# Enteral (oral or tube administration) nutritional support and eicosapentaenoic acid in patients with cancer: A systematic review

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**Abstract.** The aim of this systematic review was to determine the efficacy and potential benefits of enteral nutritional support [oral nutritional supplements (ONS) or enteral tube feeding (ETF)], and eicosapentaenoic acid (EPA, free acid, ethyl esters or fish oil; provided as capsules or enriched ONS or ETF) in patients with cancer. Clinical studies were identified using electronic databases, and studies were selected according to predetermined criteria. For each treatment modality (chemo/radiotherapy, surgery, and palliative care), the comparisons of interest were nutritional support vs. routine care (no nutritional support), EPA supplement (capsule or enriched ONS or ETF) vs. routine care (no supplement or standard supplement), ETF vs. parenteral nutrition (PN). The reviewed outcomes were dietary intake, anthropometry, clinical (mortality, length of hospital stay, complications, and quality of life) and haematological/biochemical (white blood cell count, serum transferrin and albumin, CD3-positive lymphocytes, and inflammatory markers). Meta-analyses were performed where possible. In patients undergoing radiotherapy, meta-analysis showed that ONS significantly increase dietary intake (381 kcal/day, 95% CI 193 to 569 in 3 RCTs) compared to routine care. In patients undergoing surgery, meta-analyses showed that ETF results in a significantly shorter length of hospital stay (1.72 fewer days, 95% CI 0.90 to 2.54 in 8 RCTs), lower incidence of any complications (OR 0.62, 95% CI 0.50 to 0.77 in 4 RCTs) and infectious complications (OR 0.67, 95% CI 0.55 to 0.82 in 11 RCTs) and lower sepsis scores (2.21 points, 95% CI 1.49 to 2.92 in 2 RCTs), but no difference in mortality (OR 0.72, 95% CI 0.40 to 1.29 in 7 RCTs) compared to PN. There was also no difference in mortality between ONS or ETF vs. routine care in patients undergoing chemotherapy/radiotherapy (OR 1.00, 95% CI 0.62-1.61 in 4 RCTs) or surgery (OR 2.44, 95% CI 0.75 to 7.95 in 4 RCTs). Individual studies of EPA supplementation as capsules showed improvements in survival, complications and inflammatory markers in patients undergoing bone marrow transplant (BMT). In palliative care patients receiving EPA-enriched ONS or capsules, there were inconsistent positive effects on survival and quality of life. In those undergoing surgery, EPA-enriched ETF had no effect. Further research is required to elucidate the clinical efficacy of enteral nutrition support, including the potential benefits of EPA supplementation, in patients with cancer.

**Contents**



## 1. Introduction

Malnutrition is common in patients with cancer. Estimated prevalence rates of malnutrition vary according to tumour site, stage of disease, type of treatments and the methods used to identify malnutrition. The prevalence of malnutrition can range from 9% and 46% in urological and lung cancer patients, respectively, to 85% in pancreatic cancer patients (1).

Malnutrition and weight loss in patients with cancer may be caused by reduced food intake due to a number of factors including systemic effects of the disease (e.g. anorexia, hypermetabolism, alterations in taste and smell, nausea,

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*Abbreviations*: BMT, bone marrow transplant; CT, clinical trial; CCT, controlled clinical trial; CRP, C-reactive protein; EPA, eicosapentaenoic acid; ETF, enteral tube feeding; ONS, oral nutritional supplements; OR, odds ratio; PN, parenteral nutrition; RCT, randomised controlled trial

*Key words*: meta-analysis, supplement, enteral, formula, cachexia, eicosapentaenoic acid, cancer

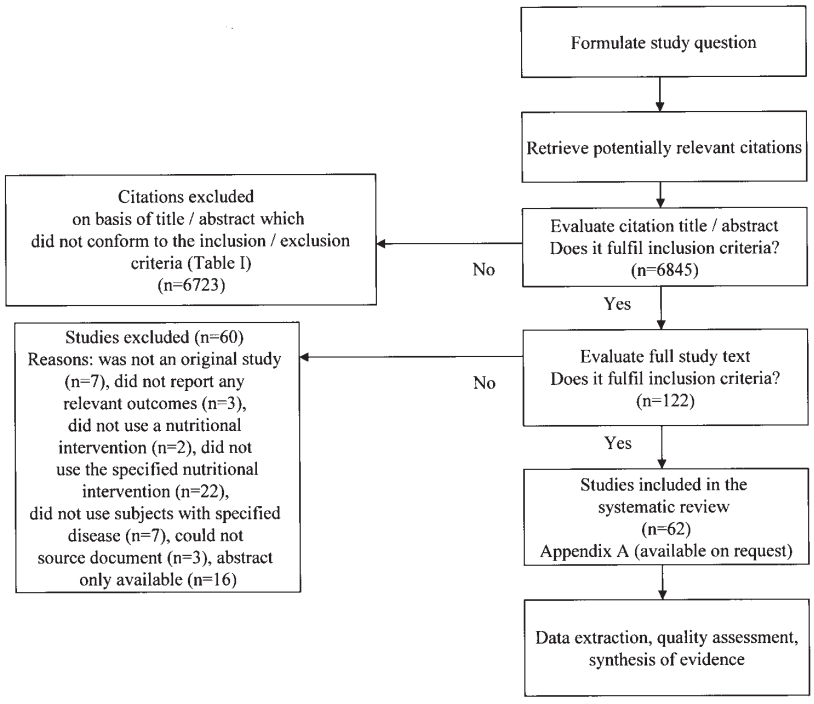


Figure 1. Summary of study methodology stages and process of the systematic review.

vomiting, and pain), local effects of the tumour (e.g. odynophagia, dysphagia, gastrointestinal obstruction, early satiety, and malabsorption), psychological factors (e.g. fear, depression, and anxiety), and side effects of treatment (2-8).

Most patients with advanced cancer lose weight during the course of their disease, and a proportion of them develop cancer cachexia, a progressive involuntary weight loss condition (9). Cancer cachexia is a complex multifactorial syndrome, attributable to factors arising from the tumour itself, the host response to the tumour, and treatments (3,5-7,10,11). This condition is associated with metabolic abnormalities, anorexia, early satiety and reduced food intake, depletion of lean body mass, muscle weakness, oedema, fatigue, impaired immune function, and a decline in attention span and concentration (3,5-7,11).

Reported consequences of malnutrition in cancer patients include lower quality of life, reduced effectiveness of chemotherapy, increased risk of chemotherapy-induced toxicity, reduced performance status and muscle function, increased risk of postoperative complications, longer hospital stay, higher prescription and consultation rates, and shorter survival time (12-35).

Nutritional support is therefore indicated in malnourished patients with cancer; this is often provided as oral nutritional supplements (ONS) and enteral tube feeding (ETF). Although there have been previous reviews to address the efficacy of enteral nutritional support (36), there appears to have been no formal systematic review with meta-analyses that considers the impact of ONS and ETF vs. routine care in cancer patients according to the type of therapy received.

When oral food intake is insufficient or difficult, ETF can be used with cancer patients. Post-pyloric ETF can be undertaken when tolerance to nasogastric feeding is poor (e.g. after abdominal surgery); PN may also be used in such cases. Previous reviews of studies comparing ETF with PN (37-39) have generally not been systematic reviews, excluded meta-analyses and, in some cases, have not considered studies on patients with cancer separately from other conditions (37). One review on this topic only considered preoperative studies in cancer patients (38), and another did not separately consider the effects of ETF using standard feeds from 'immunonutrition' feeds (39).

Eicosapentaenoic acid (EPA), an n-3 long chain polyunsaturated fatty acid found in oily fish, has recently been introduced as a treatment for patients with cancer for a variety of reasons. EPA may modulate aspects of the inflammatory response implicated in the metabolic changes associated with weight loss and muscular atrophy in cancer patients. EPA supplementation in cancer patients has been shown to down-regulate the production of pro-inflammatory cytokines (e.g. IL-6, IL-1, and TNF) (21) and attenuate progression of the acute-phase protein response e.g. C-reactive protein response (CRP) (40-49). Furthermore, an anti-tumour effect has been demonstrated, which is thought to occur through a number of mechanisms (50). EPA has also been associated with the halting or reversal of weight loss (51-54) and prolongation of survival (21). However, no systematic review has been performed to date.

In clinical practice, EPA has been given either as capsules or enriched ONS or ETF in patients with cancer. However, there is no consensus about the value of using EPA in the treatment of patients with cancer as yet. An earlier review by Baracos summarised some trials of EPA supplementation, but this was not a systematic review, studies on EPA capsules were not discussed separately from those on EPA-enriched feeds, and meta-analysis was not undertaken (55).

In summary, there have been few systematic reviews of the efficacy of nutritional support, including the use of EPA, in patients with cancer, and those published previously included limited therapy types (37), were qualitative rather than

Table I. Inclusion and exclusion criteria.

| Selection criterion | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Population | All adult patients.<br>Nutritional status either well-nourished or malnourished.<br>All types/stages of cancer.<br>Any type of therapy.<br>Hospital or community setting (e.g. hospital, out-patient and home). | Animal data. |
| Intervention nutritional support studies) | All studies using ONS and/or ETF (all routes/ methods), including those simultaneously using dietary counselling and/or PN and/or simultaneous standard diet. | Dietary counselling only.<br>PN only.<br>Interventions with <2 macronutrients.<br>Interventions with no micronutrients.<br>Concurrent use of appetite stimulants.<br>Immune-modulating diets (e.g. incorporating arginine, designed to modulate the immune system in the critically ill). |
| Intervention (EPA studies) | All studies using EPA (free acid, ethyl esters or fish oil). Route of administration: capsules or enriched ONS or ETF. | Parenteral route of administration of EPA.<br>EPA enriched immune enhancing diets.<br>All other forms of EPA.<br>Concurrent use of appetite stimulants. |
| Outcome measures | Dietary intake.<br>Anthropometry.<br>Mortality.<br>Length of hospital stay.<br>Complications.<br>Quality of life/performance status.<br>Biochemical (white blood cell count, serum transferrin and albumin, CD3-positive lymphocytes and inflammatory cytokines). | |

quantitative (56), and have been restricted to randomised controlled studies with limited outcome measures (57). Therefore, this systematic review was undertaken to comprehensively examine the efficacy of nutritional support in patients with cancer. The aim was to determine the extent to which (i) enteral (oral or tube administration) nutritional support vs. routine care, (ii) EPA supplementation (capsules or enriched ONS or ETF) vs. routine care, and (iii) ETF vs. PN improves the outcome of cancer patients undergoing radio/chemotherapy (including BMT) or surgery, or in palliative care.

