CONTEXT AND POLICY ISSUES

People with cancer who are well nourished and who are capable of maintaining a healthy body weight may have better outcomes than patients who are undernourished or underweight. Survival is generally shorter for those patients who lose weight prior to starting cancer treatment. Maintaining a healthy diet through cancer treatment may help maintain the immune system and the general well-being of patients. Weight and nutrition can be managed by eating more protein, eating more calories, drinking more water, and reducing alcohol consumption. Calories and protein may come from foods that would regularly be consumed in the diet or through high-calorie and high-protein shakes or beverages. When ingesting adequate nutrition by mouth is not a possibility due to nausea, swallowing difficulty, or a very sore mouth or throat, alternative feeding methods could be necessary. These methods may include providing fluids and nutrition through a feeding tube (enteral nutrition) or intravenous line (parenteral nutrition).

The purpose of this review is to evaluate the evidence and guidelines regarding the effect of nutritional supplementation on the clinical outcomes of patients with cancer.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of nutritional supplementation (from food or other sources) for patients with cancer?

2. What is the comparative clinical effectiveness of nutritional supplementation with food compared with other nutritional sources for patients with cancer?

3. What are the evidence-based guidelines for nutritional supplementation for patients with cancer?
KEY FINDINGS

The authors of the included studies concluded that oral nutritional interventions may be effective for increasing the nutritional intake of cancer patients, preserving body weight, and improving some aspects of their quality of life. One guideline recommends patients at risk of poor nutrition be assessed for the need for nutritional support and that nutritional support should not be offered as standard treatment for cancer patients undergoing surgery or chemotherapy. It is unclear which type or formulation of nutritional supplementation may be most beneficial to patients with cancer.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Medline, PubMed, The Cochrane Library (2013, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and December 2, 2013. Internet links were provided, where available.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Nutritional supplementation with food</td>
</tr>
<tr>
<td></td>
<td>Nutritional supplementation from other sources (e.g. Ensure, Boost, etc.)</td>
</tr>
<tr>
<td>Comparator</td>
<td>No supplementation</td>
</tr>
<tr>
<td></td>
<td>Different supplementation sources</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Treatment effectiveness, quality of life, mortality, weight increase</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), evidence-based guidelines</td>
</tr>
</tbody>
</table>
Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2008.

Critical Appraisal of Individual Studies

The included systematic review was critically appraised using the AMSTAR Checklist,\textsuperscript{3} the randomized studies were critically appraised using the Downs and Black instrument,\textsuperscript{4} and the guideline was appraised using the AGREE II Instrument.\textsuperscript{5} Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 392 citations were identified in the literature search. Following screening of titles and abstracts, 385 citations were excluded and seven potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 2 publications were excluded for various reasons, while 5 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Details of study characteristics, critical appraisal, and study findings are located in Appendices 2, 3, and 4, respectively.

Study Design

One systematic review was identified that included 13 RCTs or quasi-RCTs, written in any language, and published up to February 2010.\textsuperscript{6} Three additional RCTs were identified and were described as double-blind, placebo controlled,\textsuperscript{7} open label,\textsuperscript{8} and simply as randomized.\textsuperscript{9} Patients were randomized to receive oral nutritional supplements, with\textsuperscript{6,9} or without,\textsuperscript{6,8} dietary counseling or usual dietary care in the systematic review\textsuperscript{6} and two RCTs.\textsuperscript{8,9} In the third RCT, patients were randomized to receive either an energy and protein enriched oral nutritional supplement or an isocaloric oral nutritional supplement in addition to their usual diet.\textsuperscript{7}

One evidence-based guideline was identified.\textsuperscript{2}

Country of Origin

The included systematic review was undertaken in the United Kingdom. Studies were not excluded from the review based on where they were undertaken or published.\textsuperscript{6} The three included RCTs were conducted in Switzerland,\textsuperscript{9} the Netherlands,\textsuperscript{7} and Turkey.\textsuperscript{8} The included evidence-based guideline was created by a professional society in the USA.\textsuperscript{2}
Patient Population

The included systematic review,6 two RCTs,7,9 and the guideline2 included adult patients and one RCT8 included children. All patients had been diagnosed with cancer. Patients were clearly malnourished6,9 or determined to be at risk of malnourishment6 and were undergoing active treatment (chemotherapy,8 chemoradiotherapy,7 or unspecified6) or were in palliative care.6

Clinical Outcomes

Major clinical outcomes reported in the included studies were change in weight,6-9 energy intake,6,9 protein intake,9 quality of life,6,9 and mortality.6 The clinical outcomes of interest for the formulation of the guidelines were not explicitly stated.2 A description of recommendation grading and levels of evidence is provided in Appendix 5.

