

Nutritional support of the cancer patient: issues and dilemmas

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Abstract

Malnutrition in cancer patients results from multifactorial events and is associated with an alteration of quality of life and a reduced survival. A simple nutritional assessment program and early counselling by a dietitian are essential to guide nutritional support and to alert the physician to the need for enteral (EN) or parenteral nutrition (PN). A daily intake of 20–35 kcal/kg, with a balanced contribution of glucose and lipids, and of 0.2–0.35 g nitrogen/kg is recommended both for EN and PN, with an adequate provision of electrolytes, trace elements and vitamins. EN, always preferable for patients with an intact digestive tract, and PN are both safe and effective methods of administering nutrients. The general results in clinical practice suggest no tumor growth during nutritional support. The indiscriminate use of conventional EN and PN is not indicated in well-nourished cancer patients or in patients with mild malnutrition. EN or PN is not clinically efficacious for patients treated with chemotherapy or radiotherapy, unless there are prolonged periods of GI toxicity, as in the case of bone marrow transplant patients. Severely malnourished cancer patients undergoing major visceral surgery may benefit from perioperative nutritional support, preferably via enteral access. Nutritional support in palliative care should be based on the potential risks and benefits of EN and PN, and on the patient's and family's wishes. Research is currently directed toward the impact of nutritional pharmacology on the clinical outcome of cancer patients. Glutamine-supplemented PN is probably beneficial in bone marrow transplant patients. Immune diets are likely to reduce the rate of infectious complications and the length of hospital stay after GI surgery. Further studies are needed to determine the efficacy of such novel approaches in specific populations of cancer patients, and should also address the question of the overall cost-benefit ratio of nutritional pharmacology, and the effect of nutritional support on length and quality of life. © 2000 Published by Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Malnutrition, and its ultimate form cachexia, are encountered every day in cancer and hematology wards. Malnutrition results from the 'parasitic' metabolism of the tumor at the expense of the host, from the impact of the tumor on the metabolism of the host, and from more and more aggressive cancer therapies. The major consequence is an increased risk of complications and death during the course of chemotherapy, radiation therapy and major surgery. In addition, malnutrition is associated with depression, which consumes the patient, a marked alteration of quality of life and a drastic reduction in performance

status [1]. It is thus important to offer nutritional support, in order to stop or reverse the process of malnutrition. Nutritional interventions should be founded on the abundant literature devoted to cancer cachexia, including the pathophysiology of the disease, the technical aspects of enteral and parenteral nutrition, and the results of clinical trials. One must keep in mind that nutritional intervention is only conceivable in combination with potentially efficacious anti-cancer treatment, and is not for moribund patients. The aim of this review is to highlight recent advances in the metabolic and nutritional management of cancer cachexia, together with hopes and disappointments.

2. Is malnutrition the unavoidable fate of the cancer patient?

2.1. Incidence of malnutrition during the course of cancer

Weight loss and malnutrition are common in cancer patients and lead to poor quality of life, susceptibility to infection, socio-economic problems and reduced survival. The global incidence of malnutrition during the course of cancer ranges from 30 to 90%, according to the type, location, grade and stage of the tumor, tumor spread and anticancer treatments, but also individual susceptibilities. Patients with cancers of the upper digestive tract (esophagus, stomach, pancreas, etc.) and of the head and neck often have moderate to severe malnutrition at diagnosis. In a multicenter cooperative study of more than 3000 cancer patients, DeWys et al. found that about one-third of those with gastric or pancreatic adenocarcinomas had lost more than 10% of their body weight [2]. Patients with hematological disorders had the lowest frequency and severity of weight loss, probably because these diseases often develop rapidly in relatively young patients: the initial nutritional status of patients suffering from acute leukemia is usually normal [3–5]. However, it is noteworthy that most available data refer to studies done in the hospital setting, where patients are usually more severely ill and submitted to aggressive anticancer treatments. The incidence of malnutrition in ambulatory cancer patients may be markedly lower, as suggested by Edington et al, who found an incidence of 10.3% in a group of 213 patients consulting for gastrointestinal, lung and pro-

static cancers [6]. However, in the study by Tchekmedyan et al., 59% of the 644 patients who were followed on an ambulatory basis had lost > 5% of their body weight, underlying how the assessment of malnutrition in cancer patients is dependent on the type of nutritional measurements [7].

Malnutrition increases the duration of the hospital stay [8,9], reduces the cost-benefit and risk-benefit ratios of anticancer treatments [9], and is directly or indirectly responsible for excess mortality among cancer patients [10]. Malnutrition evolves during the course of cancer and is modulated by therapeutic interventions. It must be seen as a continuum, and be periodically reassessed, in the same way as the white cell count or respiratory status.

The current challenge is clear: can we counteract the deleterious consequences of cancer cachexia by nutritional intervention, at the beginning or during the course of the disease, and especially during the successive phases of treatment which often worsen nutritional status [11]. The future challenge is to develop a specific approach to the problem, in other words to better understand the pathophysiology of cancer cachexia and thus to use pharmaco/immunological nutrients more efficiently [12].

2.2. Pathophysiology of cancer cachexia

As pointed out by many authors [13–22], cancer cachexia must be seen as the result of multifactorial events that can be grouped into three major categories: (1) inadequate food intake; (2) metabolic alterations resulting in a wasting disease, and (3) specific humoral and inflammatory responses (Fig. 1).

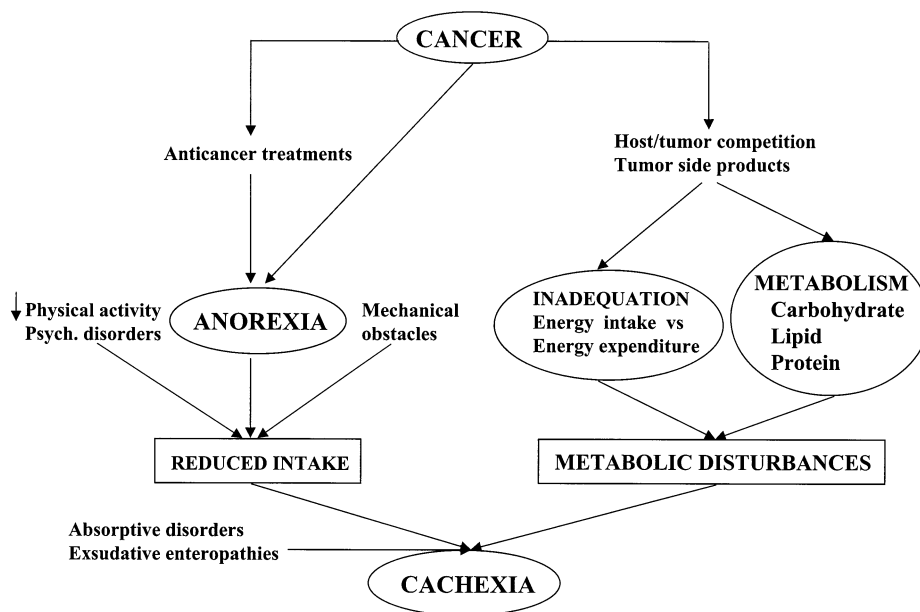


Fig. 1. Mechanisms of cancer cachexia. Cancer cachexia results from the combination of multiple events. Among them, appetite loss (anorexia) and metabolic alterations are the most important factors in nutritional deterioration, and are compounded by the side-effects of treatments.

2.2.1. Anorexia and related factors in decreased food intake

Appetite loss, or anorexia, is the most frequent and the most important contributory factor in nutritional deterioration among cancer patients, and results from several intricately linked physiopathological mechanisms [19]. Psychological factors such as depression are frequent [23]. About half of these patients have some degree of altered taste and smell. Changes in the recognition of sweet taste occur in approximately one-third of patients, while bitterness (responsible for meat aversion), sourness, and saltiness are less frequently affected [24]. Numerous studies have suggested that these changes in taste and smell correlate with decreased nutrient intake, a poor response to therapy, and tumor extension (including metastasis) [25].

Delayed digestion can lead, possibly by increasing the intestinal contents, to a sensation of early satiety. Other factors directly or indirectly affect the gastro-intestinal tract. Intestinal and gastric atrophy have been described, and are most often correlated with the degree of muscle wasting [24]. Dysphagia and odynophagia are particularly marked in head and neck cancer and esophageal cancer. Tumors in the gastrointestinal tract and hepatobiliary tract, but also the extrinsic pressure exerted by metastatic cancers, are often complicated by partial or total digestive obstruction leading to nausea, vomiting and early satiety. In some patients, relapsing episodes of obstruction or blind-loop syndromes can seriously affect nutrient absorption. Severe atrophy of the small bowel mucosa with malabsorption, and even exsudative enteropathies, have been described, similar to those seen in other wasting diseases. Other anorectic factors have been incriminated, such as a decreased response to insulin [26], increased circulating lactate [27] secondary to anaerobic metabolism of cancer cells and exacerbated by hepatic impairment [28], modification of the blood level of free fatty acids, altered plasma amino acid and cytokine levels, etc.

It has been proposed that the increased cerebral production of tryptophan and serotonin induce anorexia through their activity on the hypothalamic area. However, there is little evidence that the results obtained in animal studies are relevant to hypothalamic dysfunction in humans [29].

Anticancer treatments can also be a major cause of malnutrition. Chemotherapy can cause nausea, vomiting, abdominal cramping and bloating, mucositis, paralytic ileus and even malabsorption. Despite the recent advent of antiemetic drugs such as the setrons, and optimization of their timing of administration, vomiting remains an important cause of malnutrition in cancer. Some antineoplastic agents such as fluorouracil, adriamycin, methotrexate and cisplatin induce severe gastrointestinal complications [30]. Enterocytes are rapidly dividing cells, which make them prone to the cytotoxic

effects of both chemotherapy and radiotherapy. Both treatments are responsible for erosive lesions at various levels of the digestive tract, such as tongue ulceration, mucositis, and esophagitis, that markedly impair food intake. Combined protocols can cause acute and sub-acute enteropathies combining mucosal atrophy, ulcerations and necrosis, leading to severe radiation enterocolitis complicated by fistulas, complete obstruction or peritonitis, and contributing to the poor nutritional status of these patients who subsequently require long-term nutritional support [31]. Technical progress in radiation therapy (high energy, fractioning, dosing and timing) and protective bowel shielding should reduce the incidence of such complications [32].

In summary, the importance of anorexia as a contributing factor in malnutrition and cachexia is not sufficiently recognized. Indeed, it is often a primary factor in weight loss, and increases as the disease progresses. Furthermore, it is compounded by the side-effects of treatments. However, nutrient intake is not always diminished during the course of cancer, and there is no clearcut relationship between the level of food intake and nutritional status, emphasizing the fact that cancer-induced malnutrition involves both systemic and metabolic alterations.

2.2.2. Metabolic disturbances

The widespread disorders associated with cancer, which affect both energy expenditure and the metabolism of protein, fat, carbohydrates, vitamins and trace elements, have been extensively explored in experimental and animal models, as well as in various clinical settings. They are summarized in Table 1. In animal models, studies of tumor metabolism and its effects on overall host metabolism are limited by the fact that, in most models, cachexia occurs only when tumor burden represents $\approx 10\%$, and may be up to 40%, of the animal's weight. This situation contrasts with that seen in clinical practice, where cachexia develops in patients whose tumors represent about 1% of body weight, are sometimes undetectable, and rarely exceed 1 kg. Nevertheless, such tumors can have profound effects on host metabolism. New animal models have recently been developed to study protein metabolism, and may yield results that are more relevant to human metabolism of cancer [33].

The tumor escapes all the normal mechanisms of metabolic control. Most tumor tissue develops whatever the host's nutritional status and maintain a high level of metabolic activity at the expense of the host [34]. Malignant cells have a high degree of anaerobic glycolysis and produce large amounts of lactate. An investigation of amino acid metabolism showed net uptake of amino acids by human tumor tissue (in [22]), suggesting that cachexia is caused by increased metabolic demands by the tumor. In this case, why

Table 1
Metabolic effects of starvation and cancer cachexia

	Starvation	Cancer cachexia
Energy expenditure	Decreased	Variable
<i>Protein metabolism</i>		
Protein turnover	Decreased	Increased
Whole body synthesis	Decreased	Increased
Whole body catabolism	Decreased	Increased
Skeletal muscle synthesis	Decreased	Decreased
Skeletal muscle catabolism	Decreased	Increased
Hepatic protein synthesis	Decreased	Increased (acute phase proteins)
Plasma aminoacidogram	Unchanged	Variable
Nitrogen balance	Negative	Negative
<i>Carbohydrate metabolism</i>		
Glucose turnover	Decreased	Increased
Hepatic gluconeogenesis	Increased	Increased
Cori cycle activity	Unchanged	Increased
Insulin sensitivity	Decreased	Decreased
<i>Lipid metabolism</i>		
Lipolysis	Increased	Increased
Lipogenesis	Unchanged	Variable
Lipoprotein lipase activity	Unchanged	Decreased
Serum FFA level	Unchanged	Increased

does the cancer patient's body respond by reducing nutrient intake, and why is cachexia not readily reversed by adequate fuel provision? Clearly, although the alterations of tumor metabolism associated with appetite loss are two important components of the cachectic syndrome, underlying abnormalities of host metabolism play a major role.

