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Contra:

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NUTRITIONAL SUPPORT in cancer patients should show a beneficial impact on survival, disease-free survival, response to antineoplastic therapy, toxicity, nutritional status or quality of life. Additionally, nutritional interventions should not enhance tumour growth while repleting lean body mass and fat stores. There is (conflicting) evidence that intravenous hyperalimentation may stimulate tumour growth and mitotic activity in animals, while caloric restriction results in inhibition of tumour growth [1]. Tumour growth in response to starvation and refeeding is rapid and reproducible [2], a process in which sugars seem to have the most pronounced stimulating effect. So far, these effects have been shown in an animal model; hyperalimentation does not seem to promote tumour growth in humans [3]. A large study demonstrated that maintenance of a good nutritional status in patients with malignant lymphoma does not have any deleterious effect on tumour growth [4]. Such research is relevant, since some more recent nutritional concepts are based on the assumption that the tumour and the tumour-bearing host have a different energy substrate utilisation [5]. Today, the following facts are accepted concerning nutrition-related tumour growth: starvation is more harmful to the tumour-bearing human than to the tumour itself; energy substrate composition may have an impact on tumour growth (low carbohydrate content, high fat content); the role of glutamine, arginine, fatty acids and polyribonucleotides is becoming evident [6–12].

The prevalence of nutritional deficits in cancer patients is high; cachexia has a dramatically negative influence on patient outcome. Besides the well-known immunological abnormalities with impaired tolerance of antineoplastic therapy leading to an increased morbidity and mortality, low quality of life is the main concern for the patient. Nutritional support in this situation would, of course, make good sense, but until now, scientific data have not been convincing evidence that nutritional interventions, at least in the conventional way, are really beneficial to the patient with incurable malignancy. Nutritional therapy alone or in conjunction with antineoplastic therapy (surgery, radiotherapy, chemotherapy, immunotherapy) has failed to become an accepted supportive modality, and there is no consensus regarding its therapeutic role so far.

The reasons for this dilemma are found in inappropriately designed nutritional intervention trials and nutrition-related inefficiencies [13–19]. However, subsequent randomised studies have been unable to demonstrate a clear positive effect on tumour response, toxicity or survival [20, 21]. In more recent studies with improved methodology (and better energy substrates), no other conclusions can be drawn [22]: more than 70 prospective randomised controlled trials have evaluated the use of nutritional support in cancer patients, but many trials had serious shortcomings in study design that limited the ability to draw definitive conclusions from the data. In general, the data failed to demonstrate the clinical efficacy of providing nutritional support to most patients with cancer. Nutritional effects may be limited, due to the usually short duration of nutritional support, while malnutrition in cancer patients occurs over several months [23]. Unfortunately, quality of life issues have usually not been considered important endpoints [24]. In special settings, such as chronic gastrointestinal insufficiency (short bowel, radiation enteritis) or prolonged intestinal toxicity (bone marrow transplantation as an example), nutritional support has an established role; in the settings mentioned the patient is either cured (nutritional rehabilitation) or treated with curative intent [25, 26].

Peri-operative nutritional support is still under debate; preoperative total parenteral nutrition (TPN) is able to reduce postoperative morbidity and mortality [27]. Pooled data from 18 controlled clinical trials of peri-operative TPN demonstrated that only certain subgroups of patients who are at a particularly high risk would have benefitted [28]. It still remains unclear, again due to inadequate sample sizes and suboptimal nutritional support, which patient may benefit from peri-operative nutritional therapy. A randomised trial of postoperative TPN after pancreatic surgery for malignancy demonstrated a detrimental effect (infectious complications) [29]. Multicentre randomised trials with relevant endpoints, including quality of life, are warranted. It must be noted that conventional parenteral or enteral nutritional support may influence postoperative outcome positively (hence also justifying the procedure in patients with advanced incurable cancer), but most probably not the general outcome of malignant disease.

Nutritional support as an adjunct to radiotherapy may have a role concerning tolerability. Radiation therapy, depending on dose and location, can influence nutritional status considerably; patients with head and neck cancer demonstrate a high risk for intestinal toxicity, often precluding normal enteral intake. Concomitant nutritional support,

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preferably by modern enteral means, can have a positive effect on tolerability and quality of life [30]. In abdominal and pelvic cancer treated with radiotherapy, parenteral nutrition failed to demonstrate a positive effect on mortality or median survival, although methodological flaws were again evident in these early randomised investigations [31–34].

