Clinical Nutrition Highlights
Science supporting better nutrition

Nutrition and Patients’ Outcomes in Oncology

Special Issue
September 2013

Nestlé Nutrition Institute
Nutrition and Patients’ Outcomes in Oncology

Cancer Treatment and Nutrition
Zeno Stanga, MD

Approaches to Nutritional Supplementation in Patients Undergoing Neoadjuvant Chemoradiotherapy and Surgery for the Treatment of Esophageal and Esophagogastric Cancer
Donald E Low, MD, FACS, FRCS(C)

Nutrition Modulation of Chemotherapy Efficacy and Toxicity
Vickie E Baracos, PhD

Nutritional Interventions Improve QoL
Jens Kondrup, MD, PhD

Specialised Nutritional Intervention During Chemotherapy
Alessandro Laviano, MD
Cancer Treatment and Nutrition

Zeno Stanga, MD
Head of the Nutritional Support Team, Division of Endocrinology, Diabetes and Clinical Nutrition, and Division of General Internal Medicine, University Hospital, Bern, Switzerland

Introduction

Deterioration of nutritional state and persistent weight loss may have deleterious consequences for cancer patients. The prevalence of cancer-related malnutrition ranges from 30-74% in in- and out-patients, and is related to an increased risk of adverse clinical outcome13, poor quality of life, and lower survival rates8,10. In addition, as many as 20% of cancer patients die from the effects of malnutrition rather than from the malignancy11. Nutritional state tends to decline during the course of hospitalization and malnutrition is associated with increased morbidity and mortality, prolonged hospital stay and increased health care costs12-16. Furthermore, malnutrition worsens the responsiveness and tolerance to anti-cancer therapy13. On the other hand, early and adequate provision of nutritional support for those identified as malnourished has demonstrated an improved outcome16-17. It is therefore essential that nutritional issues are addressed at the time of diagnosis and throughout the course of anticancer treatment. In a recent multicenter, prospective cohort study Pan et al. showed the impact of malnutrition, nutritional risk, and nutritional treatment on clinical outcomes18. High nutritional risk score was significant when related to the increased rate of adverse events. Moreover the research group demonstrated that enteral and parenteral nutrition in hospitalized cancer patients significantly reduces the risk of adverse events19.

Goals of nutritional support in cancer patients

Cancer disease and nutrition are key determinants of patients’ quality of life. In oncology patients the quality of life scores are determined mainly by cancer location (30%), weight loss (30%) and nutritional intake (20%)19. The therapeutic goals of nutritional support in cancer patients - prior to, during, and after anticancer treatment - are to maintain and/or improve nutritional status, function and outcome. This is done by:

• Preventing and treating cancer-related or therapy-related malnutrition
• Preventing or reversing weight loss
• Enhancing compliance and minimizing nutrition-related discomfort (adverse effects) associated with anti-tumor therapy
• Improving treatment efficacy
• Improving strength and quality of life.

Impact of food on anticancer drugs (e.g., interactions between anticancer drugs and nutritional supplements)

There is a paucity of clinical data in the literature regarding this issue. Use of herbal supplements and vitamins in patients receiving chemotherapy is common: McCune et al. reported a frequency of 78%, with 27% of the study participants being at risk of a detrimental chemotherapy-herbal and/or vitamin interaction20. Food interactions with chemotherapy are often difficult to assess, given the polypharmacy that exists in oncology patients and the frequent inability to distinguish which factor is responsible for a specific toxicity. Food can interact with chemotherapy through reduction of the bioavailability and/or by induction or inhibition of the metabolism of the administered drug, often due to their metabolism by the cytochrome P450 system21. The most popular are herbal supplements and micronutrients such as calcium, multivitamins, and antioxidants. Sudden and unexplained changes in the clinical response of a patient to prescribed chemotherapy could be the result of a food-drug interaction.

Nutrition support during cancer treatment

Since malnutrition can have a major influence on general well-being, performance status, and even symptoms (e.g., fatigue), it also seems reasonable that they might have a negative impact on various oncological outcomes, such as treatment success. Weight loss is one of the factors that defines malnutrition in patients with cancer, and it is a major cause of morbidity and mortality18,22. Furthermore, an impaired nutritional state during cancer treatment has been associated with a number of clinical consequences and a range of poor outcomes, including more emergency room visits, increased in-hospital complication rates, increased length of hospital stay, more treatment interruptions, compromised treatment efficacy, reduced quality of life, and decreased survival18,23. The global pandemic of obesity has recently yielded to an increase in mean body mass index of cancer patients at presentation24. Indeed, it is now frequently reported that a relevant proportion of cancer patients at admission is overweight or even obese. However, those patients should receive the same nutritional attention as their underweight counterpart, since weight loss is a negative prognostic factor for obese or malnourished cancer patients. It is increasingly supported by evidence that weight loss might not be detected in those patients, yet the cancer patients are at nutritional risk for the presence of sarcopenic obesity (i.e., simultaneous presence of excessive fat mass and depleted muscle mass)25.
Malnutrition in cancer patients, also known as cachexia, is a continuum of progressive depletion of nutritional state (loss of skeletal muscle mass) and worsening of metabolic alterations. Its clinical manifestations range from pre-cachexia (i.e., minimal, if any, weight loss, but presence of metabolic alterations) to refractory cachexia (i.e., severe weight loss and wasting, characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism)\textsuperscript{24}. Therefore, in cancer patients some suggest that actual body weight is not a sufficient criterion to diagnose malnutrition or the nutritional risk, but validated nutritional screening tools should be used, or weight loss history collected (weight loss >5%, or weight loss >2% in individuals already showing depletion according to current body mass index <20 kg/m\textsuperscript{2}), or, preferably, changes in muscle mass assessed\textsuperscript{24}.

Various authors have focused on nutritional risk as a cause of delay and even failure in the scheduled administration of antineoplastic treatments\textsuperscript{27}. Malnutrition may also be responsible for increased toxicity of antitumoral drugs, and for several complications following the treatment. It may cause changes in the ESPEN's nutritional guidelines, and ultimately elimination, as already reported for some drugs in the literature. Therefore, maintaining adequate energy intake during therapy is mandatory, and requires considerable commitment and motivation on the part of most patients. Nutritional support should be based on nutritional state, general conditions, patient tolerance, tumor site, stage of disease, treatment, and related side effects\textsuperscript{27}.

Nutritional counseling and psycho-oncologic support may be needed to help and encourage patients to comply with their nutritional support requirements. According to a recent study by Ravasco et al. early individualized nutritional counseling and education during radiotherapy is valuable and is effective at improving long-term prognosis in cancer patients\textsuperscript{28}. An impaired nutritional state, identified with a nutritional screening tool, will consequently lead to a nutritional care program. For this purpose, a simple, reliable, easily applied and reproducible scoring system, such as the Nutritional Risk Screening 2002 (NRS 2002) tool developed in collaboration with the ESPEN, could be used. The NRS 2002 is a reliable, applicable and reproducible tool to easily identify hospitalized patients at nutritional risk\textsuperscript{29}. Management by dieticians is available in most cancer centers and hospitals.

Oral nutrition is always the first method of choice. Individualized approaches are important in order to set realistic and achievable goals\textsuperscript{30}. Substrate requirements depend on the pathological condition of the patient, with energy intake varying between 25 to 40 kcal/kg body weight/day, depending on physical activity. To minimize weight loss and facilitate repair and regeneration of damaged tissues, dieticians will formulate various suggestions for consideration by treating physicians, such as a high-energy and high-protein diet providing adequate macro- and micronutrients, allowing specific deficiencies to be replaced. If oral intake drops below 20% to 40% of daily energy requirements, the measures should include a patient-adapted intervention plan, starting with easy but essential measures such as the creation of a daily meal schedule (quantity, quality and presentation of menu), introduction of small and frequent snacks between meals, and addition of oral sip drinks and nutritional supplements. Fruit shakes should be offered to tempt the appetite. The modification of food texture may be required to facilitate chewing and swallowing. Dry mouth and changes in taste perception may increase the effort required for optimal intake. The goal of oral intake is to achieve more than 75% of the daily energy requirements. If this objective cannot be met, other types of nutritional support, such as enteral or parenteral nutrition, have to be evaluated\textsuperscript{31-33}.

In the presence of inflammation, dietary supplementation of omega-3 fatty acids may provide beneficial effects by modulating several aspects of the inflammatory response. During chemotherapy, omega-3 fatty acids may contribute to the reduced inflammatory response, but whether cancer treatment toxicity can be prevented remains to be assessed\textsuperscript{34,35}. Recent small studies demonstrated that omega-3 fatty acids increase response rate to chemotherapy\textsuperscript{36}.

