



European Partnership for Action Against Cancer (EPAAC)

D6.1: Nutrition in Cancer Patients: A summary of the evidence

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Nutrition in Cancer Patients:

A summary of the evidence

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General: Providing evidence for the ESPEN evidence-based guidelines

The workflow for accruing and evaluating evidence to support the ESPEN evidence-based guidelines is summarized below. The first stages (clinical question and preliminary search) should take a few weeks. The duration for the whole effort to address a specific clinical question will be settled only after the preliminary search, depending on the kind of work that is needed (please see #3 below).

Formulating the clinical question:

The clinical question includes short but exact definitions of the population of interest, the intervention, comparators, and outcome. We emphasize the choice of the main outcome (before the review starts) as the outcome that matters most to the patients, and not necessarily the outcome in the original studies. The clinical question will be formulated by the relevant ESPEN committee, and finalized after a short discussion with our group.

Preliminary search and decision on the work to be done:

According to the clinical question, a search strategy and search phrases will be drawn by us. As a rule we will look in Pubmed and the Cochrane Library. We will look for recent, sound systematic reviews and meta-analysis that answer our clinical question; in their absence, for other systematic reviews and meta-analysis (old and in need of updating; or partially answering our question; or with methodological flaws in need of repair). Recent, sound systematic reviews will be summarized (see later for summary of results) and GRADEd for use in evidence-based guidelines. Partial systematic reviews will be updated, and again summarized. In the absence of systematic reviews, together with the relevant ESPEN committee we will decide whether to perform one, and whether to include in the review only RCTs or observational studies as well.

Performing a systematic review:

As a rule, we will use the Cochrane Handbook and Revman 5 to work on the systematic reviews and meta-analyses. We need to decide beforehand whether each systematic review will be performed as a Cochrane review or not; for separate publication; or for internal use only. We will use a hierarchy of evidence: randomized controlled trials (RCTs), matched-design observational comparative studies, prospective non-matched-design and retrospective non-matched design. The highest-level available evidence will be used. We will

use the domain-based approach to assess risk of bias in RCTs. For assessing the methodological rigor of observational, comparative studies we will use the Newcastle Ottawa Scale, modified as appropriate.

Evaluating a systematic review

To use a systematic review without any modifications, the requisites are detailed below. For any systematic review that does not fulfill the standards, we will update and amend it.

- Recent
- The main outcome is identical or similar to the one chosen by us.
- The inclusion and exclusion criteria for studies were detailed; make sense; and do not exclude studies in a way that might create bias (e.g. by language).
- The search string and databases are similar to ours (in the preliminary search).
- Major decisions and extraction of data were done by more than one researcher.
- The methodological rigor of the included studies was assessed and used for sensitivity analysis.
- The extraction of data was correct (mainly: used intent to treat analysis).
- Possible biases and heterogeneity were explored.
- If meta-analysis was performed, the correct model was used.

