

## Module 26.3

### Benefits and Limitations of Conventional Nutritional Support (CNS) for Cancer Patients (CP)

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#### Learning Objectives

- Understand the mechanisms behind the pathogenesis of malnutrition/cachexia in cancer patients;
- Understand the ways in which malnutrition can adversely affect patient outcome and quality of life;
- Understand the benefits and limitations of different forms of nutritional support.

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1. Introduction
2. Does poor nutritional state relate to adverse outcome from surgery, chemotherapy or radiotherapy?
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5. What causes the sub-optimal response to conventional nutritional support in a proportion of cancer patients?
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#### Key Messages

- Cancer cachexia represents a wasting syndrome involving loss of muscle and fat directly caused by tumour factors, and/or indirectly caused by an abnormal host response to tumour presence;
- Patients with cancer cachexia develop chronic negative energy and protein balance driven by a combination of reduced food intake and metabolic change;
- Malnutrition is associated with adverse outcomes in cancer patients;
- Nutritional support alone is beneficial but there is considerable scope for improvement;
- Oral nutritional supplementation is superior to total parenteral nutrition in the majority of cases.

## 1. Introduction

Patients with cancer frequently develop weight loss and in a proportion this becomes so severe that they appear to die of starvation. The syndrome of cachexia has been considered to be synonymous with severe weight loss. However, it is important to recognise that this is a multilayered, multifaceted syndrome of complex aetiology of which weight loss is only one component (Fig. 1). At the core of the cachexia syndrome lays the problem of progressive tumour growth and the catabolic side-effects of conventional anti-neoplastic therapy (1). These two phenomena subsequently give rise to alterations in the activity of the neuro-endocrine system, to the production of a variety of pro-inflammatory cytokines and to the release of cancer-specific cachectic factors. In turn, these mediators cause either a reduction in food intake, abnormalities in metabolism (including hypermetabolism) or a combination of the two. The resulting negative energy and nitrogen balance induced changes in the mass and function of a variety of organs and finally these changes are translated into a variety of symptoms and signs not the least of which is a reduction in the quality and perhaps the duration of life.

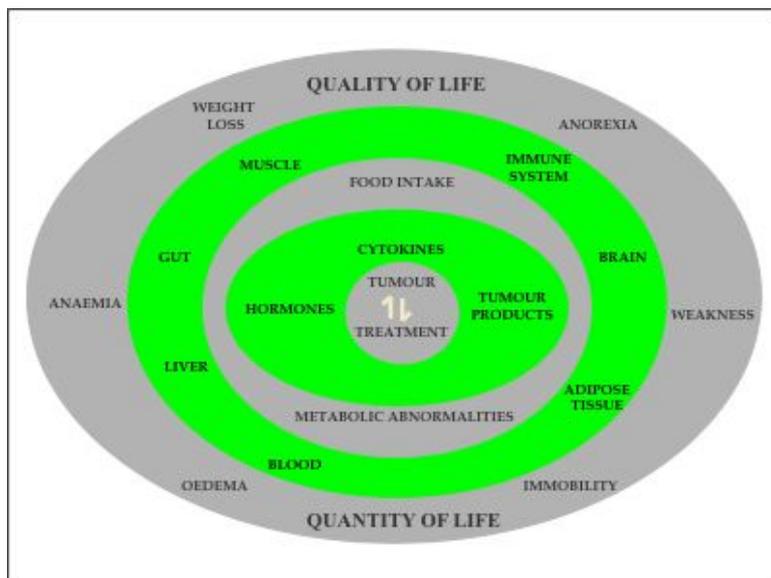


Figure 1 Multi-layered nature of cancer cachexia

Clearly advanced cachexia represents the end-stage of a process that has started much earlier in a patient's illness. Moreover, many patients experience weight loss and nutritional problems of mild to moderate severity and it is in this context that we should consider current issues surrounding the nutritional support of cancer patients. The aim of this module is to review current knowledge about usefulness of nutritional support in patients undergoing treatment (either surgery or chemotherapy), to discuss whether there is a suboptimal response to conventional nutritional support in cancer patients, and to suggest mechanisms whereby the efficacy of nutritional support might be improved in the future.

## 2. Does Poor Nutritional State Relate to Adverse Outcome from Surgery, Chemotherapy or Radiotherapy?

The correlation between poor nutritional status and adverse outcome is well recognised. In surgical patients, pre-existing malnutrition increases post-operative morbidity and mortality rates, and the duration and cost of hospital stay (2, 3). Interestingly, the routine use of pre- and/or post-operative nutritional supplementation does not increase the cost of standard surgical patient care (4). Post-operatively, nutritional status can continue to decline for several months (5).

In patients undergoing chemotherapy, weight loss is prevalent at the time of presentation (Fig. 2) and correlates with survival duration, decreased treatment response, reduced quality of life (Fig. 3) and decreased performance status (6, 7). It has also been shown that patients who stop losing weight demonstrate superior overall survival (7).