Interventions and Comparators

The systematic review6 included studies that compared oral nutritional interventions consisting of dietary advice, oral nutritional supplements (food products markets for the management of disease-related malnutrition), or a combination of dietary advice and nutritional supplements to usual care (optional dietary counseling or no intervention) in patients who were malnourished or at risk of malnourishment.

Two RCTs included ProSure protein and energy-dense oral nutritional supplement containing EPA (eicosapentaenoic acid) and DHA (docosahexanaeic acid).7,8 One RCT7 randomized adult patients to receive either two cans per day of ProSure (1.01g/can EPA and 0.46g/can DHA) or an isocaloric nutritional supplement without EPA or DHA (Ensure) in addition to their usual diet. The second RCT8 randomized pediatric patients to receive either two containers per day of ProSure (1.09g/can EPA) in addition to their normal diet or usual dietary care alone.

In the third RCT,9 patients were randomized to receive nutritional counseling followed by an individual nutrition plan with various dietary interventions including food enrichment, vegetable oil, protein powder, protein-rich snacks and beverages, and energy and protein-dense oral nutritional supplements (Resource 400 kcal and 18 g protein per day) or usual dietary care.

Summary of Critical Appraisal

The strengths and limitations of the included studies are summarized in Appendix 3.

Overall, the systematic review6 was well conducted. The authors provided an a priori study design. The literature search strategy was comprehensive and well described. Duplicate study selection and data extraction was undertaken. The methodological quality of the studies included in the review was assessed by two investigators. The authors indicated that all of the included studies were at risk of bias from one or more characteristics of the studies. There was clinical and statistical heterogeneity between the studies included in the analyses. In the identified RCTs, randomization8,9 and blinding methods9 were not well described and one study was described as open label.8 The lack of appropriate randomization and blinding may impact the internal validity of the studies and decrease the confidence in the association between the use of nutritional supplementation and improved outcomes in cancer patients. In the Uster study,9 there was a difference in baseline characteristics between groups after randomization.
This difference might also have impacted the internal validity of the study by introducing selection bias. It was unclear if confounders were accounted for in all statistical analyses. In the Uster study, a high drop-out rate and early study termination resulted in low statistical power of analyses and a reduced confidence in hard endpoints of the study. Statistical power calculations were not described in the Bayram study. Poor patient compliance and higher drop out rate in the intervention group may have impacted the reliability of the results from van der Meij.

An evidence-based guideline from the American Society for Parenteral and Enteral Nutrition (ASPEN) was included. The strengths of the guideline include a clear objective, a systematic search of the literature was conducted, the strength of the evidence and a grading scheme is described, recommendations are clearly outlined, the guideline development group included doctors, nurses, pharmacists, and dieticians from ASPEN, and input was sought form the target population. Limitations of the guideline include the lack explicitly predefined research questions developed a priori, lack of information provided on the barriers and aids to implementing the recommendations, lack of discussion of potential resource implications, no information on if or how the guideline will be updated, and no information regarding conflicts of interest or funding sources.

Summary of Findings

A summary of study findings is provided in Appendix 4.

What is the clinical effectiveness of nutritional supplementation (from food or other sources) for patients with cancer?

Mortality data was available in 11 of the 13 studies included in the systematic review. No statistically significant differences in mortality were observed between the intervention and control groups (RR = 1.06; 95% CI, 0.92 to 1.22; \( P = 0.43 \)). Data regarding changes to body weight was available in eight of the 13 studies. Nutritional interventions were associated with significant improvements in body weight and increased energy intake but significant heterogeneity was observed between studies. When the data from two studies, which was determined to be the main source of heterogeneity, was removed from the analysis, there was no longer a significant association between nutritional interventions and weight gain or energy intake. Quality of life (QoL) was assessed with the European Organization for Research and Treatment of Cancer (EORTC) questionnaire in five studies. When compared with routine care in the meta-analysis, nutritional interventions resulted in significant improvements in all function scales (physical functioning, role functioning, cognitive function, emotional function, and social functioning) and global QoL scores.

