxine binding prealbumin and ceruloplasmin concentrations as well as protein kinetics are in general unaffected by the treatment, and results concerning the effect of enteral nutrition on serum albumin concentrations are conflicting (Table II).

With regard to immune function, increases in some fraction of the complement cascade have been described and in a number of studies increases in lymphocyte counts have been reported (Table III).

TABLE II The effect of enteral nutrition on serum proteins and whole body protein kinetics

Tumour site	Regimen per kg per day		Duration (days)	Results*	Authors
	kcal	N ²			
Serum proteins					
Total protein					
Oesophagus	44	0.14	14	=	Burt <i>et al</i> ⁶
Oesophagus	37	0.33	35	=	Cozzaglio <i>et al</i> ⁷
Head-neck	49	0.30	49	=	Palmo <i>et al</i> ¹⁹
Heterogeneous	42	0.38	18	=	Ravera <i>et al</i> ¹³
Albumin					
Oesophagus	44	0.14	14	—	Burt <i>et al</i> ⁶
Oesophagus	37	0.33	35	=	Cozzaglio <i>et al</i> ⁷
Head-neck	39	0.24	28	—	Daly <i>et al</i> ⁹
Head-neck	49	0.30	49	=	Palmo <i>et al</i> ¹⁹
Gastrointestinal	44	0.20	15	=	Braga <i>et al</i> ¹⁰
Heterogeneous	35	0.21	14	=	Bennegard <i>et al</i> ¹¹
Heterogeneous	43	0.28	28	+	Cristallo <i>et al</i> ¹²
Heterogeneous	42	0.38	18	=	Ravera <i>et al</i> ¹³
Total iron binding capacity					
Oesophagus	44	0.14	14	=	Burt <i>et al</i> ⁶
Gastrointestinal	44	0.20	15	=	Braga <i>et al</i> ¹⁰
Heterogeneous	43	0.28	28	+	Cristallo <i>et al</i> ¹²
Heterogeneous	42	0.38	18	=	Ravera <i>et al</i> ¹³
Cholinesterase					
Oesophagus	37	0.33	35	=	Cozzaglio <i>et al</i> ⁷
Head-neck	49	0.30	49	=	Palmo <i>et al</i> ¹⁹
Heterogeneous	43	0.28	28	+	Cristallo <i>et al</i> ¹²
Heterogeneous	42	0.38	18	=	Ravera <i>et al</i> ¹³
Thyroxin binding prealbumin					
Head-neck	49	0.30	49	+	Palmo <i>et al</i> ¹⁹
Heterogeneous	35	0.21	14	=	Bennegard <i>et al</i> ¹¹
Ceruloplasmin					
Oesophagus	44	0.14	14	=	Burt <i>et al</i> ⁶
Whole body protein kinetics					
Protein flux synthesis, catabolism	44	0.14	14	=	Burt <i>et al</i> ⁶

*+, increase; -, decrease; =, no change; †radiotherapy; ‡radiotherapy plus chemotherapy.

In general the data suggest a limited efficacy of enteral nutrition in restoring a depleted nutritional state; most commonly, nutritional state is maintained as a consequence of enteral nutrition.

A number of studies have now been carried out to compare the efficacy of enteral nutrition in cancer and non-cancer patients (Table IV).

Cancer patients receiving enteral nutrition show smaller increases in body weight, arm muscle circumference, and some mineral balances than non-cancer patients. Dresler *et al*²¹ recently investigated the metabolic efficacy of enteral feeding in malnourished cancer and non-cancer patients. They showed that a defined enteral diet with a calorie: nitrogen ratio of 200:1 prescribed to 120% of the basal

TABLE III The effect of enteral nutrition on humoral immune response and non specific cellular response

	<i>Regimen per kg per day</i>		<i>Duration (days)</i>	<i>Results*</i>	<i>Authors</i>
<i>Tumour site</i>	<i>kcal</i>	<i>N²</i>			
Humoral immune response					
<i>IgG, IgA, IgM</i> Oesophagus	77	0.41	7-21	=	Haffeejee and Angorn ¹⁷
<i>C3, C3, C3PA</i> Oesophagus	77	0.41	7-12	+	Haffeejee and Angorn ¹⁷
<i>C3</i> Gastrointestinal	44	0.20	15	+	Braga <i>et al</i> ⁴
<i>CH50</i> Oesophagus	77	0.41	7-21	=	Haffeejee and Angorn ¹⁷
Non-specific cellular response					
<i>Lymphocytes</i> Oesophagus	77	0.41	7-21	+	Haffeejee and Angorn ¹⁷
Gastrointestinal	44	0.20	15	=	Braga <i>et al</i> ⁴
Heterogeneous	42	0.38	18	+	Ravera <i>et al</i> ⁴
<i>T lymphocytes</i> Oesophagus	77	0.41	7-12	+	Haffeejee and Angorn ¹⁷
<i>B, T, N, FT lymphocytes</i> Oesophagus	77	0.41	7-12	=	Haffeejee and Angorn ¹⁷

*+, increases; =, no change.