In cachectic cancer patients, low serum carnitine levels have been reported, and this change has been suggested to play an important contributory role in the development of cachexia. Based on these data, carnitine supplementation has been tested in preliminary studies concerning human cachexia, resulting in improved fatigue and quality of life\textsuperscript{37-40}.

In recent decades progress has led to reduced morbidity and mortality after cancer surgery. However, even with such efforts, perioperative complications are frequent in oncology patients, and therefore adequate nutritional support needs to be introduced to minimize the risk of potential complications in the preoperative phase. There is substantial evidence that a deteriorated preoperative nutritional state adversely affects outcome in terms of increased complications and reduced quality of life, which again have cost implications for the health care system\textsuperscript{41}. An impaired nutritional state before major surgery is related to increased incidence of nosocomial infections, longer length of stay (i.e., intensive care unit), frequently re-admission to hospital and higher mortality\textsuperscript{42}. Malnutrition may also influences multiple organ dysfunction, functional recovery, wound healing and the incidence of postoperative surgical wound infections. The stress of surgery or trauma additionally increases protein and energy requirements by creating a hypermetabolic, catabolic state. As a result, identifying and treating malnutrition in cancer patients prior to the operation is critical to achieve favorable patient outcomes. Preoperative nutritional support of the patient gained increased attention due to several landmark randomized controlled studies by Braga et al. showing that severe morbidity could be reduced by approximately 50% in patients undergoing major surgery for upper gastrointestinal cancer\textsuperscript{35}. With special regard to patients with obvious severe nutritional risk, those undergoing major cancer surgery of the neck (laryngectomy, pharyngectomy) and of the abdomen (oesophagectomy, gastrectomy, and pancreaticoduodenectomy) benefit from the use of immune modulating formulae, namely enriched with arginine, omega-3 fatty acids, ribonucleotides, with or without glutamine\textsuperscript{43-45}. Four recent meta-analysis showed that preoperative immunonutrition improves outcome in major abdominal surgery, even in patients not at nutritional risk\textsuperscript{46-49}.

**Monitoring of nutritional state and nutritional support during cancer treatment**

First-line monitoring strategies should include a routine, accurate, practical and non-time-consuming nutritional screening (i.e. NRS 2002), which should be performed at diagnosis, before and during anti-cancer treatment. It is mandatory to identify patients at nutritional risk who can profit from adequate and rapid nutritional support. Patients at nutritional risk should be assessed with a carefully performed medical history, a clinical examination, and collection of selected laboratory data.

Although screening and monitoring of the nutritional status can often be performed with simple tools, the following personalized parameters should be taken into account:

- Primary tumor site affected and presence of metastases.

---

\textsuperscript{27} Ravasco et al.
\textsuperscript{28} Four recent meta-analysis
\textsuperscript{29} Braga et al.
\textsuperscript{30} Malnutrition may also influences multiple organ dysfunction
\textsuperscript{31} Functional recovery, wound healing and the incidence of postoperative surgical wound infections.
\textsuperscript{32} Stress of surgery or trauma additionally increases protein and energy requirements by creating a hypermetabolic, catabolic state.
\textsuperscript{33} As a result, identifying and treating malnutrition in cancer patients prior to the operation is critical to achieve favorable patient outcomes.
\textsuperscript{34} Preoperative nutritional support of the patient gained increased attention due to several landmark randomized controlled studies by Braga et al.
\textsuperscript{35} With special regard to patients with obvious severe nutritional risk, those undergoing major cancer surgery of the neck (laryngectomy, pharyngectomy) and of the abdomen (oesophagectomy, gastrectomy, and pancreaticoduodenectomy) benefit from the use of immune modulating formulae, namely enriched with arginine, omega-3 fatty acids, ribonucleotides, with or without glutamine.
• Pre-existing medical conditions.
• Type and frequency of treatments and potential side effects, such as nausea, vomiting, lack of appetite, mucositis, disturbances of taste and smell, dryness of the mouth, swallowing difficulties, constipation and/or diarrhea.
• The effect of malignancy on the ingestion, digestion, and absorption of nutrients.
• Current food intake and appetite quality. To demonstrate a reduced intake of normal food, a simple 24-48-hour recall is usually sufficient. Calculation of the actual energy and protein intake.
• Both physical functioning and components of the psychosocial effect should be assessed. Therefore, performance state (i.e., patient-reported physical functioning according to European Organization for Research and Treatment of Cancer, EORTC) and quality of life (i.e., quality of life questionnaire QLQ-C30) should be measured with a standardized tool and the follow-up evaluation is important.
• Height, weight, and weight loss.
• Dehydration or edema (hydration state).
• Muscle mass: Fearon et al. stated in a consensus paper that the assessment of the muscle mass can be performed by anthropometry (mid-arm muscle area), bioimpedance analysis (BIA), cross-sectional imaging (CT or magnetic resonance imaging) or dual energy x-ray imaging (DXA). In the daily practice the use of simple and low-cost evaluation tools as anthropometry or BIA should be preferred.
• Muscle strength: As muscle function reacts early to nutritional deprivation, hand-grip strength has become a popular, useful and non-invasive indicator of nutritional state, and is can be employed as outcome variable.
• Laboratory tests such as serum albumin can be used as a pretreatment prognostic factor in cancer patients, with low levels being associated with poor outcome. Testing for serum concentration of c-reactive protein at baseline may identify a subset of patients for whom a decline in nutritional state is linked to the presence of an active inflammatory response, a recognized precursor of cachexia. The interpretation of laboratory results must be done carefully, as cancer and/or its treatment often results in pathological values independent of nutritional state.
• Calculation of the daily energy, protein and micronutrient requirements, with a drwan up nutritional support concept (action plan).

Use/indications of enteral nutrition (EN) and parenteral nutrition (PN) during cancer treatment

Before the decision is made to use artificial nutrition, the caregiver must be completely informed about the patient’s overall circumstances (disease development, general and performance state, social situation, etc.). The functioning and capacity of the gastrointestinal tract, the underlying disease, and patient tolerance must be assessed in order to determine the appropriate method of administration.

Enteral nutrition (EN)

EN is used to provide nutritional support when oral consumption is inadequate but gastrointestinal function is normal. Enteral nutrition preserves intestinal function and promotes efficient nutrient use. The insertion of an enteral access is an interdisciplinary decision. The primary medical team, the patient, and the patient’s family must be involved in the evaluation process. A decision as to whether enteral tube access is appropriate will be made after taking into consideration the underlying disease, clinical situation, prognosis, ethical issues, and the patient’s wishes. Patients with swallowing difficulties or mucositis can usually use nasogastric (duration up to 3 weeks) or gastrostomy (>3 weeks) tubes to overcome nutritional obstacles. Feeding tubes are beneficial in facilitating adequate nutrition and hydration during cancer treatment. The percutaneous endoscopic gastrostomy (PEG) has rapidly become a standard procedure for nutritional purposes - for example, in patients with severe mucositis, to prevent weight loss and interruption of radiation therapy. Percutaneous tubes are preferred over nasogastric tubes in patients with head and neck cancer. Prophylactic PEG placement at treatment initiation, prior to development of mucositis and weight loss, is now recommended more frequently. Although PEG insertion is considered relatively safe and has low rate of significant associated complications, it is not a completely benign non-invasive procedure. Frequent complications associated with PEG are local site infections, tube blockage, and migration or dislodgement. Serious complications, such as peritonitis, fistula development, or abscess, are relatively rare. The major complications of enteral tube feeding are diarrhea and abdominal cramps secondary to the high osmotic load. Tube feeding may be contraindicated in situations of severe gastrointestinal dysfunction or bleeding, intractable vomiting, or diarrhea.

EN can be administered in a continuous (over 20-22 hours/day), in a cyclic mode (over 8-12 hours, often overnight) or in combined modus intermittend/bolus (3-4 times per day over a 30-60 minute period). Use of and indications for EN in cancer patients are listed in Table 1.

Parenteral nutrition (PN)

For selected patients, parenteral delivery of nutrition through a central venous catheter will represent the only practicable way to guarantee receipt of the scheduled daily energy requirements (short-term PN: 2-3 weeks). Long-term (home) PN (duration >3 weeks) should be applied through a tunneled central venous catheter (e.g., Hickman® device) or implanted port systems (e.g., Port-a-Cath®), and may be recommended, for instance, in hypophagic/subobstructed (e.g., peritoneal carcinomatosis) patients if there is an acceptable performance state and if they are expected to die from malnutrition prior to the tumor dissemination. A careful and in-depth risk-benefit analysis should be performed to justify use of PN in cancer patients, because of a high potential for life-threatening complications, such as catheter-related and metabolic problems.