Chemotherapy, inducing anorexia and direct toxic effects at the cellular level, usually contributes to malnutrition and impaired quality of life. Since well-nourished cancer patients will have a better response to chemotherapy, it seems logical that patients undergoing chemotherapy should benefit from nutritional support (less serious side-effects leading to dose reductions) [35, 36]. Recent meta-analysis of pooled data from individual studies of parenteral nutrition in cancer patients receiving chemotherapy revealed that TPN was detrimental in this setting: mortality was increased in patients under TPN even when catheter-related septicaemia was excluded [35, 37]. Standard TPN does not allow protection of normal body composition and thereby preservation of body function in conjunction with chemotherapy. The American College of Physicians published a position paper discouraging the routine use of TPN in cancer patients undergoing chemotherapy and recommending further trials to determine the patient subgroups which might benefit from nutritional support [38].

Unfortunately, we do not know whether nutritional interventions, such as TPN or aggressive enteral nutrition, have a positive impact on the quality of life, which would also warrant its use in a palliative setting. The increase in quality of life with nutritional interventions depends on the clinical setting; in cancer rehabilitation clinical nutrition has an established role.

So far one must conclude that conventional nutritional support, the way it is applied, parenterally or enterally, has rarely shown the desired positive impact on survival, tumour response or toxicity. The impact on quality of life remains undetermined. Is it correct to make a distinction between curative and palliative therapeutical intent? In the curative setting, a patient will accept a transient deterioration of well-being in order to have an option for a long-lasting remission. In contrast, a patient with incurable progressive disease which can be influenced only marginally by diverse therapeutical modalities will usually choose a quality of life as good and consistent as possible. The only indications for nutritional support in this situation are the patient's desires and concerns. Although survival or the general medical condition can hardly be influenced by nutritional support, quality of life could be positively affected in some palliative situations: home parenteral (or enteral, if possible) nutrition may be an alternative to hospitalisation for patients who are unable to swallow or who are suffering from obstruction or previous gastrointestinal complications [39–41]. In patients whose main problem is tumour-induced anorexia, invasive clinical nutrition is usually not beneficial [38] and may have a negative impact on the quality of life [42]. The benefit of home parenteral or enteral nutrition, which has doubled in the past few years in the U.S.A., in the patient subset with terminal conditions, remains unclear [43].

The European Association for Palliative Care has published guidelines on artificial nutrition versus hydration in terminal cancer patients [44]: part of the controversy relates to the definition of the terminal cancer patient as a group with different needs, expectations and potential for medical intervention. Prediction of life expectancy and the patient's likely response to vigorous nutritional support are further difficulties. The paper proposes a three-step process for decision on treatment modalities (artificial nutrition versus hydration): step 1 relates to key elements necessary to reach a decision (oncological/clinical condition; symptoms; expected survival time; hydration and nutritional status; spontaneous or voluntary nutrient intake; psychological profile; gut function and potential route of administration; need of special services based on type of nutritional support prescribed). Step 2 involves the overall assessment of pros and cons, based on information determined in step 1, in order to reach an appropriate decision based on a well-defined endpoint (i.e. improvement in quality of life; maintaining patient survival; attaining rehydration). Step 3 involves the periodic re-evaluation of the decision made in step 2 based on the proposed goal and the result attained. In several cases the decision (based on the key elements) may still be difficult; the patient should be directly and actively involved in deciding what form of treatment will be provided. The main goal should be symptom relief and home care. It remains unclear whether terminal nutritional support will have an impact on the quality or quantity of life, since prospective protocols are required to answer this question. It is concluded that the role of nutrition and/or simple hydration is an area for future investigation, and one in which well-defined endpoints should be planned.

In summary, standard (conventional) enteral or parenteral nutritional support rarely has a clear beneficial impact on the general outcome or quality of life in cancer patients. It is likely that some malnourished patients undergoing major cancer surgery can profit from peri-operative TPN; possibly few patients with incurable gastro-intestinal neoplastic disease may benefit subjectively from home parenteral or enteral nutrition. Important well-known changes in host metabolism and inadequate consideration of quality of life aspects contribute to a lack of success in a nutritional support so far practised with conventional nutrients.

Recently, characteristic metabolic changes in host metabolism have met with considerable attention, leading to the development of 'designer diets' and better, more complete parenteral substrates. Glutamine, arginine, polyunsaturated fatty acids, ribonucleotides and gestational hormones apparently have an established role in more recent nutritional concepts [8–12].

Today, we should move away from rarely effective standard nutritional support consisting of crude caloric substrates; the more promising approach of 'nutritional pharmacotherapy', which has an established role in the post-operative setting, may be expected to have a similar positive impact on nutritional deficits in patients with incurable disease, with aspects of long-term effects and quality of life receiving paramount attention.

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HAVING ACCEPTED my requested assignment to write this bridging editorial, I read the preceding pro and contra position articles. Reflecting on these two articles it became apparent that these debators are actually singing very similar tunes. So much so, that I am not sure I would have been able to pick out the 'pro' piece from the 'contra' piece if they had not been so labelled.

Both articles clearly agree that there are no data to support the routine use of parenteral or enteral nutrition in patients with advanced incurable malignancies. Both agree