## 2. Methods

The review was planned, conducted and reported according to published guidelines, which included those issued by the Cochrane Collaboration (58), UK National Health Service Centre for Reviews and Dissemination (CRD) (59,60), and Quorum guidelines (61). A flow chart illustrates the principle stages and processes undertaken (Fig. 1).

*Identification and retrieval of studies*. Potentially relevant studies were identified by searching electronic databases (all conducted on 23/07/04). These included Pub Med (62), Cochrane (58), Turning Research Into Practice (63), Clinical Evidence (64), National Electronic Library for Health guidelines finder (65) and National Service Frameworks (66). The search terms included: fish oil*, epa, eicosapentaen*, icosapentaen*, omega-3, omega3, n-3 fatty acid*, n 3 fatty acid, neoplasm, cancer*, carcinoma, lymphoma, leukaemia, tumour*, tumor*, malignan*, nutrition*, nutrie*, enteral*, supplement*, sip, feed, formula*, liquid, tube, nasogastric, nasojejunal, nasoduodenal, gastrostomy, jejunostomy, and clinical trial. Bibliographies were checked, and experts in the field were contacted for additional studies.

*Study selection criteria*. Studies were deemed eligible for inclusion in the review if they conformed to predetermined inclusion and exclusion criteria (Table I). The inclusion criteria specified subjects, intervention, outcome measures and study design. Subjects eligible for inclusion were adult

patients (>18 years age) with cancer of any type and stage, any nutritional status (well-nourished or malnourished) and based in any setting (e.g. hospital, out-patient, or home). Eligible nutritional support interventions contained at least two macronutrients as well as micronutrients, and were administered enterally as either ONS or ETF. The intervention could either provide a portion of or the complete daily requirement for energy and be nutritionally complete or incomplete. Eligible EPA interventions incorporated EPA administered as a free acid, EPA ethyl esters, or fish oil; this could be administered alone as a discrete dose (e.g. capsule) or an enriched ONS or ETF. In all cases, supplements containing other immune modulating nutrients (e.g. arginine) were excluded, although these comparators could be included in the review if such studies incorporated other interventions as comparators. Studies using concurrent PN or dietary advice were admissible, but those utilising only PN or only dietary counselling were excluded. Only full papers were admissible, thereby excluding abstracts that are often published as preliminary findings and not subjected to peer review. No other restrictions were placed on studies with regard to the type of comparator (e.g. no nutritional support, dietary advice or PN), year of publication, language (provided an English translation was available) and source. Randomised controlled trials (RCT) were considered a priority, although non-randomised controlled clinical trials (CCT) and before-after clinical trials (CT) were also admissible; observational study designs (e.g. cohort, case study) were excluded.

Following the identification of potentially relevant studies based on titles and abstracts, full papers were obtained and evaluated by one researcher; a second assessor verified inclusion/exclusion decisions.

*Data extraction and outcome measures*. A predetermined data extraction table was designed to capture study characteristics and outcome data, and allow the assimilation of data from differing study designs. Outcome measures of interest were dietary intake, anthropometry, clinical (mortality, length of hospital stay, complications, and quality of life) and haematological/biochemical (white blood cell count, serum transferrin and albumin, CD3-positive lymphocytes, and inflammatory cytokines). Outcomes were recorded based on definitions provided by the original authors of each study.

*Quality assessment*. Using two methods, the quality of individual studies was assessed by one researcher and verified by a second (67,68). The first method was a six-point scale adapted from the Quality of Evidence Quality Assessment scale (Agency for Health Care and Policy Research) (67), and the second was a method used by Jadad *et al*, reported previously (68).

*Synthesis of data and statistical methods*. Following the extraction of data, meta-analysis was conducted where appropriate and feasible for any measured outcome that was represented by two or more comparable studies.

For each treatment modality of surgery, chemotherapy/radiotherapy and palliative care, the main comparisons of interest were: nutritional support (ONS or ETF) vs. routine care (no nutritional support); EPA supplementation (administered as a capsule or as enriched ONS or ETF) vs. routine care; and ETF vs. PN. Separate analyses were intended for cancer type, setting and nutritional status (malnourished vs. well-nourished).

For categorical data, the method of Woolf was used to calculate a weighted average of the log odds ratio (OR) in each study (69). The odds ratios were considered statistically significant if the 95% CI did not span the value of 1. A fixed effects model was used to combine the treatment estimates, which assumes no heterogeneity between the study results. The meta-analysis estimate of the odds ratio was calculated as a weighted sum of the odds ratio for each study, where the weight was calculated as the reciprocal of variance of the absolute odds ratio for each individual study.

For continuous data, the selection of data for analysis was conducted as follows: changes from baseline data were used, except if one or more studies in the meta-analysis failed to report baseline data in which case post-intervention data were used. The correlation between baseline and post intervention data was assumed to be zero (r=0), which results in the most conservative method of analysis. The sensitivity of this assumption was tested by conducting additional analyses using r=0.5. Hedges' unbiased estimator of the standardised mean difference for relevant treatment comparisons was calculated (70). The mean treatment difference was considered statistically significant if the 95% CI did not span the value of 0. A fixed effects model was used to combine the treatment estimates, which assumes no heterogeneity between the study results. Meta-analysis estimate of the treatment effect size was calculated as a weighted sum of the effect size for each study, where the weight was calculated as the reciprocal of Hedges' estimated variance of effect size for each individual study.

Forest plots were used to present the odds ratio or effect size of each study and meta-analysis estimate. Heterogeneity was investigated with the Q test of heterogeneity derived from the Mantel-Haenszel method (71). Due to the small number of studies included in the meta-analyses, it was deemed inappropriate to investigate publication bias through the use of funnel plots (72). All statistical analyses were conducted using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA.). All data are presented as mean ± SD unless otherwise stated.

## 3. Results

*Overall search findings*. A total of 6845 studies were identified by the search strategy (Fig. 1). Following evaluation of the title/abstract, 122 papers were deemed potentially relevant and obtained in full. Upon reading the full text of these 122 papers, 62 complied with the inclusion criteria and were included in the review (21,46,47,51,52,54,73-128). The study details are provided in Appendix A (available upon request).

The other 60 studies were rejected for reasons that included not being an original experimental study, use of an ineligible nutritional intervention and not using a nutritional intervention. Studies published only in abstract form were also excluded, as were studies for which English translations could not be obtained. Details of the excluded studies and reasons for exclusion are included in Appendix B (available upon request).

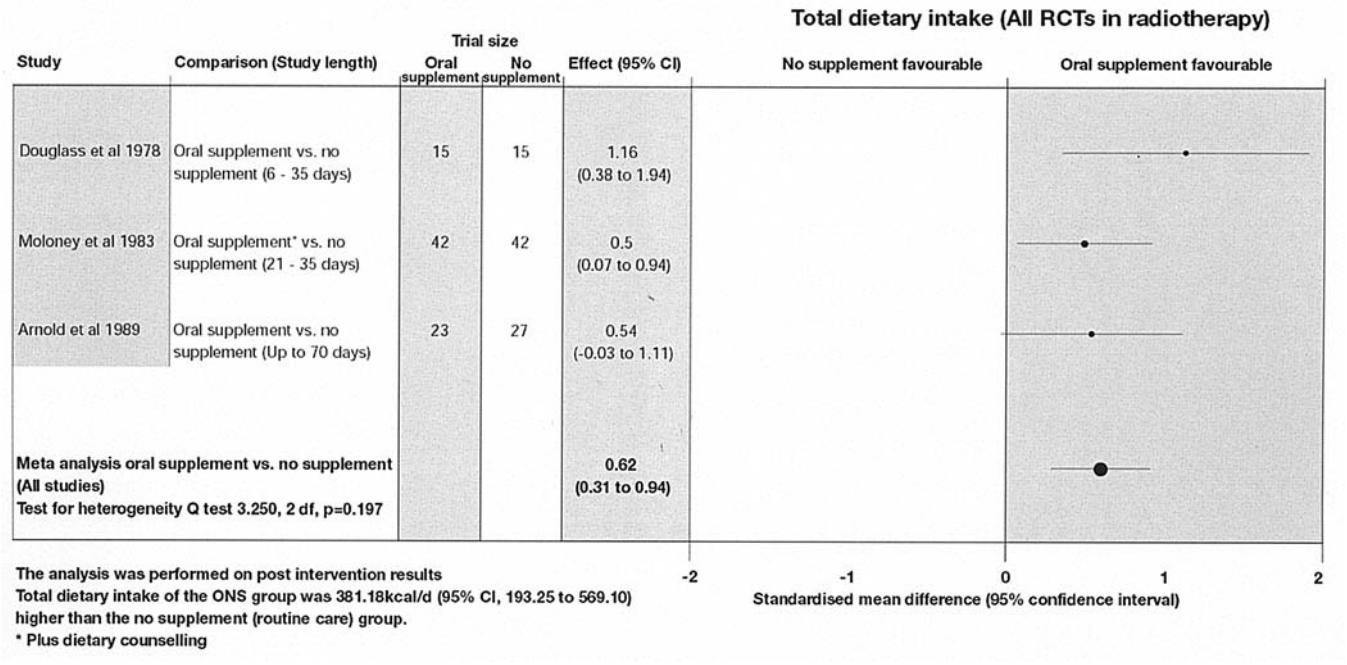


Figure 2. Total energy intake. The effect of oral nutritional support vs. routine care in patients with cancer undergoing radiotherapy based on a meta-analysis of 3 RCTs (77,94,107).

*Description of included studies*. There were 17 eligible studies on patients undergoing chemotherapy or radiotherapy for inclusion in the review, including 8 RCTs (77,79,87,94,95, 97,107,109) and 6 non-RCTs (78,81,92,105,121,128) comparing nutritional support with routine care, 2 RCTs comparing EPA supplementation (capsules) with routine care (47,74), and 1 RCT comparing ETF with PN (108). The majority of studies (n=12) utilised ONS, with only 5 studies using ETF (78,81,92,108,121). The type of cancer varied widely and included head/neck (77,109,121,128), abdominal/pelvic (79,87,94,97), lung (128), breast (95,105), gastrointestinal (81), leukaemia (47,74,92), or a variety of sites (78,107,108). Three of the studies were on patients undergoing bone marrow transplantation (47,74,108).