Anologue to EN, PN can be administered in a continuous (over 20-22 hours/day) or in a cyclic mode (over 8-12 hours, often overnight). In patients with transient and partial gastrointestinal failure, peripheral PN can be administered as a complement to enteral or oral nutrition. Use of and indications for PN in cancer patients are listed in Table 2.

Conclusions

During cancer treatment it is critical that body weight loss is prevented or at least minimized in order to reduce morbidity and to enhance effectiveness; by the timely use of the tools available (i.e., nutritional counseling, oral nutritional supplements, complementary EN and/or PN) will help achieve this.
References

Table 1: Use of/indications for enteral nutrition (EN) in cancer patients according to the guidelines of the European Society of Clinical Nutrition and Metabolism

<table>
<thead>
<tr>
<th>Use/indications</th>
<th>Grade of recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional state</td>
<td></td>
</tr>
<tr>
<td>• In general, start (complementary) EN if malnutrition already exists or if it is anticipated that the patient will be unable to eat for &gt;7 days.</td>
<td>C</td>
</tr>
<tr>
<td>• Start EN if inadequate food intake (&lt;60% of estimated energy expenditure for &gt;10 days) is anticipated.</td>
<td>C</td>
</tr>
<tr>
<td>• In patients losing weight due to insufficient nutritional intake, EN should be provided to improve or maintain nutritional state.</td>
<td>B</td>
</tr>
<tr>
<td>• Use tube feeding if an obstructing head and neck or esophageal cancer interferes with swallowing or if severe local mucositis is expected.</td>
<td>C</td>
</tr>
<tr>
<td>• In general use standard formulae.</td>
<td>A</td>
</tr>
<tr>
<td>• Prefer the enteral route whenever feasible.</td>
<td>A</td>
</tr>
<tr>
<td>• EN should be preferred in cancer patients because it is more cost-effective than PN and results in fewer complications.</td>
<td>A</td>
</tr>
<tr>
<td>• Regarding omega-3 fatty acids, the evidence is controversial and at present it is not possible to make any concrete conclusion with regard to improved nutritional state and physical function.</td>
<td>C</td>
</tr>
<tr>
<td>During radio-chemotherapy</td>
<td></td>
</tr>
<tr>
<td>• Use dietary advice and oral nutritional supplements to increase dietary intake and to prevent therapy-associated weight loss and interruption of radiation therapy.</td>
<td>A</td>
</tr>
<tr>
<td>• During radio- or radiochemotherapy EN can be delivered via either transnasal or percutaneous routes.</td>
<td>A</td>
</tr>
<tr>
<td>• Because of radiation-induced oral and esophageal mucositis, a PEG may be preferred.</td>
<td>C</td>
</tr>
<tr>
<td>• Routine EN is not indicated during radiation therapy.</td>
<td>C</td>
</tr>
<tr>
<td>• Routine EN during chemotherapy has no effect on tumor response to chemotherapy or on chemotherapy-associated undesirable effects, and therefore is not considered useful.</td>
<td>C</td>
</tr>
<tr>
<td>Hematopoietic stem cell transplantation</td>
<td></td>
</tr>
<tr>
<td>• The routine use of EN during stem cell transplantation is not recommended.</td>
<td>C</td>
</tr>
<tr>
<td>• If oral intake is decreased, PN may be preferred to EN in certain situations (i.e., increased risk of hemorrhage and infections associated with enteral tube placement in immuno-compromised and thrombocytopenic patients).</td>
<td>C</td>
</tr>
<tr>
<td>• Enteral administration of glutamine or eicosapentanoic acid is not recommended due to inconclusive data.</td>
<td>C</td>
</tr>
<tr>
<td>Peri-operative care</td>
<td></td>
</tr>
<tr>
<td>• Administer preoperative EN preferably before admission to the hospital.</td>
<td>C</td>
</tr>
<tr>
<td>• Use preoperative EN preferably with immune modulating substrates for 5-7 days in all patients undergoing major abdominal surgery independent of their nutritional state.</td>
<td>A</td>
</tr>
<tr>
<td>Incurable patients</td>
<td></td>
</tr>
<tr>
<td>• Provide EN in order to minimize weight loss as long as the patient consents and the dying phase has not started.</td>
<td>C</td>
</tr>
<tr>
<td>• When the end of life is very near, most patients require only minimal amounts of food and water to reduce hunger and thirst.</td>
<td>B</td>
</tr>
<tr>
<td>• PEG can also be considered in order to produce decompression of the upper gastrointestinal tract, typically in the situation of (malignant) bowel obstruction.</td>
<td>C</td>
</tr>
<tr>
<td>Tumor growth</td>
<td></td>
</tr>
<tr>
<td>• There are no reliable data that show any effect of EN on tumor growth.</td>
<td>C</td>
</tr>
</tbody>
</table>

*Grades of recommendation:
A: Meta-analysis of randomized controlled trials, at least one randomized controlled trial
B: At least one well-designed controlled trial without randomization or one other type of well-designed, quasi-experimental study or well-designed non-experimental descriptive studies such as comparative studies, correlation studies, case-control studies
C: Expert opinions and/or clinical experience of respected authorities
Table 2: Use of/indications for parenteral nutrition (PN) in cancer patients according to the guidelines of the European Society of Clinical Nutrition and Metabolism

<table>
<thead>
<tr>
<th>Use/indications</th>
<th>Grade of recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional state</td>
<td></td>
</tr>
<tr>
<td>• The majority of patients requiring PN for only a short period of time do not need a special formulation.</td>
<td>C</td>
</tr>
<tr>
<td>• A higher percentage of the lipid component (e.g., 50% of non-protein energy) may be beneficial for those patients with frank cachexia needing prolonged PN.</td>
<td>C</td>
</tr>
<tr>
<td>• PN is ineffective and probably harmful in non-aphagic patients in whom there is no gastrointestinal reason for intestinal failure.</td>
<td>A</td>
</tr>
<tr>
<td>Nutritional provision</td>
<td></td>
</tr>
<tr>
<td>• Cyclic administration is recommended in patients with home PN.</td>
<td>B</td>
</tr>
<tr>
<td>• The use of infusion pumps is recommended, but is not practiced in all European countries.</td>
<td>B</td>
</tr>
<tr>
<td>• Supplemental PN is recommended in patients if inadequate oral/enteral intake (&lt;60% of estimated daily energy requirements) is anticipated for more than 10 days.</td>
<td>C</td>
</tr>
<tr>
<td>• PN is not recommended in patients with adequate oral/enteral intake.</td>
<td>A</td>
</tr>
<tr>
<td>During chemo-radiotherapy</td>
<td></td>
</tr>
<tr>
<td>• Short-term PN is recommended in patients with acute gastrointestinal complications (gastrointestinal toxicity) from chemotherapy and/or radiotherapy, because it is usually better tolerated and more efficient in preventing nutritional deterioration.</td>
<td>C</td>
</tr>
<tr>
<td>• Long-term PN is often indicated in patients with sub-acute/chronic radiation enteropathy.</td>
<td>C</td>
</tr>
<tr>
<td>• PN is recommended in patients with severe mucositis or severe radiation enteritis.</td>
<td>C</td>
</tr>
<tr>
<td>• The routine use of PN during chemotherapy, radiotherapy or combined therapy is not recommended.</td>
<td>A</td>
</tr>
<tr>
<td>Peri-operative care</td>
<td></td>
</tr>
<tr>
<td>• If patients are malnourished or facing a period &gt;1 week of starvation and enteral nutrition support is not feasible, PN is recommended.</td>
<td>C</td>
</tr>
<tr>
<td>• Peri-operative PN is recommended in malnourished candidates for artificial nutrition when enteral nutrition is not possible.</td>
<td>A</td>
</tr>
<tr>
<td>• Peri-operative PN should not be used in well-nourished patients.</td>
<td>A</td>
</tr>
<tr>
<td>Incurable patients</td>
<td></td>
</tr>
<tr>
<td>• In incurable patients with intestinal failure, long-term PN should be offered if (a) enteral nutrition is insufficient, (b) expected survival due to tumor progression is longer than 2-3 months, (c) it is expected that PN can stabilize or improve performance state and quality of life, and (d) the patient desires this type of nutritional support.</td>
<td>C</td>
</tr>
<tr>
<td>Hematopoietic stem cell transplantation</td>
<td></td>
</tr>
<tr>
<td>• In hematopoietic stem cell transplantation, PN should be reserved for those patients with severe mucositis, ileus, or intractable vomiting.</td>
<td>B</td>
</tr>
<tr>
<td>• No clear recommendation can be made as to the time of introduction of PN in those patients. Its withdrawal should be considered when patients are able to tolerate approximately 50% of their requirements enterally.</td>
<td>C</td>
</tr>
<tr>
<td>• Hematopoietic stem cell transplantation patients may benefit from glutamine-supplemented PN.</td>
<td>B</td>
</tr>
<tr>
<td>Tumor growth</td>
<td></td>
</tr>
<tr>
<td>• Although PN provides nutrients to the tumor, there is no evidence that this has detrimental effects on outcome. This fact should not have an influence on the decision to feed the oncologic patient when PN is clinically indicated.</td>
<td>C</td>
</tr>
</tbody>
</table>
Approaches to Nutritional Supplementation in Patients Undergoing Neoadjuvant Chemoradiotherapy and Surgery for the Treatment of Esophageal and Esophagogastric Cancer