2.2.2.1. Modifications of energy expenditure. There has been major controversy over whether cancer patients have elevated energy expenditure (EE) relative to malnourished non cancer patients. Initial reports suggested that both resting and non resting EE is elevated in cancer patients and contributes to significant weight loss [35–37], but these studies were criticized for using non specific methodologies and heterogeneous groups of cancer patients, and for rarely including matched controls [38,39]. EE must in fact be interpreted as a function of several factors, including the topography, size and spread of the tumor, the patient's nutritional status, and antineoplastic treatments. Studies based on indirect calorimetry have shown no change, or a minimal increase, or even lower EE in cancer patients than in weight-losing non cancer patients or weight-stable cancer patients [40–42]. The normalization of EE after

tumor resection favors the hypothesis that increases in EE are tumor-driven [40]. For a given type of tumor, EE seems to be related to an elevated adrenergic state [43] and/or an active inflammatory process [44]. Hematologic malignancies are not a homogeneous group when evaluated metabolically. Lymphoma patients are similar, in metabolic terms, to healthy volunteers, but patients with myeloproliferative disorders form a distinct group with major abnormalities [45]. Increases in EE are usually attributed to increased activity of the Cori cycle, resulting in wasting futile cycling [46] and accelerated protein turnover, with a failure of normal adaptive mechanisms to starvation. Although the increases in EE associated with cancer are generally small (10–15% in many studies), they can explain the loss of several kilograms of body weight over a period of months.

2.2.2.2. Carbohydrate metabolism. For more than half a century, tumors have been regarded as 'glucose-traps' producing lactates by anaerobic glycolysis. These lactates can be oxidized or recycled into glucose by hepatic and renal neoglucogenesis in the Cori cycle. This energy-wasting ('futile') metabolic pathway, however, seems to play only a minor part in the total energy expenditure of the host. Neoglucogenesis can also start from glycerol and alanine, but the contribution of these substrates appears to be minor. The share of neoglucogenesis in the use of the energy substrates in the cancer patient seems to increase during the course of cancer. It does not correspond to any usual mechanism of homeostatic regulation [47].

The carbohydrate metabolism of the cancer patient is also characterized by glucose intolerance, with a reduction in the sensitivity of peripheral tissues to insulin [48]. The reduction in hepatic sensitivity to insulin, and the lesser insulin secretion by the pancreas in response to feeding, are the two main features in this dysregulation.

2.2.2.3. Lipid metabolism. Increased mobilization of peripheral fat and excessive oxidation of fatty acids are the most consistent metabolic abnormalities in cancer patients [49]. They lead, more or less quickly, to a depletion of lipid stores. The increase in the plasma concentrations of glycerol and free fatty acids (produced by triglyceride hydrolysis), reflects the mobilization of lipid stores. An increase in the activity of lipoprotein lipase, an enzyme required for triglyceride clearance, has been observed in cancer patients. However, using isotopic techniques, Shaw et al. [50] showed that there were no difference in the level of glycerol and free fatty acid metabolism between cancer patients with stable weight and healthy volunteers; only cachectic cancer patients released glycerol and free fatty acids from the adiposities in the circulation more quickly

than normal subjects [50]. In fact, although the increase in endogenous lipolysis contributes to malnutrition in cancer patients, the possible part played by the reduction in lipogenesis has never been correctly evaluated. The reduction in fat mass in cancer patients could be due to anorexia, but also to a primary imbalance between lipolysis and lipogenesis.

2.2.2.4. Protein metabolism. In fasting healthy subjects, muscle amino acids and some visceral proteins are used as precursors for neoglucogenesis. Protein catabolism decreases slowly and functional lean body mass is more or less preserved. This adaptive mechanism seems to be completely absent in cancer patients [51], leading to noticeable protein depletion and, in some patients, spectacular muscle atrophy.

The most frequent protein metabolism alterations in cancer patients include an increase in protein turnover, a reduction in muscle protein synthesis, an increase in inflammatory ('acute phase') hepatic protein synthesis, a constantly negative nitrogen balance and various change in the plasma aminoacidogram profile [52]. The circulating concentrations of amino acids have been extensively studied in cancer patients. No cancer-specific profile has been established [53], although certain changes have been forwarded as potential markers of the extent of malignancy and as a basis for nutritional intervention [54]. In most studies, based on whole body kinetic measurements, total protein turnover was accelerated as a result of increased hepatic protein synthesis coupled to an increase in muscle protein breakdown [15,55]. By contrast, direct measurements of 3-methyl-histidine release from peripheral tissues in weight-losing cancer patients demonstrate reduced protein breakdown compared to healthy individuals; however, protein synthesis is more reduced, leading to a negative net protein balance [56]. Recent studies suggest that muscle proteolysis is largely mediated by ATP-dependent proteases, and especially by a ubiquitine-dependent proteolytic system [57].

A deterioration of the intestinal barrier function has also been described, without significant changes in crypt height or villusities, and could serve as a basis for

new nutritional strategies in cancer patients with combinations of specific nutrients and growth factors. In cachectic states the regional changes in protein metabolism, which lead to marked hypoalbuminemia, might thus be due to a redistribution of peripheral proteins towards the visceral protein synthesis of the host and/or the tumor [58].

2.2.3. Humoral and inflammatory responses in the host-tumor relationship

Many circulating factors have been incriminated in the appetite loss and metabolic disturbances associated with cancer [59]. The precise role of cytokines and other mediators in appetite regulation and in metabolic loss of homeostasis in cancer patients is poorly documented [21,60] (Table 2). An increase in cytokine activity (IL-1, IL-6, gamma-interferon), abnormal eicosanoid production, excessive monocyte and macrophage activation (with TNF production), altered lymphocyte functions, and abnormal IL-2 production have all been described in various animal models and in cancer patients. These acute or chronic disorders are variously associated with one another and with other hormonal disturbances [18], inducing and maintaining a catabolic state. A better knowledge of these mechanisms, which also no doubt play a part in the genesis and persistence of metabolic disturbances, might lead to new therapeutic strategies against cancer cachexia [61,62].

However, it has proven difficult to correlate levels of tumor necrosis factor-alpha and interleukin-6 with cancer cachexia, and the weight loss induced by leukemia-inhibitory factor may be due to its toxicity. Recently, Todorov et al. isolated a peptidoglycan responsible for skeletal muscle catabolism in an animal model of colonic malignancy [63]. The purified peptidoglycan caused intense muscle protein catabolism in vivo [64]. It is present in the urine of cachectic cancer patients but undetectable in healthy subjects, malnourished multiple-trauma patients, and weight-stable cancer patients. The clinical implications of this remain to be determined [65]. Finally, because cytokines regulate circulating leptin levels in humans, it has been hypothesized that leptin could mediate cancer-associated cachexia, but conflicting data were obtained. Thus, further studies are needed to elucidate the exact role of leptin in this context [66].

Table 2
Potential mediators of cancer cachexia

<i>Cytokines</i>	
TNF- α	(Beutler and Cerami Nature, 1986)
Interleukin-1	(Strassman JCI, 1992)
Interleukin-6	(Tsujiyama JCI, 1996)
Interferon- γ	(Matthys Int J Cancer, 1991)
<i>Leukemia-inhibitory factor</i>	(Mori Cancer Res, 1991)
<i>Neuropeptide Y</i>	(Chance Ann Surg, 1995)
<i>Proteoglycan 24K</i>	(Todorov Nature, 1996)

2.3. Influence of nutritional support on tumor growth

Ideally, nutritional support should benefit the patient without feeding the tumor or, better, while starving the tumor. Drastic restriction of the amount of protein in food inhibits tumor growth in most animal models, but limitation of protein intake is also detrimental to a malnourished host. The stimulation of tumor growth by enteral or parenteral nutrition has never been clearly

demonstrated in humans [67]. In vivo evaluation of tumor growth is technically difficult, and most studies rely on data gathered in very small populations. Several studies have involved patients with head and neck cancer or gastrointestinal tumors who were on enteral or parenteral nutrition with various amounts of calories and protein, and the results favor a lack of change in cancer cell volume under nutritional support (Table 3).

Modulation of tumor growth by nutritional manipulation is a nice idea. Administration of carbohydrates that cannot be metabolized by tumor cells is one approach: for example, replacing halogenated carbohydrates, 2-deoxyglucose or pentoses with dextrose. Lipids, especially medium-chain triglycerides and omega-3 fatty acids, are weakly metabolized by cancer cells: a regimen containing 90% of non protein calories in the form of lipids (MCT and LCT mixtures) was well tolerated and was associated with stable patient weight and tumor volume for 5 months [68]. Other interventions, such as blocking the neoglucogenesis pathway by the use of hydrazine-sulfate have failed to improve clinical outcome [69], but these negative results may be biased because patients receiving hydrazine-sulfate were left to a free (glucose-rich) diet. The impact of new pharmaconutrients, such as arginine, glutamine and omega-3 fatty acids, on immune status is dealt with below.

2.4. Nutritional assessment of the cancer patient

The purpose of the nutritional assessment is to identify the subset(s) of patient who might benefit from dietary counseling by a dietitian, as well as to determine the severity and cause(s) of malnutrition, to identify patients at risk of complications of chemotherapy, radiation therapy or surgery, and to assess the efficacy of nutritional support. The nutritional parameters and indices should have sufficient sensitivity and specificity to reliably reflect the course of malnutrition during the disease, from baseline at diagnosis to remission or cure, through each specific therapeutic intervention. Nutritional assessment must be combined with a careful evaluation of performance status and quality of life, so that nutritional management is correctly adapted to the patient's real needs and entails a minimum of constraints [1,70].

2.4.1. A 'rough' nutritional assessment?

A standardized tool is mandatory for the follow-up of these patients. It should be easy to use, validated in different countries and institutions, and accepted by the medical and nursing staff [71]. The subjective global assessment (SGA) popularized by the Toronto group [72] and adapted to cancer patients by Ottery [73], only estimates the degree of nutritional depletion and identifies patients at risk of malnutrition. The SGA corre-

lates closely with objective parameters such as anthropometric measurements and serum protein levels, and accurately predicts clinical outcome after major surgery, with 82% sensitivity and 72% specificity [74]. Inter-observer variability and reproducibility are satisfactory after a training period of a few days. Other nutritional indexes or scores have been proposed for the triage of patients who need simple counselling from those who require an immediate nutritional support. The recent nutritional risk score (NRS) developed by Reilly et al. is a 5-item questionnaire validated for adults and children, which involves a dynamic appreciation of weight loss, body mass index, appetite, ability to eat spontaneously, and intercurrent diseases [75]. The NRS score classifies patients as minimally, moderately or severely malnourished, and compares favorably with clinical judgment and other nutritional risk indices. In addition, this score is fairly reproducible within specialized teams and among different health professions in the field of nutrition (dietitians, nurses and nutritionists). It was recently used by a French team to detect malnourished patients needing nutritional management in a teaching hospital [76]. A 9-item questionnaire has been developed by an Icelandic team, and showed an excellent correlation with objective data when used to identify malnourished patients and patients at risk of malnutrition in a general hospital [77]. All these questionnaires are non invasive, cost-free, time-sparing, and easy to use, and can accurately identify patients who are malnourished or at risk of malnutrition. We feel they should be part of the global initial assessment of cancer patients. After this first rough nutritional assessment, a subset of patients at risk can undergo a thorough evaluation to guide nutritional management.

2.4.2. Accurate assessment of candidates for nutritional support

Several variables can be combined to complete the information provided by the subjective assessment, such as anthropometric measurements, serum protein levels and impedancemetry.

Recent weight change is a good indicator of a nutritional deficit and can be used to classify patients into nutritional categories of normality, or mild or severe malnutrition (Table 4). A weight loss of 10% or more within the previous 6 months, or 5% or more within the previous month, indicates alarming malnutrition and correlates well with clinical outcome. Subscapular and triceps skinfold, and mid-arm muscle circumference and area, provide an estimate of body fat and fat free mass [78], but values may vary with hydration status, should be matched with normal values in each country [79], and have not been validated in cancer patients. In addition, inter-observer reproducibility is poor, even after several weeks of special training [80].

Table 3
Total parenteral nutrition and tumor growth in humans^a

Authors	Ota et al. (1984)	Baron et al. (1986)	Franchi et al. (1991)	Westin et al. (1991)	Dionigi et al. (1991)	Heys et al. (1991)	Franck et al. (1992)
<i>15 Number of cases</i>	25	8	18	19	7?	9	10
<i>TPN characteristics</i>							
Kcal/kg/day	40–60	59	25	35	48	25	?
% Glucose	60–100	90?	20–100	55	?	40	?
% Lipids	40–0	?	80–0	45	?	60	?
gAA/kg/day	2–3	1.9	1.5	1.5	2.3	1.25	?
<i>Duration of TPN</i>	11	9	15	5–7	18	1	7
<i>Tumor</i>	Mixed	Head/neck	Digestive Tract	Head/neck	Stomach	Rectum	Head/neck
<i>Tumor growth detection</i>	RBC polymine	% Hyperploid cells	³ H-TdR	ODC, Ki-67 % aneuploid	³ H-TdR % aneuploid	Protein synthesis	BrdU
<i>Tumor growth</i>	+	+	NC	NC	NC	+	+
<i>Control group/Randomized</i>	Yes/no	Yes/no	Yes/no	No	Yes/yes	Yes	No

^a RBC, red blood cells; ³H-TRD, ³H-thymidine labelling index; ODC, ornithine decarboxylate activity; Ki-67, immunohistological chemical reactivity with monoclonal antibody Ki-67; BrdU, bromodeoxyuridine labelling index; NC, no charge; +, increase; ?, data not available. Adapted from Cozzaglio et al. [173] and Bozzetti et al [67].