There were 27 eligible studies on patients undergoing surgery for inclusion in the review. These included 9 RCTs (82,84,90,104,111,120,123,125,126) and 1 non-RCT (116) comparing nutritional support with routine care, 3 RCTs comparing EPA provided as either enriched ETF (102,124) or capsules (46) with routine care, and 15 RCTs comparing ETF with PN (76,80,83,85,86,90,93,98,103,112,115,117,118, 122,127). One study provided data both for analysis of nutritional support vs. routine care, and ETF vs. PN (90). The majority (n=23) utilised ETF, with only 4 studies using ONS (84,104) or a combination of oral and tube routes (46,82). The type of cancer varied; most (n=24) were gastrointestinal (46,76,80,82-86,90,93,98,102-104,111,112,115,117,118, 120,123-125,127), with 3 studies on patients with head/neck (116,126) and liver cancer (122).

There were 11 eligible studies on patients in palliative care for inclusion in the review. There was 1 non-RCT that compared ETF with routine care (99). The remaining studies (n=10) compared EPA with routine care, including 3 RCTs (75,96,101) and 2 non-RCTs (51,52) using EPA-enriched ONS, and 3 RCTs (21,88,114) and 2 non-RCTs (54,73) using EPA capsules. There were no studies comparing ETF with PN in patients in palliative care. The type of cancer included gastrointestinal (51,52,54,75,96,99) or a variety of sites (21,73,88,101,114). One study (75) largely duplicated data published previously (96); only unique data was utilised from this paper (physical activity level).

Seven studies, which complied with the inclusion criteria for the review-utilised designs, were not considered relevant to the topic in question (e.g. comparison of one enteral product vs. another) and were not included in the analyses (89,91,100,106,110,113,119).

The type of cancer varied greatly, as did the stage of disease (see Appendix A, available upon request). In general, however, the disease stage and details of diagnosis confirmation were poorly reported. Separate analyses were intended for cancer type, setting and nutritional status (malnourished vs. well-nourished), but there were insufficient data to allow these.

*Quality assessment*. The majority of studies were RCTs (n=47) (21,46,47,74-77,79,80,82-88,90,91,93-98,100-104, 106-109,111-115,117,118,120,122-127), scoring the highest grade of 1 for quality of evidence in accordance with the assessment scale (67). However, the methodology of individual RCTs was generally judged to be poorly described or planned (with regard to methods of randomisation, blinding and recording the number of drop-outs) with only 7 studies (75,80,82,88,96,104,120) scoring the top grade of 5 on the Jadad scale (68). The remaining RCTs scored 4 (n=3; (46,101,124), 3 (n=9; 21,84,95,108,111,114,118,125,126), or 2 (n=27; 47,74,76,77,79,83,85-87,90,91,93,94,97,98,100, 102,103,106,107,109,112,113,115,122,123,127).

The review also included 9 CCTs scoring 2 (78,81,89,92,99,105,110,119,128) on the Quality of Evidence scale (67), and 6 CTs scoring 4 (51,52,54,73,116,121).

Table II. Dietary intake and clinical outcomes; data used in the meta-analysis.

| Parameter | Citation (ref.) | Comparison | Sample size | Change from baseline | | Post-intervention | | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | Mean | SD | Mean | SD | |
| Total dietary intake (kcal/day) | Douglass *et al* 1978 (94) | No Supplement | 15 | * | * | 1270.0 | 534.0 | * |
| | | ONS | 15 | * | * | 2070.0 | 814.0 | * |
| | Moloney *et al* 1983 (107) | No Supplement | 42 | * | * | 1456.0 | 569.0 | * |
| | | ONS | 42 | * | * | 1769.0 | 673.0 | * |
| | Arnold *et al* 1989 (77) | No Supplement | 27 | * | * | 1624.3 | 528.7 | * |
| | | ONS | 23 | * | * | 1929.8 | 605.3 | * |
| Mortality | Braga *et al* 1996 (85) | Postoperative ETF | 20 | * | * | * | * | 0/20 |
| | | Postoperative PN | 20 | * | * | * | * | 0/20 |
| | Gianotti *et al* 1997 (98) | Postoperative ETF | 87 | * | * | * | * | 2/87 |
| | | Postoperative PN | 86 | * | * | * | * | 2/86 |
| | Reynolds *et al* 1997 (115) | Postoperative ETF | 33 | * | * | * | * | 2/33 |
| | | Postoperative PN | 34 | * | * | * | * | 1/34 |
| | Sand *et al* 1997 (117) | Postoperative ETF | 13 | * | * | * | * | 0/13 |
| | | Postoperative PN | 16 | * | * | * | * | 1/16 |
| | Di Carlo *et al* 1999 (93) | Postoperative ETF | 35 | * | * | * | * | 0/35 |
| | | Postoperative PN | 32 | * | * | * | * | 2/32 |
| | Bozzetti *et al* 2001 (80) | Postoperative ETF | 159 | * | * | * | * | 2/159 |
| | | Postoperative PN | 158 | * | * | * | * | 5/158 |
| | Braga *et al* 2001 (83) | Postoperative ETF | 126 | * | * | * | * | 3/126 |
| | | Postoperative PN | 131 | * | * | * | * | 4/131 |
| | Lim *et al* 1981 (103) | Preoperative ETF | 10 | * | * | * | * | 2/10 |
| | | Preoperative PN | 10 | * | * | * | * | 1/10 |
| | Van Bokhorst 2001 (126) | Preoperative ETF | 15 | * | * | * | * | 1/15 |
| | | No ETF | 17 | * | * | * | * | 0/17 |
| | Braga *et al* 2002 (84) | Preoperative ONS | 50 | * | * | * | * | 0/50 |
| | | No supplement | 50 | * | * | * | * | 1/50 |
| | Douglass *et al* 1978 (94) | No supplement | 17 | * | * | * | * | 13/17 |
| | | ONS | 13 | * | * | * | * | 8/13 |
| | Elkort *et al* 1981 (95) | No supplement | 23 | * | * | * | * | 3/21 |
| | | ONS | 24 | * | * | * | * | 4/24 |
| | Smith *et al* 1985 (123) | No ETF | 25 | * | * | * | * | 1/25 |
| | | ETF | 25 | * | * | * | * | 4/25 |
| | Arnold *et al* 1989 (77) | No supplement | 27 | * | * | * | * | 0/27 |
| | | ONS | 23 | * | * | * | * | 3/23 |
| | Page *et al* 2002 (111) | No ETF | 20 | * | * | * | * | 0/20 |
| | | ETF | 20 | * | * | * | * | 0/20 |
| | Moloney *et al* 1983 (107) | No supplement | 42 | * | * | * | * | 26/42 |
| | | ONS | 42 | * | * | * | * | 27/42 |
| | Bozzetti *et al* 1998 (81) | No ETF | 21 | * | * | * | * | 1/21 |
| | | ETF | 29 | * | * | * | * | 0/29 |
| Mean length of hospital stay (days) | Braga *et al* 1995 (86) | Postoperative ETF | 24 | * | * | 15.2 | 5.1 | * |
| | | Postoperative PN | 27 | * | * | 19.3 | 7.3 | * |
| | Braga *et al* 1996 (85) | Postoperative ETF | 20 | * | * | 15.0 | 2.5 | * |
| | | Postoperative PN | 20 | * | * | 17.0 | 9.0 | * |

*, not recorded.

Table II. Continued.

| Parameter | Citation (ref.) | Comparison | Sample size | Change from baseline | | Post-intervention | | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | Mean | SD | Mean | SD | |
| Mean length of hospital stay (days) | Schilling *et al* 1996 (118) | Postoperative ETF | 14 | * | * | 14.0 | 19.0 | * |
| | | Postoperative hypocaloric PN | 14 | * | * | 14.0 | 10.3 | * |
| | Gianotti *et al* 1997 (98) | Postoperative ETF | 87 | * | * | 19.2 | 7.9 | * |
| | | Postoperative PN | 86 | * | * | 21.6 | 8.9 | * |
| | Di Carlo *et al* 1999 (93) | Postoperative ETF | 35 | * | * | 17.8 | 6.9 | * |
| | | Postoperative PN | 32 | * | * | 19.3 | 8.0 | * |
| | Aiko *et al* 2001 (76) | Postoperative ETF | 13 | * | * | 34.0 | 4.0[a] | * |
| | | Postoperative PN | 11 | * | * | 40.0 | 9.0[a] | * |
| | Bozzetti *et al* 2001 (80) | Postoperative ETF | 159 | * | * | 13.4 | 4.1 | * |
| | | Postoperative PN | 158 | * | * | 15.0 | 5.6 | * |
| | Braga *et al* 2001 (83) | Postoperative ETF | 126 | * | * | 19.9 | 8.2 | * |
| | | Postoperative PN | 131 | * | * | 20.7 | 8.8 | * |
| | Van Bokhorst 2001 (126) | Preoperative ETF | 15 | * | * | 46.0 | 30.0 | * |
| | | No ETF | 17 | * | * | 41.0 | 32.0 | * |
| | Braga *et al* 2002 (84) | Preoperative oral | 50 | * | * | 12.0 | 4.5 | * |
| | | No supplement | 50 | * | * | 12.2 | 3.9 | * |
| | Smith *et al* 1985 (123) | No ETF | 25 | * | * | 15.0 | 6.4 | * |
| | | ETF | 25 | * | * | 20.0 | 8.9 | * |
| | Page *et al* 2002 (111) | No ETF | 20 | * | * | 13.4 | 5.0 | * |
| | | ETF | 20 | * | * | 13.6 | 5.2 | * |
| Patients with any complication | Sand *et al* 1997 (117) | Postoperative ETF | 13 | * | * | * | * | 5/13 |
| | | Postoperative PN | 16 | * | * | * | * | 8/16 |
| | Di Carlo *et al* 1999 (93) | Postoperative ETF | 35 | * | * | * | * | 14/35 |
| | | Postoperative PN | 32 | * | * | * | * | 19/32 |
| | Bozzetti *et al* 2001 (80) | Postoperative ETF | 159 | * | * | * | * | 54/159 |
| | | Postoperative PN | 158 | * | * | * | * | 78/158 |
| | Braga *et al* 2001 (83) | Postoperative ETF | 126 | * | * | * | * | 45/126 |
| | | Postoperative PN | 131 | * | * | * | * | 53/131 |
| Patients with infectious complications | Braga *et al* 1995 (86) | Postoperative ETF | 24 | * | * | * | * | 4/24 |
| | | Postoperative PN | 27 | * | * | * | * | 4/27 |
| | Braga *et al* 1996 (85) | Postoperative ETF | 20 | * | * | * | * | 3/20 |
| | | Postoperative PN | 20 | * | * | * | * | 3/20 |
| | Schilling *et al* 1996 (118) | Postoperative ETF | 14 | * | * | * | * | 40% |
| | | Postoperative hypocaloric PN | 14 | * | * | * | * | 40% |
| | Gianotti *et al* 1997 (98) | Postoperative ETF | 87 | * | * | * | * | 20/87 |
| | | Postoperative PN | 86 | * | * | * | * | 24/86 |
| | Reynolds *et al* 1997 (115) | Postoperative ETF | 33 | * | * | * | * | 13/33 |
| | | Postoperative PN | 34 | * | * | * | * | 20/34 |
| | Sand *et al* 1997 (117) | Postoperative ETF | 13 | * | * | * | * | 3/13 |
| | | Postoperative PN | 16 | * | * | * | * | 5/16 |
| | Shirabe *et al* 1997 (122) | Postoperative ETF | 13 | * | * | * | * | 1/13 |
| | | Postoperative PN | 13 | * | * | * | * | 4/13 |