Donald E Low, MD, FACS, FRCS(C)
Department of Thoracic Surgery and Thoracic Oncology
at Virginia Mason Medical Center, Seattle, Washington, USA

Background
Historical outcomes with respect to the surgical management of patients presenting with esophageal cancer show documented differences between high- and low-volume centers. Esophagectomy also remains an outlier compared to other major cancer surgical procedures with a mortality rate in all Medicare patients in the United States, approaching 10% as recently as 2008. The application of Enhanced Recovery Protocols programs and standardized clinical pathways has led to significant improvement in outcomes in high-volume centers. Nutritional assessment and support are typically part of the standard assessment in most Enhanced Recovery Protocols programs and clinical pathways. Nutritional assessment is also now recommended as an routine component of care in current NCCN guidelines, and is increasingly targeted as a quality indicator in the overall management of esophageal cancer.

Previous assessments have demonstrated that malnutrition is a clearly-defined negative prognostic factor in patients undergoing definitive chemoradiotherapy for esophageal cancer. It is currently estimated that up to 80% of patients presenting with esophageal cancer will be malnourished at the time of diagnosis. The reasons for malnutrition at the time of presentation are easy to understand considering the frequency with which patients presenting with esophageal cancer demonstrate dysphagia, odynophagia, altered tastes, regurgitation, anorexia and altered gastric motility. The addition of neoadjuvant therapy can increase the potential for malnutrition due to the increased incidence of anorexia, nausea, vomiting, diarrhea, and especially with the utilization of radiotherapy, mucositis and xerostomia which can significantly increase problems with dysphagia and odynophagia.

Nutritional support has documented benefits regarding decreasing morbidity and mortality, associated with tri-modality therapy (chemoradiation followed by surgical resection) while also decreasing the incidence of hospitalizations during neoadjuvant therapy and length of stay associated with surgical resection. Early initiation of nutritional support can decrease complications associated with the treatment of esophageal cancer. Selected nutritional support can also help maintain quality of life in patients with esophageal cancer and, especially in the era in which multi-modality therapy is becoming more common, it increases the potential that patients will receive and tolerate their entire recommended therapy. Table 1 summarizes the issues affected by malnutrition and improved with nutritional support in patients undergoing treatment for cancer.

Rationale for Neoadjuvant Chemoradiotherapy Followed by Surgery in the Treatment of Esophageal Cancer
Neoadjuvant chemoradiotherapy is currently recommended under NCCN guidelines for the treatment of locoregional (T2-3 N1-3 MX) esophageal cancer. Multiple studies have demonstrated that the utilization of neoadjuvant chemoradiotherapy is not associated with significant increases in morbidity and mortality and leads to improvements in R0 resection rates. A recent randomized controlled clinical trial comparing chemoradiotherapy followed by surgery versus surgery alone (CROSS trial), reinforced these previous issues but also demonstrated improvements in two-year survivorship of 15% and three years survivorship of 11% in the tri-modality treatment group.

Although the opinion regarding the best treatment approach in patients with locoregional esophageal cancer remains controversial. The international trend in the treatment of esophageal cancer is increasingly toward the application of tri-modality therapy.

A systematic review of the benefits and risks of neoadjuvant chemoradiotherapy was recently completed and, in spite of documented advantages, nutritional support was provided in only 6-35% of patients receiving neoadjuvant chemoradiotherapy. Previous general assessments have clearly demonstrated that nutritional status deteriorates in a significant proportion of patients with the application of radiotherapy and chemotherapy. Nutritional supplementation can not only increase the likelihood of patients tolerating all of their proposed treatment, but there is also strong evidence to document that it can decrease grade III or IV toxicities associated with neoadjuvant therapy which has been directly related to perioperative mortality.

Nutritional Assessment
There are currently multiple recognized standardized assessment tools available for grading nutritional status (Table 2). The application of these assessment tools is variable, but several randomized controlled trials have documented the positive effect of enteric supplementation on mortality, complication rates, length of stay, reoperations and early return of gut function in major gastrointestinal cancer surgery. The assessment of nutritional status has been made increasingly complex with the recognition that BMI (body mass index) is demonstrating a progressive increase over time within Western society but particularly in patients...
presenting with esophageal adenocarcinoma. Although obesity as an individual factor does not seem to increase the risk of complications associated with surgery, these patients can present overweight, but also malnourished. As shown in Table 3, irrespective of presenting weight or BMI, significant malnutrition should be suspected when a change in weight or BMI of greater than 10% is documented. However, a BMI of <18.5 has been associated with a five-fold increase in perioperative mortality. Increasingly, carcinogenesis is specifically associated with visceral obesity and metabolic syndrome. This association is particularly well-documented in esophageal and esophagogastric adenocarcinoma.

More high-volume centers are now routinely recommending embedding nutritional assessment into “routine clinical practice.” At our institution, nutritional assessment is now a component of discussion and review in every esophageal cancer patient at the time of presentation at multidisciplinary tumor board. The information in Table 3 is available for review at every tumor board and, if the patient is found to have three of these factors positive, then they are considered for nutritional supplementation as outlined in our institutional nutritional treatment algorithm (Figure 1).

Methodologies for Providing Nutritional Supplementation during Neoadjuvant Chemoradiotherapy

1. Oral Supplementation

There are a wide variety of oral nutritional supplements available in liquid form which can aid in maintaining or restoring nutritional status during neoadjuvant therapy. Dietician-delivered intensive nutritional support can help preserve pre-operative weight and decrease complications associated with esophagectomy. Peri-operative immunonutrition diets, especially those containing glutamine, arginine, and omega-3 fatty acids have been demonstrated to decrease operative morbidity and length of hospital stay. Diets containing glutamine have especially been shown beneficial in preserving small bowel function and maintaining T-cell responsiveness associated with major surgery. Recent meta-analyses demonstrate the potential benefits of enteral pre-operative immunonutrition for 5-7 days in both well-nourished and malnourished patients.

Oral nutritional supplementation and dietary supervision is clearly an important issue in patients undergoing treatment for esophageal cancer. However, a component of patients will have severe esophageal obstruction associated with significant pre-existent weight loss which has the potential to be exacerbated by the esophagitis and loss of appetite often associated with chemoradiotherapy.

The role and efficacy of immunonutrition in patients undergoing neoadjuvant chemoradiation and surgery for esophageal cancer is not well-defined. There is a current international multicenter Phase III randomized controlled trial (NCT 01423799) assessing immunologically active components in nutritional support on tolerance to neoadjuvant therapy and overall outcomes including quality of life of trimodality therapy for esophageal cancer.

2. Parenteral Nutrition

Current recommendations of the American Society for Parenteral and Enteral Nutrition is to utilize enteral nutrition whenever feasible due to the recognized benefits of maintaining normal gastrointestinal function and flora as well as mucosal barrier, providing a more physiologic approach to nutrition, improved support of the immune response and overall decreased costs. Previous studies comparing parenteral nutrition to standard supplementation of oral diet has not demonstrated defined advantages to parenteral nutrition. A randomized controlled trial comparing enteral and parenteral nutrition in patients receiving neoadjuvant therapy for esophageal cancer demonstrated that enteral nutrition was superior at limiting chemotherapy-related toxicity. There is also the issues surrounding the maintenance of central venous catheters and the potential for increase catheter-related complications including infections and thrombosis which supports the desirability of utilizing enteral nutritional approaches whenever feasible.

3. Nasoenteric Feeding Tubes

These catheters can routinely be placed in either radiology or with endoscopic guidance and can be positioned in the stomach or upper small bowel. Except for premature removal, they have a very low complication rate and, provide the most overall cost-effective approach to enteral nutritional supplementation. Understandably, these tubes are considered unacceptable to the vast majority of patients on the basis of both personal comfort and social acceptability. They should be reserved for situations in which nutritional supplementation is planned for a short period, likely not exceeding 7-14 days.