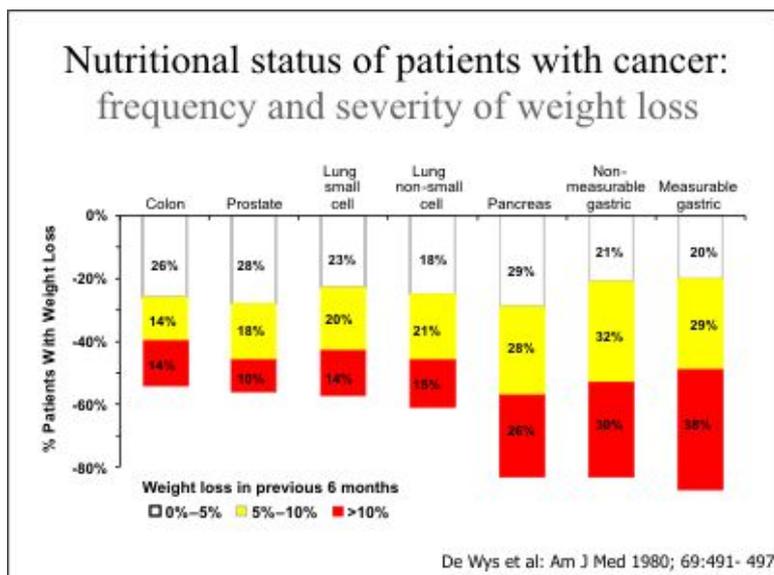


Figure 2 Nutritional status of patients with cancer: frequency and severity of weight loss (6)

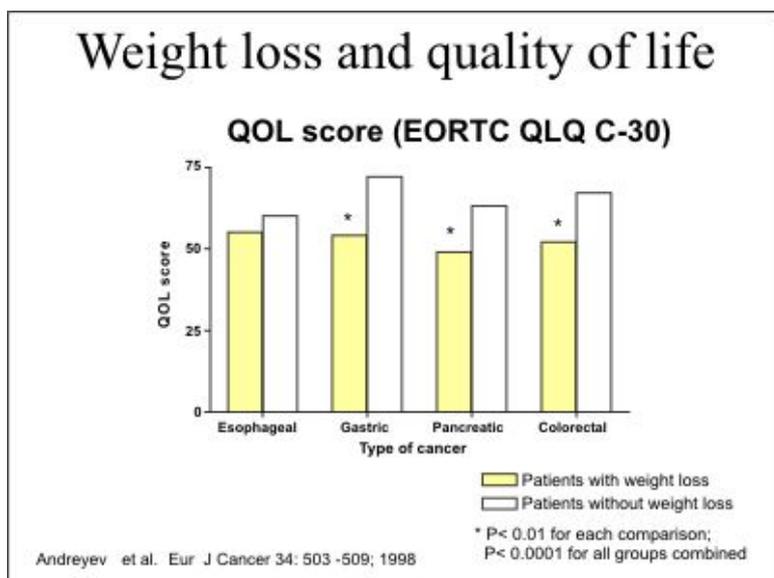


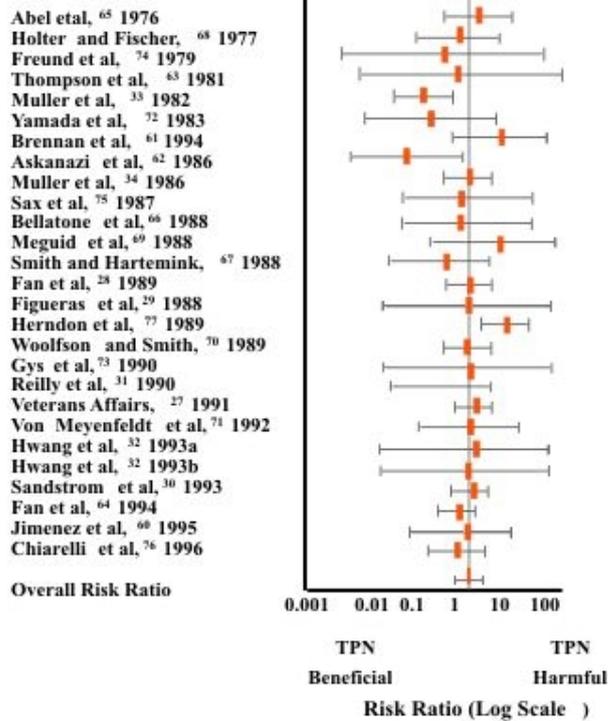
Figure 3 Weight loss and quality of life in patients with GI malignancy (7)

### 3. Does Conventional Nutritional Support Improve the Outcome of Anti-cancer Therapy?

#### 3.1 Surgery

The past 30 years have seen an extensive evaluation of the potential of perioperative total parenteral nutrition (TPN) to reduce the major complications and mortality of patients undergoing major upper abdominal surgery. Initial reports were positive (8). However, subsequent studies suggested, not surprisingly, that TPN around the time of surgery is not an insurance policy for poor surgical technique or bad patient selection and is most likely to benefit only patients who are severely malnourished in the first place (9). A recent meta-analysis based on critically ill surgical patients (but focussed primarily on upper gastrointestinal (GI) cancer patients) has demonstrated no overall benefits of TPN in terms of complications or mortality (Fig. 4) (10).