*, not recorded. [a]SEM not SD.

Table II. Continued.

| Parameter | Citation (ref.) | Comparison | Sample size | Change from baseline | | Post-intervention | | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | Mean | SD | Mean | SD | |
| Patients with infectious complications | Di Carlo *et al* 1999 (93) | Postoperative ETF | 35 | * | * | * | * | 6/35 |
| | | Postoperative PN | 32 | * | * | * | * | 8/32 |
| | Aiko *et al* 2001 (76) | Postoperative ETF | 13 | * | * | * | * | 1/13 |
| | | Postoperative PN | 11 | * | * | * | * | 1/11 |
| | Bozzetti *et al* 2001 (80) | Postoperative ETF | 159 | * | * | * | * | 25/159 |
| | | Postoperative PN | 158 | * | * | * | * | 42/158 |
| | Braga *et al* 2001 (83) | Postoperative ETF | 126 | * | * | * | * | 25/126 |
| | | Postoperative PN | 131 | * | * | * | * | 30/131 |
| | Lim *et al* 1981 (103) | Preoperative ETF | 10 | * | * | * | * | 5/10 |
| | | Preoperative PN | 10 | * | * | * | * | 3/10 |
| | Smith *et al* 1985 (123) | No ETF | 25 | * | * | * | * | 11/25 |
| | | ETF | 25 | * | * | * | * | 14/25 |
| | Page *et al* 2002 (111) | No ETF | 20 | * | * | * | * | 1/20 |
| | | ETF | 20 | * | * | * | * | 3/20 |
| | Braga *et al* 2002 (84) | Preoperative oral | 50 | * | * | * | * | 16/50 |
| | | No supplement | 50 | * | * | * | * | 15/50 |
| Mean sepsis score | Gianotti *et al* 1997 (98) | Postoperative ETF | 87 | * | * | 7.8 | 3.7 | * |
| | | Postoperative PN | 86 | * | * | 10.6 | 4.5 | * |
| | Braga *et al* 2001 (83) | Postoperative ETF | 126 | * | * | 8.5 | 3.5 | * |
| | | Postoperative PN | 131 | * | * | 10.4 | 3.7 | * |

*, not recorded.

**4. Patients undergoing radiotherapy, chemotherapy and BMT**

*Nutritional support vs. routine care*

*Dietary outcomes and anthropometry*

*Intake*. The data from 3 RCTs, all using ONS for 6-70 days in patients undergoing radiotherapy for a variety of cancers, were combined to investigate the effect of nutritional support vs. routine care on total dietary energy intake (77,94,107). This meta-analysis (effect size 0.62, 95% CI 0.31 to 0.94) (Fig. 2 and Table II) demonstrated that patients receiving ONS had a significantly higher energy intake (381 kcal/day, 95% CI 193 to 569) (Fig. 2), than those receiving routine care. Another RCT using ONS in abdominal/pelvic cancer patients undergoing radiotherapy documented non-significant results for this comparison, and this trial could not be included in the meta-analysis due to the lack of consistency in the way outcomes were reported (79).

Two CCTs also showed improvements in energy intake with ONS/ETF in patients with cancer undergoing treatment (radiotherapy/chemotherapy) (78,105). In many trials, food intake was not substantially decreased by supplementation (77,78,105).

Protein intake may also be increased following nutritional supplementation; however, the identified studies were not suitable for meta-analysis. One RCT, using ONS for 70 days in patients with head/neck cancer undergoing radiotherapy, demonstrated a significantly higher protein intake in those receiving nutritional support (88.4± SEM 31.9 g/day) compared to routine care (66.9± SEM 26.1 g/day) (77). A further RCT in patients undergoing radiotherapy was difficult to interpret due to significant differences in protein intake at baseline (107). However, a CCT reported that patients (cancer stage 1 or 2) undergoing radiotherapy receiving ONS for 4 weeks had a significantly higher protein intake (g/day) compared to controls (original data provided graphically) with no concurrent reduction in food-protein intake (105).

*Anthropometry*. One RCT demonstrated a significant increase in the body weight of patients undergoing radiotherapy who received ONS compared to routine care patients (79). Similar trends in another RCT were not statistically analysed (79). Other RCTs reported non-significant effects of ONS in patients undergoing radiotherapy or chemotherapy for a variety of cancers (77,87,94,95,97).

CCTs have reported a significant benefit from ONS vs. routine care with regard to reducing weight loss in patients with lung cancer receiving radiotherapy (128), ONS/ETF vs. routine care in patients with advanced metastatic cancer receiving chemotherapy or radiotherapy (78), ETF vs. routine care in patients with oesophageal cancer receiving chemotherapy or radiotherapy (81) and ETF vs. routine care in patients with leukaemia undergoing chemotherapy (92).

Table III. Biochemical outcomes; data used in the meta-analysis.

| Parameter | Citation (ref.) | Comparison | Sample size | Baseline | | Post-intervention | | Change from baseline | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Mean | SD | Mean | SD | Mean | SD |
| Changes in blood albumin (g/l) | Foster *et al* 1980 (97) | No supplement | 12 | 42.0 | 1.0[a] | 41.0 | 1.0[a] | * | * |
| | | ONS | 20 | 44.0 | 1.0[a] | 42.0 | 1.0[a] | * | * |
| | Elkort *et al* 1981 (95) | No supplement | 14 | * | * | * | * | -0.1 (mg/l) | 0.8 |
| | | ONS | 12 | * | * | * | * | -2.0 (mg/l) | 1.4 |
| | Bozzetti *et al* 1981 (95) | No ETF | 21 | 40.0 | 4.0 | 35.0 | 5.0 | * | * |
| | | ETF | 29 | 39.0 | 4.0 | 38.0 | 4.0 | * | * |
| Changes in C-reactive protein in blood (g/l) | Schilling *et al* 1996 (118) | Postoperative ETF | 14 | 8.8 (mg/l) | 17.3 | 67.1 (mg/l) | 104.0 | * | * |
| | | Postoperative hypocaloric PN | 14 | 12.4 (mg/l) | 14.2 | 52.5 (mg/l) | 56.3 | * | * |
| | Braga *et al* 2001 (83) | Postoperative ETF | 126 | 109.0 | 38.0 | 51.0 | 22.0 | * | * |
| | | Postoperative PN | 131 | 117.0 | 31.0 | 63.0 | 24.0 | * | * |
| Changes in $CD3^+$ T cells (%) | Braga *et al* 1996 (85) | Postoperative ETF | 20 | 69.4 | 8.3 | 75.3 | 7.1 | * | * |
| | | Postoperative PN | 20 | 69.5 | 7.7 | 75.6 | 6.7 | * | * |
| | Schilling *et al* 1996 (118) | Postoperative ETF | 14 | 70.5 | 8.5 | 71.0 | 7.5 | * | * |
| | | Postoperative hypocaloric PN | 14 | 75.0 | 17.0 | 77.0 | 10.0 | * | * |

*, not recorded. [a]SEM not SD.

Subgroup analysis investigating the benefit of ONS vs. routine care in patients with head and neck cancer failed to demonstrate statistical significance (128).

*Haematological and biochemical outcomes*

One RCT using ONS undergoing radiotherapy reported that whereas those patients receiving routine care exhibited a significant reduction in white blood cell count compared to baseline, those receiving ONS maintained their white blood cell count (97). In contrast, a CCT reported no significant difference in white blood cell count following ETF (nasogastric) vs. routine care in oesophageal cancer patients undergoing radiotherapy (81).

An RCT of ETF (jejunostomy) in oesophageal cancer patients undergoing radiotherapy found no significant effect from nutritional support on serum transferrin (90). Likewise, another RCT of ONS in breast cancer patients undergoing chemotherapy, found no difference in transferrin concentrations following nutritional supplementation (95). These trials were not suitable for meta-analysis.

Two RCTs using ONS, one with pelvic cancer patients undergoing radiotherapy (97) and the other with breast cancer patients undergoing chemotherapy (95), and a CCT using a nasogastric route (81) in oesophageal cancer patients undergoing radiotherapy were combined to investigate the effect of nutritional support on serum albumin concentrations. Meta-analysis suggested no significant effect from nutritional support (effect size -0.06, 95% CI -0.47 to 0.34; Table III). Another RCT of ONS in head/neck cancer patients, which could not be included in meta-analysis as data were presented graphically, found a significant reduction of serum albumin in the control group compared with no significant change in the supplemented patients (77). Statistical differences between groups were not reported.

*Clinical outcomes*

*Mortality*. Meta-analysis of the data from 4 RCTs using ONS in chemotherapy or radiotherapy patients with breast (95), abdominal (94), head/neck (77) or various (107) cancers, and 1 CCT using 32 days ETF (nasogastric) in oesophageal cancer patients undergoing radiotherapy (81) demonstrated no significant effect (OR 1.00, 95% CI 0.62 to 1.61, Table II) from nutritional support vs. routine care on mortality.

