Efficacy of Enteral and Parenteral Nutrition in Cancer Patients

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Before attempting to analyze the potential efficacy of the two different routes of administering nutrients to cancer patients, enteral nutrition (EN) versus total parenteral nutrition (TPN), it should be appreciated that patients who are usually fed via a vein are not the same as those who receive EN. In fact, nowadays, the option for TPN only emerges if a patient is not suitable for EN because his/her gut is not working. Consequently, the different effects of EN and TPN cannot be attributed only to the administration route of nutrients, but also to the different basic conditions of these two groups of patients.

There are, however, some exceptions: at the beginning of the era of artificial nutrition, TPN was more developed than EN probably because the impetus of this new approach relied on an urgent need to solve the problems of patients with intestinal failure. In fact, initially TPN was developed in surgical departments to meet the nutritional requirements of patients with short-bowel syndrome or abdominal catastrophes. This translated into the use of TPN also in patients with a working gut, and finally rendered a comparison between TPN and EN not only possible, but even scientifically rational and ethically acceptable. At this point we were roughly in the 1980s.

Another field where TPN and EN are frequently compared is the perioperative setting. Nutritional support in the perioperative period is not nutrition in the traditional meaning of the word: it is the attempt to control the metabolic reaction to surgical trauma and to potentiate the defenses of the patient through the administration of nutrients.

The indication for nutritional support in this patient population was questioned for a long time and the simple provision of a saline solution for a few days was usually accepted in many institutions. Consequently, in the literature, there are studies comparing not only different nutritional regimens and...
routes of administration in the perioperative period, but also nutritional sup-
port with saline solutions.

Finally, today the vast majority of patients receiving artificial nutrition is
fed enterally or intravenously depending on whether the gut is working or
not. Moreover, the current idea nowadays is that maintaining a working gut is
beneficial for patients and they are often administered minimal enteral feed-
ing in order to accomplish this aim even though macronutrient requirements
are mainly covered by the intravenous route.

EN and TPN have now completely reversed their original positions: in the
1970s, TPN was given to some patients even though they were able to be fed
enterally, whereas now strong emphasis is put on giving some nutrients enter-
ally even if the majority of the nutritional support can only be administered
venous route.

**Prospective Controlled Studies on Metabolic 
Effects of TPN and EN**

Only a few randomized [1–3] or prospective and controlled [4] studies have
compared TPN and EN (table 1). It appears that TPN was more effective
than EN in promoting weight gain [3] even though this gain may simply be
due to accrual of fat or water. Nevertheless TPN was able to maintain a bet-
ter nitrogen balance and plasma amino acid level [1, 3] and a positive balance
of K, Na, Cl, P and Mg [4].

In their study in 1983 Burt et al. [3] did not find any difference between
EN and TPN as far as whole body flux, protein synthesis and catabolism were
concerned. However, during the control (basal) period, whole-body protein
catabolism was uniformly and significantly higher than synthesis, and during
the period of nutritional repletion through EN or TPN the rate of whole-body
synthesis tended to be greater than that of catabolism. In addition, during the
period of nutritional support, the percentage of nitrogen entering the meta-
bolic pool that was derived from catabolism of protein was significantly
decreased in both EN and TPN groups.

The study by Dresler et al. [5] showed that before nutritional repletion,
the flux of nitrogen entering the metabolic pool originated solely from the
breakdown of body protein and about 75% of this flux was utilized in protein
synthesis. However, when an exogenous supply of amino acids was intro-
duced in cancer patients, utilization efficiency decreased to 58% during EN
and to 39–43% in cancer patients during TPN [3, 6]. There appeared to be a
definite advantage for the enteral route in terms of utilization for synthesis of
body proteins.

Overall, both EN and TPN tend to stabilize the nutritional status and
whole-body protein economics and, depending on the type of metabolic
parameter adopted, TPN or EN appears to be slightly more effective.
**Randomized Controlled Trials on the Efficacy of Perioperative TPN and EN**

Whereas there are a large number of articles comparing EN to TPN, the number decreases when randomized studies are considered. These studies only include cancer patients (both as a total or as the majority of the series) are homogeneous with regard to the nutritional status and are particularly well matched as far as the calorie and nitrogen intake of the nutritional regimens of the 2 groups are concerned.
There are in fact some excellent metabolic studies [7, 8] demonstrating the benefits on whole-body protein kinetics and the hormonal pattern with postoperative EN as compared with simple standard intravenous nutrition. However, they do not solve the dilemma of whether the benefit is due to the quality of the nutritional regimen or to the route of administration of nutrients.