4. Surgical, Endoscopic and Radiographically Placed Gastrostomy Tubes

Gastrostomy tubes have historically provided an excellent option for enteral nutritional supplementation in cancer patients. Gastrostomy tubes can typically be placed as an outpatient procedure, and can be used for either gastric feeding which can be provided as bolus feeds or it can be converted to jejunal feeding if gastric function is impaired. Certain high-volume centers have demonstrated that radiologically placed gastrostomy tubes can be utilized feasibly and safely prior or during neoadjuvant chemoradiotherapy in patients with esophageal cancer. There remains controversy regarding gastrostomy tubes in other centers because the stomach is the most commonly utilized conduit for reconstruction after esophageal resection, and there remains the hypothetical risk of interrupting a crucial blood supply to the stomach during the insertion of a gastrostomy tube inserted either with endoscopic or radiologic guidance. There are also reports indicating the potential for malignant cell seeding with percutaneous endoscopic gastrostomies in patients with oral pharyngeal and esophageal cancers. With appropriate planning, gastrostomy tubes will remain an option for a nutritional augmentation in esophageal cancer patients. It has been our practice, however, to utilize jejunostomy tubes as we routinely advocate continued jejunostomy tube nutritional augmentation after surgical resection and therefore, patients who require nutritional supplementation during neoadjuvant therapy can use the same enteral approach throughout their entire therapy.

5. Surgical, Endoscopic and Radiographically Placed Jejunostomy Tubes

Jejunostomy tubes can be utilized throughout the entire course of therapy in patients undergoing tri-modality therapy for esophageal cancer. There is also little potential that they will impact conduit selection at the time of esophageal resection. Jejunostomy tubes, however, are more inconvenient to the patient in that bolus feeding is typically not feasible, and feedings must be provided through a pump, although nutritional supplementation can usually be given within 12 hours, much of which can be concentrated at night so the patient is free during the daytime hours.
When a patient is recommended for nutritional supplementation at our tumor board according to the treatment algorithm (Figure 1), it has been our practice to insert the jejunostomy surgically in conjunction with the insertion of the Port-A-Cath to facilitate chemotherapy or in conjunction with a diagnostic laparoscopy in patients who require this additional staging procedure due to extensive gastric involvement. This approach improves both costs and efficiency of initiating therapy. We initially inserted these catheters laparoscopically but now use a 2 cm supraumbilical incision to simplify the operation and reduce costs. Table 4 shows the incidence of nutritional supplementation prior to chemoradiotherapy in 245 consecutive resections at our institution between 2005 and 2011. Of the 50 jejunostomy tubes that were inserted, 44 (88%) were placed in conjunction with an additional surgical procedure. We typically use a large 14 French jejunostomy tube (Kimberly-Clark Worldwide Sales, LLC, Roswell, Georgia, USA) which decreases potential for tube blockage and allows the jejunostomy tube to be used not only for nutrition but also for crushed medications. See Figure 3.

We advocate the surgical approach to jejunostomy insertion as studies demonstrating the safety of endoscopic percutaneous jejunostomy have demonstrated a 10% incidence of major adverse events and death. Percutaneous radiologic-directed jejunostomy tubes demonstrate even higher levels of risk for major adverse events and therefore are not to be recommended.

6. Insertion of Temporary Self-Expanding Plastic and Metal Stents

Many of the issues directly contributing to malnutrition in patients presenting with esophageal cancer have to do with esophageal obstruction and dysphagia. Previous reports have presented the concept of inserting a metal or plastic stent which can immediately relieve dysphagia and provide improved opportunities for maintaining oral nutrition. There are now a wide variety of stents available which can be placed endoscopically as an outpatient (Figure 3) and can produce immediate improvement in dysphagia scores and patients’ ability to support their nutrition with an oral diet. There are now a series of papers highlighting that this approach can be done safely. The majority of these studies utilize an expanding plastic stent and to our knowledge have demonstrated a 10% incidence of stent migration that is reported between 18% and 46%. Stent placement is not appropriate in all patients, especially those with severe loss of appetite, nausea and abdominal gastric motility.

A retrospective review comparing self-expanding plastic stent versus surgical jejunostomy demonstrate equal levels of technical success, complications and improvement in peri-treatment albumin levels and all stents were removed uneventfully prior to surgery.

The most significant unresolved controversy regarding the application of these stents is whether they should remain in place during the entire course of neoadjuvant chemoradiotherapy or be removed electively three to four weeks after the initiation of chemoradiotherapy. A study examining this issue demonstrated that dysphagia scores improved equally in patients who had their stents remain in place or where electively removed at four weeks. However, interventions and stent-related complications were seen to be less in the patients that underwent elective stent removal. Although biodegradable stents are conceptually an interesting option, the evolution of these devices is not at a point where they should be considered for current application.

It is our current practice to consider temporary stent placement (see Figure 4) in conjunction with staging with endoscopic ultrasound when it is recommended at our multidisciplinary tumor board (Figure 1). We are currently recommending elective removal of the stent three weeks after insertion and prior initiation of chemoradiotherapy where improvements in swallowing typically continue due to the chemoradiation effect and pressure necrosis associated with the stent.

Conclusions

Neoadjuvant chemoradiation followed by surgery is becoming the most common multi-modality approach for patients presenting with locoregional cancer. A significant component of these patients will present with malnutrition which can be exacerbated by the initiation of chemoradiotherapy. This scenario not only leads to poor overall outcomes but also impacts the patients’ ability to receive their entire course of planned therapy and increases costs. Having a specific orchestrated institutional plan embedded in a standardized clinical pathway or Enhanced Recovery Protocols program to assess and support nutrition in these patients will certainly be a recognized quality parameter in the future.

References

21. Cerentola Y, Hubner M, Grass F, Demartines N, Schaller M. Immunonutrition in
Figure 1. VMMC Institutional Nutritional Algorithm Associated with Neoadjuvant Chemoradiation for Esophageal Cancer

Presentation Assessment: Wt Loss >10% in 3 Mo.
BMI <18.5 Kg/m²
Dysphagia to all solids
Zubrod score 2 or 3
Albumin <3.25 g/dl

Staging Assessment
CT, PET, Physiologic Assessment
EGDUS – long esophageal stricture
Consider SEMS

Tumor Board
Stage IIA (+), IIb, III Resectable Stage IV
Recommendation for neoadjuvant chemoradiation

Nutritional Concerns

Nutritionally Stable

SEMS
Routine CXR 2 Weeks
Elective Stent Removal 2-4 Weeks

Feeding Jejunostomy
14 FG
Placed in conjunction with
1. Port Placement
2. Diagnostic laparoscopy and washings

Cycle to Nocturnal Feeds

Figure 2. Examples of SEPS (self-expanding plastic stents) and SEMS (self-expanding metal stents)

Figure 3. Demonstrates the 14 Fr jejunostomy tube and the incision used for insertion

Figure 4. Deployment of temporary expandable metal stent in patient with near complete obstruction due to distal esophageal adenocarcinoma
Introduction

The premise of nutritional oncology is to deploy nutritional assessment and nutrition therapy to optimize cancer therapy in both the short term and longer-term. Cancer treatment with chemotherapy is always a delicate balance between the efficacy and toxicity of the treatment. The objective of both the oncologist and of the nutritionist is to increase the therapeutic index of treatment [i.e. increase the efficacy and/or reduce the toxicity].

Cancer chemotherapy is a balancing act between efficacy and toxicity

The term therapeutic index which refers to the amount of a therapeutic agent (drug) that causes the therapeutic effect (anti-cancer), to the amount that causes toxicity (Figure 1).

Figure 1. Nutritional modulation of therapeutic index

A higher therapeutic index is preferable to a lower one: a patient would have to take a much higher dose of such a drug to reach the toxic threshold than the dose taken to elicit the therapeutic effect. Anti-cancer drugs generally have a low therapeutic index (i.e. having little difference between toxic and therapeutic doses). Since doses are standardized for a population of patients, for some individuals there is potential for significant overdose with toxicity which may be life threatening or even fatal, as well as for substantial under-dosing with risks of cancer progression or recurrence. It is accepted that there will be a trade-off between efficacy and toxicity in cancer therapy. The recommended chemotherapy dose in Phase II studies of a single new drug or drug combination is determined by a dose-finding study. The upper limit of the recommended dose is the dose at which <33% of patients experience dose-limiting toxicity (DLT)1. These doses become the standard of care if a treatment is found to be effective in subsequent phase III studies2.