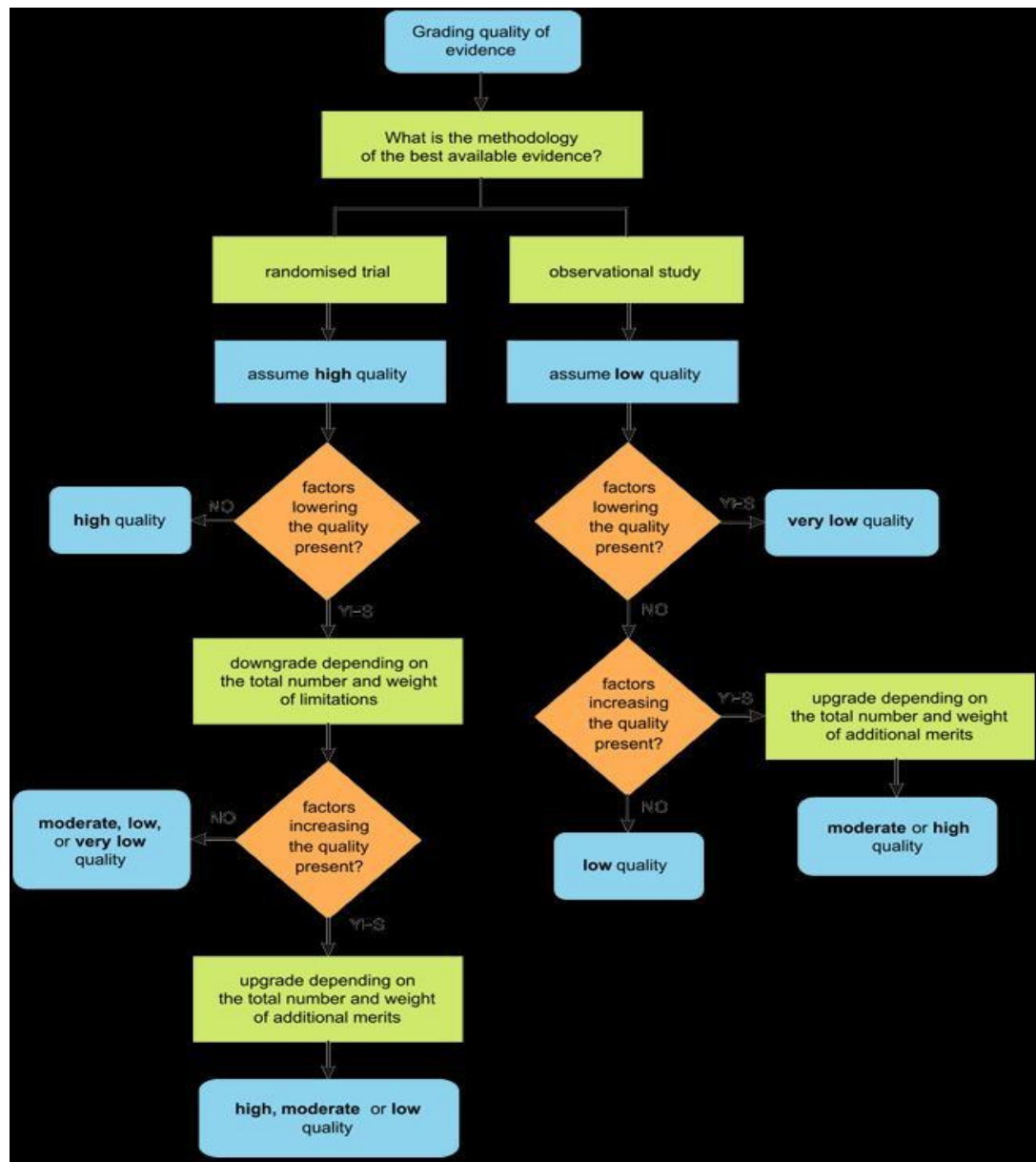
Presentation of results

Each topic will be summarized in a document detailing the clinical question, the search strategy, the source of data (existing systematic review, updated review, our own systematic review); results expressed as relative and absolute differences (if possible); GRADE summary of findings tables of the evidence; and implications (including needed research).

GRADEing the evidence

The GRADE system for assigning strength of evidence to outcomes of research is best explained in the GRADE profiler help (GRADE profiler can be downloaded for free at

<http://ims.cochrane.org/gradepr>). For a short explanation I have copied a few relevant figures and paragraphs below:



In general we consider whether a study is randomized or not; if comparative non-randomized, the order of strength of evidence is highest for prospective cohorts and lowest for historical controls; if comparative non-randomized we use a modification of the Newcastle Ottawa Scale to assess for methodological quality and lack of bias.

Factors that can reduce the quality of the evidence:

Factor	Consequence
Limitations in study design or execution (risk of bias) (eg inadequate allocation concealment in RCT)	1 or 2 levels
Inconsistency of results (eg large heterogeneity in treatment effect)	1 or 2 levels
Indirectness of evidence (indirect comparison, population, intervention or outcome)	1 or 2 levels
Imprecision (relatively few patients and few outcomes)	1 or 2 levels
Publication bias	1 or 2 levels

Factors that can increase the quality of the evidence:

Factor	Consequence
Large magnitude of effect	1 or 2 levels
All plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed	1 level
Dose-response gradient	1 level

PICO: Questions as defined by the ESPEN study group

The clinical questions are described in terms of population/s of interest, interventions, comparison, outcomes. On a general note, the interventions of interest and outcomes depend on the populations (e.g. in terminal cancer patient survival should not serve as an outcome).

Population:

The populations of interest are defined by the multiplications of the following matrices: cancer type; condition; treatment of cancer; nutritional status; age groups.

Cancer type: hematological, acute leukemia and bone marrow transplantation (BMT); hematological, all others; solid: lung, GI, head and neck cancer, other.

Condition: Terminal, treated or smoldering; functional capacity.