**Risk ratios and associated 95% confidence intervals for effect of total parenteral nutrition (TPN) on mortality .**



*Heyland et al 1998, JAMA, 280:2013-9*

Figure 4 Risk ratios and associated 95% confidence intervals for effect of total parenteral nutrition (TPN) on mortality in critically ill surgical patients (10)

Moreover, it is evident that severely malnourished patients form less than 5-10% of the overall population undergoing major cancer surgery and that within this group it is the risk of nutritional decline should complications develop that is the key issue.

Recent trends in perioperative nutritional support have been away from TPN and towards enteral or oral nutrition. In the context of traditional perioperative care, use of oral nutritional supplementation (ONS) together with voluntary food intake in the post-operative period has been shown to be cheap, robust and complication-free. Importantly, post-operative ONS has been shown to have a beneficial effect on outcome after surgery (5, 11, 12).

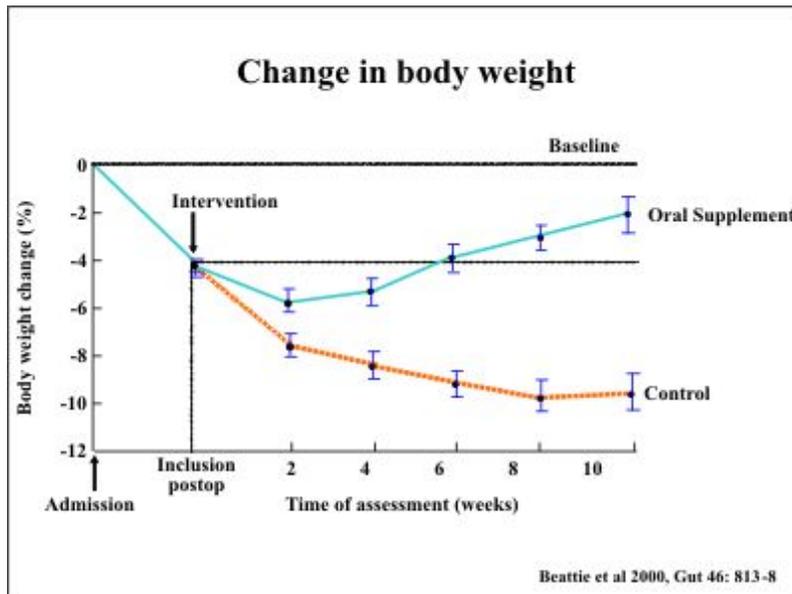


Figure 5 Effect of ONS on post-operative weight loss in malnourished patients undergoing major surgery (5)

Recent studies have evaluated the efficacy of ONS administration to surgical patients over an extended period before hospital admission, during the hospital stay and after discharge. Such an approach appears to diminish post-operative weight loss and the incidence of minor, but not major, complications (4). The use of perioperative ONS using immunonutrition has also been advocated as a method to reduce infectious complications, and has been suggested to be cost-effective (13).

A further evolution of the nutritional and metabolic care of the cancer patient undergoing major surgery has been to develop multimodal care pathways to reduce post-operative organ dysfunction and return the patient to normality as soon as possible (14). Such a “stress-free” approach to perioperative care includes the use of pre-operative oral fluid and carbohydrate loading and early post-operative oral nutrition (including the use of ONS). Thus, the patient is in a less catabolic state and undergoes less starvation resulting in more rapid recovery and reduced length of hospital stay.

### 3.2 Chemotherapy and Radiotherapy

Combination cytotoxic chemotherapy is associated with fairly frequent gastrointestinal toxicity that can result in oral ulceration, anorexia, nausea, vomiting and diarrhoea. It has long been recognised that such toxicity can lead to reduced food intake and nutritional decline and it was hoped that artificial nutritional support might obviate these problems, sustain the patient during toxic therapy and allow them to tolerate the full course of therapy thereby leading to improved response rates and survival. During the 1980’s, numerous trials tested this hypothesis in groups of patients with a wide variety of both chemosensitive and relatively chemoresistant tumour types. The overall result was disappointing with no improvement in response rates or survival and a suggestion that, if anything, TPN resulted in an increased level of septic complications (15). There are, however, specific circumstances where TPN is of value. For example, it has been shown to increase body weight and improve nutritional status in patients undergoing bone marrow transplantation (BMT) (16).

Furthermore, TPN supplemented with branched-chain amino acids can maintain a BMT patient’s visceral protein better than standard TPN (16).

The recognition that highly invasive and costly chemotherapy led to a series of studies evaluating the potential of dietary counselling and oral supplements in the context of out-patient chemotherapy. However, the metabolic sequelae of the systemic and gastrointestinal toxicity of chemotherapy coupled with the very limited improvement in oral intake that could be achieved (an additional 100-300 kcal and 10-15 g protein per day) meant that no net benefit in terms of nutritional variables such as total body weight could be achieved (17, 18).