In the study by van der Meij, after correcting for individual energy requirements and energy intake per kilogram, energy balance and protein intake were the same between the ProSure and Ensure groups. After weeks one, two, and four the nutritional therapy group demonstrated better weight maintenance (\( P = 0.07, 0.02, 0.04 \)). The treatment effects were stronger in the per protocol analysis (\( P <0.01, <0.01, 0.04 \)). The nutritional therapy group had a significantly higher energy and protein intake over time. No serious adverse events were reported in either group. The authors indicated that patients enrolled in this study had less advanced disease and a lower prevalence of malnutrition at baseline as compared to patients included in previous studies. The dropout rate was higher in the intervention than in the control group (6/20 vs 1/20).
Uster et al. found that daily energy and daily protein intake were significantly greater in the intervention group (+379 kcal; \( P = 0.0007 \) and +10.4g; \( P = 0.016 \)). However, the increased dietary intake of energy and protein were not related to significant changes in body weight, physical functioning, or QoL measures. The participants enrolled in this study had advanced disease and poor nutritional status before the initiation of the study intervention. The authors hypothesized that the nutritional intervention was initiated too late in these patients to have any important impact on their nutritional status.

In the study by Bayram et al., The participants began the intervention (ProSure) soon after cancer diagnosis. Significantly fewer patients in the treatment group showed loss in body weight \( (P = 0.001) \) or BMI \( (P = 0.002) \) after three months, compared with usual care. In a subgroup of patients who were followed for six months, the decreased loss in body weight in the treatment group was maintained \( (P = 0.03) \). Cancer remission rate was also reported to be higher in the treatment group \( (P = 0.021) \).

**What is the comparative clinical effectiveness of nutritional supplementation with food compared with other nutritional sources for patients with cancer?**

No literature was identified that explicitly compared the effectiveness of nutritional supplementation with food to similar supplementation from other nutritional sources. While the systematic review and two of the identified RCTs compared nutritional supplements to usual care, usual care was not well defined.

**What are the evidence-based guidelines for nutritional supplementation for patients with cancer?**

The ASPEN guideline recommends that patients with cancer who are determined to be nutritionally-at-risk and should undergo nutrition screening to identify whether they require a formal nutrition assessment that would include the development of a nutrition care plan (Grade D). Nutrition support therapy should not be used routinely in patients undergoing major cancer operations (Grade A) or as an adjunct to chemotherapy (Grade B). Omega-3 fatty acid supplementation is recommended as it may help to stabilize the weight of cancer patients on oral diets who are experiencing unintentional and continuing weight loss (Grade B). The grading of the guidelines and levels of evidence used in the ASPEN guideline are provided in Appendix 5.

**Limitations**

The inclusion criteria for the oral nutritional supplements included in the systematic review were not explicitly described other than "food products marketed for the management of disease-related malnutrition". The authors of the van der Meij study indicated that enrolled patients showed a less advanced state of disease and malnutrition than was present in previous studies. Due to drop outs, there were not the required number of patients in the intervention group and may have impacted the statistical power of the analysis. In the Uster study, although nutritional supplements were only intended to be consumed by the treatment group, they were also reported to have been consumed by members of the control group. The cut off score of the screening tool used to determine eligibility of participants in this study may have been set too high and resulted in included patients having a stage of cancer that was too far advanced to be improved by nutritional interventions. This study was terminated early due to low recruitment and had a high drop out rate.
None of the included studies was undertaken at a Canadian center; therefore, the findings of the non-Canadian studies might not be applicable to the Canadian setting because of local differences in clinical practice and the availability of the nutritional products used in the studies.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The authors of the included studies concluded that oral nutritional interventions may be effective for increasing the nutritional intake\textsuperscript{6,9} of cancer patients, preserving body weight,\textsuperscript{6-8} and improving some aspects of their quality of life.\textsuperscript{6,9} The guideline recommends patients at risk of poor nutrition be assessed for the need for nutritional support and that nutritional support should not be offered as standard treatment for cancer patients undergoing surgery or chemotherapy.\textsuperscript{2} It is unclear which type or formulation of nutritional supplementation is most beneficial to patients with cancer.