Treatment of cancer: Under chemotherapy or radiotherapy: by intensity (causes nausea/anorexia); radiotherapy to head and neck; radiotherapy to GI; surgery.

Nutritional status: Malnourished/not malnourished; anorexia.

Age groups

Interventions:

Psychosocial support, screening, enteral nutrition, parenteral nutrition, increase calories intake, increase protein intake, glutamine, immunonutrition, N3-FA, ONS.

Outcomes:

Primary, by order of importance:

- Survival (in all populations but for terminal patients)
- Disease free survival (in all populations but for terminal patients)
- Quality of life
- Performance status
- Completion of therapy

- Complications /LOS

Secondary by order of importance:

- Weight change
- Weight
- BMI
- Other

Search strategy

Search phrase

((Cancer OR carcinoma OR malignancy OR lymphoma OR leukemia OR myeloma OR melanoma OR metasta* OR bone marrow transplant) AND (nutrition* OR diet OR nourishment OR nutrient OR nutriment OR malnutrition OR malnourishment OR undernourishment OR calorie* OR lipid OR trace OR vitamin* OR protein OR taurine OR arginine OR glutamine OR fatty OR micronutrient* OR supplement* OR enteral OR parenteral OR EN OR TPN OR PN))

Search results

6600 records were examined.

A note of caution

We search for the best evidence. The best evidence, in evidence-based medicine terms, is gained from methodologically sound randomized controlled trials (RCTs). However the decision to do an RCT does not always follow the burden of disease. RCTs might be done to test a lucrative me-too drug; while trials might be missing for important, clinical questions for which no sponsor can be found. Guidelines should address these questions as well.

Summary of evidence

General

In general we found good systematic reviews to answer the majority of questions, although only for some populations of interest. The inclusion criteria and description of the population did not allow us to reach the level of resolution agreed on by the ESPEN guideline group. The randomized controlled trials included in the systematic reviews were often of medium or low quality, with small sample size, often with no calculation of sample size, and with poor or unreported allocation concealment.

For some cells in the matrix of the clinical questions we found no evidence, and the guidelines should rely on expert opinion.

The effort on writing guidelines should also include an effort to outline future studies that are needed: questions to be addressed (in terms of PICO); outcomes; design.

The evidence: short summary

Dietary interventions

Dietary counseling

A methodologically sound and recent systematic review (E1 – please see below) included randomised controlled trials (RCTs) looking at the efficacy of dietary counselling on the quality of life of patients with colorectal, GI, head and neck, lung, ovarian and breast cancer. It included 5 RCTs to a total of 488 patients. The change in the quality of life was not statistically significant, the heterogeneity huge, but the point estimate was in favour of the intervention. The evidence does not support counselling to improve the quality of life of cancer patients, but it does not rule out a significant efficiency.

GRADE: low quality.

Oral nutritional intervention

A methodologically sound and recent systematic review (E2 – please see below) included randomised controlled trials (RCTs) looking at the efficacy of any oral nutritional intervention: dietary advice, oral nutritional supplements, or both; on the survival and quality of life of adult patients with cancer (all sites and stages; receiving active treatments or palliative care) who were clearly malnourished or judged to be at risk of malnutrition on the basis of their clinical condition. It included 13 RCTs to a total of 1414 patients.

No difference in survival was found (relative risk = 1.06, 95% CI = 0.92 to 1.22, P = .43; no heterogeneity, $I^2 = 0\%$). Quality of life was significantly improved (both when including all studies and when removing the studies that accounted for high heterogeneity) on the global QOL scale, on “emotional functioning”, “dyspnea” and “loss of appetite” scales.

The interventions were associated with statistically significant improvements to weight (mean difference in weight = 1.86 kg, 95% CI = 0.25 to 3.47, P = .02), but there was statistically significant heterogeneity. Groups receiving nutritional interventions had a statistically significantly greater energy intake than groups receiving routine care, again with high heterogeneity.

Studies that offered both dietary advice and oral nutritional supplements had the greatest effect, but this is a post-hoc observation made by us.

GRADE: moderate quality

In summary: Dietary advice and oral nutritional supplements in cancer patients who were clearly malnourished or judged to be at risk of malnutrition improved quality of life, weight and energy intake, but not survival.

GRADE: moderate quality.