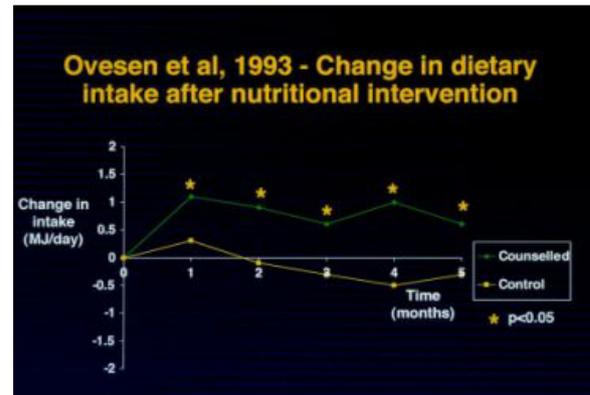
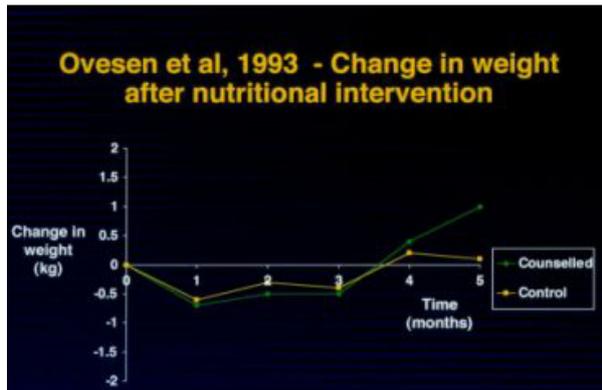


Figure 6 Change in dietary intake:

(a) and body weight

(b) in advanced cancer patients undergoing chemotherapy and randomised to nutritional counselling/ONS or no intervention (18)

More recent studies have, however, suggested that dietary counselling (and, to a lesser extent, ONS) following radiotherapy for colorectal cancer can significantly improve patient-related outcomes, including symptoms (e.g. anorexia, nausea, vomiting and diarrhoea) and quality of life (19). These studies emphasise a shift in the concept of what nutritional support is trying to achieve - away from conventional morbidity/mortality and towards the patient-centred outcomes such as improved physical activity and quality of life (Fig. 7).

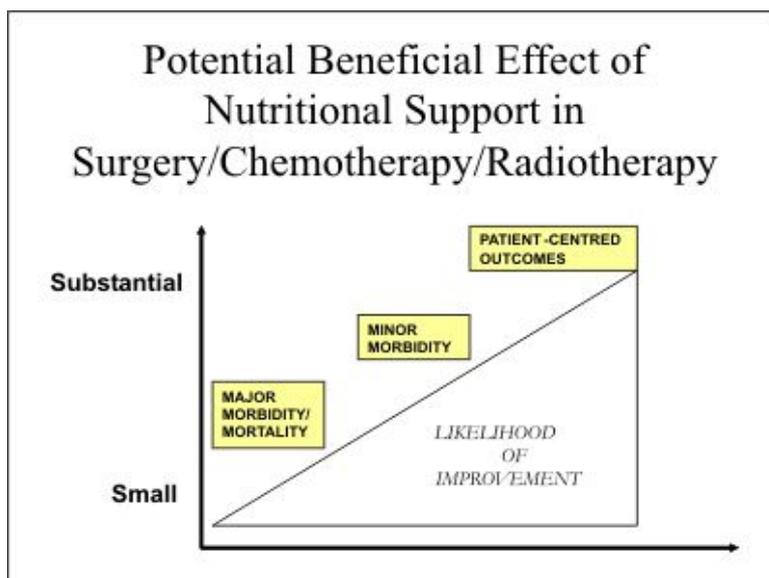


Figure 7 Potential beneficial effect of nutritional support in surgery, chemotherapy, radiotherapy

Given the limited efficacy demonstrated by nutritional support vis-à-vis the outcome of either surgery or chemotherapy, a re-evaluation of whether conventional nutritional support alone is capable of maintaining or improving the nutritional status of patients with cancer is called for. Instead of nutritional support alone, the development and implementation of combination strategies incorporating nutritional support should be implemented. Such techniques have shown significant promise in recent trials.

#### 4. Is there a Partial Block to the Efficacy of Conventional Nutritional Support in Cancer Patients?

Early body composition studies by Cohn and co-workers (20) examined the effects of 6 weeks of either TPN or oral supplementation in a heterogeneous group of cancer patients. It was demonstrated that patients who received TPN gained weight and this was distributed between both adipose tissue and lean body mass (Fig. 8).