Table 4
Classification of nutritional status as a function of the percentage and rate of weight loss

Time	Mild Malnutrition	Severe Malnutrition
	Weight loss (% of usual weight)	
1 week	1 to 2	>2
1 month	5	>5
3 months	7.5	>7.5
6 months	10	>10

Plasma concentrations of so-called anabolic proteins such as albumin, transferrin and transthyretin are frequently used to estimate nutritional status and to monitor the efficacy of nutritional support [81]. However, many clinical conditions encountered in cancer patients may interfere with these measurements, such as hyperhydration, nephrotic syndrome and hepatocellular insufficiency. Moreover, transferrin and transthyretin have short half-lives (merely reflecting recent nutritional changes), and their assay is costly compared to the little information they provide. Transthyretin may be used as a marker of nutritional recovery during nutritional support [82]. Albumin has a half-life of 20 days, so that a decrease in its concentration is related to long periods of nutritional deficit, assuming that hydration is stable. A strong relationship has been found between low albumin concentrations and poor outcome in cancer patients [71]. Nutritional proteins have been incorporated in various and complex nutritional risk indexes [83]. Most of these indexes are of limited value, except in the perioperative period, mainly because they often include immunological parameters, such as the lymphocyte count or delayed hypersensitivity testing, that are modified by immunosuppression independently of malnutrition. New biological measurements, especially the serum concentration of IGF-1, have shown some promise in complex clinical settings such as coexisting malnutrition, sepsis and renal failure: IGF-1 levels remain fairly well correlated with nutritional status and nitrogen balance [84]. We do not recommend this expensive assay until it is validated in cancer patients.

New techniques to estimate the functional consequences of malnutrition and body composition deserve attention. Because changes in muscle function occur before changes in protein concentrations, hand-grip strength has been proposed as an indicator of nutritional status and has been shown to correlate with postoperative complications [85]. Impedancemetry is currently making a breakthrough thanks to its feasibility and reduced cost. It has been validated in intensive care patients (mono-frequency or bi-frequency mode), with a good correlation with isotopic dilution [86]. It can be used with acceptable feasibility and discrimination between malnourished and normonourished pa-

tients, even in case of edema of nutritional or other causes [87,88]. Bi- or multifrequency impedancemetry can thus be used in oncologic practice to evaluate nutritional status and follow the effectiveness of nutritional support, provided the operators are well trained and highly motivated.

Data on the identification of patients at risk and on serial nutritional assessment of cancer and hematology patients can be used to build a decision tree, in which a specialized nutrition team must be integrated, like that proposed by Ottery [89] (Fig. 2).

3. How to preserve oral intake during the course of cancer and cancer treatments?

3.1. Alteration of taste and smell during the course of cancer

Modifications of taste and smell are frequent among patients with metastatic cancer and those receiving radio-chemotherapy. These alterations of perception can be related to direct injury of the papillary mucosa. Mucositis frequently occurs during combined chemotherapy, radiotherapy for head and neck cancers, oropharyngeal or esophageal candidiasis, and during deficiencies in water-soluble vitamins (B2, B3, folates, B12, etc.). Taste and smell can be deteriorated by certain cytokines (IL-1 β and TNF- α), which directly block olfactory and gustative neurotransmission. The plasma concentration of TNF- α may correlate with gustative alteration, particularly for bitter taste. Certain drugs, including most antimetabolic agents and particularly cyclophosphamide [90], some antibiotics (including metronidazole), and certain deficiencies in trace elements like zinc and nickel, lead to dysgeusias or hypogeusias. Xerostomia, which is either drug-induced (imipraminics, H1-antihistamines, etc.) or secondary to radiotherapy, leads to deterioration of taste. Finally, poor oral hygiene can be responsible for unpleasant taste perceptions.

A third of cancer patients have a reduction in their perception of sweet taste. Less frequent are aversions for or reductions in the taste of bitter, sour or salt. A metallic taste is described during chemotherapies containing cyclophosphamide, antibiotic treatments with imidazoles, and zinc deficiency. Supplementation with zinc sulfate can improve these symptoms during head and neck irradiation [91]. An aversion for new tastes is particularly frequent during chemotherapy, possibly because of the Pavlovian character of taste acquisition. Moreover, a dislike for meat and all kinds of food with strong odors, either naturally or after cooking (meat, fish, cabbage, etc.), is common.

New antiemetics may have a beneficial action on taste disorders, particularly setrons and corticosteroids.

But the most effective measure is dietary adaptation to these taste alterations, with exclusion of all foods deemed unpleasant, and reinforcement of sweet and salt according to sensitivity.

The outcome of these taste disorders follows that of the disease. In the particular case of allogenic marrow transplantation, complete recovery was noted in 80% of cases at 1 year and 100% of cases at 5 years [92]. During chemotherapy these alterations disappear within a few days to a few weeks after the last cycle.

3.2. Place of the dietitian in the management of cancer: simple nutritional counseling or thorough management?

Simple dietary recommendations can significantly increase oral protein-energy intake by cancer patients in the course of treatment or in palliative care, even if this does not appear to have a beneficial effect on weight or albuminemia [93]. In a recent study, Bachmann et al. underlined the poor dietary follow-up in a major cancer center in France, despite its reputation for high-quality nutritional management [94]. Whereas 60% of the patients were regarded as malnourished, only 27% had a dietary consultation during their stay. Thirty of the 98 patients studied had received dietary advice during a

previous hospitalization, but only a third of them were reassessed. A specialized consultation by a dietitian is thus required in many cases. The dietitian should intervene as soon as possible after the diagnosis of cancer. His or her role is to calculate food consumption, evaluate nutritional status, and anticipate the nutritional risks of both the cancer and its treatment. The aims are to maintain adequate nutrition in normonourished patients and to minimize the risk of cachexia in malnourished patients. These objectives must take account the tumor type, its extension, the planned treatments, and also the socio-economic context and the patient's former lifestyle. Regular monitoring must be conducted both during hospitalization and between hospitalizations. In close liaison with oncologists, surgeons, anesthesiologists, and members of the nutritional team (if there is one...), the dietitian evaluates the nutritional status of consulting and hospitalized patients, evaluates their oral intake, and gives advice aimed at maintaining oral nutrition (Table 5). In addition, he or she proposes oral supplements, assesses the effectiveness of dietary advice, and should alert the physician to the need for enteral or parenteral support. Moreover, dietitians should take part in training staff on nutritional management and support.

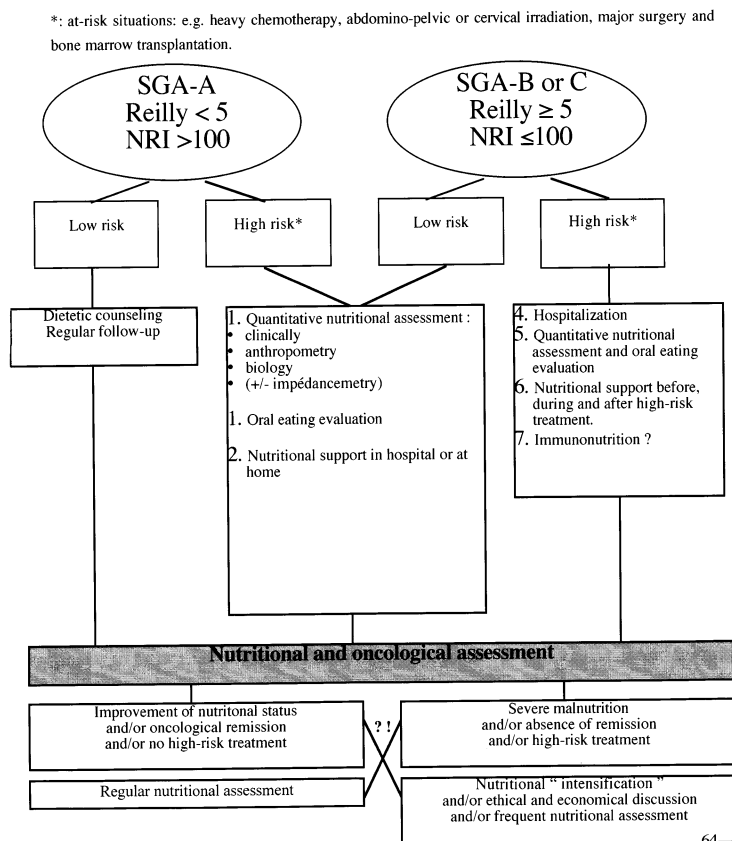


Fig. 2. Decision tree for nutritional intervention based on a risk assessment and nutritional status (after Ottery [88]). *: At-risk situations: e.g. heavy chemotherapy, abdomino-pelvic or cervical irradiation, major surgery and bone marrow transplantation.

Table 5
Dietary counselling for the maintenance of oral nutrition

<i>Schedule of meals</i>	Fixed Fractionated (6 to 8 meals per day)
<i>Ambiance of meals</i>	Quiet Slowly Sitting Accompanied Suppression of strong smells (cooking, smoking, etc.)
<i>Quality of meals</i>	Small quantities Avoid drinking during meals 'Rich' food: honey, sugar, butter, eggs, cheese, etc. Modulate restrictive regimens (diabetes, hypercholesterolemia, nephrotic syndrome, edema, etc.) Modify the texture of meals according to the intensity of the symptoms (minced, mixed or liquid) Avoid hot and spicy food
<i>Around meals</i>	No naps! Maintain some level of physical activity Take medications in the middle or at the end of meals

3.3. Oral nutritive supplements or artificial nutrition?

Oral nutritive supplements (ONS) are indicated when spontaneous oral protein-calorie intake is insufficient despite observance of dietary advice. A recent meta-analysis selected five randomized controlled studies comparing supplemented oral nutrition to a placebo or no supplementation [95]. Weight gain was greater and survival better in the supplemented group, but apparent benefits were not evident if trials with less robust methodology were excluded, and there were insufficient data in trials which meet strict methodological criteria to be certain if mortality was reduced.

Many oral supplements are available. They vary according to the type of proteins, energy density, osmolarity, lactose, gluten and fiber content, commercial formulation (liquid, powder, cream, soup, etc.), and the range of flavors (44). ONS are usually served cold to attenuate their taste, but they can be heated according to the patient's preferences. The flavor can be modified by adding industrial perfumes, including alcoholic additives. Observance of ONS consumption requires a careful explanation of the prescription to both the patient and close relatives. The daily cost of oral nutritive supplementation ranges between 9 and 20 Euros (or \$...) according to the number of units prescribed and the type of product. Unfortunately, in France only RENUTRYL[®] is completely reimbursed by the social security system, because oral supplementation is still considered as a comfort measure and not as a medica-

tion. The cost-benefit ratio of oral supplementation remains to be evaluated.

The clinical benefit of oral supplementation in cancer patients could be increased by enrichment with immunonutrients. In one study, preoperative supplementation of oral nutrition with arginine, nucleotides and n-3 fatty acids led to a significant postoperative improvement in immune defenses [96], but this advantage was not found by another team [97].

3.4. Orexigens: indications and results

In the past few years oncologists have better accepted the fact that is unlikely that all patients will respond to a given anticancer treatment, and there has been a shift from traditional oncological outcomes to symptomatic outcomes such as functional status and quality of life [98]. This is the main reason for the recent development of symptomatic treatments for the management of anorexia [99].

Orexigens such as corticosteroids and pentoxifylline are given to increase appetite by reducing the action of cytokines at the level of both monocytes and the central nervous system. Other approaches include a reduction in serotonergic neurotransmission with the use of cyproheptadine, inhibition of gluconeogenesis by hydrazine sulfate, attenuation of nausea and vomiting with metoclopramide, mixed pathways for 5-HT₃ receptor antagonists, or remain dubious in the case of progestational drugs such as megestrol acetate [100]. About 30 randomized studies focus primarily on corticosteroids and megestrol acetate. On the whole, they showed a significant positive effect on appetite and non fluid weight gain with megestrol acetate [69]. The side effects of corticosteroids (neuropsychiatric disorders, edema, etc.) and megestrol (deep venous thrombosis, vaginal bleeding, edema, etc.) were seen in 10 to 30% of patients in these studies. In addition, the most effective corticosteroid and optimal dose remain to be determined, and the effect of steroids seems to wane after 1 or 2 months of treatment. The recommended megestrol dose (800 mg/day) requires the ingestion of five tablets at a daily cost of 15 Euros. Recently, Bruera et al. obtained interesting results with a reduced dose of megestrol acetate (160 mg 3 times daily) in 84 patients with advanced cancer: in the 43 assessable patients, treatment rapidly and significantly improved appetite, activity and well-being (but not quality of life), and these results could not be explained by a change in nutritional status [101].

As regards other compounds such as orexigens, no firm recommendations can be made because of the few available studies or because of the product is not available in some European countries (e.g. dronabinol). Hydrazine sulfate, pentoxifylline and cyproheptadine showed some promise, but all recent randomized stud-

ies are disappointing. Some emerging drugs, such as thalidomide, melatonin and clenbuterol (see below) seem to warrant further clinical research, but none of them can yet be recommended in clinical practice [98]. Certain drug combinations have been proposed, such as megestrol acetate plus ibuprofen (a non steroidal anti-inflammatory drug). When compared to megestrol plus a placebo, this combination led to significant weight gain after 12 weeks of treatment and, more importantly, to an improvement in the quality of life of gastrointestinal cancer patients [102]. The risk of such combinations is an increase in side effects.