*Response to treatment*. Two RCTs, both using ONS for 21-70 days with patients undergoing radiotherapy for head/neck or various cancers, reported no significant effect from nutritional support on the number of patients in complete remission (77,107). The number of head/neck cancer patients completing a course of uninterrupted radiotherapy was similar to another RCT using ONS (109).

*Complications*. One CCT using 21 days ETF (nasogastric) in leukaemia patients undergoing chemotherapy (92) reported similar rates of infectious complications in those receiving nutritional support vs. routine care. Other studies were difficult to interpret due to the lack of control data (121).

*EPA supplementation (capsules) vs. no EPA supplementation (routine care)*

*Dietary outcomes and anthropometry*
No data were reported on dietary outcomes and anthropometry in studies comparing EPA supplementation vs. routine care in patients undergoing chemotherapy or radiotherapy.

*Haematological and biochemical outcomes*
Two RCTs providing EPA (47) or EPA ethyl ester capsules (74) to bone marrow transplant patients demonstrated significant reductions in TNF-α, IFN-γ, leukotriene B4 (47,74) and IL-10, thromboxane $A_2$ and prostaglandin $I_2$ (47) compared to routine care. An RCT using approximately 200 days of EPA capsules in bone marrow transplant patients reported no significant difference in the CRP between those receiving EPA and routine care (47).

*Clinical outcomes*
*Mortality*. An RCT, using EPA capsules for approximately 200 days in bone marrow transplant patients, reported that patients receiving this intervention had a significantly lower mortality rate of 0/7 (0%), whereas 4/8 (50%) of those receiving no supplement (routine care) died (47).

*Complications*. Two RCTs, providing approximately 200 days of EPA (47) or EPA ethyl ester capsules (74) to bone marrow transplant patients demonstrated a significant reduction in post-transplant complications between patients receiving EPA vs. routine care; both the incidence (50% of EPA supplemented vs. 63% of unsupplemented patients) (47) and severity (a significant reduction in severity for EPA supplemented patients) of graft vs. host disease was reduced (74).

*Enteral tube feeding vs. parenteral nutrition*

An RCT reported no significant differences in body weight, infectious complications, serum transferrin, serum albumin or white blood cell count in bone marrow transplant patients receiving partial PN and ETF nasogastrically (108).

## 5. Patients undergoing surgery

*Nutritional support vs. routine care*

*Dietary outcomes and anthropometry*
*Intake*. Individual RCTs suggest that nutritional support may improve dietary intake in patients undergoing surgery for cancer. One RCT reported an intake of 2232 kcal/day for postoperative oesophageal cancer patients fed ETF (nasojejunal) vs. 0 kcal/day in those receiving routine care (bowel rest) (129), and a study of home ETF (80% nasogastric) in head/neck or oesophageal surgical cancer patients reported an intake of 2100 kcal/day (116). A further RCT reported a protein intake of 83 g/day for postoperative oesophageal cancer patients fed ETF (nasojejunal) vs. 0 g/day in those receiving routine care (bowel rest) (111). Other studies are difficult to interpret due to the use of stratified groups (90).

*Anthropometry*. Individual RCTs reported no significant effects from pre- and postoperative ETF on body weight and body composition measurements in a variety of cancer patients undergoing surgery (90,111,123,126).

*Haematological and biochemical outcomes*
One RCT using postoperative ETF (nasojejunal) for 7 days in oesophageal cancer patients reported that whereas patients receiving routine care exhibited no significant change in white blood cell count compared to baseline, those receiving ONS significantly increased their white blood cell count (111).

ONS and ETF had no significant effects on other biochemical parameters in patients undergoing surgery. One RCT using postoperative ETF (nasojejunal) for 7 days in oesophageal cancer patients reported no significant effect from nutritional support on serum transferrin (111); another RCT was more difficult to interpret due to missing control data (82). Five RCTs with surgical patients reported no significant difference in serum albumin concentration following nutritional support vs. routine care, but were not meta-analysable due to undefined units (111), incomplete data (126) or missing data (123). Further RCTs with ONS/ETF found no significant changes in CRP (111), CD3-positive cells (126) or IL-6 (84) concentrations in patients undergoing surgery, while other studies were more difficult to interpret due to the lack of a control group (82,104).

*Clinical outcomes*
*Mortality*. In total, 4 RCTs examining cancer patients pre- and postsurgery reported mortality as an outcome (84,111,123,126). Peri-operative nutritional support in the form of ETF or ONS did not significantly influence the mortality rate compared to routine care (OR 2.44, 95% CI 0.75 to 7.95). The removal of preoperative studies from meta-analysis did not alter the result (135,96). Other identified studies were difficult to interpret due to the lack of control data (82,104,116,120).

*Length of hospital stay*. Two RCTs, both using 7 days post-operative ETF (nasojejunal or jejunostomy) in gastrointestinal cancer patients, were combined to investigate the effect of nutritional support vs. routine care (bowel rest) on the length of hospital stay (111,123). Meta-analysis demonstrated no significant effect (1.89 days, 95% CI 0.66 to 4.43; Table II). The inclusion of 2 preoperative RCT studies on head/neck (126) and colorectal (84) cancer patients did not affect the overall outcome (0.40 days, 95% CI -0.95 to 1.82; Table II). Other identified relevant studies were difficult to interpret as no control data were provided (82,104,120).

*Complications*. Three RCTs reporting infectious complications in peri-operative cancer patients were identified for meta-analysis. Two studies on postoperative gastrointestinal cancer patients (111,123) and one on preoperative colorectal cancer patients (84) were combined to investigate the effect of nutritional support vs. routine care on infectious complications. Meta-analysis demonstrated no significant difference in the incidence of infectious complications (OR 1.36, 95% CI 0.86 to 2.13; Table II) following nutritional support when compared to routine care. Combining only the

postoperative studies using ETF for 7-10 days (nasojejunal or jejunostomy) also did not achieve significance (OR 1.81, 95% CI 0.90 to 3.64; Table II). Other identified studies were difficult to interpret due to the lack of adequate control data (104,120).

*Quality of life and performance status*. There were insufficient data to allow the meta-analysis of quality of life outcomes for the comparison of nutritional support vs. routine care. One RCT, using 7-10 days preoperative ETF (nasogastrically) in head/neck cancer patients, reported a significant benefit of ETF vs. routine care with regard to preoperative physical functioning, emotional functioning and dyspnea, using both standard and disease-specific questionnaires (125). A further RCT using 9 days preoperative ETF (administered nasogastrically at home) in head/neck cancer patients reported a similar change in grip-strength in both hands (126). Moreover, a single CT using 28 days ETF in surgical/radiotherapy patients with head/neck or oesophageal cancer reported a significant improvement in global health status (116).

*EPA supplementation (capsules or enriched feeds) vs. no EPA supplementation (routine care, standard feeds and PN)*

*Dietary outcomes and anthropometry*
Meta-analysis of 2 RCTs, both using 7 days postoperative fish oil structured lipid-enriched ETF compared to standard ETF in gastrointestinal cancer patients reported no significant difference in total energy (17 kcal/day, 95% CI -151 to 186) or protein intake (-1.1 g/day, 95% CI -10.5 to 8.4) (102,124).

*Haematological and biochemical outcomes*
An RCT of pre- and postoperative EPA supplementation reported a significantly reduced CRP on postoperative day 3 compared to those patients receiving PN (46). The same study also reported a significantly reduced IL-6 measured 2 h after surgery compared to those patients receiving PN (46).

*Clinical outcomes*
*Mortality*. Two RCTs, both using 7 days postoperative fish oil structured lipid-enriched ETF in gastrointestinal cancer patients, reported similar mortality rates compared to standard ETF (102,124).

*Complications*. An RCT, conducted in postoperative gastrointestinal cancer patients, reported a significant (40%) reduction in the total number of days with reported GI complications in patients receiving fish oil-enriched feeds, and a significant (50%) reduction in the total number of actual reported GI complications in this group compared with patients given control feeds (102).

Meta-analysis of 2 RCTs, both using 7 days postoperative fish oil structured lipid-enriched ETF in gastrointestinal cancer patients, reported no significant difference (OR 0.84, 95% CI 0.39 to 1.82) in the rate of infectious complications between patients supplemented with fish oil structured lipid-enriched and standard ETF (102,124).

*Enteral tube feeding vs. parenteral nutrition*

*Dietary outcomes and anthropometry*
*Intake*. Seven RCTs comparing isocaloric ETF and PN regimens reported total energy intake (76,80,83,93,103,112,115); not surprisingly, all reported no significant difference in total dietary intakes between ETF and PN. The majority of these studies provided postoperative support following surgery in patients with gastrointestinal cancers, with one providing preoperative support (103). A variety of routes (jejunostomy, nasojejunal, gastrostomy, and nasogastric) were involved.

Of the 3 RCTs reporting total protein or nitrogen intake, all reported no significant difference between patients fed ETF and PN regimens invariably designed to be isonitrogenous (76,112,115). These studies provided postoperative support following surgery in patients with gastrointestinal cancers; jejunostomy was used in one study, but the route for the others was not described (115).

*Anthropometry*. Of the 2 RCTs reporting body weight, both reported no significant difference between ETF and PN (103).

*Haematological and biochemical outcomes*
In total, 5 RCTs reported serum transferrin concentration as an outcome; all reported no significant differences between ETF and PN, including patients fed postoperatively following surgery for gastrointestinal (76,85,127) or liver cancer (122) and patients undergoing radiotherapy for oesophageal cancer (90). However, only 2 studies were suitable for meta-analysis (76,85); there was no significant difference between ETF and PN in serum transferrin (75.11 mg/l, 95% CI -200.90 to 351.11). The ETF routes in these studies included jejunostomy, nasogastric and nasojejunal.

The majority of studies, including RCTs, reported no significant difference in serum albumin concentrations with postoperative support in patients with gastrointestinal cancer (76,83,85,86,115,117), preoperative support in patients with oesophageal cancer (103), or preoperative support in patients undergoing radiotherapy for oesophageal cancer (90). One RCT using postoperative support in patients with gastric cancer reported that serum albumin concentrations were significantly higher (39 g/l) in patients receiving ETF (route not stated) compared to those receiving a combination of ETF and PN (32 g/l) (112).