Table 2 summarizes the clinical outcome in 8 randomized controlled trials (RCTs) [1, 9–15] comparing EN (tube feeding) and TPN in malnourished and non-malnourished cancer patients. Interpretation of these studies, which belong to the past century is not easy: some authors counted the number of patients with one or more complications, others computed the number of single complications. Moreover these studies only included a small number of patients, hence the statistic power appears to be very small.

To my knowledge there are only 3 RCTs that compared two isoenergetic and isoprotein regimens, one by vein and the other by the enteral route, in a large number of patients with gastrointestinal cancer.

A study published by Braga et al. [16] included 257 patients, less than half of whom had weight loss of >10%, and serum albumin was approximately 3.7 g/dl. The nutritional intake was 24.4 and 23 kcal/kg/day in the TPN and EN groups, respectively. Overall, complications occurred in 56.4 and 49.2% of TPN and EN patients, respectively (not statistically significant). The authors considered the subgroup of malnourished patients in a post hoc analysis, and found a significantly shorter duration of hospital stay in EN than TPN patients.
In the second study, Pacelli et al. [17] randomly assigned 241 patients (>90% with gastrointestinal cancer) with moderate malnutrition (15% body weight loss and albumin 3.6 g/dl) to a daily nutritional regimen of 24.8 (TPN) or 25.3 kcal/kg/day (EN), respectively. Major complications occurred in 39.3 and 37.8% of TPN and EN patients (not statistically significant), respectively, with no difference in mortality (2.5 and 5.9%, respectively). The duration of postoperative stay was 15 and 16 days in the EN and TPN groups, respectively.

The third study was launched by the Italian Society for Parenteral and Enteral Nutrition (SINPE) [18] and was conducted in 317 patients with moderate to severe malnutrition (13–14% body weight loss, serum albumin 3.4–3.5 g/dl and 1,541–1,573 peripheral lymphocytes/mm³). Those patients were randomly assigned to early EN or TPN (mean 26 kcal/kg/day and 1.4 amino acids/kg/day) for 1 week, starting on the 1st postoperative day. There was a benefit for the EN versus TPN patients with respect to postoperative complications (34.0 and 49.4%, respectively; risk differential 15%; p ≤ 0.02) and to postoperative stay (13.4 and 15.0 days, respectively; p = 0.009). Adverse effects of nutritional support were more frequent in EN patients (35%) than in TPN patients (14%; p < 0.001), however.

How can these conflicting results be reconciled? A possible explanation is that the advantage of EN is confined to malnourished patients. The majority of patients in the study of Braga et al. [16] were not malnourished, those in the study of Pacelli et al. [17] were moderately malnourished, and those in the SINPE study [18] were more malnourished because their serum albumin was somewhat lower and peripheral lymphocytes were often below the normal range; only within this latter group of patients was there a clinical benefit from EN.

Quite recently a large study [19] on 54,215 patients reported that in regression models, the albumin level was the strongest predicting factor of surgical mortality and morbidity, and similarly Kudsk et al. [20] confirmed on 526 candidates for abdominal surgery that preoperative albumin correlated inversely with complications, length of stay, postoperative stay, intensive care unit stay, mortality and resumption of oral intake. They write that ‘this lack of appreciation for nutritional risk ... can explain discrepancies in outcome noted in several randomized, prospective nutrition studies’. More precisely, by categorizing the patients according to the level of serum albumin at intervals of 0.5 g/dl, they were able to demonstrate that each class of patients had a statistically different frequency of major complications.

Second, malnourished patients need to receive an adequate amount of protein if they are to benefit from EN. It is worth noting that the SINPE study [18] patients received 30% more nitrogen daily in comparison with those from the study by Pacelli et al. [17]. This might account for the quicker and safer recovery from surgery in the former group.

Finally, criticism concerning the quality of complications that could account for the discrepancy in benefits from EN [21] is not substantiated by
the fact that patients randomized to EN in the SINPE trial also had a shorter postoperative stay.