Artificial nutrition and hydration in the last week of life

A methodologically sound systematic review published in 2000 (E3 – please see below) included one RCT and 9 observational studies examining the influence of nutrition and hydration in the last days of life. The one RCT included in the review (RCT1, please see below) examined the efficiency of hypodermoclysis to relieve thirst, nausea and delirium in 42 cancer patients in the terminal stages of the disease. No difference in the relief of symptoms at 24 hours was shown, and at 48 hours the only parameter improved in the intervention group was nausea (by an average of 1 on a scale of 10) (GRADE: very low quality).

The systematic review including observational studies showed no improvement in symptoms or survival, but the data were far from conclusive.

In summary: Hydration or artificial nutrition for cancer patients at the end of life showed no improvement in symptoms or in survival.

GRADE: low quality.

Enteral feeding methods for nutritional management in patients with head and neck cancers being treated with radiotherapy and/or chemotherapy

A recent Cochrane review of sound methodology compared methods of enteral feeding in adult patients with head and neck cancers treated with radiotherapy and/or chemotherapy (E4 – please see below) . The review included 1 RCT with 33 patients randomized to PEG placement vs nasogastric tube. Patient's satisfaction did not differ between groups. Quality of life was not formally assessed. Survival was not reported. PEG patients gained significantly more weight (but probably because of loss of fat in the NG group) at 6 weeks but not at 6 months. The duration of PEG feeding (range 56 to 488 days) was significantly longer than for the NG group (range 23 to 136 days) ($P = 0.0006$). There was no difference in chest infection rates between the two groups. Twelve NG patients experienced feeding tube dislodgement, with no tube dislodgement in the PEG group. Four of the PEG group had site infections.

In summary: In this small RCT PEG patients gained significantly more weight than patients in the nasogastric tube group, none experienced tube dislodgement, and about a fourth of them had site infections.

GRADE: low quality.

Nutrition support for bone-marrow transplant patients

A Cochrane systematic review of sound methodology included all RCTs that examined any nutrition intervention for bone-marrow transplant patients (please see E5 below). The interventions are summarized below (E5).

Parenteral nutrition vs. IV hydration showed no benefit on survival up to 200 days, graft vs host disease, and days in hospital. The change in body weight was higher with parenteral nutrition (2.81% of change in body weight [95% CI 1.34, 4.29]). Line infections were significantly increased, RR 21.23 [95% CI 4.15, 108.73].

Glutamine: A more recent systematic review was performed – please see below.

In summary: Parenteral nutrition showed no effect on survival or length of hospital stay. Weight was increased, but at the expense of a significant increase in line infections. The intervention cannot be recommended.

GRADE: good quality.

Glutamine supplementation

Glutamine for chemotherapy induced diarrhea

A recent systematic review of poor methodology included 8 RCTs with 298 cancer and bone marrow transplant patients comparing prophylactic glutamine (given IV or PO) with placebo or no treatment for prevention of diarrhea (E6 – please see below) . Glutamine reduced the duration of diarrhea by 1 day, but not its severity. Other outcomes were not assessed.

GRADE: low quality.

Glutamine in patients with stem cell transplantation:

A systematic review of sound methodology examined glutamine supplementation in stem cell transplantation patients (E7). It included 22 RCTs (generally of poor methodology) to a total of 2331 patients. No positive effect on mortality was shown. Two studies of autologous transplants only suggested an increased mortality with glutamine (combined effect RR=3.21, 95% CI 1.17–8.79, $I^2=0\%$) whereas the single study that suggested decreased mortality investigated allogeneic transplants only and the excess deaths in the control arm all occurred in the first 100 days.

In seven studies the effect on infection was examined, and glutamine reduced clinically documented infections, RR 0.77, 95% CI 0.60–0.98, no heterogeneity, $I^2=0\%$. In 3 studies of sound methodology the effect was no longer significant. Days of fever (2 studies) and days of antibiotic treatment (5 days) did not differ between groups.

The overall effect of oral and i.v. glutamine was a reduced average mucositis score (SMD - 0.24, 95% CI -0.42 to -0.05, $I^2=48\%$). Subgroup analyses revealed a trend towards a lower

average score if the glutamine was started before day 0 compared to after. There was no statistically significant effect on days of opioids with glutamine (MD -0.21 days, 95% CI -1.52 to 1.10, high heterogeneity, $I^2=84\%$).

The overall effect of i.v. and oral glutamine on GVHD was a reduction in GVHD (RR=0.73, 95% CI 0.53–0.99, $I^2=47\%$), 6 studies.