Several strategies are adopted by medical oncologists to manage toxicity of cancer therapy. Scaling drug doses is used to reduce variation in drug exposure, efficacy and toxicity. Cytotoxic chemotherapy is generally scaled to an individual’s height and weight, most often using the anthropometric scaler body surface area (BSA) which is calculated by equations such as Mosteller’s formula (BSA (m²) = ([Height(cm) x Weight(kg)]/3600)½). For drugs that have a renal pathway of elimination, dosing is adjusted to estimated glomerular filtration rates in addition to height and weight. Rarely, dosage may be adjusted according to measurements of the actual blood levels achieved in the person taking it. In addition to dose scaling, stringent criteria for eligibility are applied to individual patients based on their performance status (PS), renal, hepatic and hematological functions and co-morbidities.

Despite the precautions described above, significant numbers of patients are made seriously ill by chemotherapy3. Some patients with apparently good PS experience treatment toxicity that is severe, life threatening and even fatal3-5. Adverse events in cancer treatment are precisely defined. The standard scale is the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0[4]. Grade 1 or 2 adverse events are considered mild and tolerable, Grade 3 is considered serious, Grade 4 life-threatening and Grade 5 toxicity is fatal. Adverse events occur in every tumor group. For example, Schiller et al.7 summarized a series of trials on 1207 patients with advanced non–small-cell lung cancer (NSCLC) treated with cisplatin- and carboplatin-based therapies. Despite restricting treatment to patients with PS 0, 1 or 2 and adequate hematologic, hepatic and renal function, 4-6% of patients had fatal toxicity of infectious, cardiac or renal origin and 68% had Grade 4 toxicity.

Severe toxicity in treatment is managed by reducing or delaying the next dose, or stopping treatment, thus limiting benefits of a complete course of anti-cancer therapy. Patients may even stop treatment even though it is controlling their cancer, if toxicities are intolerable8. Stopping cancer treatment early is an obvious detriment to the patient in terms of controlling cancer progression, and it is also to patient physical and emotional well-being. The serious nature of treatment toxicity raises the question of our ability to accurately predict treatment toxicity and appropriately manage susceptible individuals3.
Nutrition risk = Toxicity Risk

Cancer treatment toxicity in some individuals is unusually severe. Some aspects of nutritional status including weight loss and depletion of the lean body mass [skeletal muscle] are predictive of such high risk toxicity. Screening/assessment of nutritional risk is used by the nutrition support team to plan individual nutrition counseling and therapy, but also yields valuable information concerning patients' fitness to tolerate chemotherapy. The prognostic effect of weight loss prior to chemotherapy was shown 30 y ago using data from 3,047 patients enrolled in 12 chemotherapy protocols of the Eastern Cooperative Oncology Group. Weight loss has repeatedly been shown to be a significant independent predictor of severe toxicity and of cessation of treatment. The term sarcopenia was coined to denote a reduced quantity of skeletal muscle. The generally accepted definition of sarcopenia is an absolute muscle mass >2 standard deviations below that typical of healthy adults. Sarcopenia is not restricted to people who appear thin or wasted. Aging is often paralleled by decreased muscle and increased fat, which may culminate in sarcopenic obesity. Starting in 2008, computed tomography imaging has been adopted to detect this underlying muscle wasting in patients with cancer. Patients with sarcopenia behave as if overdosed and had toxicity of sufficient magnitude to require dose reductions, treatment delays or definitive termination of treatment. This was consistent across a range of drugs (5-fluorouracil (5FU), capecitabine, sorafenib, sunitinib), a chemotherapy regimen (adjuvant FEC: 5FU, epirubicin; cyclophosphamide) and in patients with cancers of the colon, breast and kidney. Sarcopenia may reflect a generalized inability to respond appropriately to stress.

Mechanisms underlying drug toxicity in patients with sarcopenia are not well understood. One measure of drug exposure [area under the concentration time curve, in patients with hepatocellular carcinoma treated with sorafenib, was nearly double in patients with sarcopenia compared to that of patients without this feature (102.4 vs. 53.7 ng/mL.h)]\(^{21}\). This is suggestive of overexposure in patients with sarcopenia, however additional pharmacokinetic data are needed. Cancer is clearly more advanced in patients with sarcopenia, and it has been shown in large population based cohorts\(^{13,14}\) that their survival times are shorter than in non-sarcopenic individuals of the same age, sex, stage and PS.

While none of the currently employed scaling systems for chemotherapy drug dosing formally incorporate elements of nutritional assessment such as weight loss or sarcopenia, the presence of these factors, either individually or together, may provide key independent indicators of the likelihood of developing DLT. For example, the simultaneous presence of low BMI and sarcopenia associated with >70% incidence of DLT in patients with renal cell carcinoma. The sensitivity and specificity of these measures for predicting DLT requires testing in large data sets including nutritional parameters and detailed toxicity data. Robust predictors would be of immediate value for choosing patients for reduced dosages in standard therapy. The relevance of early identification of patients with sarcopenia, is that they are at risk for a rapid decline, with a high risk for toxicity leading to exacerbation of malnutrition and wasting, with further depletion of the lean tissue mass (Figure 2) and further enhanced risk of toxicity in subsequent chemotherapy cycles.

Nutritional modulation of the therapeutic index of cancer therapy

The outcome of chemotherapy depends on complex interplays between tumor, host, and the anticancer drug. Diet may be used to modulate changes that favor increased anti-cancer efficacy and/or lesser injury to normal tissues. Diverse dietary elements (amino acids, fatty acids, oligosaccharides, minerals, vitamins, antioxidants) have been suggested to modulate gastrointestinal toxicities of chemotherapy. Their proposed actions include interfering with mechanisms of drug toxicity (modulating pharmacokinetics, altering key mechanisms of injury) and mitigating injury to non-tumor tissues (modulating immune responses, cytokine/hormone network, cellular protective and repair machinery, and signaling events involved in regulating cell cycle, cell proliferation or cell death). Most of the evidence for these effects come from experimental studies and suggest that specific nutrients can alter both the efficacy and the toxicity of anticancer therapy. While it is not the intention here to treat this topic systematically, an example may be made of the omega-3 polyunsaturated fatty acids (PUFA) for which there is an emerging body of clinical evidence.

In animals omega-3 PUFA decrease tumor cell proliferation, enhance tumor cell apoptosis, promote cell differentiation, limit tumor angiogenesis, and modulates tumor-extracellular matrix interaction. Dietary omega-3 PUFA can enhance toxicity of drugs to tumor cells and offer protection to nontumor tissues. Eicosapentaenoic acid, docosahexaenoic acid (DHA) and fish oil enhance anti-cancer activity of anthracyclines, cisplatin, alkylating agents, vincristine, taxanes, CPT-11, and 5-FU \(^{24-27}\). Omega-3 PUFA supplementation appears to attenuate the toxicity of cyclophosphamide, arabinosylcytosine, doxorubicin, and CPT-11 \(^{24,32}\) including gut weight, histo-pathology, intestinal epithelial apoptosis, and inflammatory mediator production.

Preliminary clinical findings suggest that dietary supplementation with omega-3 PUFA may enhance tumor response to chemotherapy. In metastatic breast cancer patients supplemented with DHA, individuals who showed robust incorporation of this fatty acid into plasma phospholipids showed increased time to progression and overall survival compared with those patients who showed weak or total incorporation\(^{36}\). Those results have led to a large randomized phase 3 placebo-controlled study (DHALYA trial, NCT01548534 \(^{17}\), which is ongoing. Patients with advanced NSCLC supplemented with 2 g / day of omega-3 PUFA (as fish oil), was associated with a higher rate (80%) of objective response of tumor to cisplatin-based chemotherapy, compared with patients receiving standard of care (20%)\(^{38}\).

Conclusions and future developments

Further studies are required to accurately define how nutritional assessment can contribute to the early identification of patients at risk for severe treatment toxicity. Further understanding of the interaction between nutritional status and drug pharmacokinetics could lead to more appropriate dosing scales for malnourished individuals. The positive interaction between omega-3 PUFA and chemotherapy to enhance treatment efficacy suggested by preliminary results, is worthy of further investigation.
Nutritional Interventions Improve QoL

Jens Kondrup, MD, PhD
Clinical Nutrition Unit, Rigshospitalet,
University Hospital, Copenhagen, Denmark

Introduction

The effect of nutrition support in controlled trials commonly include objective variables such as clinical outcomes, e.g. infections, complications in general, LOS or survival\(^1,2\). Nutritional outcome variables and clinical outcome variables show a low rate of concordance in controlled trials\(^3\) and therefore most investigators do not consider nutritional outcome variables, such as changes in body weight, to be valid outcome variables. However, controlled trials of clinical outcome variables commonly require the recruitment of several hundred patients to reach an adequate power of the study and are therefore very costly. Physiological functions, such as muscle function and cognitive function, may be considered valid interim outcome variables, as they probably require fewer participants and may be useful for smaller trials in which a new idea is tested before undertaking a large clinical outcome study. In addition, effects of nutrition support on physiological functions may be considered pathophysiologically to be a prerequisite for effects on clinical outcome\(^4\), since improvement of some cellular function must be responsible for the improved clinical outcome. In addition, muscle function and cognitive function may be related to the major components of Quality of Life (QoL) measures: physical function and mental function. In recent years, Quality of Life scores have gained increasing interest as an outcome variable in clinical trials, also in trials of nutrition support\(^5\)–\(^21\). This interest has arisen from the concept that medical treatment should not only delay mortality and decrease morbidity, but also improve the quality of the prolonged span of life. This is in accordance with the WHO definition of health: “Health is a state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity.”