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Tel: 1-866-898-8439
www.cadth.ca
REFERENCES


APPENDIX 1: Selection of Included Studies

392 citations identified from electronic literature search and screened

385 citations excluded

7 potentially relevant articles retrieved for scrutiny (full text, if available)

0 potentially relevant reports retrieved from other sources (grey literature, hand search)

7 potentially relevant reports

2 reports excluded: -irrelevant intervention (2)

5 reports included in review
# APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Studies

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Clinical Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baldwin (2011)&lt;sup&gt;6&lt;/sup&gt;, United Kingdom</td>
<td>Systematic review and meta-analysis</td>
<td>Included 13 RCTs or quasi-RCTs</td>
<td>Adult patients with cancer (all sites, all stages) who were clearly malnourished or at risk of malnutrition, receiving active treatment or palliative care</td>
<td>Oral nutritional interventions consisting of: - dietary advice - oral nutritional supplements (food products marketed for the management of disease-related malnutrition) - dietary advice and oral nutritional supplements</td>
<td>Usual care (optional dietary counseling or no intervention)</td>
</tr>
</tbody>
</table>

<p>| Uster (2013)&lt;sup&gt;9&lt;/sup&gt;, Switzerland | RCT | Patients with malignant tumors referred to a cancer center with NRS score ≥3, unintended loss of ≥5% of body weight over last two months, or ≥10% over last six months, and food intake less than usual quantity | Nutritional counselling at baseline, 6 weeks and 3 months followed by an individual nutrition plan with various dietary interventions (food enrichment, vegetable oil, protein powder, protein-rich snacks and beverages, energy and protein-dense oral nutritional supplements [Resource]) If Resource was prescribed, patients were asked to | Usual care (standard medical therapy with no specific nutritional interventions) | QoL, energy intake, protein intake, body weight, nutritional status, physical status |</p>
<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Clinical Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Meij (2010)³</td>
<td>Double-blind, placebo controlled RCT</td>
<td>Adult patients with histological or cytological proven stage IIIa-N2 or IIIb NSCLC eligible for concurrent chemotherapy and life expectancy greater than three months</td>
<td>Two cans per day of a protein and energy-dense oral nutritional supplement containing 1.01g/can of EPA and 0.46g/can DHA (480 mL ProSure) in addition to usual diet</td>
<td>Isocaloric oral nutritional supplement without EPA or DHA (400 mL Ensure) in addition to usual diet</td>
<td>Weight maintenance, FFM, MUAC, inflammatory markers</td>
</tr>
<tr>
<td>Bayram (2009)⁸</td>
<td>Prosepective, single center, open label, RCT Randomized 2:1</td>
<td>Pediatric patients diagnosed with malignant disease and receiving intensive chemotherapy</td>
<td>Two containers per day of a protein and energy dense EPA containing oral supplement (ProSure) [1.09g EPA/can] in addition to normal dietary intake</td>
<td>Usual dietary care</td>
<td>Body weight, height, BMI, weight percentile, status of primary disease, attacks of febrile neutropenia, clinical status</td>
</tr>
</tbody>
</table>

BMI = body mass index; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FFM = fat free mass; g = gram; kcal = kilocalorie; MUAC = mid-upper arm circumference; NSCLC = non-small cell lung cancer; QoL = quality of life; RCT = randomized controlled trial
Table A2: Characteristics of Included Guidelines

<table>
<thead>
<tr>
<th>Intended users/ Target population</th>
<th>Intervention and Practice Considered</th>
<th>Major Outcomes Considered</th>
<th>Evidence collection, Selection and Synthesis</th>
<th>Evidence Quality and Strength</th>
<th>Recommendations development and Evaluation</th>
<th>Guideline Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>August et al. 2009² – American Society for Perenteral and Enteral Nutrition (ASBEN), USA</td>
<td>healthcare professionals who provide nutrition support services and offer clinical advice for managing adult and pediatric patients in inpatient and outpatient settings</td>
<td>nutrition support therapy in adult cancer patients during anticancer treatment and in hematopoietic cell transplantation</td>
<td>not explicitly stated</td>
<td>Literature was obtained through MEDLINE, Cochrane trial registry, Cochrane Database, and other appropriate reference sources. No date limits.</td>
<td>Guidelines were graded based on level of evidence of the studies to support the guidelines. Grading criteria were provided.</td>
<td>Guidelines are based on general conclusions of health professionals.</td>
</tr>
</tbody>
</table>
## APPENDIX 3: Summary of Critical Appraisal of Included Studies and Guidelines