The reasons for the beneficial effects of EN versus TPN in this setting are largely unknown. It is interesting, however, that Reynolds et al. [13], who conducted a RCT of early EN feeding versus TPN (an almost isocaloric and isonitrogenous regimen) in 67 patients after major gastrointestinal surgery, observed no significant difference between the groups with respect to intestinal permeability, acute-phase response and endotoxin exposure.

In an attempt to further clarify the complex relationship between nutritional status (weight loss), postoperative complications and type of nutritional support, data on 1,410 patients entered in RCTs on perioperative nutrition, coordinated by the Istituto Tumori of Milan and San Raffaele Hospital of Milan over the last 8 years, were reviewed. Patient data were obtained from electronic databases specifically created to achieve charts of all those subjects included in RCTs designed to test the effect of different nutritional approaches on clinical outcome [16, 18, 22–25].

Figure 1 shows that, in groups of patients at varying risk of surgical complications, low or high (depending on level of serum albumin, age and type of surgery), the probability of complications changes according to the degree of weight loss, and EN and immune-enhancing EN are always better than TPN and standard isotonic fluids.
Survival of cancer patients on home artificial nutrition is largely dependent on the severity of the basic disease. Unfortunately many series mix together patients with simple sequelae of cancer, i.e. radiation enteropathy or chronic surgical complications or mutilations, patients with active cancer who are receiving oncologic therapy and finally patients with incurable cancer.

For this last group there are divergent opinions regarding the indication both between different countries and different institutions within the same country. Therefore, disparity in the composition of the series and indications for home artificial nutrition can account for different survival rates in reports on patients receiving home TPN or home EN, and when comparing the two procedures.

In a series of small retrospective studies of patients receiving home TPN [26–32], the median survival ranged from 53 to 120 days. More reliable are studies reporting large institutional experiences or data from national registers, or pooling data from several nations. Table 3 shows that most of the 1-year survival rates range between 20 and 30% [33–37]. This figure is in keeping with data of the British Artificial Nutrition Survey [38] which in 1999 reported a 26% survival at 1 year. If one considers more favorably selected series of patients (non-terminal cancer patients), a survival rate of 38% at 5 years is observed [39]. The survival rate from the Register of the Italian Society for Parenteral and Enteral Nutrition is shown in figure 2.

The survival rate in some series of patients receiving home EN is reported in table 3 [33–35]. It is noteworthy that in some of them survival at 1-year surpasses 30%. Moreover data from the British Artificial Nutrition Survey show that in patients with upper gastrointestinal cancer the 1-year survival is 70–80% [41], and in the series of the Nice group [42, 43] the 1- and the 4- to 5-year survival rates were 38.8 and 23.8–21.7% respectively.

Data on quality of life (QoL) are more sparse. There are some retrospective analyses [27, 29, 39] which would indicate a very limited benefit in patients on home TPN: the Karnofsky performance score increased in 7% of patients after 1 month [28], and in 68% of patients surviving longer than 3 months [29], the ability to sustain daily activities and oral intake improved in 27% of patients [44]. According to the data of the North American Register, 31% of patients appeared to be completely rehabilitated at 1 year.

An ad hoc study has recently been published by Bozzetti et al. [31]. Sixty-nine advanced cancer patients enrolled in a program of home parenteral nutrition in 6 different Italian centers were prospectively studied with regard to nutritional status (body weight, serum albumin, serum transferrin and total lymphocyte count), length of survival and QoL through the Rotterdam Symptom Checklist questionnaire. These variables were collected at the start of home parenteral nutrition and then at monthly intervals. All these patients were severely malnourished, almost aphagic, and beyond any possibility of cure. They reported a median survival of 4 (range 1–14) months with about
one third of the patients surviving more than 7 months, and nutritional indices maintained stable until death. QoL parameters remained stable until 2–3 months before death.

The authors concluded that home TPN may benefit a limited percentage of patients who may survive longer than the time allowed by a condition of starvation and depletion. Provided that these patients survive longer than 3 months, there was some evidence that QoL remains stable for some months and acceptable for the patients.

With reference to home EN, it appears from data of the National Register Information of the USA [32] that 79% of patients were able to achieve full rehabilitation. Similarly some retrospective studies report that 75% of cancer patients on home EN had a subjective improvement of QoL [46].