TABLE IV Response to enteral nutrition in cancer v non-cancer patients¹¹²⁰

Category	Enteral nutrition	
	Cancer	Non-cancer
Weight	+	++
Arm circumference	+	+
Triceps skinfold	=	+
Arm muscle area	=	+
Creatinine-height index	+	+
Nitrogen balance	+	+
Total body potassium	+	+
Tyrosine balance	=	+
Albumin	+	+
Prealbumin	=	=
Retinol binding protein balance of:		
Na	-	+
K	-	+
Cl	-	+
Mg	-	+
P	+	+
Ca	+	+

+, increase; ++, greater increase; -, decrease; =, no change.

energy expenditure resulted in an equivalent suppression of endogenous glucose production, suppression of alanine to glucose conversion, attainment of positive nitrogen balance, and suppression of protein catabolism. After two weeks of enteral support, however, cancer patients differed from non-cancer patients by having significantly raised lactate concentrations, decreased plasma glycine concentrations, and inability to replenish fat stores. Furthermore, cancer patients had a significant reduction in whole body protein synthesis rates whereas non-cancer patients showed no significant change.

These data suggest that there are metabolic abnormalities besides simple starvation and underfeeding that play a part in cancer malnutrition and that these in turn are difficult to reverse by nutritional support.

Randomised studies on perioperative enteral nutrition

PREOPERATIVE ENTERAL v TOTAL PARENTERAL NUTRITION

Lim *et al*⁴ randomly assigned 24 patients with carcinoma of the oesophagus to receive either total parenteral nutrition (12 patients) or enteral nutrition given by a gastrostomy tube (12 patients) for three weeks before surgery. Weight gain was significantly greater in the total parenteral nutrition group whereas improvement in serum albumin concentrations was similar in both groups. The lower morbidity and mortality seen in the total parenteral nutrition group was not statistically significant, probably, in part, because of the small numbers investigated.

Sako *et al*²² prospectively randomised 69 patients to receive total parenteral nutrition or enteral nutrition before surgery for head and neck cancer. Nutritional support was given for 14 days. Nitrogen balance was significantly better in the total parenteral nutrition group but no differences were found in the incidence of postoperative complications or death.

These studies suggest that when adequate amounts of nutrients are given in the preopera-

TABLE V Nutritional state in patients with cancer of the oesophagus receiving chemotherapy and radiotherapy⁷

Patients	Enteral nutrition* (n=20)		Control (n=17)	
	b	a	b	a
Weight (kg)	55.4	55.4	54.2	52.3**
Protein (g/dl)	6.9	6.9	7.1	6.5**
Albumin (g/dl)	3.9	3.8	4.0	3.5**
Cholinesterase (mU/ml)	1921	2107	1925	1838

*37 kcal/kg⁻¹/d⁻¹ and 2.1 g protein/kg⁻¹/d⁻¹; ** p=0.05.

tive period, there are no advantages in giving them by either the enteral or parenteral route. This is particularly so in relation to the incidence of postoperative complications and death.

Most recently von Meyenfeldt *et al*²³ randomised patients with gastric or colorectal cancer to receive pre and postoperative enteral nutrition, total parenteral nutrition or control therapy. There was no significant difference in outcome or in any of the end points of the trial.

POSTOPERATIVE EN V TPN OR V STANDARD CONTROL NUTRITION

Heylen *et al*²⁴ randomised 20 patients having total gastrectomy for cancer to a calorie regimen of 40 kcal/kg/day + amino acids through central vein or jejunostomy for eight days: there was no significant difference in postoperative outcome between the two groups except for the arm muscle circumference, which increased significantly more in the total parenteral nutrition than the enteral nutrition group.

Different results are obtained when enteral nutrition is compared with standard intravenous nutrition.

In a different study in which Sagar and associates²⁵ randomised 30 patients having major gastrointestinal surgery for presumed malignancy to receive either an elemental diet beginning on postoperative day one through a nasojejunal tube or standard intravenous fluids and a light diet, which was started on the sixth postoperative day. Control patients lost more weight, had a more negative nitrogen balance, and had a longer hospital stay than the group fed an elemental diet. Wound infection rates, however, were similar.

Daly *et al*²⁶ prospectively studied the effects of immediate postoperative jejunostomy feeding in patients having a cystectomy and ileal conduit construction for bladder cancer. Twenty patients were randomised to receive an enteral diet by needle catheter jejunostomy or the standard postoperative 5% dextrose solution. Improved nitrogen balance was noted in the patients receiving enteral nutrition. The length of hospital stay, however, was similar between the groups; the incidence of infectious complications was not reported.