Meta-analysis demonstrated no significant differences between ETF and PN in the proportion of CD3-positive lymphocytes (0.50%, 95% CI -5.24 to 6.24) using data from 2 RCTs, both providing postoperative ETF vs. PN in patients with gastrointestinal cancer (85,118), (including jejunostomy, nasogastric, nasoduodenal, and nasojejunal).

Likewise, meta-analysis of 2 RCTs, both providing postoperative support in patients with gastrointestinal cancer demonstrated no significant effect from ETF vs. PN on the CRP (16.60 mg/l, 95% CI -43.33 to 79.53; Table III) (83,118). This is supported by the findings of another RCT (115); however, 2 other RCTs demonstrated a significantly lower CRP following ETF compared to PN (76,117). These studies were not suitable for meta-analysis because they reported incompatible data (115) or only provided graphical data (76,117).

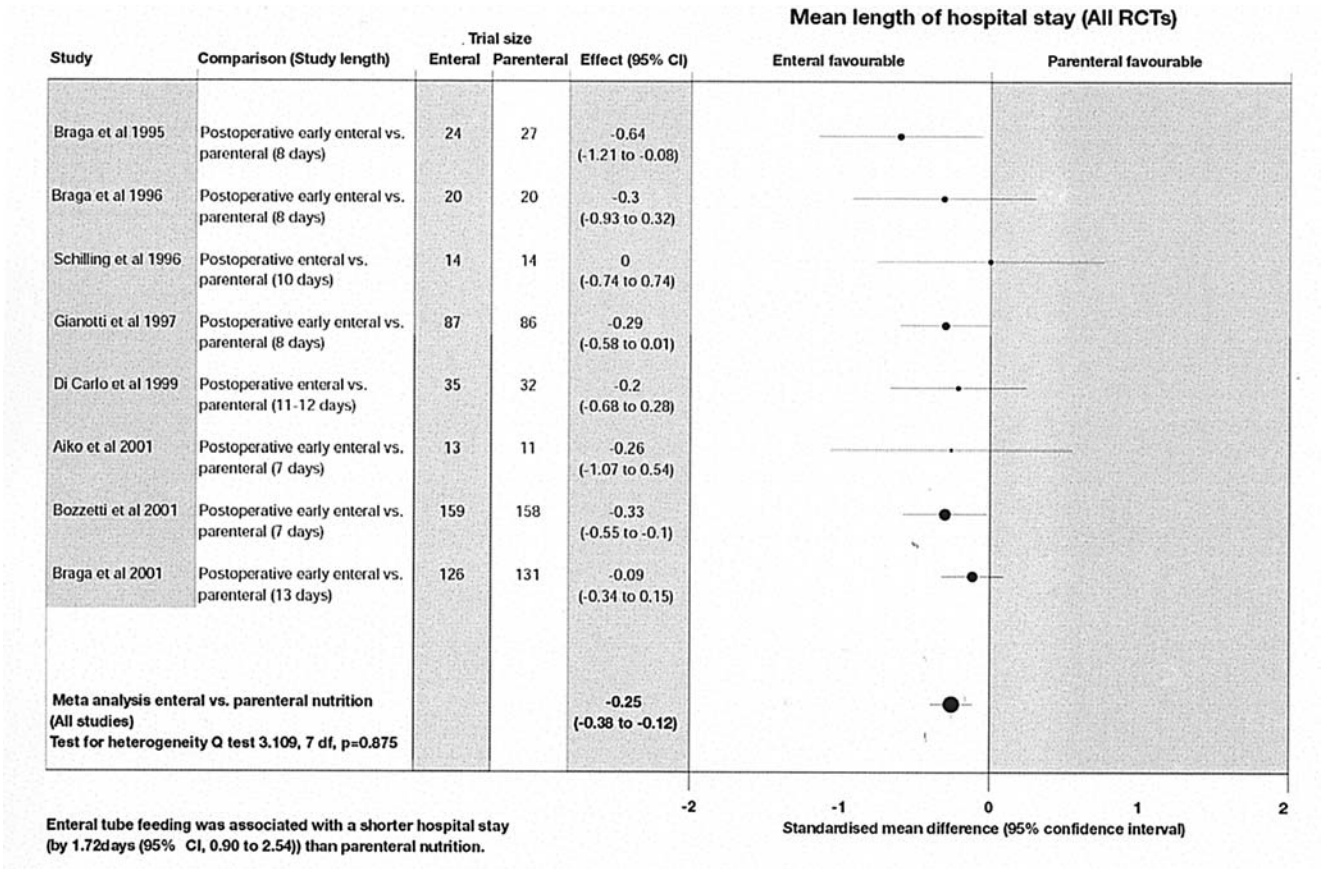


Figure 3. Length of hospital stay. The effect of enteral (tube) vs. parenteral administration in patients with cancer undergoing surgery based on a meta-analysis of 8 RCTs (76,83,85,86,93,98,118,130).

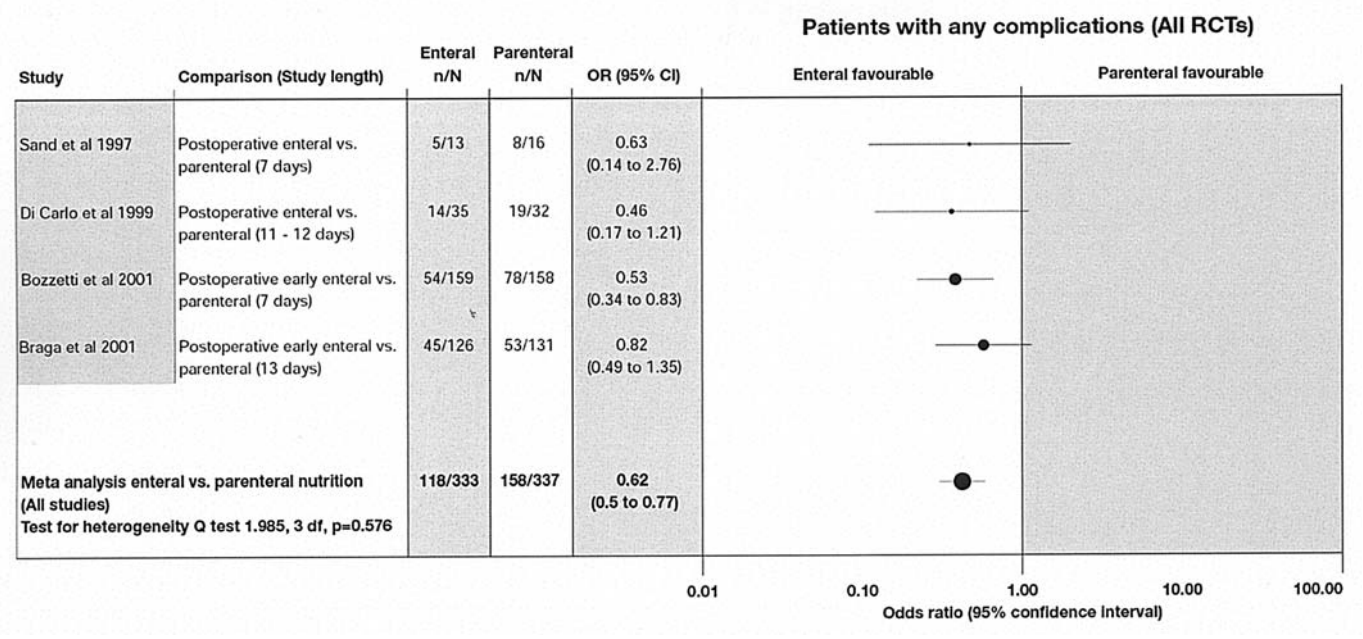


Figure 4. Complications of any type. The effect of ETF vs. PN in patients with cancer undergoing surgery based on a meta-analysis of 4 RCTs (80,83,93,117). Complications included wound infection, bacteremia, respiratory failure, renal dysfunction, pancreatic fistula, gastrointestinal bleeding, cardiac failure, pneumonia, urinary tract infection, pancreatitis, hemoperitoneum, intestinal obstruction, circulatory insufficiency, delayed gastric emptying, and death.

Only a single RCT reported white blood cell count as an outcome in which PN resulted in significantly higher absolute leukocyte numbers than ETF (nasoduodenal or nasojejunal) in postoperative patients with gastrointestinal cancer (118). This study also reported no significant difference in TNF-α, IL-1 or IL-6 for those receiving ETF vs. PN (118). Other studies have similarly reported no difference in IL-6 (83,85,98).