In a prospective study including a mixed population of cancer and non-cancer patients, Loser et al. [42] reported an improvement in Karnofsky and Spitzer indices and in the EORTC QLQ C 30 self-rating questionnaires.

Table 3. Survival of cancer patients on home TPN and EN

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>Period of study</th>
<th>Number of patients</th>
<th>Survival</th>
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<tbody>
<tr>
<td><strong>Home TPN</strong></td>
<td></td>
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<tr>
<td>Howard [33], 1993</td>
<td>1985–1990</td>
<td>1,672</td>
<td>28% at 1 year; median 6 months; mean 4 months 37% at 1 year</td>
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<tr>
<td>Howard et al. [34], 1995</td>
<td>1985–1992</td>
<td>2,122</td>
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<tr>
<td>Messing et al. [35], 1998</td>
<td>1993–1995</td>
<td>524</td>
<td>19.5% at 6 months</td>
</tr>
<tr>
<td>Van Gossum et al. [36], 1999</td>
<td>1997</td>
<td>200</td>
<td>26% at 6–12 months</td>
</tr>
<tr>
<td>Howard [37], 2000</td>
<td>1984–1988</td>
<td>1,073</td>
<td>25% at 1 year; median 6 months</td>
</tr>
<tr>
<td>SINPE Register 2004a</td>
<td>1980–2003</td>
<td>1,103</td>
<td>20% at 1 year; median 6 months</td>
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<table>
<thead>
<tr>
<th><strong>Home EN</strong></th>
<th>Period of study</th>
<th>Number of patients</th>
<th>Survival</th>
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<tbody>
<tr>
<td>Howard [33], 1993</td>
<td>1985–1990</td>
<td>1,296</td>
<td>32% at 1 year; mean/median 6 months</td>
</tr>
<tr>
<td>Howard et al. [34], 1995</td>
<td>1989–1992</td>
<td>1,644</td>
<td>41% at 1 year</td>
</tr>
<tr>
<td>Gaggiotti et al. [40], 2001</td>
<td>1992–1999</td>
<td>3,690</td>
<td>Mean</td>
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<tbody>
<tr>
<td>Head-neck</td>
<td>18.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus-stomach</td>
<td>13.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon-rectum</td>
<td>21.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary</td>
<td>16.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>10.7</td>
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*Courtesy of Dr. A. Palmo.*
Schneider et al. [43] prospectively studied the QoL-related parameters in 38 patients (11 with cancer) and reported that patients on home EN have a poorer QoL than the age- and sex-matched general population, probably because of their underlying disease. A more complete study is that by Robergé [49] who prospectively investigated 39 cancer patients using 3 questionnaires, EORTC QLQ-C30, EORTC HEN 35, OES 24, that were to be filled in after 1 week of hospital discharge and 3 weeks later. They found a slight improvement in QoL and in symptoms such as constipation, coughing, social functioning and body image/sexuality. However, one third of patients felt uncomfortable with body image.

Conclusions

The scenario of enteral and parenteral nutrition in cancer patients is not uniform. Not only do the final effects depend on the type of evaluation, metabolic versus clinical, but for both the outcome is affected by the duration of the nutritional support and by the biological-clinical aggressiveness of the malignancy.

The less aggressive the tumor, the less the impact on the nutritional status is and the longer the time allotted to the artificial nutrition is to improve the general status of the patients.

In the short-term, both EN and TPN seem to be equivalent. The metabolic benefits sometimes described for TPN versus EN or vice versa are not strong enough to endorse the choice of one route over the other. Should both routes be available, the option may depend on the availability of proper access, the need of particular formulations and other clinical and logistic factors which may render nutritional support more practical and easier in that single case.

Table 4 summarizes the advantages and disadvantages of both approaches with a particular emphasis on some of these points that can finally lead to the choice of one or the other approach.

Fig. 2. Survival of incurable cancer patients on home TPN.
In the perioperative setting there is compelling evidence that the enteral route is the first choice. It is much more evident now that perioperative EN works more as a complex drug able to favorably modulate the cytokine pattern and the immune response than as a support capable of restoring a depleted nutritional status.

When patients need a long-term nutritional support at home, the choice is definitely conditioned by the degree of intestinal failure. If this is not total, the enteral supply of small quantities of nutrients is usually recommended not only to integrate TPN but also to prevent metabolic complications. There are, however, some clinical circumstances where both procedures could be applied. In such cases consideration of patient preference should be included in decisions on the method of feeding.