Improvement of appetite in cancer patients calls for improvement of other symptoms such as pain, mucositis and depression, and the side effects of oncologic treatments. Opiates can induce or worsen constipation, which often becomes complicated by food intolerance. Some antidepressants such as fluoxetine and imipramines can lead to a marked reduction in nutrient intake. Finally, it is often difficult to assess the degree of appetite loss in the hospital setting. Apart from the individual appreciation of the gustative qualities of hospital meals, the 'iatrogenic fasting state' caused by the various programmed procedures and treatments of cancer does not lend itself to regular, sustained nutrition.

Table 6
Recommended calorie and protein intake by cancer patients

<i>Calorie requirements</i>	25-35 Kcal/kg/day Glucose \leq 5 g/kg/day Lipids (LCT or LCT+MCT) 0.5–1 g/kg/day 24 h continuous perfusion is better tolerated
<i>Protein requirements</i>	0.25-0.35 gN/kg/day Standard amino acid solutions (PN) or whole protein diets (EN)

Table 7
Recommended micronutrient intake by cancer patients

<i>Vitamins</i>	Balanced standard solutions Vitamin K (\geq 10 mg/day) Vitamins B1 and B6 ($>$ 100 mg/day) Antioxidants (vitamins A, C and E)
<i>Trace elements</i>	Complete standard solutions Zn (15–20 mg/day) Se (120 μ g/day)
<i>Electrolytes</i>	Daily adaptation (Na ⁺ , K ⁺ , Ca ⁺⁺) P ($>$ 16 mMol/day) Mg ($>$ 200 mg/day)

4. Quantitative and qualitative aspects of nutritional regimens

4.1. Calorie and protein requirements (Table 6)

The nitrogen and energy intake of malnourished cancer patients must take into account not only the patient's requirements but also those of the 'tumor trap'.

4.1.1. Calorie supply

Resting energy expenditure (REE) in normonourished cancer patients subject to therapeutic stress ranges between 20 and 25 kcal/kg of usual weight/day [103], and non protein calorie amounts ranging between 100 and 200% of the calculated REE preserve the nutritional status of these critically ill patients. Calorie intakes have to be corrected for a 'stress factor' and adapted to the intensity of physical activity. The optimal proportion of lipids and carbohydrates in oral nutritional support is highly controversial. If oral feeding is preserved, no restrictions must normally be imposed except in the case of obvious metabolic disorders (diabetes for example).

For patients who are fed exclusively by artificial nutrition, no definite recommendations can be made despite the abundant literature devoted to nutritional support of cancer patients. The literature suggests that the desirable daily calorie intake required to improve lean body mass and to increase hepatic production of 'anabolic' proteins ranges between 25 and 35 kcal/kg. However, other authors have obtained interesting results in terms of protein synthesis by increasing the energy supply to 200% of the REE, i.e. \approx 50 Kcal/kg/day, while maintaining a calorie-nitrogen ratio of 150 [36]. These data are valid for both enteral and parenteral nutrition. A balanced contribution of glucose and lipids, or slightly more glucose than fat (60% glucose, 40% fat) is generally recommended. Needless to say, the nutrition must be supplemented, especially in the case of parenteral nutrition, with electrolytes, trace elements and vitamins [104] (Table 7).

4.1.2. Is there a gold standard for nitrogen supply?

It is not certain whether the changes in protein metabolism induced by cancer are influenced by the specific admixture of PN or EN. The main goal of the nitrogen supply is therefore to limit muscle catabolism, while at the same time maintaining an adequate nutrient supply to the liver, particularly in essential AA, so that the synthesis of certain proteins, especially those involved in immune defenses, can be maintained.

Fine adjustments of protein supply can be made on the basis of nitrogen balance, using the following formula [105]:

nitrogen balance = (dietary protein intake. 6.25)

$$- \text{TUN}_a - 5 \text{ mg N/kg}_b$$

$$- 12 \text{ mg N/kg}_c$$

where 'a' represents the total urinary nitrogen excreted over 24 h, 'b' is the estimated occult nitrogen losses (add any measurable losses from other sources) and 'c' is the estimated nitrogen losses from the gastrointestinal tract

An estimate of total urinary nitrogen losses can be obtained by using various formulas according to the clinical and metabolic setting, but the accuracy of such estimations has been questioned [106].

It must be stressed that equilibrium or positivity of the nitrogen balance is not a goal in itself in this setting, and that such a goal can even be detrimental if it leads to an accumulation of urea [107]. Correctly adapted supplies can, however, reduce myofibrillar breakdown [108] and, above all, stimulate protein synthesis, generally without upsetting the balance in hypercatabolic cancer patients [109].

In practice, the optimal nitrogen supply for cancer patients cannot be determined at present. A nitrogen supply of 200–300 mg/kg/day, i.e. 1.2–2 g of protein/kg/day, appears to be sufficient. Above this value, opinions diverge. An increase in nitrogen supply to 400 mg/kg/day does not necessarily improve the nitrogen balance or largely reduce net protein breakdown, and leads to a significant increase in EE [109]. The calorie/nitrogen ratio (Cal/N = nonprotein calories/gN) corresponding to high protein supplies is no longer 150, as in conventional nutrition, but 100–120 or even less. In a randomized study of BMT recipients with severe hypercatabolism, we found that for the same calorie input (REE \times 1.7), only a Cal/N ratio of 100 clearly rendered positive the cumulative nitrogen balance over the period of aplasia, but at the price of a significant increase in protein turnover, with no increase in blood urea concentrations [3].

Despite experimental evidence that branched-chain amino acids (BCAA) have anabolic effects on muscle protein metabolism, their benefit in the clinical setting, including oncology, has not been established [55]. Administration of BCAA-enriched parenteral nutrition to preoperative colon cancer patients resulted in a slightly smaller increase in protein synthesis in comparison to conventional TPN, but this reduced stimulation was observed in both the host muscle and the tumor [110]. The available data do not support a specific advantage of nutrition with BCAA in tumor-bearing patients.

4.2. Rationale for the use of lipid emulsions in malnourished cancer patients

Many studies have shown the equivalence of exclu-

sive carbohydrate calorie intake and mixed carbohydrate-lipid calorie intake when the lipid contribution oscillates between 30 and 40% of the non protein calories [67]. When binary nutrition containing glucose plus amino acids was compared with ternary nutrition (glucose + fat + amino acids) balanced in carbohydrate and lipid energy supply, no difference was detected after 3 weeks in anthropometric parameters or biological markers such as blood concentrations of albumin, transthyretin and RBP, nitrogen balance and protein turnover. In surgical oncology a predominantly fat regimen (75% of calorie intake in the form of a 20% LCT lipid emulsion) did not decrease the nitrogen-sparing effect (as assessed by the nitrogen balance) or modifications of anabolic proteins. Although total body nitrogen and lean body mass were significantly decreased compared to total glucose nutrition, this discrete fall in protein repletion had no consequences in terms of inflammatory or immune parameters, clinical outcome (duration of hospitalization) or the incidence of infectious complications (in [111]).

Many experimental data and rare clinical studies suggest that lipid emulsions could deteriorate the immune response and thus increase the risk of infection in cancer patients [112]. Some investigators have reported that administration of conventional lipid emulsions (LCT) led to no difference between cancer patients and controls as regards humoral immune parameters (IgG, IgM, C3c, chemotaxis and phagocytosis by neutrophils) and cellular immune responses (numbers and functions of B and T lymphocytes) [113,114]. One study even suggested that lymphocyte functions, evaluated by their mitogenic response, were improved. In all available studies, 1–3 weeks of parenteral nutrition at an infusion rate of 1.4 ml/min with 20% lipid emulsions had no impact on the incidence of infections [115]. During short- or medium-term parenteral nutrition of malnourished cancer patients, glucose and mixed-energy regimens are thus probably equivalent in terms of nitrogen metabolism, immune responses and infectious risks [116].

The value of medium-chain triglycerides (MCT) for partial or total replacement of LCT is controversial, except perhaps for patients with liver failure, who have a gradual loss of apolipoprotein C, hepatic lipoprotein-lipase and carnitine synthesis. There is no clinically significant difference between MCT and LCT as regards blood gas values in patients on mechanical ventilation, or coagulation parameters when nutrition lasts > 1 month [117]. MCT can also be used safely for longer periods, especially for home parenteral nutrition in children [118], but there are no data on cancer patients.

The effectiveness of cyclosporin in reducing the risk of GVHD after bone marrow transplantation is well

Table 8
Effects of PN and EN on nutritional parameters (from Bozzetti F et al [67])

Parameter	PN	EN
<i>Weight</i>	Increased	Increased
<i>Fat body mass</i>	Increased	Increased
<i>Muscle mass</i>	Unchanged	Unchanged
<i>Lean body mass</i>		
Nitrogen balance	Improved	Improved
Total body nitrogen	Unchanged or increased	Unchanged?
<i>Serum proteins</i>		
Albumin	Unchanged	Unchanged or decreased
Transthyretin	Unchanged or increased	Unchanged or increased
<i>Protein turnover</i>	Unchanged or increased	Unchanged

Table 9
Effects of PN and EN on immunological parameters^a

Parameter	PN	EN
<i>Humoral immune response</i>		
IgG, IgA, IgM	Unchanged	Unchanged
C3, C4	Unchanged	Improved
<i>Immune cell response</i>		
Neutrophils	Unchanged	
Lymphocytes	Unchanged	Unchanged or improved
Chemotactism/Phagocytosis	Unchanged	

^a From Bozzetti et al. [67].

established. However, cyclosporin administration is associated with alterations of fat metabolism, particularly a rise in the blood concentrations of cholesterol and triglycerides: the median peak of plasma triglycerides reaches 35 mg/l in 60% of patients [119]. These disturbances of fat metabolism occur independently of other risk factors, such as hyperglycemia, parenteral nutrition, and administration of corticosteroids or estrogens. The value of MCT administration was thus tested during BMT; there was an improvement in nitrogen sparing and a reduction in hepatic toxicity (unpublished personal data), but these results require confirmation.

We have already seen that the risk of stimulating tumor growth by nutritional support is highly controversial. Schematically, any effect would be primarily related to the nitrogen component of the nutrition. Well-designed controlled studies in animals indeed showed that the risk was identical with a total glucose regimen, a mixed energy supply with LCT or with a mix of MCT-LCT emulsions. It is noteworthy that the effect on the size of visceral metastases was different from that on the primary tumor: stimulation was

greater when the fat contribution was provided by LCT, stable with exclusive glucose calorie intake, and the MCT-TCL mixture seemed to reduce the size of metastases [120]. This result needs to be confirmed. Some relatively old studies suggested that the type of lipid could modulate tumor growth, and that this effect would be partially related to prostaglandin metabolism. Based on this assumption, the effect of omega-3 polyunsaturated fatty acids (PUFAs) was evaluated in animal models: a 40% calorie contribution from fish oil reduced tumor growth in comparison with the same lipid contribution in the form of vegetable oil [121]. The results were identical when fish oil was replaced by structured lipids.

In conclusion, it should be kept in mind that data on the value and/or risks of lipid emulsions (or the lipid content of diets) in cancer patients are scarce and difficult to interpret. The type of nutritional support, its duration, its mode of administration, and the histological types of tumor differed between available studies. Moreover, few studies were specifically devoted to the individual effects of the glucose or fat content on the patients' nutritional status. These differences can easily lead to hasty, inappropriate and unnecessarily expensive conclusions!

4.3. Metabolic, immune and general effects of enteral and parenteral nutrition (Tables 8 and 9)

Correction of the metabolic alterations of malnourished cancer patients by means of artificial nutrition is the major target. Beneficial effects are apparent when truly malnourished cancer patients are compared with matched control groups, between and during periods of chemotherapy and/or radiotherapy [122]. The goal is to replenish active muscle and visceral cell mass, but often (as in critically ill hypermetabolic patients) the weight gain preferentially affects the fluid and fat compartments at the expense of active lean body mass [123]. Studies evaluating the improvement of non fat mass by measuring of total potassium or total body nitrogen in response to nutritional support [67]. Artificial nutrition does not appear to markedly modify protein turnover, and can even lead to a significant reduction in both protein synthesis and catabolism. In addition, EN and PN do not always increase blood levels of nutritional markers of anabolism, such as albumin, transthyretin, transferrin and cholinesterase, and their effects on humoral and cellular immunity during specific treatments are difficult to interpret (see below).

In summary, artificial nutrition makes it possible to limit the nutritional deterioration of cancer patients and to improve some metabolic and nutritional indices, depending on the duration of nutritional support, the

biological aggressiveness of the tumor, and on the efficacy of concomitant anticancer therapy. It must be emphasized that maintenance of nutritional status is important, as the absence of nutritional management condemns cancer patients to chronic cachexia. For this reason, improved general behavior, well-being and comfort, and especially resumption of even limited activity, are the best clinical evidence of effective artificial nutrition in cancer [1]. The nutritional response is limited and is always lower than that observed in malnourished non cancer patients receiving equivalent artificial nutrition [124].

4.4. Data comparing enteral and parenteral nutrition

It is beyond the scope of this article to examine the technical aspects of EN and PN. Readers interested in this field will find all the useful information in textbooks, recommendations [125], and several recent reviews [104,126,127]. The two techniques are similar in terms of the improvement in nutritional parameters, such as body weight, fat mass, nitrogen balance and body total potassium, and immune status. The results are probably dependent on the duration and timing of nutritional support, the type and growth rate of the tumor, and the efficacy of concomitant anticancer treat-

ment [67]. Accordingly, one or other of these two methods can have advantages in certain circumstances: in the rare controlled studies comparing EN and PN, only PN significantly improved the nitrogen balance and elementary balances of potassium, magnesium, phosphorus and chloride, whereas only EN appeared to improve immune responses. The observed differences are marginal, and the slight advantages of PN are offset by the intravenous approach, EN always being preferable for cancer patients with a (relatively) intact digestive tract.