Further, cost considerations have gained higher priority in recent years and therefore also the concept of cost-effectiveness. One example of cost-effectiveness is the cost of improving QoL for a certain period: the cost-utility analysis of Quality Adjusted Life Years (QUALYs).

Measuring Quality of Life

A large number of QoL measures have been developed. Some of these are for specific groups of patients and others are meant to be generic measures which can be used across all health conditions. A review of the latter category\(^22\) noted that SF-36 is the most commonly used measure, but also that “there are no uniformly ‘worst’ or ‘best’ performing instruments. The decision to use one instrument over another, will be driven by the purpose of the measurement and depend on a variety of factors including the characteristics of the population (e.g. age, health status, language/culture) and the environment in which the measurement is undertaken (e.g. clinical trial, routine physician visit). The appropriate selection will depend on many factors and circumstances.” It is clear from this review, and other papers, that the scientific community has not yet produced a generic health related QoL measure which is valid under all conditions.

When considering using a measure of QoL in a nutrition support study, it may be a useful to look at the methods that until now have been tested in randomized controlled trials (RCTs) of nutrition support.

- Ollenschlager et al.\(^3\) failed to show an improvement in ‘subjective well-being’ in a small study of ‘intensified oral nutrition’ patients undertaking chemotherapy.
- Rogers et al.\(^4\) failed to show an effect on ‘Sickness Impact Profile’ in a small study of nutritional supplements among COPD patients.
- Ovesen et al.\(^2\) failed to show improvement in ‘Quality of Life Index’ in a study of oral supplements among 105 patients undergoing chemotherapy.
- Saudny-Unterberger et al.\(^5\) showed a trend (\(P <0.066\)) towards improvement in a ‘general well-being score’ in a small study of oral supplements among COPD patients.
- Rabeneck et al.\(^6\) failed to show improvements in a custom made QoL measure in a study of oral supplements among 118 HIV infected patients.
- Beattie et al.\(^7\) showed an improvement in QoL (SF-36) in a study of 10 weeks’ oral supplements, initiated among 101 gastrointestinal surgery patients.
- Van Bokhorst-de van der Schueren et al.\(^8\) showed an improvement in both a disease-specific QoL measure (European Organization for Research and Treatment of Cancer [EORTC-QLQ-C30]) and a generic QoL questionnaire (Dartmouth Primary Care Cooperative Information Project [COOP-WONCA]) in a small study of oral supplements among head and neck cancer patients undergoing surgery.
- Johansen et al.\(^9\) failed to show improvement in QoL (SF-36) in a study of nurse-and-dietitian driven nutritional therapy among 212 patients recruited from a multitude of hospital departments.
- Ravasco et al.\(^10,11\) showed an improvement in QoL (EORTC-QLQ-C30) in a study of 4 weeks’ nutritional counselling or oral supplements among 75 head and neck cancer patients and 111 colorectal cancer patients undergoing radiotherapy.
- Rufenacht et al.\(^12\) showed an improvement in QoL (Functional Assessment Anorexia-Cancer Therapy [FAACT]) in a small study of dietitian-driven nutritional
therapy among patients in a department of internal medicine.

- Norman et al.16,17 showed an improvement in QoL (SF-36 and SF-6D) in a 3 months’ study of oral supplements, initiated among hospitalized non-cancer gastroenterology patients.
- Starke et al.18 showed an improvement in QoL (SF-36) in a study of nutritionist-driven nutritional therapy among 132 patients in a department of gastroenterology.
- Rondanelli et al.19 showed an improvement in QoL (SF-36) in a small study of 8 weeks’ supplementation with oral essential amino acids among institutionalized elderly patients.
- Neelmaat et al.20 failed to show improvement in QoL, expressed as QUALY derived from Euroqol-5D (EQ-5D) in a study of 3 months’ nutritional support, including oral supplements, initiated among 210 hospitalized elderly patients.
- Baldwin21 showed an improvement in QoL (EORTC) in a meta analysis of 5 studies of oral supplements among cancer patients.

It appears from this list of randomized trials that several QoL measures are responsive to nutritional support. In studies of patients for whom specialized QoL measures, such as EORTC, have not been validated (i.e. has not been shown to be responsive to nutrition support), it seems that SF-36 is the most commonly responsive QoL measure, being responsive in 4 out of 5 RCTs in which it has been applied. Of course, the success or failure of a QoL measure in an RCT is not only depending on the measure chosen, but also on the design of the study, such as the indication for nutrition supprt in the patients recruited and the actual difference in energy and protein intakes in control versus intervention patients, but these other aspects will not be discussed here.

Utility versus Quality of Life

As initially discussed by Brazier et al.22, the 36 items of SF-36 can each be answered at several levels, which can generate many millions of health states (if an average of 5 levels per item: $5^{36} = about 14 \times 10^{34}$ possible combinations of health states). For a comparison of two treatments, such as nutrition support versus spontaneous intake, the outcome on some items may be better for one treatment but worse on other items and it will be difficult to decide which health state is actually the best outcome for the patient.

The solution was first to re-arrange SF-36 to fewer items and for each item to have a limited number of possible answers, and to arrange these answers on an ordinal scale23. The result was a scale with only 249 possible health states. Secondly, these possible health states were presented to 611 healthy individuals who were each asked to rank and value a set of only 6 of these 249 health states. After mathematical modelling, all 249 health states were expressed on an ordinal scale from 0 to 1 in which 0 is close to being dead while 1 is the optimal state of health. In fact, this scale from 0 to 1 represents the states of health ranked according to the preferences of the healthy individuals. Therefore, a significant improvement on this scale, as a result of treatment, can be interpreted as a superior outcome according to the preference of healthy individuals. One advantage of this SF-6D measure is that it can be derived from available SF-36 data. SF-6D, and other similar measures, are called preference based QoL measures. Ideally, these preferences should be worked out in patients, but that has until now not been done.

Utility is originally a commercial concept dealing with how much extra the consumer is willing to pay for an added value of a product, or for a fulfillment of a desire, e.g. for attending a cultural event. In healthcare, it is the extra cost that the payer (society or insurance company) is willing to pay for a patient’s preferred improvement in QoL for a certain period, expressed per year (Quality Adjusted Life Year [QUALY]). In the UK, it appears that at a cost of about £40,000 per QUALY, about one half of new treatment modalities are accepted and that new medical technologies with costs of £20,000 - £30,000/QUALY are typically accepted25.

A very illustrative example of a cost-utility analysis of a nutrition support RCT is given by Norman et al.17. In this study, patients were randomized at discharge to a control group or a nutrition support group who received oral supplements for 3 months. Preference based QoL (= utility) was measured by SF-6D at entry and after 3 months. The control group reported an increase in utility of 0.07 (from 0.62) and the intervention group an increase of 0.13 (from 0.59). The difference between the groups was statistically significant. QUALY was calculated from the time-dependent Area-under-the-curve (0.62 in the control group and 0.66 in the intervention group). The difference in QUALY was 0.045 and the difference in cost of supplements was £ 540. Therefore, the cost/utility (extra cost per added QUALY) was £ 12,099 which is well below the threshold mentioned above for the UK.

SF-6D versus EQ-5D

EQ-5D, originally from 199024, is the traditional measure of utility. It has been adopted in a large number of countries in Europe, US, Africa and Asia25. A number of studies have shown that SF-6D and EQ-5D do not measure the same. A recent study among free living individuals, of whom a large number suffered from chronic disease conditions, showed SF-6D to be less sensitive towards these conditions compared to EQ-5D24, perhaps because the scale of EQ-5D goes below zero (health state worse than death). Another observational study comparing SF-6D and EQ-5D in patients with ankylosing spondylitis similarly showed that SF-6D discriminates less between patients with better and worse health states than EQ-5D29. They also reported that the ability to detect a treatment difference in a specific RCT was similar for the two measures. They further noted that SF-6D and EQ-5D correlate equally well with external measures of health, but agree only moderately among each other. They concluded that it is difficult to recommend one of the instruments over the other.