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AMSTAR</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Baldwin (2011) SR United Kingdom | • used Cochrane Collaboration methods for systematic review  
• double selection and extraction  
• 'a priori' design provided  
• duplicate study selection and data extraction  
• comprehensive literature search performed  
• characteristics of the included studies provided  
• scientific quality of the included studies assessed and documented  
• scientific quality of the included studies used in formulating conclusions  
• methods used to combine the findings of studies were appropriate  
• analyses adjusted for confounding variables  
• likelihood of publication bias was assessed | • does not specify which oral nutritional interventions they included  
• clinical and statistical heterogeneity between studies  
• unclear whether grey literature was searched  
• no mention of excluded studies list  
• potential sources of conflict of interest was not disclosed |

| **Downs and Black**            |           |             |
| Uster (2013) RCT Switzerland   | • aim and hypothesis described  
• inclusion/exclusion criteria clearly described  
• power calculation provided  
• patient and intervention characteristics clearly described  
• ITT analysis used  
• described patients lost to follow up | • randomization and blinding methods were not described  
• study was terminated early due to low recruitment  
• at baseline, there was a difference after randomization between groups in general performance status  
• randomization methods were not described  
• unclear if confounders were accounted for in analyses  
• nutritional supplements were consumed by members of the control group  
• 3 day food questionnaire was not fully completed by all patients  
• standardized quantities were used where food diaries were incomplete  
• high drop-out rate led to low statistical power of analyses and |
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| van her Meij (2010) RCT The Netherlands | • aim of the study was well described  
• patient characteristics, inclusion/exclusion criteria, randomization, blinding, and intervention were well described  
• statistical power of the study was based on calculations from a previous study. Specific details were provided  
• statistical analyses well described  
• used both ITT and per protocol analyses  
• analyses were adjusted for confounding variables  
• described patients lost to follow up | • the higher drop-out rate in intervention than control group may have impacted the statistical power of the calculations  
• poor patient compliance may have impacted results |
| Bayram (2009) RCT Turkey | • aim of the study was well described  
• patient characteristics, inclusion/exclusion criteria, and intervention were well described  
• statistical methods described | • open label study design  
• randomization methods not clearly described  
• no statistical power calculations  
• did not adjust analyses for confounders |
| AGREE II Instrument | SCOPE AND PURPOSE  
• The overall objectives of the guideline are specifically described  
• The target users of the guideline are clearly defined  
STAKEHOLDER INVOLVEMENT  
• The guideline development group includes individuals from all relevant professional groups  
• The views and preferences of the target population (patients, public, etc.) have been sought | SCOPE AND PURPOSE  
• The health question(s) covered by the guideline is (are) specifically described  
STAKEHOLDER INVOLVEMENT  
• The guideline development group includes individuals from all relevant professional groups  
• The views and preferences of the target population (patients, public, etc.) have been sought |

**Nutritional Supplementation for Patients with Cancer**
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
|                               | externally reviewed by experts prior to its publication  
• The methods for formulating the recommendations are clearly described  
• The health benefits, side effects, and risks have been considered in formulating the recommendations  
CLARITY OF PRESENTATION  
• The recommendations are specific and unambiguous  
• The different options for management of the condition or health issue are clearly presented  
• Key recommendations are easily identifiable                                                                                                                                                           | guideline is not provided.  
APPLICABILITY  
• The guideline does not describe facilitators and barriers to its application or advice and/or tools on how the recommendations can be put into practice  
• The potential resource implications of applying the recommendations have not been considered  
• The guideline presents monitoring and/or auditing criteria  
EDITORIAL INDEPENDENCE  
• Funding sources were not identified  
• Competing interests of guideline development group members have not been recorded and addressed                                                                                                            |

ITT = intention to treat; RCT = randomized controlled trial
## APPENDIX 4: Main Study Findings and Authors’ Conclusions