Finally, the choice of nutritional method must take account of the tumor site, the potential nutritional consequences of carcinolytic treatments, the existence of a digestive fistula and above all of an ileus—the only absolute contraindication for EN. Enteral nutrition should always be privileged, because PN is more expensive, short-circuits the digestive tract and the entero-insular axis, leads to a reduction in the height of the villi and a decrease in the activity of brush-border enzymes [128], thus potentially facilitating intestinal bacterial translocation [129]. In addition, PN is a source of catheter-related infections, and requires closer monitoring than EN. However, many of the advantages of EN have recently been called into question [130]. In practice, even if the two methods are complementary and decision to use one or/and other (Fig. 3) will depend on the expertise, experience and training of the dietary, medical and nursing staff, never forget that ‘if the gut works, use it!’.

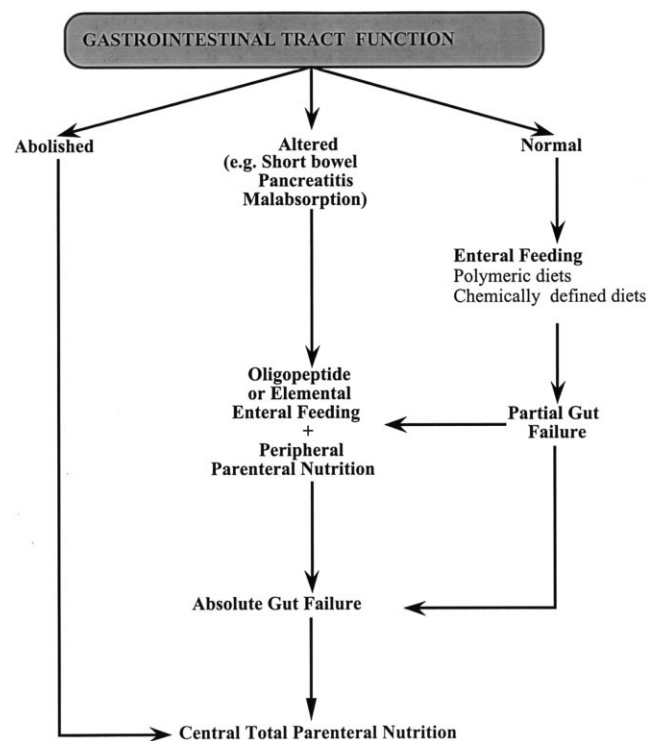


Fig. 3. Decision tree for selecting the type of nutritional support in cancer patients. Example of a decision tree for selecting the type of nutritional support. It must be kept in mind that at least a part of the nutrition can be delivered by the enteral route in about 75% of the cases.

5. When to prescribe nutritional support?

5.1. Perioperative period

Malnourished patients undergoing surgery, mainly for gastrointestinal tumors, are at a higher risk of morbidity and mortality. The essential precondition for perioperative nutrition in oncology remains the nutritional assessment, which of course should be done during the surgery or the anesthetic outpatient clinic. Simple tools such as the SGA and Reilly scores can readily be used during consultations, and will show whether a more complete evaluation or nutritional support is required [131]. As malnutrition predisposes the patient to an increased risk of postoperative complications, can it be reversed by nutritional support? This is a simplistic view, because in many patients malnutrition due to a devastating tumoral process can be stopped only by immediate surgery: in other words, the most important thing is not that patients are cachectic, but that they have a tumor which makes them cachectic! Thus, nutritional support should not be allowed to delay urgent surgery. We and others [132,133] have shown that nutritional indices are often better markers of

spreading, non resectable tumors than of nutritional status.

A number of studies have shown that nutritional support has beneficial metabolic effects, reduces the risk of infectious and non infectious morbidity, and reduces mortality (e.g. [134,135]). However, conflicting results have been reported, owing to serious methodological flaws such as variations in nutritional status before surgery, small group sizes with a large type II error, inadequate randomization, use of unmatched control groups, and inadequate nutrition [136].

The French [137] and North-American [138] consensus conferences held respectively in 1995 and 1997 pointed out that most studies on perioperative nutrition in adults concerned cancer patients, especially gastrointestinal cancer patients. The conclusions of these conferences naturally apply to oncologic surgery. The American conference in 1997 reexamined 33 randomized controlled trials concerning 2500 patients, of which 17 exclusively concerned cancer patients. It concluded, with a high level of evidence (A), on the utility of 7- to 10-day preoperative parenteral nutrition in malnourished gastrointestinal cancer patients, and that these patients should continue with nutritional support postoperatively for at least 5 days. It was suggested that severely malnourished patients respond favorably to preoperative nutrition, e.g. by a rise in serum albumin values and a loss in body weight (contraction of the expanded extracellular fluid compartment) to become good candidates for surgery; this can lead to nutritional support for up to 6 weeks [139]. This preoperative nutrition might reduce by 10% the rate of postoperative complications. Preoperative parenteral nutrition was not recommended in other cases, as it could increase the risk of complications by 10% (including catheter-related infections). In addition, it was suggested that postoperative PN be given to patients who could not resume about 60% of their calculated nutritional intake within 5 days following the operation. All these recommendations must be applied while respecting recommendations on protein-calorie needs.

With regard to enteral nutrition (EN), two studies on preoperative EN and four studies on postoperative EN failed to provide definitive conclusions on cancer patients. However, the small bowel recovers its ability to absorb nutrients almost immediately following surgery, even in the absence of peristalsis. In abdominal surgery the creation of a feeding jejunostomy seems appropriate to ensure nutrient delivery, avoiding the inconvenience and cost of PN [140]. It seems that oligopeptide diets are more efficient than whole-protein diets on amino acid kinetics during early enteral feeding after surgery [141]. However, no significant differences in efficacy were documented between PN and EN in the postoperative period [142].

To reduce postoperative morbidity, perioperative nutrition must thus ensure sufficient protein-calorie intake before and after surgery, for as long as the patient is not nutritionally autonomous. Supplementation should be given, when feasible, by the oral route rather than by nasogastric feeding, and by peripheral rather than by central lines when the gut is dysfunctional. It is ideally carried out at home, to reduce its cost and to improve psychosocial tolerability. A large number of surgical cancer patients have a central venous line (catheter or implanted port) for prolonged treatments, and hospitalization of very sick and severely malnourished patients is required to monitor their nutrition and conduct safely preoperative investigations.

Perioperative enteral or parenteral nutrition could be made more efficient by the use of immunonutrients (see below). Braga et al. recently confirmed the clinical value of oral and enteral supplementation with arginine, n-3 fatty acids and ribonucleotides when EN was administered for 1 week before and 1 week after major surgery for gastric, colo-rectal or pancreatic adenocarcinoma [143]. There was a significant difference in favor of the supplemented group in terms of overall complications, infectious complications and the duration of hospital stay. These data are in agreement with a recent meta-analysis of 6 studies (including 2 studies from the Milan team) of surgical cancer patients who received a postoperative diet supplemented with arginine, n-3 fatty acids and RNA [144]. The results of the meta-analysis favor the use of immune-enhanced diets, with a relative risk of serious complications of 0.47 (0.30–0.73), but no significant reduction in the rate of pulmonary infections or the duration of hospital stay. Hospital mortality could be judged in 3 studies, with no difference between the two groups. The cost-benefit assessment was also in favor of the supplemented diets when the direct costs of nutrition and complications were taken into account [145].

5.2. Chemotherapy

The toxic effects of chemotherapeutic agents may influence the outcome of chemotherapy, limiting the delivery of more aggressive regimens. Can PN slow the progression of cachexia before or during therapy, and thereby improve the rates of complications and therapeutic responses? The literature on the subject was relatively abundant before 1990 but since this date few well designed studies have been published. This loss of interest is partly due to the publication of the ASPEN recommendations [146] and two meta-analyses [147,148] showing that patients receiving chemotherapy did not benefit from nutritional support in the absence of clear malnutrition.

Well-nourished patients do not benefit from PN during chemotherapy, while malnourished patients are

more likely to suffer nosocomial infectious complications linked to PN, especially line sepsis. In addition, the meta-analyses cited above showed no benefits in terms of survival, tumor response, or toxicity, but an increased rate of infections and in the risk of metabolic complications. These conclusions were partly confirmed by the American consensus conference of 1997, which contra-indicated routine use of EN and PN during chemotherapy [138]. However, these conclusions may not apply to malnourished patients and patients unable to eat sufficiently during chemotherapy [148].

5.3. Bone marrow transplantation (BMT)

Parenteral nutrition is often prescribed to bone marrow transplant patients because of the mucosal injury, digestive problems, the impossibility of oral feeding, and the risk of aggravation of digestive disorders by enteral nutrition. It is also prescribed in the event of poor tolerance of enteral nutrition and as a complement for inadequate oral intake or enteral nutrition [149]. When compared to free oral feeding in this setting, optimal parenteral nutrition proved more efficacious in terms of in-hospital mortality at 3 years and relapse-free survival [150]; paradoxically, there was no significant reduction in the duration of hospital stay or in the incidence of infectious complications and graft-versus-host disease (GVHD) [150,151].

Muscaritoli et al. compared two types of energy intake in parenteral nutrition, one containing 100% dextrose and the other 80% LCT and 20% dextrose; there was no significant difference between the two groups of 30 patients in terms of infectious complications, the duration of hospitalization, or mortality during 18 months of follow-up after BMT [152]. In contrast, there was a reduced incidence of lethal episodes of GVHD and of metabolic complications such as hyperglycemia in the mixed-energy group. In the same way, the use of a conventional lipid emulsion (30% of non protein energy intake) did not increase the infectious risk after BMT [116]. Our group recently reported that mixed lipid emulsions (50% LCT-50% MCT) can improve the nitrogen balance and reduce the incidence of abnormal liver function test results (no clinical parameters were studied). A reduction in the calorie-nitrogen ratio to 100–120 kcal per gram of nitrogen can lead to increased protein turnover and a positive nitrogen balance, but without affecting clinical parameters [3,107].

Immunonutrition could play a major role in BMT patients [153]. Several teams have evaluated the contribution of glutamine (see below § for additional information) in parenteral nutrition after auto- or allo-transplantation. No studies have yet shown a favorable effect of glutamine on the intestinal mucosa after BMT. On the other hand, Ziegler et al. found

increased total lymphocyte and circulating CD4 + and CD8 + T-lymphocyte counts after glutamine supplementation of parenteral nutrition during allogenic BMT [154], together with a reduction in the incidence of infections. Finally, glutamine supplementation makes it possible to preserve the body composition of these patients by limiting the increase in the extracellular volume of water [155,156].

The main clinical benefit of glutamine-supplemented parenteral nutrition in bone marrow transplantation is a significant reduction in the incidence of clinical infections [154,156,157], and the duration of the hospital stay (26.9 versus 32.7 days in the study by Schloerb, 29.0 versus 36.0 days in the study by Ziegler) [155,157], compared with isocaloric, isonitrogenous groups in relatively similar randomised, controlled studies. However, there was no significant difference in the severity of mucositis [157], the incidence or severity of GVHD [157], or in-hospital mortality [155,157].

Oral supplementation with glutamine could reduce the severity of mucositis after autografting but not after allografting [158], and could significantly reduce the incidence of acute GVHD [159]. In this latter study, oral supplementation with glutamine seemed to reduce the need for parenteral nutrition and to decrease mortality, although the results were not statistically significant. Finally, oral supplementation with glutamine did not modify the incidence or severity of digestive symptoms (diarrhea, vomiting, dysphagia and stomatitis) after autologous transplantation in the study by Canovas [160]. The maintenance of parenteral nutrition after BMT in case of poor oral intake delays oral refeeding, when compared with simple intravenous hydration, with no difference in terms of cancer recurrence, hospital readmission, or survival [161].

Enteral nutrition has many theoretical advantages over parenteral nutrition (see above). These advantages have not been observed among bone marrow transplant patients, and moreover a certain reserve does remain to start enteral nutrition in this setting because of the important risk of worsening digestive manifestations [162]. However, Mulder showed that enteral nutrition associated with parenteral nutrition was better tolerated than total parenteral nutrition in a homogeneous population of autologous BMT patients [163], with a significant reduction in the percentage of days with diarrhea in the EN + PN group (26.8 versus 53.6%). In a population composed mainly of patients undergoing allogenic BMT for acute leukemia, Szeluga et al. showed an equal effectiveness of parenteral and enteral nutrition, with a reduction in the incidence of catheter-related infections and in the total cost of nutritional management in the enteral group (\approx 1000 Euros for 28 days on average versus 2500 Euros) [164]. However, seven (23%) of the 30 patients in this group became intolerant to enteral nutrition, and were thus switched

to parenteral nutrition. These results favoring first-line nutritional support by the enteral route in BMT patients have been confirmed in pediatric hematology [165]. Finally, enteral nutrition can be started later after BMT in case of persistent nutritional deterioration due to difficulties in the resumption of oral feeding and/or chronic GVHD [166]. In this study enteral nutrition was delivered by percutaneous endoscopic gastrostomy, with good local and general tolerance.