In this author’s opinion it is difficult to strongly recommend which of the two utility measures should be used in a new RCT on nutrition support. However, despite only 2 RCTs available, it is worthwhile to consider that SF-6D has been shown to be responsive to nutrition support27, in contrast to EQ-5D20. This favoritism of SF-6D also relates to the stronger case for SF-36 in the RCTs mentioned above.

Quality of Life and physiological functions

SF-36 records subjective parameters and it would be useful to validate objective measures that agree with these subjective parameters. Norman et al.16 reported from their RCT that the change in hand-grip strength correlated with the change in two physical items of SF-36 (physical functioning and physical role). Jakobsen et al.26 confirmed in an observational study that handgrip strength was closely related to some SF-36 physical and mental function items and suggested that handgrip strength is a valid measurement of mobility (timed
up-and-go) and QoL in patients. The same group investigated whether the mental functioning component of SF-36 could be assessed by using Addenbrooke’s Cognitive Examination (ACE) and Continuous Reaction time (CRT). Indeed, the CRT was related to ACE, supporting that CRT is a measure of cognitive function. However, neither CRT nor ACE was related to the mental component of SF-36. It was realized afterwards that the mental component of SF-36 is actually a reflection of mood and social drive, rather than cognitive function. Therefore, an objective easy bed-side correlate of the mental function component of SF-36 is still lacking.

Conclusion
To summarize, QoL measures seem to be sensitive to nutritional support. QoL may be regarded as a relevant outcome measure, not only in patients where hard end points such as death or complications are not sensitive to nutrition support but also in its own right. Measurement of QoL allows cost utility calculations which are meant to reflect the preferences of the patients, and the cost of such preferences. The subjective nature of QoL measures should be supported with validated objective measures.

References
Specialised Nutritional Intervention During Chemotherapy

Alessandro Laviano, MD
Department of Clinical Medicine, Sapienza University, Rome, Italy

Introduction

Despite decades of scientific effort, which has required significant public and private resources, cancer remains a leading cause of morbidity and mortality worldwide. Although the incidence of many human cancers has progressively declined over recent years, and the relative risk of cancer death one year after diagnosis has also improved\(^1\), these results appear to be largely due to the worldwide implementation of prevention programs and early screening procedures, which allow for timely eradicative therapies. In patients with advanced cancer, overall and progression-free survival are still limited, since the response rate to chemo- and radiotherapy is frequently below 50%. As an example, only around 30% of patients with metastatic lung cancer benefit from first-line chemotherapy\(^2\). Consequently, there is an emerging awareness among oncologists that the current pharmacologic approach to cancer patients should be substantially revised, since it impairs patients’ quality of life and frequently fails to extend survival\(^3\). It is acknowledged that the development of more “intelligent” drugs targeting specific molecular pathways may significantly improve the outcome of advanced cancer patients during the next decade. However, we are now observing a progressive shift in the focus of researchers and clinical oncologists from exclusively targeting cancer cells to a more comprehensive approach to the disease, which not only includes supportive therapies for the human body itself, but also the metabolic modulation of tumor microenvironment.

One of the major limitations of current pharmacologic anti-cancer therapies is the high level of toxicity, which frequently leads to dose limitation and interruption of the treatment schedule\(^4\). Therefore, the development of new strategies which limit toxicity, and would allow for a complete delivery of antineoplastic therapies and also improve the patient’s quality of life is required. It is unlikely however that such goals could be soon achieved by new drugs, since the time needed to devise and test a new pharmacological agent may extend over a decade. In addition, there is growing evidence of medical excess in wealthier countries, with increasing associated harms and costs\(^5\). Of more clinical relevance would be the implementation of strategies already widely available, and in this light, nutrition could be of significant help\(^6\).

Pharmanutrition and tumour growth

Cancer treatment toxicity levels are a result of both the pharmacological properties and the delivered dose of any given drug. Preventable and non-preventable factors also play a significant role, with individual genetic background repeatedly demonstrating the predicted toxicity of radio- and chemotherapy\(^7,8\). However, cancer-induced malnutrition, i.e., cachexia, is closely related with the development of complications of antineoplastic regimens. In particular, sarcopenia, which is the hallmark of cancer cachexia\(^9\), predicts dose-limiting toxicity\(^10\), post-operative complications\(^11\) and survival\(^12\) of patients with tumors of different origins and receiving different antineoplastic therapies. Therefore, prevention or restoration of muscle mass in cancer patients may result in better tolerance and improved compliance to antineoplastic regimens.

There is accumulating evidence that nutritional support improves cancer patients’ outcome by preserving/restoring nutritional status. It could also be suggested that nutrition may directly influence tumor growth. On our planet, many examples exist showing that animals use food to prevent and treat diseases\(^13\), an ability which has been lost by mankind.

The key role of inflammation in cancer initiation and progression has been first hypothesized by Virchow\(^14\). Since then, much evidence has accumulated, demonstrating that cancer cells require an inflammatory microenvironment to proliferate and disseminate\(^15\). In this light, the role of stromal cells and the tumour microenvironment in general in modulating tumour sensitivity is increasingly becoming a key consideration for the development of active anticancer therapeutics\(^16\). The mechanisms by which chronic inflammation favors tumor growth are being elucidated. Recent observations point to the cross-communication between cancer cells and non-malignant stromal cells as a key factor rendering tumor cells resistant to certain drugs\(^16\), but also enhancing the responsiveness of tumor cells to other agents (microenvironment-induced synthetic lethality). However, a key role is also played by the inflammation-induced reduction of host immune surveillance\(^17\). In line with this reasoning, we demonstrated in an experimental model of cancer cachexia that a strong decline in contact hypersensitivity, a parameter for cell-mediated immunity, occurs early in tumor-bearing mice, even before cachexia occurs, reflecting an impaired immune function prior to weight loss\(^18\).

In human cancer, it is well established that malignancy and aggressiveness of human cancers is related to the degree of stroma infiltration by inflammatory cells\(^19\). Consequently, neutralizing the tumor inflammatory microenvironment, or boosting host immune surveillance, may represent an effective strategy to enhance the response rate of cancer patients to chemo- and radiotherapy\(^17\). Arginine is an amino acid which has been extensively demonstrated to increase immune response, and therefore its use could be beneficial in...
cancer patients. Indeed, Buijs et al. showed that patients with head and neck cancer receiving an arginine-enriched enteral formula in the perioperative period have a longer survival than those receiving a standard formula.21

Tumour-induced inflammatory response can be blunted by diet modification, and in particular by increasing the intake of omega-3 polyunsaturated fatty acids (PUFAs), namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). After being incorporated in the lipid layers of cell membranes, omega-3 PUFAs are metabolized by cyclooxygenase and lipooxygenase yielding to the production of thromboxanes and prostaglandins, whose pro-inflammatory activity is less potent than that mediated by thromboxanes and prostaglandins deriving from omega-6 PUFAs, namely arachidonic acid. In fact, cancer patients supplemented with omega-3 PUFAs showed reduced levels of arachidonic acid-derived prostaglandin E2 when compared to patients receiving a standard, non-omega-3 PUFAs enriched supplement.23 Consequently, this may suggest that integration of standard chemotherapy with specialized nutrition therapy including omega-3 PUFAs may result in an increased response rate.23 Preliminary reports are encouraging with Murphy et al. reporting that omega-3 PUFAs supplementation to advanced lung cancer patients receiving first-line chemotherapy almost doubles the response rate.22 Similar results were obtained by Bougnoux et al. in advanced breast cancer patients, although clinical benefits were observed only in those patients who were high incorporators of DHA into plasma membranes.21 More recently, Arshad et al. showed that in pancreatic cancer patients treated with gemcitabine and intravenous omega-3 PUFAs, the circulating levels of cytokines and growth factors reduce with treatment over time, this effect being potentially associated with an improved outcome.22 Similarly, restoration of mannose-binding lectin component activity by gemcitabine and omega-3 PUFAs is associated with improved outcome in the same clinical setting.23

Conclusion
Nutritional modulation of tumor microenvironment is a current and available opportunity to improve the response rate to chemotherapeutic and radiotherapy. Nutrition support with specialized nutrients may reduce inflammatory infiltration of tumor mass and restore innate immunity, leading to enhanced tumor rejection. More studies are needed to assess the impact on clinical outcomes of the integration of specialized nutrition support within standard anti-cancer treatments. If the preliminary results now available in the literature can be strengthened by larger and mechanistic studies, specialized nutrition support may be used to prime host and cancer cells’ metabolism, making the former more resistant and the latter more sensitive to the cytotoxic effects of chemotherapeutic and radiotherapy.24

References
5. Godlee F. Too much medicine. BMJ 2013; 346:f1328