In an ad hoc study Scolapio et al. [50] explored the patient’s preference of therapy. They distributed a written questionnaire to 101 hospitalized oncology patients and 98 outpatients without gastrointestinal illness. Patients were asked their preference of nasogastric versus TPN feeding. In both groups, the majority preferred TPN over EN. Preference was related to patient perception of the comfort of these interventions. In logistic regression analyses, the strongest influence on preference were age and perceived comfort of TPN feeding. Consequently, awareness of patient preference should be taken into account when making decisions regarding the route of nutrient delivery.

### Table 4. Advantages and disadvantages of TPN and EN

<table>
<thead>
<tr>
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<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td><strong>TPN</strong></td>
<td>As much as is needed can be given</td>
<td>More expensive</td>
</tr>
<tr>
<td></td>
<td>A working gut is not required</td>
<td>More demanding</td>
</tr>
<tr>
<td></td>
<td>Regimen may be adjusted without withdrawal</td>
<td>Potentially more dangerous</td>
</tr>
<tr>
<td></td>
<td>Better modulation of substrates</td>
<td>More prone to stimulate tumor growth</td>
</tr>
<tr>
<td></td>
<td>Compliance may be better (patients may harbor a CVC for other purposes)</td>
<td></td>
</tr>
<tr>
<td><strong>EN</strong></td>
<td>Simple</td>
<td>It requires a functioning gut</td>
</tr>
<tr>
<td></td>
<td>Low cost</td>
<td>NG tube is often required</td>
</tr>
<tr>
<td></td>
<td>Metabolically better</td>
<td>Critical volume to meet the nutritional requirements</td>
</tr>
<tr>
<td></td>
<td>Less stimulation of tumor growth</td>
<td>Adverse effects force to withdraw nutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Compliance may be poor</td>
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References

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41 British Artificial Nutrition Survey (BANS) Annual Report, PO Box 992, Maidenhead Berks, SL6 4SH UK (BAPEN), 1999.


Discussion

Dr. Powell-Tuck: I enjoyed your very elegant presentation as much as ever. The difference internationally is largely around the use of home nutritional support for cancer patients. I obviously come from a country that uses this very little, although in parts of London occasional patients with perhaps a very high stoma or a patient with sclerosing peritonitis are supported with home parenteral nutrition (PN). I have a little bit more difficulty in really understanding how home PN and home enteral nutrition (EN) are being used by those that advocate them more widely. I wondered if you could fill in color in some of the indications for home care in your own practice in Italy which might differ from this more extreme care that we use in the UK? What do you think the difference is for home nutritional support between the countries?

Dr. Bozzetti: I think that there is large variation in the indications not only between different European countries but also between different regions in Italy or even institutions in the same town; this reflects cultural attitude. I am an oncological surgeon, and I know that when a patient has a cancer many general surgeons consider that there is nothing more to do, and this is just the opposite if we take care of a cancer patient in a cancer center. So I admit we have an aggressive policy. As oncologists we are also more and more conditioned by the fact that our cancer therapy is very often palliative. We see that we are not able to cure a cancer of the pancreas for instance, and we always need to follow our patients with a palliative approach as much as possible. But coming to your question, I think that the patients who really could benefit from this approach are patients who are more likely to die due to starvation than tumor progression. So I think that our major effort should be to try to identify the patient population who will be dying from starvation and theoretically could benefit from nutritional support. These are the patients who have an advanced tumor without involvement of the vital organs, patients without liver metastases, patients without lung metastases; on the contrary young and relatively healthy patients with abdominal carcinomatosis from a slow growing tumor. A classical example is a young female patient with ovarian cancer and abdominal carcinomatosis from ovarian cancer, and these patients do not need an excess of palliative care. Patients who receive strong analgesic therapy, which could also complicate their quality of life because they are lying in bed all the time and are treated with sedatives and this type of drugs, and patients with ascites or respiratory problems should not be considered because their condition could be worsened by the administration of fluid. So I think that perhaps if we try to select a favorable group of patients there is a benefit. Of course I agree with you that now we don't have a clear parameter to specifically select this group of patients, but I think it should be a focus for future research.