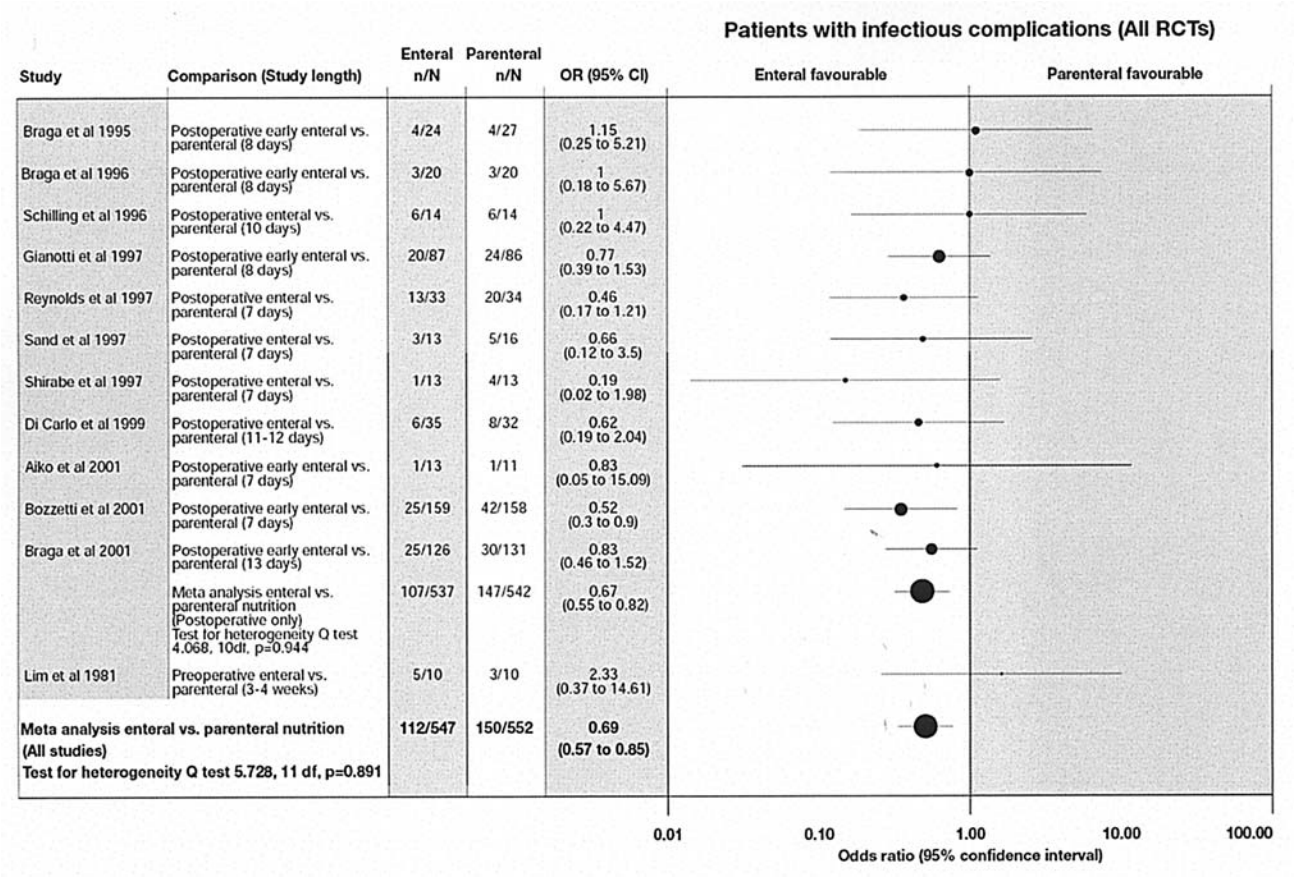


Figure 5. Infectious complications. The effect of ETF vs. PN in patients with cancer undergoing surgery based on a meta-analysis of 12 RCTs (76,80,83,85,86,93,98,103,115,117,118,122).

*Clinical outcomes*

*Mortality*. Meta-analysis of 7 RCTs, all providing postoperative nutritional support in patients with gastrointestinal cancer, demonstrated no significant difference in mortality rates associated with ETF vs. PN (OR 0.72, 95% CI 0.40 to 1.29; Table II) (80,83,85,93,98,115,117). Inclusion of an RCT examining preoperative nutritional support for 3 to 4 weeks did not affect the outcome of the analysis (OR 0.80, 95% CI 0.46 to 1.39; Table II) (103).

*Length of hospital stay*. Meta-analysis of 8 RCTs, all providing postoperative nutritional support in patients with gastrointestinal cancer, demonstrated that ETF (including nasoduodenal, jejunostomy, nasogastric, and nasojejunal) resulted in a significantly shorter length of stay compared to PN (effect size -0.25 , 95% CI -0.38 to -0.12; Fig. 3 and Table II) (76,80,83,85,86,93,98,118). This amounted to 1.72 fewer days (95% CI 0.90 to 2.54; Fig. 3) in the hospital for those fed via tube. This analysis is supported by findings in a further RCT that presented no data (112), but not another that used postoperative nasojejunal ETF in patients with gastrointestinal cancer and was not meta-analysable due to incompatible data presentation (117).

*Complications*. Meta-analysis of 4 RCTs, all providing postoperative support in patients with gastrointestinal cancer (80,83,93,117), demonstrated that ETF (including nasojejunal, jejunostomy, and nasogastric) administration resulted in a significantly lower incidence of complications compared to PN (OR 0.62, 95% CI 0.50 to 0.77; Fig. 4 and Table II). In particular, the rate of infectious complications was improved by ETF; meta-analysis of 11 RCTs, providing postoperative support for patients with gastrointestinal cancer (76,80,83,85, 86,93,98,115,117,118) or liver cancer (122), demonstrated that ETF administration resulted in a significantly lower incidence of infectious complications compared to PN (OR 0.67, 95% CI 0.55 to 0.82; Fig. 5 and Table II). Inclusion of an RCT providing preoperative ETF via gastrostomy to patients with oesophageal cancer did not affect the overall outcome of the analysis (OR 0.69, 95% CI 0.57 to 0.85; Fig. 5 and Table II) (103).

Meta-analysis of 2 RCTs, both providing postoperative support in patients with gastrointestinal cancer, demonstrated that ETF (including jejunostomy and nasojejunal) resulted in a significantly lower sepsis score (effect size -0.59, 95% CI -0.78 to -0.39; Fig. 6 and Table II) than PN by 2.21 points (95% CI 1.49 to 2.92; Fig. 6) (83,98). An additional RCT showed a trend towards decreased sepsis scores with postoperative ETF (jejunostomy) in patients with pancreatic cancer (93), while another showed the opposite trend following nasogastric or jejunostomy ETF in patients with gastric or pancreatic cancer (85); however, these did not reach statistical significance and could not be used in the meta-analysis due to missing variability measures.

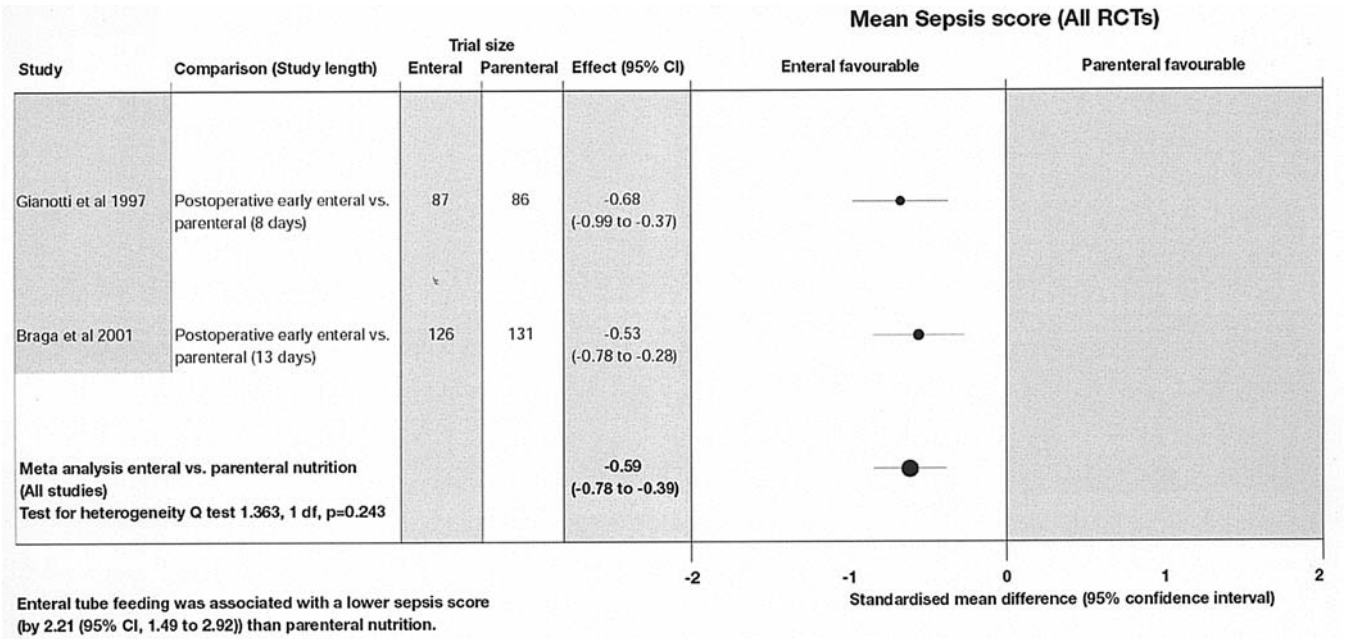


Figure 6. Sepsis scores. The effect of ETF vs. PN in patients with cancer undergoing surgery based on a meta-analysis of 2 RCTs (83,98).

## 6. Patients in palliative care

*Nutritional support vs. routine care*

A CCT reported non-significant effects from ETF vs. routine care on body weight for those in palliative care (99). In the same study, however, ETF significantly increased absolute numbers of CD3-positive lymphocytes compared to routine care (99). Other outcomes including serum albumin were more difficult to interpret due to the lack of control data (99). No other outcomes were reported for this comparison in palliative care settings.

*EPA supplementation vs. routine care*

*Dietary outcomes and anthropometry*

*Intake*. An RCT, using 8 weeks EPA-enriched ONS with pancreatic cancer patients in palliative care, reported that those receiving EPA significantly increased their total energy intake, while the intake of those receiving a standard supplement was unchanged (96). This occurred despite poor compliance, as indicated by plasma EPA concentrations and an intake of only 70% of that intended. A further 14-day RCT in palliative care patients (advanced cancer and various sites) reported no significant effect from fish oil capsules compared to placebos on total energy intake and no difference in appetite scores (88). However, compliance was low with most patients achieving only half of the intended dose (1.8 g EPA/day instead of 3.2 g/day), and the period of supplementation was short (14 days). Elsewhere, fish oil and EPA capsules have been correlated with increases in energy intake and appetite score in palliative care patients, respectively (51,54).

One RCT reported that pancreatic cancer patients in palliative care receiving 8 weeks of an EPA-enriched ONS significantly increased protein intake (15± SEM 3.5 g/day) compared to baseline, while the intake of those receiving a standard supplement did not change (6± SEM 3.3 g/day) compared to baseline (96).

*Anthropometry*. An RCT, using EPA-enriched ONS for 8 weeks in pancreatic cancer patients in palliative care, reported a significant increase in lean mass measured by bioelectrical impedance in both groups, although it was significantly greater in those receiving EPA-enriched (+0.54 kg/8 weeks) vs. standard formulae (+0.24 kg/8 weeks) (96). The authors also demonstrated a significant positive correlation between EPA-enriched ONS and an increase in lean mass (96). No significant effects on lean mass (measured by bioelectrical impedance analysis) were reported in an RCT when fish oil was delivered for 14 days as a capsule to palliative care patients with advanced cancer at various sites (88). However, significant increases of 0.75-2.00 kg lean mass (and no significant change in absolute fat mass) in patients with pancreatic cancer in palliative care following 3-7 weeks EPA-enriched ONS were reported in CTs measured by bioelectrical impedance analysis (51,52).