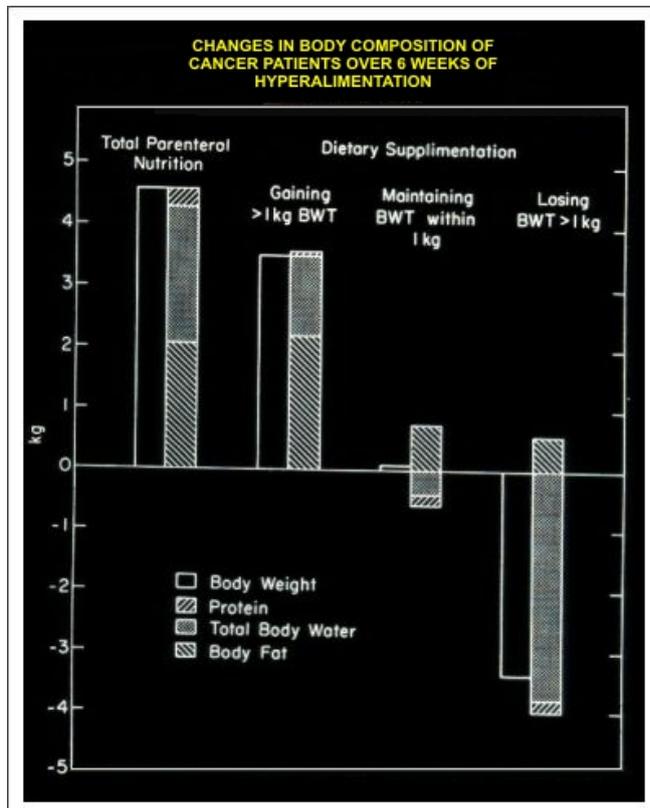


Figure 8 Changes in body composition of advanced cancer patients over 6 weeks of hyperalimentation (either TPN or dietary supplementation) (20)

In contrast, oral supplementation was much less effective with some patients gaining weight, some remaining weight stable and some continuing to decline. Moreover, even in those whose weight increased, the changes were almost entirely due to an increase in body fat and water rather than any effect on the functional protein mass. Such findings confirmed the impression that conventional oral supplementation had only limited benefits in advanced cancer patients.

Other investigators have addressed in more detail whether the lean body mass of weight-losing cancer patients can be restored by conventional nutritional support. Shaw and co-workers (21) examined the effects of TPN on whole body protein kinetics in depleted cancer and non-cancer patients. It was shown that whilst TPN could promote a shift from the net catabolism of protein to net whole body protein synthesis in the non-cancer patients, it was not possible to achieve nitrogen equilibrium in the cancer patients (Fig. 9).

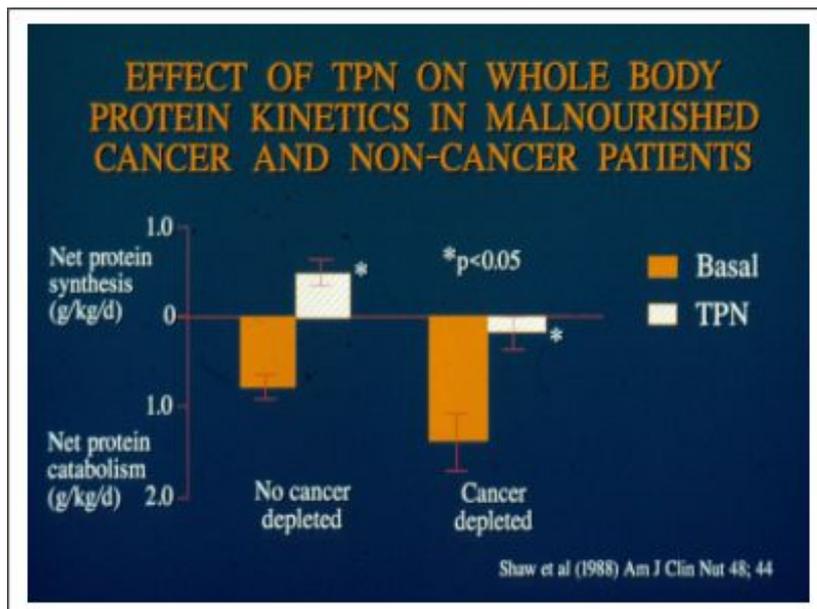


Figure 9 Effect of TPN on whole body protein kinetics in malnourished cancer and non-cancer patients (21)

Equally, Nixon and co-workers (22) demonstrated that in depleted non-cancer patients, 6 weeks of enteral feeding could result in substantial weight gain, increasing circulating albumin concentrations and increased adipose tissue mass and muscle mass (Fig. 10). In contrast, it was only possible to achieve modest weight gain, no change in albumin concentration and an increase in fat mass but no change in muscle mass in equivalent depleted cancer patients. These data suggest that at least in a proportion of cancer patients there is indeed a sub-optimal response to nutritional support and that the most resistant compartment to repletion is the vital lean body mass. It must be said, however, that other investigators have found that malnourished cancer patients are quite comparable with non-cancer patients in terms of whole body and peripheral metabolism both before and during the response to enteral feeding (23).