In practice, the usual duration of aplasia after autologous BMT is between 2 and 3 weeks. Digestive complications (mucositis, anorexia and diarrhea) are usually less frequent and less severe than after allografting. Oral feeding can be preserved and adjunctive parenteral nutrition should be prescribed only if oral intake provides less than 70% of the patient's needs. Parenteral nutrition is stopped as soon as oral intake can once more provide most of the patient's requirements. Total parenteral nutrition must be started if serious digestive complications arise. In contrast, the duration of aplasia after allogenic BMT usually exceeds several weeks and digestive complications (mainly diarrhea) are often severe, especially when they result from acute GVHD; parenteral nutrition is difficult to avoid in these circumstances. However, 'never forget to use the gut', at least partially, when it is functional [167].

5.4. Radiotherapy

A poor treatment response can be predicted in patients whose dose of radiotherapy is reduced because of the severe malnutrition it induces. Thus, a careful nutritional assessment should be an integral part of the management of cancer patients who are candidates for radiotherapy, particularly abdomino-pelvic or cervical radiotherapy [168,169]. The negative effects of radiotherapy on oral feeding are clear, and must be prevented by starting nutritional support from the very beginning of irradiation [170]. This early nutritional management may allow patients to complete the planned course of therapy, and may reduce morbidity in head and neck cancer patients treated with radiotherapy [171,172]. However, four prospective randomized studies analyzing the value of parenteral nutrition during abdominal radiotherapy failed to show an improvement in survival or a reduction in infectious and non infectious complications [148]. Conversely, enteral nutrition made it possible to reduce weight loss and to decrease the degree of digestive intolerance to abdominal or pelvic radiotherapy. Survival was not affected.

5.5. Palliative care

The American recommendations of 1993 on artificial nutrition highlighted the lack of benefit from parenteral

nutrition in patients with progressive disease despite specific treatments. However, in the United States cancer patients represent about one-third of patients receiving home parenteral nutrition, compared to about one-half in Italy. In addition, 50% to 75% of these patients have loco-regional and/or metastatic progressive disease [173]. The one-year survival rate in these conditions was 32% in the 1995 American survey, with preservation of satisfactory social and/or professional activity in 25% of cases during the first year [174]. In the Italian study the improvement in quality of life depended on functional status and the survival time. Among patients with a Karnofsky index lower than 40, the average survival time was shorter than 3 months, and an improvement in quality of life was found only in 9% of cases. The likely duration of survival must thus be predicted before considering parenteral nutrition, which induces a risk of deterioration of quality of life for patients with no hope of cure or long-term survival. Nevertheless, some teams recently reported that immune nutrition could improve the duration of survival and/or functional status during palliative care. Barber proposed oral supplementation with n-3 fatty acids for patients who had unresectable pancreatic adenocarcinoma [175]. After 7 weeks there was a significant gain in weight and lean body mass, and an increase in oral food intake and functional performance. In the same way, a Greek team carried out a controlled study comparing oral supplementation with n-3 fatty acids and vitamin E or a placebo in 60 metastatic patients, and showed an increase in survival in the supplemented patients, regardless of whether they were undernourished [68].

The choice between home parenteral or enteral nutrition is problematic. The risk of infection and thrombophlebitis linked to the use of central venous catheters or subcutaneous ports is well known, and could be increased by lipid perfusions and daily catheter manipulations in an unfavorable environment. However, a central access is generally already available. This central line can thus be used, avoiding nasogastric intubation or gastrostomy. Esthetic and psychological problems must also be considered. A naso-gastric tube can deteriorate the body image and compromise quality of life in patients in whom the validity of nutritional support is questionable. Moreover, enteral nutrition is often seen by the patient and family as a purely palliative treatment, contrary to parenteral nutrition. These psychological aspects must be taken into account when starting home nutrition as part of the palliative care framework. These patients must have a scheduled nutritional assessment, focusing on complications and quality-of-life impact [176]. Home nutrition is no longer appropriate when a patient enters the terminal phase of the disease. Such patients usually have severely restricted oral intake or are dehydrated, and the decision

to administer fluids should be made on the basis of a careful assessment that considers problems related to dehydration, the potential risks and benefits of fluid replacement, and the patient's and family's wishes [127,177].

5.6. Future prospects

It is currently impossible to draw definite conclusions from published data. Nutritional support is probably desirable in the perioperative period and during bone marrow transplantation, but the results are disappointing in patients undergoing chemotherapy, radiation therapy and combined approaches. Efforts are required in three (synergistic) directions:

- Well-designed controlled clinical trials involving only malnourished patients with a reasonable chance of a response to chemotherapy or radiotherapy. Such studies should ideally include a sufficient number of patients in each arm, a reliable assessment of malnutrition, a control group of normally eating malnourished patients, and a measurable tumor with a reasonable expected response rate. This should enable tumoral sensitivity to treatment and the effectiveness of nutrition to be distinguished from each other.
- Traditional nutritional approaches are unlikely to have an impact in the treatment of cancer. Research is currently directed towards new modalities such as bolus parenteral nutrition, and potentiation of chemotherapy by nutritional modulation of the cell cycle [178,179].
- The impact of nutritional pharmacology on the host-tumor relationship must be investigated [136]. The theoretical goal is to offer nutritional supplies that are used more efficiently by the patient than by the tumor, whose growth would thus be slowed [180]. Results obtained in animal models with formulas lacking methionine are contradictory [181]. Glucose being the privileged energy substrate of tumor cells, some researchers have suggested that the lipid supply should be enhanced, but positive results observed in animal models, especially with MCT alone or combined with n-3 fatty acids [120], must be clearly confirmed in humans.

6. Is immune nutrition the holy grail?

The limited benefit, if any, of standard parenteral or enteral nutrition in cancer patients has led to the concept that the quantity of nutrients may not be the only issue, and that qualitative modulation of nutritional substrates could restore the nutritional and immunological status of the host, without enhancing tumor growth. Ideally, such substrate supplementation-or de-

pletion-should enhance immunological defences, replete protein stores in the host, and sensitize the tumor to specific treatments. We will address certain aspects of pharmacological/immunological nutrition, with special emphasis on glutamine, arginine, omega-3 fatty acids and growth factors [10,136,182,183].

6.1. Is glutamine supplementation beneficial to tumor-bearing patients?

Glutamine, the most abundant amino acid in the body, is a preferential substrate of rapidly dividing cells and tissues *in vivo*, such as lymphocytes, macrophages and intestinal epithelial cells, and is also mandatory for optimal *in vitro* cell culture [184]. Unfortunately, glutamine is also actively consumed by rapidly growing tumors, in both animals and humans, but net glutamine retention by the tumor is not consistently observed in human cancer [185].

This potential 'glutamine trap', and the metabolic alterations mediated by tumor-secreted mediators [186] and cytokines [187], result in a severe imbalance in glutamine homeostasis. Despite accelerated glutamine release from enhanced muscle protein breakdown and from the lungs, the gradual glutamine depletion of the host leads to a reduced glutamine supply to the gut and immune cells. It may be hypothesized that this glutamine depletion, which occurs mainly in advanced cancer disease when the host loses weight, favors the occurrence of infectious complications and poor tolerance of antineoplastic treatments [188].

It has been proposed to 'fast' the tumor either by using exogenous glutaminase, or by giving glutamine analogs acting as antagonists (e.g. acivicin) of the first metabolic step. Although some tumor growth inhibition has been reported, especially with combined acivicin and insulin therapy, clinical results are globally disappointing and offset by unacceptable toxicity, especially in the form of severe mucositis and reversible, dose-limiting CNS toxicity.[189].

In an alternative concept glutamine supplementation is expected to support immune [190], muscle and gut functions [191], reduce infectious complications and improve tolerance of anti-tumor therapy. This assumes that glutamine is primarily beneficial to the host and causes only minor stimulation of tumor growth, if any [192]. Finally, glutamine enhances the activity of natural killer lymphocytes (one of the main lines of defense against tumor cells) *in vitro* and *in vivo*, and it has been suggested that the beneficial effects of glutamine on tumor growth may be related to a modulation of glutathione metabolism, as also postulated in critically ill patients [193].

The gastrointestinal toxicity of radiation therapy and anticancer drugs such as methotrexate (MTX) and 5-

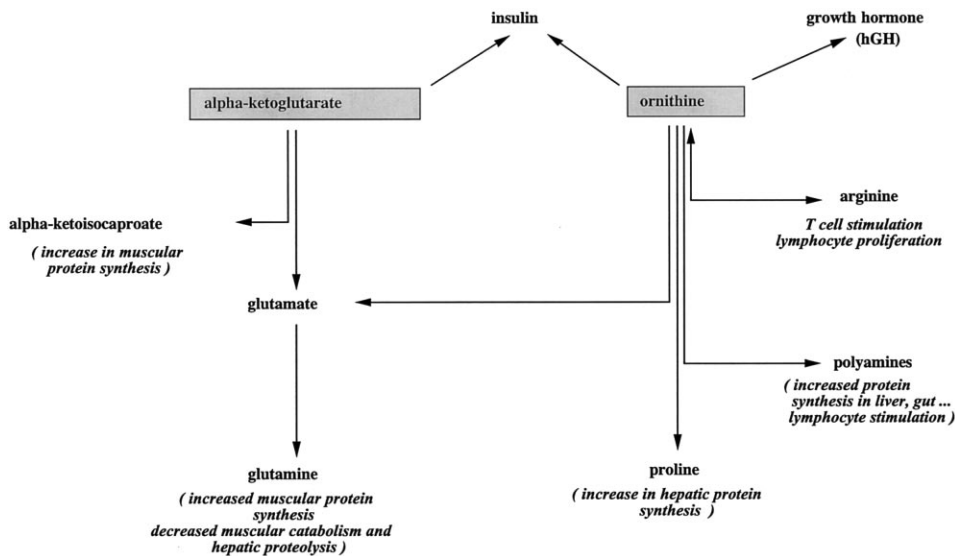


Fig. 4. Metabolic Pathways of Ornithine alpha-ketoglutarate. Ornithine alpha-ketoglutarate possesses anabolic properties via the stimulation of insulin and GH secretion, and anticatabolic properties via the stimulation of glutamine and arginine synthesis that are theoretically adapted to the hypermetabolic states. Ornithine is a precursor of polyamines, that are essential for cell growth and protein synthesis.

fluorouracil (5FU) results from direct damage to the rapidly proliferating intestinal epithelium. Thus, glutamine provision might be expected to preserve integrity of the digestive tract or enhance its recovery after injury. As oral or enteral glutamine supplementation is thought to be preferable to parenteral administration [194], the effect of oral glutamine on chemotherapy-induced toxicity has been explored in several clinical studies. Short-term fractionated oral administration of a relatively low dose of glutamine (16 g per day) in patients with advanced gastrointestinal cancer, during one course of 5-FU and leucovorin combination therapy, had no significant effect on the mucositis score [195]. In contrast, a suspension of L-glutamine (4 g 'swish and swallow' twice a day), given from day 1 of chemotherapy for 28 days resulted in a significant decrease in the total number of days with mucositis in 13 of the 14 patients in a similar cross-over study [196]. Recently, oral glutamine supplementation was found to be effective on arthralgias and myalgias during chemotherapy containing paclitaxel [197].

In patients undergoing bone marrow transplantation for hematologic malignancies, supplementation of parenteral nutrition with either free glutamine or glutamine-containing dipeptides gave controversial results. In the study by Ziegler et al, patients received either a standard or a glutamine-enriched formula providing 0.57 g of free glutamine/kg per day. Not only was the nitrogen balance significantly less negative in the glutamine-supplemented group, with a parallel reduction in 3-methyl-histidine urinary excretion, but the incidence of infectious complications and the duration of hospital stay were also significantly reduced [157], with a clear improvement in mood and a valuable cost

reduction in the treated group [198]. A similar reduction in hospital stay was reported by Schloerb et al. [155], although a statistically significant reduction in infectious complications was only found in the subgroup of patients undergoing allogeneic transplantation. Conversely, Van Zaanen et al. (42) failed to find any beneficial effect of glutamine-supplemented parenteral nutrition in a heterogeneous group of hematologic patients [199]. More recently, Bozzetti et al., in an elegant double-blind study involving 65 patients with advanced breast cancer, found that glutamine (30 g/day) neither prevented the occurrence of doxifluridine-induced diarrhea nor had any impact on the tumor response to chemotherapy [200].

Thus, the clinical benefits of glutamine-enriched nutrition have to be confirmed in various types of cancer [153]. In addition, the potential stimulation of tumor growth by glutamine cannot be ruled out, suggesting that further clinical studies of glutamine supplementation in cancer patients should include a careful assessment of tumor kinetics, to comply with ethical requirements.

6.2. Ornithine alpha-ketoglutarate (OKG) and cancer

OKG is a very old product but its anabolic properties (stimulation of insulin and GH secretion) and anticatabolic properties (stimulation of glutamine and arginine synthesis) [201] are theoretically adapted to catabolic illnesses such as cancer (Fig. 4). OKG is easy to administer, enterally or parenterally, over 24 h or, preferably, in short infusions [202]. Some authors have found that OKG is as effective as glutamine for the maintenance of muscle ribosome and polyribosome lev-

els, apparently reflecting a sparing effect on muscle protein synthesis capacity [203]. A clinical benefit was recently shown in severe burns patients, who had a better quality of wound healing after skin grafts while on enteral OKG supplementation [204].