Overall the result of oral and i.v. glutamine on time to neutrophil recovery was MD -0.62 days (95% CI -1.48 to 0.25, $I^2=0\%$).

When the oral and i.v. glutamine studies were combined, there was no effect of glutamine on length of stay (MD 0.41 days, 95% CI -0.89 to 1.71, $I^2=36\%$).

Two studies (70 patients) found increased number of patients with relapses with i.v. glutamine (RR 2.91, 95% CI 1.34–6.29, $I^2=0\%$). When oral and i.v. studies were combined, glutamine appeared to increase the number of patients with relapses (RR 1.61, 95% CI 1.01–2.55, $I^2=64\%$). There were too few studies to investigate heterogeneity further but the two i.v. studies included autologous transplants only. When random effect measures were used the overall RR was not significant, RR 1.50 (95% CI 0.64–3.50).

Weight, days on TPN and red blood cell transfusions were not significantly affected.

GRADE: moderate quality.

A note of caution

In a randomized controlled trial of high methodological quality (N Engl J Med 2013; 368: 1489-97) glutamine supplementation significantly increased mortality in critically ill patients. These are not the patients addressed in the present review, but note should be taken.

In summary: The effects of glutamine are not consistent; neither is the difference between the oral and IV administration. In our opinion glutamine should not be recommended; however the large margins of uncertainty could justify RCTs of good designs and appropriate sample size.

GRADE: moderate quality.

Eicosapentaenoic acid for treatment of cancer cachexia

In a Cochrane systematic review of sound methodology (please see below: E-8) the effectiveness of eicosapentaenoic acid (EPA) to alleviate cachexia and related symptoms was

tested in patients with incurable or advanced cancer. The review included 5 RCTs, a total of 587 patients. The exact interventions are detailed below: please see E-8.

EPA vs placebo

Only one RCT reported on survival: in the EPA arm, well-nourished (WN) patients survived 870 days and malnourished (MN) patients survived 600 days compared to all patients (n = 30) in the placebo arm (WN = 480 days, MN = 242 days). This study had a very high risk for bias (methods of low quality).

One study reported on quality of life, and showed no significant improvement. Functional status was reported in 2 RCTs: improved in one and no change in the second. Weight gain was reported in one trial and was not significant.

EPA versus matched active treatment control

In two studies that reported on survival there was no significant advantage to the EPA arm; nor were the quality of life or performance status improved. Gain in weight was not influenced by the addition of EPA.

In summary, the efficiency of EPA in cancer patients was not proven.

GRADE: low quality.

Fish oil for the treatment of cachexia

A recent systematic review of poor methodology (please see E-9 below) included 11 RCTs (1707 patients) that tested treatment with EPA, fish oil, or n-3-FA (including studies that were comprised in E-8). The systematic review found no evidence for influence on survival, performance status, complaints or weight gain.

Adverse effects of EPA and other n-3-FA were reported in only a few studies: most often gastrointestinal effects such as mild abdominal discomfort, flatulence, nausea or vomiting, transient diarrhoea or steatorrhoea. Toxicity of the central nervous system and severe paraesthesia were reported in one patient each in a randomized study.

In summary, fish oil cannot be recommended for cachexia in cancer patients.

GRADE: low quality.

n-3 PUFAs in cancer, surgery, and critical care

Another recent systematic review (please see E-10 below) aimed to review effects of oral or enteral and parenteral n-3 FA supplementation on clinical outcomes in patients with cancer who underwent surgery or critical care. For non-surgical patients the included studies are identical to the ones in E-8 and E-9, and the conclusions are similar.

For surgical patients none of the studies showed an effect on mortality. There was no consistent effect of enteral supplementation of n-3 FAs on post-operative complications, length of stay or nutritional status.

In summary, n-3 FA supplementation cannot be recommended for surgical cancer patients.

GRADE: very low quality.

Lycopene in prostate cancer

Two RCTs (89 patients) of very low methodological quality were included in a systematic review (please see E11 below). Longer overall survival was observed in the supplemented group than in the control group in the trial by Ansari (2003) after a mean follow-up period of 25.5 months, 19 patients (35%) died, 12 (22%) in the control group and 7 (13%) in the supplemented group ($P < 0.001$). A significantly higher proportion of patients had a complete response (normal bone scan) in the intervention group compared with control group.