Dr. Lochs: I was quite surprised by your very nice summary. Thank you for summarizing all the literature so well, because our standard assumption is that EN is better metabolically and immunologically and usually this is not true in cancer patients. Why is that so? Is that probably the main reason that most cancer patients do not have a functioning gut or is there another reason that the immune situation of
the cancer patients is so deteriorated that even EN does not save them from complications? Because this was really surprising to me. Metabolically you showed that PN is better and quality of life, so there seems to be almost no reason to start EN in these patients.

**Dr. Bozzetti:** No, I think that EN is better. I think that in the cancer patient population perhaps the most frequent indication is an obstruction or a sub-obstruction of the bowel so in this kind of patients you cannot use this route. The other problem is that if the patients are anorexic for a variety of reasons and they have a central venous catheter, sometimes it is practically easier to give them nutritional support by a vein because the alternative would be to place a nasogastric tube and this is psychologically bad. So in many patients I support this way because I agree with the statement made by the study of Scolapio [1] that fluid via a vein is a well-accepted procedure. But I agree with you, from the physiological metabolic point of view, especially for long-term nutrition, EN is definitively better and probably also with regard to tumor growth. In the literature there are 7 or 8 studies comparing tumor growth by the incorporation of specific indicators and the results show that PN better supports tumor growth than EN. So it is the type of population that forces you to modulate the nutritional approach, but I agree with you that EN is better than PN.

**Dr. DeLegge:** I have a statement and a question. The statement is that your data on home PN are very similar to those published August et al. [2] back in the early 1990s regarding malignant bowel obstruction and home total PN (TPN) where they also showed that if the patients had a good Karnofsky scale prior to starting home TPN they did quite well at home. That is a suggestion we should make use of and in fact perhaps we need to use it for home EN evaluation, a functional scale. In the case of someone having a malignant biliary obstruction there wouldn’t be very much hesitation in the US to put in a metal biliary stand at the cost of thousands of dollars, but yet there is a reluctance to utilize home nutrition support in a very similar patient population. I don’t see the difference. My question to you is invariably on the PN to EN studies. Patients on EN receive less calories because of the fact that someone is withholding their tube feeding for a gastric residual or perhaps going off to the X-ray suite. So in most of those studies although they were supposed to get similar amounts of calories, was that really so? Meaning, in the studies you showed us, the TPN patients and the PN patients invariably received more calories and more nitrogen per day than the EN patients, but yet they still had very similar results.

**Dr. Bozzetti:** With the exception of the study by Lim et al. [3] in 1981 in the *British Journal of Surgery* where the TPN included a hypercaloric regimen, both the studies by Nixon et al. [4] and Brennan et al. [5] perfectly matched the quantity of nitrogen and calories and there were no significant differences between the groups. But in the practice of home TPN and home EN, I agree with you that patients receiving EN usually receive less calories and this may be a crucial point. Especially if you have a gastric approach the patients may experience a full satiety feeling and you are obliged to stop the administration of nutrients. This doesn't occur with TPN. So you are obliged to use a hypercaloric formula.

**Dr. Labadarios:** I just want to pick up from Dr. DeLegge’s point. You know there is a lot of lip service paid to nutrition, but when it actually comes to budgetary issues, both at the policy and the practice level, there is very little that is actually made available to support nutrition. Now at the policy level, we have tremendous problems to convince the administrators that nutrition is important is life-saving, and is a cost-saving practice. But I wonder to what extent is it appropriate for us in the nutrition field to call any form of nutritional support expensive. In what sense is it expensive? What is the reference point for comparison? One wonders, or is it just a point of debate? It is a life-saving therapy that needs to be administered like any other therapy, and yet
when it comes to nutrition support, it is expensive. I have a problem with that, or a little bit of difficulty in understanding the approach to it.

Dr. Thomas: I have a couple of questions with regard to the route of administration and duration. This was mostly in oncology patients and the mean duration is fairly short; there is another group of patients who are more long-term in home care. So the question would be first, in the preference study you showed from the Mayo Clinic was for nasogastric intubation versus vein, and no mention of percutaneous intubation. I wonder if it is different when you give that option rather than nasogastric? Second, can you comment on the maximum duration or main duration that you are able to maintain these patients on in terms of parenteral nutrition? Did you use percutaneous tubes, the jejunostomy tubes? What is the duration you can expect to be able to maintain these tubes?