In a controlled, non-randomised study performed in our Institute⁷ in patients with squamous cell carcinoma of the oesophagus receiving chemotherapy and radiation therapy, we showed that an enteral nutrition regimen of 37 kcal/kg/day and 2.1 g protein/kg/day for one month could maintain the nutritional state of patients in the treatment group, which in turn

deteriorated in the control group. No other benefits in terms of either compliance or response to the oncological treatment, or survival was described (Table V).

Enteral nutrition and oncological therapy

There is a paucity of prospective, controlled evaluations of aggressive oral/enteral nutritional support as adjunctive therapy for oncology patients. Douglass *et al*²⁷ compared a supplemental oral elemental diet with between meal feedings in addition to standard diet in 30 patients receiving radiotherapy with or without adjuvant chemotherapy for a variety of locally advanced, non-resectable gastrointestinal malignancies. In this small study there was a trend toward improved skin test responses in those receiving the elemental diet. No differences in weight, total lymphocytes count, or survival were noted.

Daly *et al*⁹ investigated intensive nasogastric tube feeding (22 patients) v optimal oral nutrition (18 patients) in patients with advanced head and neck cancer who were receiving eight weeks of radiation treatment. There was less weight loss in the tube fed group, and median albumin values returned towards normal in the tube fed group by the end of the treatment. There were no differences in response or survival rates; tube fed patients had significantly longer radiation toxicity, mean (SEM) (3.3 (1.9) weeks v 1.8 (0.8)).

Enteral nutrition and tumour growth

Scientific data on the effect of enteral nutrition on the tumoral growth in humans are scanty, anecdotal,^{28 29} and the results of two studies on patients with head-neck cancer is conflicting (Table VI).

We speculated that, if it is true that there is a relation between nutrient availability and tumour growth, then we should see the highest cancer cell proliferation rate in well nourished patients; consequently we tested this hypothesis statistically by evaluating the correlation between some nutritional variables (albumin, cholinesterase, number of lymphocytes, and body weight loss) with the labelling index in 136 adult patients with non-Hodgkin's lymphoma. The results obtained (Table VII) in this large population of patients do not support the view that a good nutritional state could result in a faster tumour growth as the opposite statistical association was found.

Our present view therefore is that any

TABLE VI Enteral nutrition and tumoral growth in patients with head-neck cancer

	Baron ³⁰	Edstrom ³¹
No of patients	6	13
Regimen		
kcal/kg/day	43.1	RME 1.2-1.5
AA/kg/day	1.4	1
Follow up (days)	8-0	6-8
Tumoral growth	No change in % HC or AC	Increase in % AC, DNA index, ODC

HC=hyperdiploid cells; AC=aneuploidic cells;
ODC=ornithin decarboxylase activity; RME=resting metabolic expenditure.

TABLE VII Association between labelling index and nutritional variables in 136 patients with non-Hodgkin's lymphoma

	Labelling index (%)		χ^2
	Low (n=72)	High (n=64)	
Albumin (g/dl)			8.1*
0-3.53	21.9	44.4	7.4*
3.54-3.99	37.5	30.6	
≥4	40.6	25	
Cholinesterase (mU/ml)			11.9*
0-2139	23.4	43.1	4.3
2140-2739	25	33.3	
≥2740	51.6	23.6	
Lymphocytes (No/mm ³)			5*
0-1479	25	41.7	
1480-2129	35.9	26.4	
≥2130	39.1	31.9	
Body weight loss			
Yes	23.4	41.7	
No	76.6	58.3	

*p=0.05.

conclusion about the relation between nutrition and tumour growth is premature, and that if indicated no patient should be denied nutritional support for fear that this will result in stimulation of tumour growth.

Home enteral feeding in cancer patients

Malignancy accounts for more than 40% of 1676 patients registered at the Oley Foundation and at different Commercial Home Nutrition Services.³³ Gastrointestinal cancer particularly those with upper gastric intestinal tract disease accounts for about two thirds of the overall population of cancer patients. The average survival of these patients receiving home enteral nutrition is about four months longer than in the normal Italian experience of patients not receiving enteral nutrition support.³⁴

We conclude that enteral nutrition is usually feasible in malnourished anorexic cancer patients even when they are receiving radiotherapy or chemotherapy. The nutritional efficacy of enteral nutrition is, however, limited.

Evidence from controlled clinical trials suggest that the main benefits are the maintenance of, or prevention of, further deterioration in nutritional state rather than restoration of normal nutritional state. At present there is no evidence that the effectiveness of radiotherapy or chemotherapy is enhanced by concomitant enteral nutrition. Nevertheless, it is indicated in patients receiving such treatment to preserve nutritional state. In our view, it would be unethical to randomise such patients in clinical trials to receive no nutritional support. As yet there is no proof that nutritional support enhances the kinetics of tumour kinetics. Clearly further work is required to characterise the cause of cancer cachexia. If it proves possible to counteract these then more benefits of concomitant nutritional support will probably, and hopefully, be identified.

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