To match the clinical situation in which tumor burden is small at diagnosis and at initiation of treatment, diets containing OKG or an isonitrogenous, isocaloric diet containing glycine were tested in rats treated by tumor excision at a limited stage of the disease. By comparison with glycine-fed rats, OKG-fed rats had a more positive nitrogen balance, higher concentrations of muscle glutamine, and accelerated protein deposition in the small intestine ($P < 0.05$) [205]. These results may explain the failure of nutritional support in untreated cancer and underline the need for clinically relevant animal models.

However, in spite of these exciting new effects of OKG supplementation on protein metabolism and immunoregulation in tumor-bearing animals, the potential value of OKG administration to cancer patients must still be confirmed.

6.3. Pharmacological nutrition with arginine

Arginine is a specific example of a nutrient with immunomodulatory potential [206]. It is a semi-essential amino acid in adults and becomes indispensable when its endogenous synthesis is inadequate, as in cancer. Apart from its role in urea and protein (collagen) synthesis and as a stimulant of several endocrine secretions (insulin, growth hormone and IGF-1, among others), arginine has been found to have several immunomodulatory actions [207], such as accelerated wound healing and stimulated thymus growth, lymphocyte proliferation and mononuclear cell responses to mitogens; it also enhances lymphokine-activated killer cell generation via a nitric oxide-mediated mechanism, and stimulates the release of polyamines by the small bowel [208]. These immunostimulant effects of arginine have been shown in several animal studies with experimentally induced infections or trauma [209]. Although the mechanisms responsible for the immunomodulatory effects of arginine are unclear, it is likely that nitric oxide (NO) generated from arginine by the action of NO-synthase is the major pathway [210].

The potential benefits of supplemental arginine in cancer patients are poorly documented. In patients with breast cancer, Park et al. found a stimulation of protein synthesis after 3 days of arginine-supplemented feeding [211]. These findings are in marked contrast with most of the above animal data, but may be explained by differences in the doses and the resulting plasma arginine concentrations. In addition, stimulation of proliferation may be beneficial if it sensitizes the tumor to the action of antimitotic drugs or host defenses, as

suggested by Britten et al., who showed that dietary supplementation with arginine in patients with breast cancer significantly increased lymphocyte mitogenic reactivity as well as natural killer and lymphokine-activated killer cell cytotoxicity [212]. Finally, Caso et al. recently showed that arginine supplementation for 3 days before surgery for head and neck cancer did not enhance tumor protein synthesis, suggesting that arginine supplements are safe in this type of cancer [213].

In summary, available data on the use of arginine for immunonutrition of cancer patients are mainly experimental, with controversy over the optimal dose and route with respect to the type and immunogenicity of the tumor. Clinical studies on the safety and efficiency of arginine in the clinical setting of cancer are urgently needed.

6.4. Immunomodulatory effect of polyunsaturated fatty acids (PUFAs)

The immunomodulatory effects of new lipid formulations may be useful in cancer patients. As essential fatty acids are the sole precursors of eicosanoids, the former may alter the rate of eicosanoid production, which in turn modulates the immune response [214]. The induced alterations of membrane phospholipids affect cell functions and membrane fluidity [112]. Conventional lipid emulsions are relatively rich in ω -6 PUFA (linoleic and arachidonic acids); the breakdown of arachidonic acid leads to increased dienoic prostaglandin and thromboxane production (e.g. prostaglandin E2 (PGE2) and thromboxane A2 (TBA2) and increased tetraenoic leukotriene production (e.g. leukotriene B4 and LTB4), which are mainly responsible, particularly in macrophages, for their immunosuppressive properties and for the generation of free oxygen radicals (Fig. 5). In contrast, such emulsions are poor in ω -3 PUFA (linolenic acid) which inhibit the breakdown of arachidonic acid via the cyclooxygenase pathway and, thus, the synthesis of PGE2; they lead, via the eicosapentaenoic acids, to trienoic prostaglandins (e.g. PGE3 and PGI3) and thromboxane A3, and to pentaenoic leukotrienes (e.g. LTB5). Omega-3 PUFA therefore give rise to a decrease in platelet activation and thrombogenesis, and inhibit the inflammatory reactions related to the activation of target cells by cytokines [215].

Omega-3 fatty acids have protective effects on the development of carcinogen-induced tumors, the growth of solid tumors, cachexia, and metastatic diseases in experimental models [216]. It appears that the metastatic process can effectively be reversed in vivo by eicosapentaenoic acid (EPA), but not by other PUFA of either the n-3 or n-6 series [217,218]. Dietary supplementation with n-3 fatty acids has been tested in several clinical trials. In pancreatic cancer, a malignancy asso-

ciated with a persistent inflammatory response and increased energy expenditure, 3 months of dietary supplementation with a median of 12 g/day fish oil (eicosapentaenoic acid 18% and docosahexaenoic acid 12%) led to a significant median weight gain of 0.3 kg/month, accompanied by a temporary but significant reduction in acute-phase protein production and by stabilization of resting energy expenditure [219]. The same group recently determined that a combination of EPA with a conventional oral nutritional supplement produced significant weight gain, improved performance status and

improved appetite in patients with pancreatic cancer [220]; if this can be translated in prolonged survival is under investigation. Gogos et al. randomized 60 patients with generalized solid tumors to dietary supplementation with either fish oil or a placebo daily until death. Omega-3 PUFA had an impressive immunomodulating effect, as reflected by the T-helper/T-suppressor cell ratio, in the subgroup of malnourished patients. There were no significant differences in cytokine production among the various groups. In addition, omega-3 fatty acids prolonged the survival of all the patients [68].

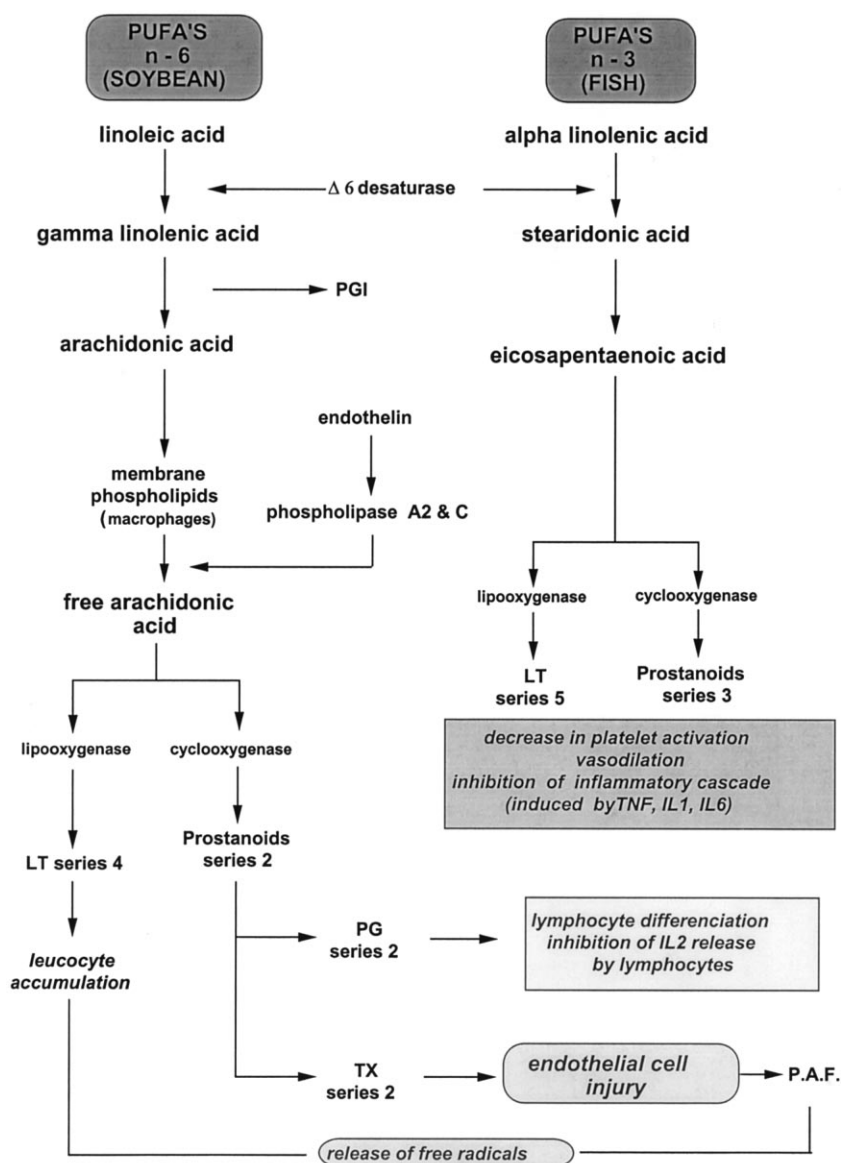


Fig. 5. Metabolic pathways ω -3 and ω -6 polyunsaturated fatty acids (PUFA'S). Free arachidonic acid (AA) and eicosapentaenoic acid (EPA) are respectively released from membrane macrophage phospholipids by the action of phospholipases A2 and C. Free AA and EPA are rapidly metabolized through two main pathways involving the action of lipooxygenase and cyclooxygenase. Prostanoids are synthesized by Cyclo-oxygenase; Leukotrienes are formed by lipooxygenase. AA, via both these pathways, yield superoxydes and is thought to be mainly responsible for for the immunosuppressive poperties of ω -6 polyunsaturated fatty acids. EPA leads to trenoic prostaglandins and pentaenoic leukotrienes that are supposed to decrease platelet activation and to inhibit the inflammatory reaction. PG; prostaglandin, LT; leukotriene, PAF; platelet activating factor, TNF; tumor necrosis factor, IL; interleukin.

Table 10
Main characteristics of immune-enhancing diets^a

	Impact	Immun-Aid	AlitraQ	Stresson
Protein (Cal%)	22	32	21	24
Free GLN (g/l)	0	12.5	14.2	13
Arginine (g/l)	14.0	15.4	4.5	6.7
Nucleotides (g/l)	1.25+RNA	1.0	0	0
Lipids	Palm, Saffl. Menhaden	Canola MCT	Saffl. MCT	Veg+fish, LCT/MCT = 1.5
ω-3 Fatty acids (g/l)	1.68	1.1	–	30 mg
Anti-oxidants	–	–	–	Vitamins A, C, E

^a RNA, ribonucleic acid; saffl., sunflower oil.

These stimulating results warrant further clinical trials to establish the exact benefits and limitations of n-3 PUFA supplementation in cancer patients.

6.5. Hormones, insulin and growth factors

Several attempts have been made to reverse muscle protein breakdown by means of hormones such as insulin, growth hormone, insulin-like growth factor (IGF-1), and anabolic agents. The main danger of this approach is to stimulate tumor growth.

Studies of insulin monotherapy of cancer cachexia have had limited success, due to insulin-induced hypoglycemia and subsequent glucagon secretion. Bartlett et al. reported that blockade of endogenous hormonal secretion by somatostatin and exogenous supply of insulin and growth hormone significantly improved skeletal muscle protein content and reduced protein incorporation by the tumor in rats with MAC-33 mammary adenocarcinoma [221]. However, as usual, there is a long way from the bench to the bedside. Cancer patients underwent a preoperative metabolic study during administration of insulin with or without a previous 3 day treatment with GH: combined hormone administration was the most effective to ameliorate whole-body balance. The effect of insulin was mainly an inhibition of protein breakdown, while GH improved protein synthesis [222]. The same group recently explored the effect of combined administration of insulin and GH in 30 patients undergoing surgery for upper GI tract malignancy and receiving total parenteral nutrition [223]. Patients who received GH and insulin had improved skeletal muscle protein net balance compared with the TPN only group, but GH and insulin combined did not improve whole body net balance more than GH alone. However, improved protein kinetics only represent biochemical changes, and a clinical trial with clinical end-points is now warranted.

Finally, administration of beta2-adrenergic agonists to tumor-bearing rats resulted in partial recovery of skeletal muscle and heart mass [224]. Treatment of tumor-bearing animals with salbutamol, salmeterol and clenbuterol did not influence tumor growth. Any of the

three beta2-adrenergic agonists, but particularly salmeterol perhaps, could be evaluated clinically in the treatment of cancer cachexia.

6.6. Immune diets: do combinations of several immune nutrients resolve the problem?

The enrichment of nutrient mixtures with arginine and vitamin C, a reduction in omega-6 PUFA and enrichment with omega-3 PUFA, all considered to be immunomodulatory, has given interesting results in animal models and is currently under clinical investigation [136,144,183]. The novel concept of 'nutritional pharmacology' or 'immune-enhancing nutrition' underlies the development of four specific enteral formulas commercially available (Impact, Sandoz Nutrition; Immun-Aid, McGaw; AlitraQ, Ross Laboratories and Stresson, Nutricia Laboratories) to modulate the inflammatory and immune response to tissue injury. The PUFA, arginine and purine content of the formulations is modified, while still providing nutritional support for immunocompromized patients (Table 10). At present, only Impact has been studied in randomized, prospective clinical trials, utilizing early enteral feeding techniques and relative to cancer patient related outcomes. In the context of cancer, all the available data come from studies performed in surgical oncology. No such studies are currently available in medical (chemotherapy or radiotherapy) oncology.

The immunostimulant effect of Impact was evaluated in several well-designed studies devoted exclusively or partially to cancer patients [225–227]. Although these studies evaluated variations of a broad range of immune and inflammatory parameters retrospectively, the overall results favored the use of Impact over the standard control nutrition.