<b>Change in Nutritional Status in Malnourished Cancer and Non - Cancer Patients during EN <sup>+</sup></b>				
	$\Delta$ Weight (kg)	$\Delta$ alb (g/l)	$\Delta$ TSF (% of standard)	$\Delta$ MMA (% of standard)
Cancer (n=6)	3.5(2 -7)	0.0(0.2 -0.3)	14.5(3 -29)	3(3-13)
Non-cancer (n=5)	9(7-13)*	3.0(0.3 -11)	11(7 -18)	10.5(9 -13)**

\* $p < 0.01$ , \*\* $p < 0.05$ , \*EN: 30 -35 Kcal/d, 0.15 -0.2g N/Kg/d

*Nixon et al, 1981; Cancer Res.: 2038-45*

Figure 10 Change in nutritional status in malnourished cancer and non-cancer patients during a six week period of enteral nutritional support (22)

## 5. What causes the Sub-optimal Response to Conventional Nutritional Support in a Proportion of Cancer Patients?

Two important factors may influence the response to conventional nutritional support in patients with cancer. On the one hand there are the effects of nutrients on the tumour and, on the other hand, the effects on the host (Fig. 11). There is no doubt that in certain animal cachexia models, refeeding the host leads to the stimulation of tumour growth (24). The tissue of the host may undergo some degree of repletion but at best the host: tumour ratio remains the same. It is, however, widely recognised that rodent tumours are different from human malignancy and tend to be more responsive to limitations/excesses in nutrient supply.

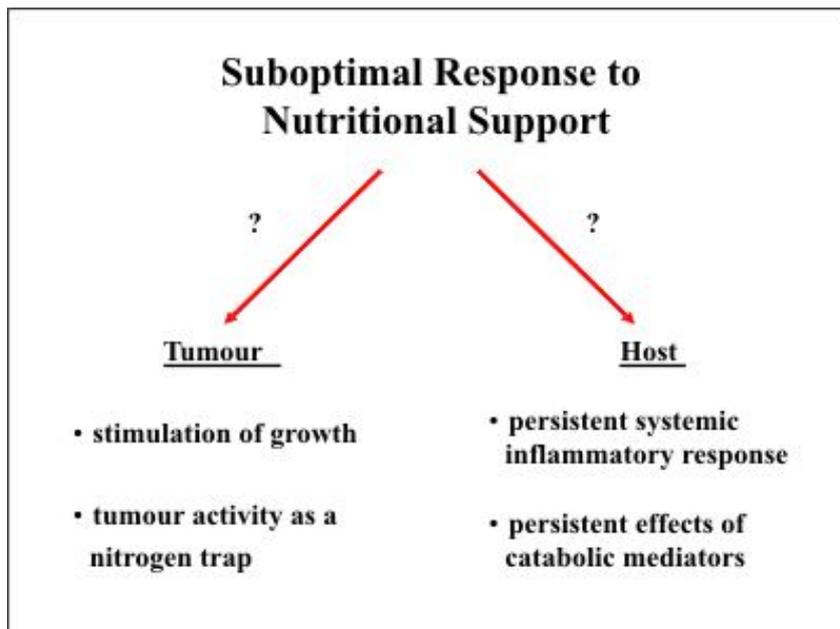


Figure 11 Role of host and tumour in the aetiology of the suboptimal response to nutritional support in patients with cancer

Data on the effect of nutritional support in human malignancy are scarce and somewhat difficult to interpret. Heys and co-workers (25) have demonstrated that in patients with colorectal cancer, a period of 24 h of TPN immediately prior to surgery results in stimulation of tumour protein synthesis. However, it is not clear whether this effect would persist if TPN was continued for more than 24 h. Moreover, it is possible that the effect observed mainly pertained to host cells within the tumour mass (about 50% of a tumour is host stromal tissue). It is also possible that protein degradation was increased and that there would have been no net stimulation of tumour growth. Overall, there is no well-documented clinical evidence of accelerated tumour growth in patients receiving long-term artificial nutrition.

The host factors which might contribute to a partial block to the accretion of lean tissue during artificial nutrition are probably similar to the mechanisms and mediators that contribute to the loss of weight in the first place (Fig. 12). In particular, the persistent effects of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6 inducing the reprioritisation of host nitrogen metabolism away from peripheral lean tissues and towards the liver (in order to allow the synthesis of acute phase proteins) may be important.

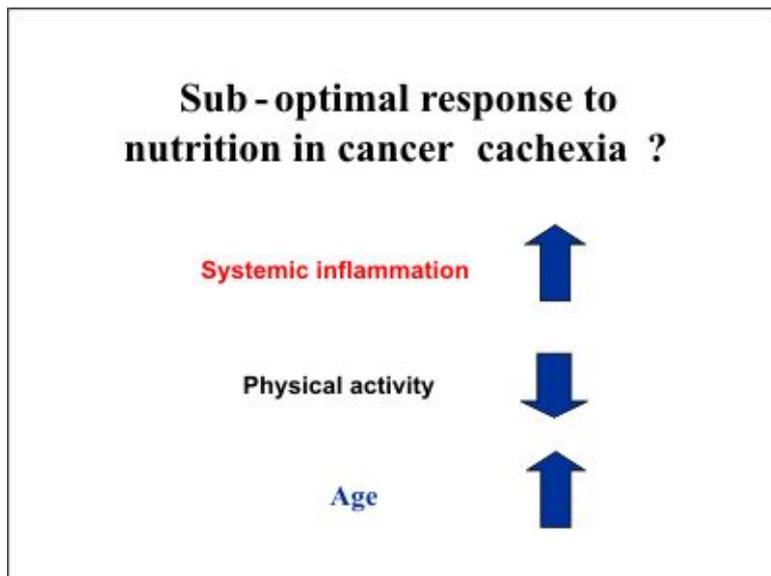


Figure 12 Host related factors which may contribute to the sub-optimal response to nutrition in cancer cachexia