In one RCT urinary tract symptoms were improved in the intervention arm compared to the control arm. No significant change in serum PSA was shown.

No adverse effects or reactions were reported during and after supplementation in the intervention arm.

In summary, although the results are positive the small sample size and the weak methodology of the trials preclude drawing of any conclusions. Further RCTs of solid methodology could be justified given these results.

GRADE: very low quality.

Impact of antioxidant supplementation on chemotherapeutic efficacy

A systematic review (E-12) of medium methodological rigor included 19 RCTs addressing a variety of interventions (vitamin C, vitamin E, vitamin A, melatonin, glutathione, N-

acetylcysteine, polyphenols, green tea catechins, carotenoids, carnitine, selenium, ellagic acid, curcumin, coenzyme Q10, lycopene, flavonoids, isoflavones). Most of the RCTs suffered from a weak design. Glutathione (in one study), melatonin (4 studies), n-acetyl cysteine (1 study), vitamin C, A and E, ellagic acid, all showed positive effect on different outcomes.

In summary, the weak methodology, multiple interventions and the diverse outcomes examines preclude any strong conclusions.

GRADE: very low quality.

Efficacy of vitamin D supplementation in cancer patients

A systematic review of low methodological rigor (please see E-13 below) looked at 3 studies that included 1273 prostate cancer patients. Vit D provided no effect on survival, with significant heterogeneity.

In summary, Vit D cannot be recommended indiscriminately to prostate cancer patients or to other cancer patients (for lack of evidence).

GRADE: low quality

Immunoenhanced enteral nutrition formulas in head and neck cancer surgery

A systematic review (please see E-14 below) examined whether preoperative immunonutrition has a role in the treatment of patients undergoing surgery for head and neck cancer. Fourteen studies (836 patients) were included. The studies are of weak methodology, and no conclusive conclusions could be drawn.

GRADE: very low quality

Perioperative immunonutrition for gastrointestinal cancer

A systematic review (please see E15 below) of medium methodological rigor examined the effect of perioperative immunonutrition (IN) diet with standard diet in RCTs. IN diet included at least two of following nutrients: arginine, glutamine, u-3 PUFA or RNA. The review included 19 RCTs to a total of 2331 patients. For the exact interventions please see below, E15.

Given postoperatively, infections were lower in the intervention arms, RR, 0.69; 95% CI, 95% CI 0.57 to 0.84, no heterogeneity. Length of hospital stay (in days) was shorter in the intervention arm: . WMD, -2.95; 95% CI, -4.57 to -1.32. For the preoperative intervention,

similar results were shown for infections: RR, 0.45; 95% CI, 0.31 to 0.65; and hospital stay: WMD, -2.62; 95% CI, -3.26 to -1.97.

No differences were shown when the postoperative intervention was compared directly to the pre-operative.

Survival and quality of life were not reported.

In summary, the meta-analysis results are in favor of the intervention. Concerns are raised by the low quality of the evidence, the heterogeneity of the interventions that were included and the lack of data on survival and quality of life. The recommendation depends on experts' opinion.

GRADE: low quality.

Nutritional screening in cancer patients

We looked for comparative studies (whether randomized or not) that addressed the efficacy of nutritional assessment/screening tools based on anthropometric measures or nutritional questioners or combined. We found no studies that addressed the efficacy of screening on any of the outcomes that were defined in this review (please see E16 below).

Included systematic reviews

E1: Does dietary counselling improve quality of life in cancer patients? A systematic review and meta-analysis

[PMID: 18551861](#)

Reference: Halfdanarson, T. R., Thordardottir, E., West, C. P., & Jatoi, A. (2008). Does dietary counseling improve quality of life in cancer patients? A systematic review and meta-analysis. *J Support Oncol*, 6(5), 234-237.

Objectives:

To assess the effect of dietary counseling on quality of life (QOL).

Studies Inclusion criteria:

Only randomized clinical trials of dietary counseling versus no dietary counseling (or a less aggressive form of dietary counseling) were included. All had to have used a validated tool for global QOL assessment as a study endpoint.

Intervention:

Dietary counseling was defined as any dietitian consultation that was undertaken to increase nutritional intake. In the specific studies:

Intervention:

Dietary counseling was defined as any dietitian consultation that was undertaken to increase nutritional intake.

Persson 2002: Patients were randomized in a 2×2 design between 1) IS, including nutritional support, 2) group rehabilitation (GR), 3) IS + GR (ISGR), or 4) standard care (SC).