An RCT, using EPA-enriched ONS for 8 weeks in weight-losing patients with pancreatic cancer in palliative care, reported similar losses of weight compared to respective baselines in those receiving standard formulae and those receiving EPA-enriched formulae (96). As stated previously, this study was confounded by poor compliance. However, the authors demonstrated a significant positive correlation between EPA-enriched ONS and an increase in body weight (96). Similarly, no significant effects on body weight were reported in an RCT when fish oil was delivered for 14 days as a capsule to weight-losing patients in palliative care with advanced cancer at various sites (88). However, a 14-day RCT using fish oil capsules with advanced cancer patients in palliative care reported that the change in body weight during supplementation was directly related to plasma EPA concentrations (114).

CTs have reported weight gain, normalisation or stabilisation of weight loss using fish oil or ethyl ester capsules (51,52,73). However, these findings were neither consistent nor experienced by all patients. Nonetheless, a significant correlation has been demonstrated between weight change and the number of days receiving EPA for weight-losing patients who take capsules for at least 30 days (73). Other studies were more difficult to interpret due to the lack of control data (101).

*Haematological and biochemical outcomes*

One RCT reported no significant effect from 40 days of fish oil capsules vs. placebos on absolute numbers or relative proportion (% lymphocytes) of CD3-positive lymphocytes in patients with metastatic solid tumours in palliative care (21). Also, 2 studies reported on CRP, but were difficult to interpret due to the lack of a control group (51,54).

*Clinical outcomes*

*Mortality*. Two RCTs found an improvement in survival time, but were not suitable for meta-analysis (21,96). An RCT, using 8 weeks EPA-enriched ONS in patients with pancreatic cancer in palliative care, reported a longer median survival time of 142 days compared to those receiving a standard supplement (128 days) (96). A further RCT using fish oil capsules for 40 days with advanced cancer patients in palliative care reported a significant increase in survival in EPA-supplemented patients compared with placebo patients (21). In addition, longer survival was noted in well-nourished patients compared to those who were malnourished (51,54,73,101). Other studies were more difficult to interpret due to the lack of control data (96).

*Quality of life and performance status*. In an RCT comparing 8 weeks supplementation with EPA-enriched ONS vs. a standard supplement in pancreatic cancer patients in palliative care, no significant differences in quality of life were observed (96). However, it was noted that quality of life correlated positively with EPA intake in the EPA group and not controls (75). A further RCT, using EPA-enriched ONS for 8 weeks in pancreatic cancer patients, demonstrated significant increases in physical activity level (calculated as total energy expenditure/resting energy expenditure by doubly labelled water) compared to respective baselines for both those receiving EPA and those receiving standard ONS; however, the difference between groups failed to reach significance (101). Little effect on the global health score was reported in another RCT following EPA-enriched ONS in advanced cancer (various sites) patients in palliative care (21).

One RCT reported an increase in Karnofsky performance status in patients with metastatic solid tumours in palliative care following 40 days of fish oil capsules (88); however, another RCT, again with advanced cancer patients advanced in palliative care, reported no change in Karnofsky performance status in the fish oil capsule-supplemented group, but a decline in the placebo group after 14 days (51). A significant increase in Karnofsky performance status was shown in a CT on fish oil-enriched ONS used for 7 weeks in patients with pancreatic cancer in palliative care (88). However, little effect on fatigue, well-being and Edmonton functional assessment in an RCT (54) or WHO performance status in a CT (107) have been reported following EPA capsule administration.

## 7. Discussion

Nutritional support in the form of ETF or ONS was generally found to improve total nutritional intake in patients with cancer undergoing surgery, chemotherapy or radiotherapy. A meta-analysis of 3 RCTs, of patients undergoing radiotherapy demonstrated that ONS significantly improved total energy intake compared to routine care (Fig. 2). Concurrent with the increase in energy provided by ONS and ETF is the associated increase in the intake of micronutrients as part of the feeds; in one of the ONS trials, the authors also reported that the intake of other nutrients, including vitamin C and folate, was greater in the supplemented group (35). In general, supplementation was achieved without suppressing food intake, concordant with observations in other clinical conditions (77,78,94,107,111,116).

Since reduced food intake is a major cause of malnutrition, an improvement in nutrient intake using ONS and ETF may help ameliorate or prevent malnutrition in patients with cancer (76,80,83,85,86,93,98,118). However, from the data currently available, it was not possible to assess if the response varied according to nutritional status because subgroup analysis according to nutritional status was not reported in the studies.

Since studies suggested that ONS and ETF improved nutritional intake, an increase in body weight might also be expected. Although there was some information on weight change in studies of ONS and ETF in patients undergoing chemotherapy and radiotherapy, surgery and palliative care, the results were varied and no consistent effects on body weight and composition were noted. Heterogeneity of patients included in the studies, duration and quantity of feeds, palatability and compliance with ONS and confounding factors, such as hydration and initial nutritional status, make it difficult to interpret the existing data. A variety of clinically measured outcomes, such as mortality, morbidity and responsiveness to treatment, were not found to differ between the intervention and control groups.

In this review, separate meta-analyses of studies on patients undergoing surgery or chemotherapy/radiotherapy demonstrated that ETF/ONS does not significantly affect mortality, length of hospital stay or rates of infectious complications. This may partly be explained by poor study design, including small sample sizes (n=18 to 120), the varying length of nutritional support, which ranged from 5 days to 12 months (see Appendix A), and poor compliance with most studies presenting no information on ONS compliance, which can decrease over time, or ETF provision (87). In addition, many ONS and ETF trials contained heterogeneous groups of cancer patients with a variety of cancer sites and stages given different types of therapy. In contrast, some clinical benefits were observed in the more homogeneous studies comparing ETF with PN in cancer patients undergoing surgery (typically post-gastrointestinal surgery). In these studies, ETF was typically delivered to the jejunum and generally achieved the desired nutritional goals (equivalent to ~20-25 kcal/kg/day) by postoperative day 3 or 4. Meta-

analyses of these studies showed that patients receiving postoperative ETF experienced significantly shorter hospital stays (1.72 fewer days; Fig. 3) compared to those receiving PN (76,85,98,117). Furthermore, although no significant differences in mortality were identified, patients fed via ETF also experienced significantly fewer complications (Figs. 4 and 5) and less sepsis (Fig. 6) than PN-fed patients.

The differences in clinical outcome may be due to different inflammatory and immune responses, but information on such processes was patchy and no significant differences were observed in some markers (e.g. serum transferrin, CD3-positive lymphocytes or acute phase proteins). There was also no evidence of significant differences in dietary intake or body weight between enterally and parenterally fed patients. It is also possible that catheter-related sepsis, which was occasionally reported in patients receiving PN, contributed to the greater incidence of septicaemia and complications in this group.

Other factors may also complicate the interpretation of these results. For instance, in an attempt to ensure isoenergetic feeding, patients receiving ETF may have also received PN in the early postoperative period (days 1-4) (80,93,98). In other cases, it was not possible to assess the separate contributions of carbohydrates (80,93,98), fat (117) and protein (80,83,85,86,93,115) to the final outcomes of studies. Moreover, nutritional status was generally not reported, and although malnutrition (including weight loss) was reported to be common in some studies (117,118,122), they did not provide stratified analysis; other studies provided no baseline information (47,74). From a practical perspective, the overall findings of these meta-analyses provide a rationale for the trend in current clinical practice to use ETF in preference to PN if feasible.

A smaller number of trials involved the use of fish oil capsules and feeds enriched with fish oil (and additional antioxidants to protect the fish oil) in patients with cancer undergoing BMT (47,74), surgery (46,102,124) and palliative care (21,51,52). In these studies, the typical intake of EPA was 1.8-4.0 g, substantially greater than normal dietary intake. In some groups (e.g. BMT), significant reductions in mortality and complications and improvements in inflammatory markers were observed with the use of EPA capsules, and this particular trial was suspended early due to the marked differences in survival observed between groups (47). In other groups (e.g. surgery), no evidence of clinical benefit has been documented with the use of EPA-enriched ETF. Indeed, many of the studies showed inconsistent effects on dietary intake, weight, body composition, or clinical outcomes, such as mortality or morbidity.

In the studies of EPA-enriched oral feeds involving advanced cancer patients receiving palliative care, it is possible that the effects of fish oils are overwhelmed by the tumour load at this stage of disease, preventing the manifestation of clinical benefits that might be apparent under other circumstances. Therefore, further studies on patients with less advanced cancer and undergoing different treatment modalities would be valuable for comparison. Another explanation for the overall lack of effect by ONS enriched with EPA is that there is variable and generally poor compliance. Since this was the case in the study by Fearon *et al*, a dose-response analysis was undertaken (96). Here, a relationship was demonstrated between the amount of EPA-enriched sip feed consumed and the net gain in weight, lean tissue and quality of life. No such relationship was found in the control group of subjects receiving a standard feed. However, these results were based on a post-hoc analysis, and prospective evaluation is therefore needed to confirm the findings. Compliance and intake of EPA capsules or EPA-enriched feeds in other studies were generally not well-reported. The differential effect of treatment with EPA in patients with cancer according to nutritional status could also not be examined. Therefore, further studies on patients with less advanced cancer undergoing different treatment modalities would be valuable for comparison. Another explanation might be the duration of supplementation with EPA, which was particularly short in surgical patients. It has been suggested that a sufficient duration is required for EPA to induce a metabolic effect (79). Burns *et al* demonstrated a duration-dependent effect on outcomes such as weight in those receiving EPA supplementation (73). Although many studies have also investigated the role of feeds containing EPA and other immune modulating nutrients, this is beyond the scope of this review and has been considered elsewhere (77).

## Conclusions

Enteral nutritional support, either orally or by tube, may help ameliorate the nutritional decline (malnutrition) in patients with cancer compared to routine care, although there is little evidence of improved clinical outcome (mortality). However, more research is needed to assess the clinical efficacy of ONS and ETF according to cancer type and treatment modality. In cancer patients undergoing gastrointestinal surgery, meta-analyses show that the delivery of nutritional support via ETF reduces the length of hospital stay and incidence of complications compared to PN. Although there were some clinical benefits to using EPA as capsules or enriched feeds in the treatment of cancer patients, further studies are required to confirm this.

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