Recently we have demonstrated that albumin synthesis is not suppressed in hypo-albuminaemic cancer patients and that during a meal, both albumin and to a much greater extent fibrinogen synthesis is markedly stimulated (Fig. 13) (26). This contrasts with the situation in healthy subjects where although albumin synthesis is stimulated by oral meal feeding, fibrinogen synthesis is not. Under normal conditions, albumin and fibrinogen synthesis together are thought to account for approximately 50-70% of total hepatic export protein synthesis. Thus, as far as liver nitrogen metabolism is concerned, feeding a wasted cancer patient with an ongoing acute phase response may be accelerating the latter and thus diverting the amino acids away from the synthesis of peripheral lean tissue such as skeletal muscle.

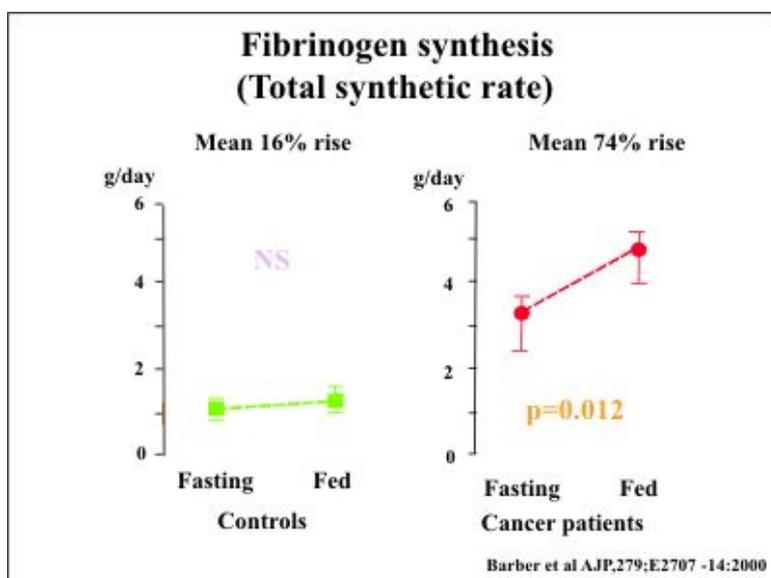


Figure 13 Fibrinogen synthesis (Total synthetic rate) in advanced cancer patients and healthy controls (26)

Increasing patient age is a further cause of poor anabolic response to dietary amino acids. Elderly patients demonstrate less anabolic sensitivity and responsiveness of muscle protein synthesis to the administration of essential amino acids, possibly due to decreased intramuscular expression and activation of amino acid sensing/signalling proteins (Fig. 14) (27). These effects are independent of insulin signalling and are therefore unaffected by the increased insulin availability found in the

elderly. Associated with these anabolic deficits are marked increases in NFkappaB, the inflammation-associated transcription factor. All of these factors contribute to the failure of muscle maintenance in the elderly.

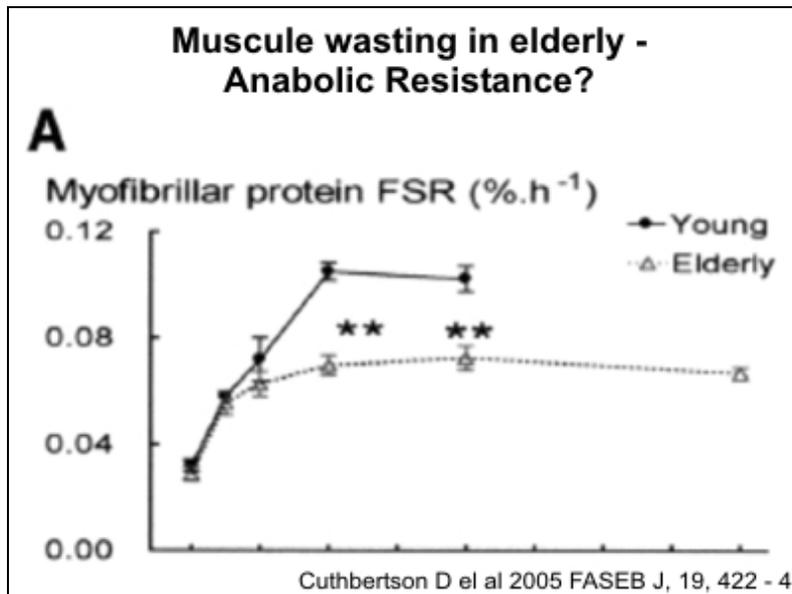


Figure 14 Muscle wasting in the elderly - evidence of reduced muscle protein synthesis in response to feeding: anabolic resistance? (24)

A reduction in patient physical activity is a further cause of reduced response to nutritional support. Weight-losing cancer patients have markedly reduced levels of physical activity (28). In hypermetabolic, weight losing pancreatic cancer patients total energy expenditure (TEE) is significantly reduced due to a lower Physical Activity Level (PAL: ratio of TEE to resting energy expenditure (REE)) (Fig. 15) (28). Measured PAL is much lower than that recorded in healthy adults of similar age, and are comparable to those observed in spinal cord injury patients living at home or in patients with cerebral palsy (29-31). It is entirely plausible that such low levels of activity may further exacerbate the muscle wasting seen in cachexia (32).