Nutritional support: three to seven subsequent interviews were scheduled at baseline and every 3–6 months for 2 years based upon the extent of disease. After having completed a 24-h recall, the dietitian gave dietary advice aimed at recommended levels of daily intake directly over the telephone when immediate improvement of intake was judged to be necessary and by mail on the basis of the calculation of intake. If necessary, extra contacts were provided. In addition, family members contacted the dietitian on several occasions.

GR intervention: eight-session group intervention with a booster session. The dietitian participated in one of the sessions.

Isenring 2004: Patients received individualized Nutrition intervention (NI) in the form of regular and intensive nutrition counseling by a dietitian, following a predetermined standard nutrition protocol, the Medical Nutrition Therapy (Cancer/Radiation Oncology) protocol of the American Dietetic Association (ADA) for a 12-week study. Nutrition counseling by the dietitian was provided within the first 4 days of commencing radiotherapy and weekly for the course of radiotherapy (approximately 6 weeks) and fortnightly for the remainder of the study period.

Telephone reviews were conducted between nutrition counseling sessions.

Individually tailored sample meal plans, recipe suggestions and hints to minimize the side effects of the tumor and therapy were provided. Standard patient handouts from the ADA Oncology Nutrition Dietetic Practice Group, as well as snack and high energy and protein exchange lists, were used. If deemed appropriate, the dietitian provided a weekly supply of oral nutrition supplements for up to 3 months.

Ravasco 2005: dietary counseling for 3 months with the research dietitian aimed at achieving calculated energy and protein requirements at baseline and weekly during therapy. Patients were randomized to the following groups: group 1, patients who received dietary counseling with regular foods; group 2, patients who maintained usual diet plus supplements; and group 3, the control group, patients were instructed to maintain their ad libitum intake. Dietary counseling involved the prescription of a therapeutic diet that used regular foods, which was further modified to provide for individual requirements. The prescription identified the type, amount, and frequency of feeding and specified the caloric/protein level to attain, together with any restrictions and limited or increased individual dietary components.

Oral nutrition commercial supplements, were ready-to-use, high-protein, energy-dense liquid polymeric formulations intended to act as a supplement to the patients' usual diets. Supplement were offered to patients who were able to select their preferred flavors and were instructed to use them as drinks to be consumed between meals, in addition to any other meal.

Ravasco 2005: dietary counseling for 3 months with the research dietician aimed at achieving calculated energy and protein requirements at baseline and weekly during therapy. Patients were randomized to the following groups: group 1, received individualized dietary counseling based on regular foods; group 2, were asked to consume two cans per day of a high-protein liquid supplement in addition to their usual diet; and group 3, the control group, patients were instructed to maintain their ad libitum intake. Dietary counseling involved the prescription of a therapeutic diet that used regular foods, which was further modified to provide for individual requirements. The prescription identified the type, amount, and frequency of feeding and specified the caloric/protein level to attain, together with any restrictions and limited or increased individual dietary components.

Oral nutrition commercial supplements, were ready-to-use, high-protein, energy-dense liquid polymeric formulations intended to act as a supplement to the patients' usual diets. Supplement were offered to patients who were able to select their preferred flavors and were instructed to use them as drinks to be consumed between meals, in addition to any other meal.

Ovesen 1993: patients received dietary counseling before starting chemotherapy and twice monthly for 5 months. If the patient had no major nutritional problems, counseling was reduced to once monthly. The goal for the nutritional counseling was an intake that met or exceeded protein and energy requirements according to Nordic Recommended Allowances' (daily energy intake in the range of 1.5 to 1.7 X basal energy expenditure [BEE], calculated from the Harris-Benedict equation,¹⁰ and protein intake of 1.0 to 1.2 g/kg body weight). Patients were counseled on an individual basis according to advocated lines of recommendations, and were offered supplementation with commercial liquid diets, protein supplements, and/ or maltodextrin if indicated. Patients could chose from several commercial diets according to individual preference.

Population:

Cancer patients: Colorectal, GI, head and neck, Lung, ovarian, breast.

Primary outcomes:

Quality of life

Primary outcomes as defined by us:

Survival

Quality of life

Performance

Completion of therapy

Complications /LOS

Does it appear in the SR and meta-analysis? YES.

Years included in the search: Not mentioned.

Were additional RCTs on the subject published since then? NO.

Methodological rigor:

Data extraction by more than one researcher: YES.