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Author’s Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baldwin (2011)</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean difference in weight NT vs UC = 1.86 kg (95% CI, 0.25 to 3.47; (P = 0.02))</td>
<td>The authors concluded that “oral nutritional interventions are effective at increasing nutritional intake and improving some aspects of QoL in patients with cancer who are malnourished or are at nutritional risk but do not appear to improve mortality.” p.1</td>
</tr>
<tr>
<td></td>
<td>Mean difference in energy intake NT vs UC = 432 kcal/d (95% CI, 172 to 693; (P = 0.001))</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mortality RR = 1.06 (95% CI, 0.92 to 1.22; (P = 0.43))</td>
<td></td>
</tr>
<tr>
<td></td>
<td>When main sources of heterogeneity were removed from the analysis, the differences in weight and energy intake were no longer statistically significant</td>
<td></td>
</tr>
<tr>
<td><strong>Uster (2013)</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Daily energy intake NT vs UC = +379 kcal (95% CI, 117 to 642; (P = 0.007))</td>
<td>nutritional intervention significantly improved energy and protein intake</td>
</tr>
<tr>
<td></td>
<td>Daily protein intake NT vs UC = +10.4 g (95% CI, 2.3 to 18.5; (P = 0.016))</td>
<td>patients were able to maintain body weight independently of study treatment and regardless of whether calculated energy and protein requirements were met</td>
</tr>
<tr>
<td></td>
<td>Mean oral supplement consumption NT (n = 16) = 0.9 ± 0.6 cups/d UC (n = 2) = 1.1 ± 0.2 cups/d</td>
<td>patients in the usual care group also showed improved QoL</td>
</tr>
<tr>
<td></td>
<td>Average global QoL/health status scores UC vs NT ((P = 0.046))</td>
<td>the authors hypothesized that the nutritional intervention was implemented too late in study patient who already had advanced cancer and poor nutritional status.</td>
</tr>
<tr>
<td></td>
<td>Total VAS scores UC vs NT ((P = 0.04))</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• at baseline, performance status was significantly lower in nutritional therapy group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• no significant changes were reported in body weight or physical functioning</td>
<td></td>
</tr>
<tr>
<td><strong>van her Meij (2010)</strong>*</td>
<td>Mean oral supplement consumption NT = 1.1 ± 1.0 can/d UC = 1.0 ± 0.9 can/d</td>
<td>oral nutritional supplements containing fatty acids resulted in preservation of body weight and FFM during chemoradiotherapy</td>
</tr>
<tr>
<td></td>
<td>Patients remaining in the study at week 5 NT (n = 14) UC (n = 19)</td>
<td>the authors concluded that a protein and energy dense oral nutritional supplement containing (n-3) fatty acids was beneficial to patients with</td>
</tr>
<tr>
<td>First Author, Publication Year</td>
<td>Main Study Findings</td>
<td>Author’s Conclusions</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>EPA intake at week 5 NT vs UC = difference of 0.6 g/d ((P = 0.01))</td>
<td></td>
<td>stage III NSCLC</td>
</tr>
<tr>
<td>ALA intake at week 5 NT vs UC = difference of 1.3 g/d ((P = 0.003))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHA intake at week 5 UC vs NT = difference of 0.2 g/d ((P = 0.25))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFM at week 5 NT vs UC = difference of 1.9 kg ((P = 0.02))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUAC at week 5 NT &gt; UC ((P = 0.06))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayram (2009)(^5)</td>
<td>Loss in body weight at 3 months NT = 6.1% (P = 0.001) UC = 47.4%</td>
<td>The authors concluded their data showed pediatric patients with cancer who are given protein and energy dense, EPA containing nutritional supplement along with standard of care had improved clinical outcomes when compared with patients receiving standard of care alone</td>
</tr>
<tr>
<td></td>
<td>Loss in BMI at 3 months NT = 12.1% (P = 0.002) UC = 52.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loss in body weight at 6 months (n = 23) NT = 6.7% (P = 0.03) UC = 50%</td>
<td>Suggest this type of supplement should be considered a safe adjunct therapy for children with cancer</td>
</tr>
</tbody>
</table>

\(BMI = body \ mass \ index; EPA = eicosapentaenoic \ acid; FFM = fat \ free \ mass; d = day; g = gram; kcal = kilocalorie; kg = kilogram; NSCLC = non-small \ cell \ lung \ cancer; NT = nutritional \ therapy; QoL = quality \ of \ life; RR = relative \ risk; UC = usual \ care; VAS = visual \ analog \ scale\)
APPENDIX 5: Grading of guidelines and levels of evidence in the ASPEN Guideline

(Table 1, page 474)

<table>
<thead>
<tr>
<th>Grading of Guidelines</th>
<th>Levels of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Supported by at least two level I investigations</td>
<td>I. Large randomized trials with clear-cut results; low risk of false-positive (alpha) and/or false-negative (beta) error</td>
</tr>
<tr>
<td>B. Supported by one level I investigation</td>
<td>II. Small, randomized trials with uncertain results; moderate-to-high risk of false-positive (alpha) and/or false-negative (beta) error</td>
</tr>
<tr>
<td>C. Supported by at least one level II investigation</td>
<td>III. Nonrandomized cohort with contemporaneous controls</td>
</tr>
<tr>
<td>D. Supported by at least one level III investigation</td>
<td>IV. Nonrandomized cohort with historical controls</td>
</tr>
<tr>
<td>E. Supported by level IV or V evidence</td>
<td>V. Case series, uncontrolled studies, and expert opinion</td>
</tr>
</tbody>
</table>