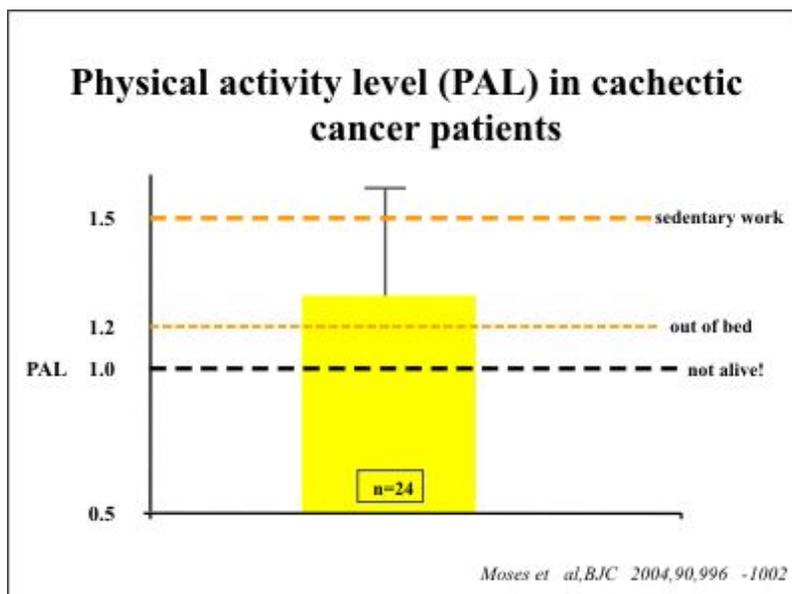


Figure 15 Physical activity level (PAL) can be markedly reduced in cachectic cancer patients (30)

In experimental post-prandial states, muscle inactivity has been shown to impair the amino-acid-mediated stimulation of protein synthesis (Fig. 16) (33).

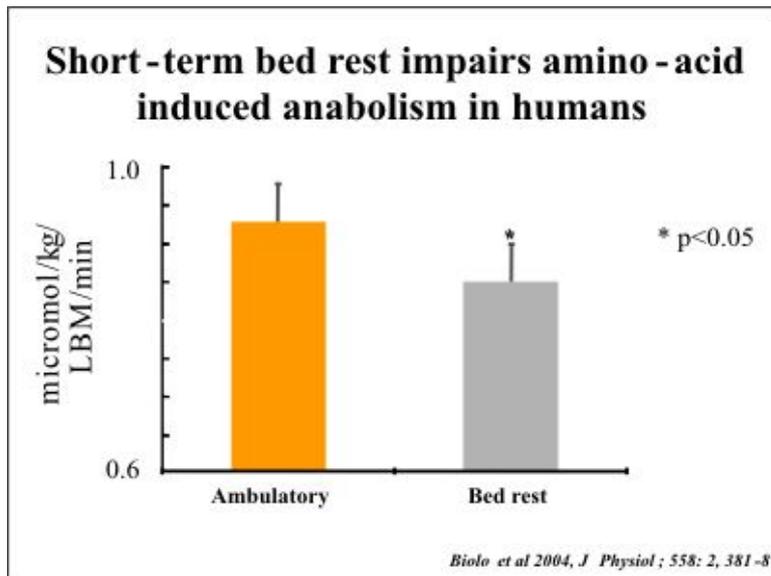


Figure 16 Short-term bed rest impairs amino-acid induced anabolism in humans

However, the ability of combined insulin and glucose infusion to decrease whole-body proteolysis is not affected (33). Thus, an impaired ability of protein/amino acid feeding to stimulate body protein synthesis may be the major catabolic mechanism for the effect of bed rest/physical inactivity on protein metabolism. This suggests that a protein intake level greater than normal may be required during nutritional supplementation of cachectic cancer patients to achieve the same postprandial anabolic effect during muscle inactivity. It is worth noting that in weight-losing pancreatic cancer patients, it was possible to increase TEE and PAL with a specialised nutritional supplement containing eicosapentaenoic acid administered over an 8-week period, but not with an isocaloric, isonitrogenous control supplement (28).

In conclusion, in the face of ongoing skeletal muscle protein degradation and suppressed synthesis, it may be difficult to reverse muscle wasting by feeding alone. Combination strategies should therefore be advocated.

## 6. Summary

- Nutritional support alone has limited benefits in terms of reducing major morbidity/mortality but may be particularly helpful in improving patient-centred outcomes;
- The complex multifactorial natures of cancer cachexia and modern oncological therapy demand a more sophisticated management approach than nutritional support alone.

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