Dr. Bozzetti: With regard to the Scolapio [1] study, you are right, Scolapio investigated the preference of the patients and the choice was between intravenous catheters and the nasogastric tube. As an abdominal surgeon I think there are very few patients with advanced disease, anorectic and malnourished, who could benefit from a gastrostomy or a jejunostomy because the main indication for nutritional support is undernutrition due to intestinal obstruction or peritoneal carcinomatosis. I don’t exclude this, but there is little room for this approach. In my experience it was possible to perform surgically a jejunostomy in some patients because when during the operation we realized that there was no possibility of cure. There is a small percentage of the patients who are managed by jejunostomy which, in this condition, is not so different from the patients receiving TPN. The long survival of patients receiving EN is due to the fact that these patients had a less aggressive tumor of the upper digestive tract with no problem in the abdominal cavity. In my experience gastrostomy or jejunostomy can be performed for this purpose in a few patients who are candidates for nutritional support, so I don’t exclude it but it is a rare occurrence.

Dr. Buchman: Tumors are rapidly growing in dividing cells and therefore they act as nutrient sinks. Do you think therefore that there are actually any carefully controlled studies that clearly demonstrate that the tumors of patients who were fed by PN grew at a more rapid rate than those in patients fed enterally? But in any case do you think that the fact that invariably in every study that has ever been published (there is one unpublished study that I am aware of), patients who received PN always receive more calories than EN, as Dr. DeLegge has pointed out? Do you think this could be the reason for the fact that, if it is true, tumor growth is enhanced with PN? In Europe glutamine dipeptide has been used in great proportions, and given the fact that some tumors are exclusively sensitive to glutamine, and in animal models tumor growth is enhanced by glutamine [6], do you think that glutamine-supplemented TPN would also be part of the reason that tumor growth could be enhanced?

Dr. Bozzetti: Quite interesting questions. With regard to the first one: I can say that I disregard many of the studies in experimental tumors. Experimental tumors are different from the human tumors. In experimental tumor the weight of the tumor can account for 20 or 30% of the weight of the carcass and so when we feed a tumor-bearing animal we directly feed the tumor. The condition in humans is totally different because even in patients with a big tumor it usually never accounts more than 0.1% of the body weight of the patients. With reference to your question we have tried to explore this problem by giving a glucose-based regimen or a lipid-based regimen to cancer patients with liver metastases and to study the [fluorodeoxyglucose uptake of the tumor with positron emission tomography [7]. The two regimens were quite identical but all the non-protein calories were given in the lipid group as fat, and no glucose was given at all. We saw that the utilization of glucose was the same in the patients receiving the mixed regimen and the lipid regimen. Even if the tumor is
utilizing glucose and not lipid, we cannot support the statement that a glucose-based nutrition is dangerous for the patient, because when the size of the tumor and its metabolic capacity are calculated we realize that the quantity of the glucose necessary to support tumor growth is very small, and anyway the small quantity of glucose made by the gluconeogenesis is enough to support tumor growth. What we have also observed is that tumor growth within the liver had a such a high metabolic capitation of the glucose that it seems to have worked at the maximal capacity possible. So it was not affected at all by the administration of glucose or the administration of a lipid regimen. The second question: theoretically you are right, in the laboratory it is possible to stimulate tumor growth and the growth of some cells by adding glutamine. I am not skeptical; I accept that cancer patients could receive glutamine for two reasons. One because as a surgeon I accept the risk; I accept that when I perform an operation there can be some infection, there can be some complications or some morbidity and so on, so I can also accept that if the patient needs glutamine for bone marrow function or for immune system function, this could be deleterious for the tumor growth. Secondly, I am aware of a wonderful study published in *Cancer Research* by Holm et al. [8] who measured the flux across the tumor in vivo and the dynamic balance of the substrate. They were able to demonstrate that glutamine is not introduced and utilized by the cancer cell, at least colon cancer cell and gastric cancer cell; the colon cancer cell because the study was done in patients with colon cancer. So I think that this is a theoretical possibility that glutamine stimulates tumor growth, but it has not been substantiated in human studies. Probably glutamine can be utilized and can be useful for other purposes, so I don’t see any major contraindication to use it.

**References**