With regard to clinical effectiveness, an increasing number of randomized double-blind studies are available (Table 11). In the study by Daly, 85 patients having undergone major surgery for gastrointestinal malignancies received post-operative enteral nutrition with either Impact or Osmolite HN, but the two diets were neither isocaloric nor isonitrogenous [228]. There

Table 11
Randomized double-blind studies^{a1}

Author (year) Reference	Patients (<i>n</i>); Diet(s)	Isocaloric/Isonitrogenous	Results, statistical significance	Efficacy?; (comments)
Daly (1992) [228]	GI surgery (<i>n</i> = 77) Impact vs osmolite HN	Yes No (IED > Std)	↓ Infections (<i>P</i> < 0.05) ↓ LOS (<i>P</i> < 0.05) in the impact group	± (see text) Definition a posteriori of the types of infection and of criteria of judgment ±
Daly (1995) [229]	GI surgery (<i>n</i> = 60) Impact vs traumacal	Yes	↓ Infections (NS), wound infections (<i>P</i> < 0.005) and LOS (<i>P</i> = 0.02) in the impact group	Very high incidence of complications in the control group
Kenler (1996) [236]	GI surgery (<i>n</i> = 50) FOSL-HN vs osmolite HN	Yes	↓ Infections (NS) ↑ digestive tolerance (<i>P</i> = 0.05) in the FOSL-HN group	No 37/50 evaluable patients post-hoc stratification
Schilling (1996) [237]	GI surgery (<i>n</i> = 41) Impact (A) vs Std (B) and low-lipid diet (C)	No/no	↓ Infectious compl. group A (A versus C, <i>P</i> = 0.15). No difference in ICU and hospital LOS	No Questionable statistical analysis, major differences in the quantitative and qualitative supplies
Senkal (1997) [145]	GI surgery (<i>n</i> = 154) Impact vs Std	Yes	↓ Late (<i>P</i> < 0.05) and total (NS) complications in the impact group Similar costs and LOS	± Important and homogeneous population, weak statistical benefit
Heslin (1997) [230]	GI surgery (<i>n</i> = 195) Impact vs IV cristaloids	No	No difference for minor and major complications, LOS and mortality	No 61% (Impact) and 22% (T) of energy requirements, provocative study and results
Gianotti (1997) [96]	GI surgery (<i>n</i> = 260) Impact (A) vs Std vs TPN	Yes	% Infections: A < Std < TPN (<i>P</i> = 0.06) Hospital LOS: A < Std (<i>P</i> = 0.01) < NPT (<i>P</i> = 0.004)	Yes Death knell for TPN? value of statistical analysis?
Braga (1998) [231]	GI surgery (<i>n</i> = 166) Impact (A) vs Std vs TPN	Yes	↓ Infections, sepsis score and LOS (NS) in the impact group	± Post-hoc stratification dissociated and non conclusive results
Braga (1999) [143]	GI surgery (<i>n</i> = 206) Impact vs Std	Yes	↓ Infected patients, antibiotic days, LOS (all <i>P</i> < 0.01) in the impact group	Yes but... similar mortality (close to 0%) Similar incidence of infections??
Snyderman (1999) [238]	Head and neck surgery (<i>n</i> = 136) Impact vs Std	Yes	No differences in wound healing and LOS ↓ Infections (<i>P</i> = 0.02) in the impact group	Yes? concordant ITT and per protocol analyses perioperative IED > posoperative IED?

^a GI, gastrointestinal; Std, standard enteral formula; FOSL, fish oil structured lipid; HN, high nitrogen; IED, immune-enhancing diet; LOS, length of stay; ICU, intensive care unit.

was no difference between the two groups with regard to the length of hospital stay in the intention-to-treat analysis. Likewise, there was no significant reduction in individual infections (such as pneumonia) in the Impact group, but when the various infectious complications were combined with anastomotic dehiscence, the difference became statistically significant in favor of Impact. This result was confirmed by another similar study from the same group [229] (Fig. 6). Comparison of the three studies by Heslin [230], Senkal [145] and Braga [231] is intriguing. All three evaluated the effects of Impact in the postoperative period of major surgery in a large population of GI cancer patients, but the three study designs differed notably. Schematically, Senkal

compared Impact with an isocaloric, isonitrogenous placebo, while Braga added a 3rd group receiving equivalent TPN, and Heslin challenged the dogma of obligatory postoperative nutrition by comparing Impact with simple post-operative hydration... The only convincing conclusion is that the concept of post-operative TPN is on the wane. The authors' conclusions diverged, no doubt because of the methodological biases of each study: (a) in Senkal's study, only late infectious complications, after the 5th day, were fewer in the Impact group (5 versus 13; *P* < 0.05) and a sound medico-economic evaluation showed a saving of ≈ 22 000 Euros per 150 patients; (b) Braga et al found a clear clinical advantage of EN over TPN, and suggested that this

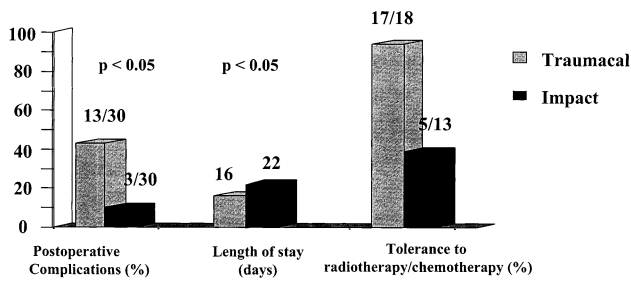


Fig. 6. Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients [229]. When combining wound complications with the occurrence of infection, Impact was superior to the control diet ($P < 0.05$). Mean length of stay was also reduced in the Impact group. The baseline mortality rate was very low in both groups. It is noteworthy that 94% of the patients randomized to receive long term tube feeding completed their postoperative chemoradiation therapy whereas 61% not randomized to tube feedings required crossover to jejunostomy nutritional support.

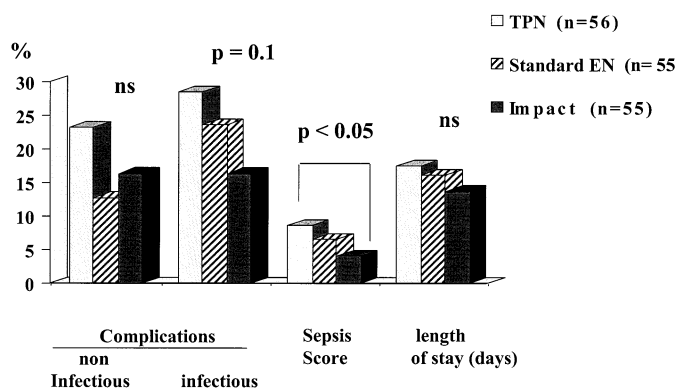


Fig. 7. Impact of route of administration and composition of the diet after major abdominal surgery [231]. Impact was compared with an isocaloric, isonitrogenous enteral diet after GI cancer surgery, and a 3rd group received an equivalent TPN. There is slight clinical advantage of EN over TPN, and this advantage could be increased by the use of an 'immune diet', especially in severely malnourished patients and patients with multiple blood transfusions. However the rate of postoperative infections and the length of ICU stay do not differ between the 3 groups.

advantage could be increased by the use of an 'immune diet' such as Impact, especially in severely malnourished patients and patients with multiple blood transfusions ($P < 0.05$), but the statistical analysis was questionable, particularly the analysis of variance (Fig. 7); (c) finally, Heslin found no difference between the groups in terms of mortality, infectious morbidity or the duration of the hospital stay, but the randomized groups were not perfectly balanced, and the effective calorie intake was only 61 and 22% of calculated energy needs, respectively, in the Impact and hydration groups. Overall EN, or better immune-enhancing EN, would appear to be effective only for particularly compliant

patients, in GI cancer patients except patients with esophageal cancers or would it be necessary to associate for the first days a complementary (immune?) PN? The most recent studies and meta-analyses do not permit to elucidate these problems, although the innovative study of Braga et al. clearly suggests that a consistent efficacy of immunonutrition in GI surgery is firmly dependent on the preoperative administration of immunonutrients [143].

7. Methodological and ethical considerations

Apart from works directly aimed at correcting the most serious states of cachexia, most clinical trials of nutritional support in cancer have ended in failure. To solve this problem, sophisticated meta-analyses have been developed by statisticians, yielding a much more precise estimate of the therapeutic effect than provided by the individual studies. However, it should be stressed that the clinical trials selected for these meta-analyses, although similar, often differ significantly in terms of therapeutic regimens and the study populations. Yet tumors of different types and locations, with different effects on appetite and different risks of malnutrition, cannot reliably be subjected to identical criteria of analysis [232].

Outstanding questions can be summarized thus:

- Can nutritional support stop the course of cachexia, or even improve malnutrition, whatever the cause? Is there a link between the malnutrition resulting from GI obstruction and that due to the deleterious effects of the tumor on host metabolism?
- Can the specific effects of anti-cancer treatments, especially chemotherapy and radiotherapy, be improved by new substrates in artificial nutrition?
- Can artificial nutrition be beneficial to the patient without increasing tumor growth?
- Are improvements in cost-benefit ratios on the one hand, and quality of life on the other hand, suitable goals in the nutritional management of cancer patients, taking into account the fact that nutritional support is usually regarded as 'supportive care' rather than potentially curative? This point is fundamental.

The improvement in quality of life by nutritional intervention is particularly difficult to prove, for two main reasons, one conceptual, the other practical.

Conceptual difficulties can be overcome by refining and clarifying the definitions and indexes of quality of life [70,233]. Practical difficulties are more complex and depend primarily on the characteristics of the underlying disease, the type of nutritional intervention, and the context in which the clinical trial is carried out. We must keep in mind that, in the present socio-economic

context, with increasingly scarce resources, quality of life assessment will undoubtedly become an essential element in the evaluation of all medical interventions [234]. They will make it possible to integrate the results of our future studies in an adequate and ethical evaluation of the costs and benefit of a treatment, taking into account improvements in both physical and mental well-being [235].

8. Conclusion

Malnutrition is encountered everyday in cancer patients and is associated with an alteration of quality of life and a reduced survival. It results from multifactorial events such as inadequate food intake, alterations of taste and smell, wasteful metabolic disturbances, specific humoral and inflammatory responses, host and tumor competition for nutrients, and side effects from anti-cancer treatments in a previously undernourished host. A simple, standardized and affordable nutritional assessment program can determine which cancer patients might benefit from dietary counselling or the need for a thorough nutritional evaluation to guide nutritional support. Early counselling by a dietitian is essential to give advice aimed at maintaining oral nutrition, to propose the various oral supplements commercially available, to monitor the evolution of the nutritional status of the patients, and to alert the physician to the need for enteral or parenteral nutrition. No firm recommendations can be made presently about the clinical indications of orexigens such as corticosteroids and megestrol acetate which seem to be beneficial only as palliative therapy and for limited periods.

Although there is no definitive consensus on the optimal calorie and protein requirements for cancer patients, a daily intake of 25–35 kcal/kg and of 0.2–0.35 g nitrogen/kg is recommended both for EN and PN to preserve the lean body mass. A balanced contribution of glucose and lipids, or slightly more glucose than fat, is generally recommended, with an adequate provision of electrolytes, trace elements and vitamins. The available data do not support a specific advantage of BCAA, and of MCT over LCT, in cancer patients. EN and PN are both safe and effective methods of administering nutrients in cancer patients. The two techniques are similar for improvement of nutritional parameters and immune status, but EN is always preferable for cancer patients with a (relatively) intact digestive tract. In practice, EN and PN are complementary, and decision to use one or the other depends on the tumor site, the potential adverse effects of treatment, and on the experience and training of the nutritional support service. The most common result is prevention of further deterioration of the nutritional status, rather than true improvement. Although *in vivo* evaluation of tumor growth is technically difficult, the general results in clinical practice suggest no change

of cancer cell volume during parenteral nutrition.

Many prospective randomized controlled trials have evaluated the role of PN, and a lesser extent of EN, as adjuvant therapy of cancer. The quality of the studies is variable and diminishes the quality of the conclusions. The indiscriminate use of conventional EN and PN is not indicated in well-nourished cancer patients or in patients with mild malnutrition when resumed oral intake is anticipated within one week. A clear benefit from nutritional support seems to be limited to a specific, small subset of patients. EN or PN is not clinically efficacious for patients treated with chemotherapy or radiotherapy, unless there are prolonged periods of GI toxicity, as in the case of bone marrow transplant patients for whom EN and/or PN may increase long term survival and decrease tumor relapse. Severely malnourished cancer patients undergoing major visceral surgery may benefit from a 7–10 days preoperative PN followed by a postoperative nutritional support, preferably via enteral access, for at least 5 days. Nutritional support in palliative care should be based on a careful evaluation of the potential risks and benefits of EN and PN, and on the patient's and family's wishes.

Research is currently directed toward a better understanding of the metabolic alterations of cancer patients, the definition of nutritional regimens that can efficiently support the host without promoting tumor growth, and on the impact of nutritional pharmacology on the host-tumor relationship. Glutamine, arginine, ornithine-alphaketoglutarate, omega-3 fatty acids, nucleotides, antioxidants and growth factors are presently under extensive investigation. Glutamine-supplemented PN is probably beneficial in bone marrow transplant patients. A recent meta-analysis suggests that immune diets reduce the rate of infectious complications and the length of hospital stay after GI surgery for cancer. In the future, carefully designed clinical trials are needed to determine the efficacy of such novel approaches in specific populations of cancer patients with an adequate definition of nutritional and oncological goals. Further studies should also address the question of the indications for conventional and immune-enhancing EN, of the overall cost-benefit ratio of nutritional pharmacology, and the effect of nutritional support on length and quality of life.

Reviewers

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