Search strategy detailed: YES.

Untoward restriction of search parameters: NO

Was the methodological rigor of the individual studies appraised, and did it serve for analysis? YES.

Were sub-group analyses of interest performed? NO.

Was heterogeneity tested? YES.

Was an attempt to explain heterogeneity made? YES.

Was the meta-analysis conducted according to the degree of heterogeneity? YES.

No of included studies: **5**

No of included patients: **488**

Mean number of patients per study: **97**

Main outcomes:

Three trials reported benefits of nutritional counseling in improving or maintaining QOL, and two did not. When all five trials were assessed in aggregate, the standardized mean difference in QOL scores was 0.56 (95% CI, -0.01–1.14; $P = 0.06$; $I^2 = 87.7\%$).

NNT for main outcome: not relevant

GRADE: low quality

Study limitation: negligible

Inconsistency: serious

Imprecision: serious

Publication bias: impossible to address

Conclusions:

This systematic review and meta-analysis observed that dietary counseling did not result in a statistically significant improvement in global QOL in cancer patients. From a clinical practice standpoint, the observed borderline statistical significance and the point estimate in favour of dietary counselling suggest that this intervention nonetheless may be justified in select patients suffering from especially poor oral intake and weight loss. In short, the findings from this study should provide the impetus for further high-quality trials.

E2: Oral Nutritional Interventions in Malnourished Patients with Cancer: A Systematic Review and Meta-Analysis

[PMID: 22345712](#)

Reference: Christine Baldwin, Ayelet Spiro, Roger Ahern, Peter W. Emery. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. J Natl Cancer Inst. 2012 Mar 7;104(5):371-85. doi: 10.1093/jnci/djr556. Epub 2012 Feb 15.

Objectives:

The aim of this systematic review was to examine the evidence for an effect of oral dietary interventions in patients with cancer who were malnourished or were at risk of malnutrition.

Studies: Inclusion criteria:

Randomized controlled trials

Quasi-randomized controlled trials.

Intervention:

Oral nutritional intervention could consist of: 1) dietary advice, 2) oral nutritional supplements, or 3) dietary advice and oral nutritional supplements given together.

Trial	Intervention
Baldwin et al., 2008	Comparison details: Group 1 received no additional intervention, group 2 received dietary advice to increase intake by 600 kcal/d, group 3 received an oral nutritional supplement providing 588 kcal/d, group 4 received dietary advice to increase intake by 600 kcal/d and an oral nutritional supplement.

	Length of intervention: 6 weeks
Dixon, 1984	<p>Comparison details:</p> <p>Nutritional counseling provided by nurses or nutritional counseling plus oral nutritional supplements vs. no advice.</p> <p>Length of intervention: 4 months</p>
Elkort et al., 1981	<p>Comparison details:</p> <p>Optimal diet (information from author indicated equivalent to dietary advice to meet nutritional requirements) + 500 kcal of nutritional supplement vs. routine care + no supplement.</p> <p>Length of intervention: 12 months</p>
Evans et al., 1987	<p>Comparison details:</p> <p>Nutritional counseling to achieve a target caloric intake, using supplements if required vs. routine care (ad libitum food intake).</p> <p>Length of intervention: 12 weeks</p>
Isenring et al., 2004 and 2007	<p>Comparison details:</p> <p>Intensive nutritional counseling and nutritional supplements, if required vs. usual care (which included standard booklet and the patient could request a referral to a dietitian). Five of 31 patients saw a dietitian during the 12-wk study.</p> <p>Length of intervention: 12 weeks</p>
Lovik et al., 1996	<p>Comparison details:</p> <p>Intensive dietary instruction including advice to use nutritional supplements if required vs. routine care (a standard information sheet providing information on all aspects of treatment, including advice to eat a nutritious diet).</p>

	Length of intervention: 6 weeks
Macia et al., 1991	Comparison details: Dietary instruction was given verbally and in writing vs. no advice. Length of intervention: unclear.
Moloney et al., 1983	Comparison details: Dietary counseling and supplements of Sustagen or Isocal vs. routine care. Length of intervention: 3-5 weeks
Ollenschlager et al., 1992	Comparison details: Daily dietary instruction and modification of diet vs. no advice. Length of intervention: unclear
Ovesen et al., 1993	Comparison details: Dietary instruction to exceed the Nordic recommended allowances using supplements if required vs. routine care. Counseling was performed by a dietitian, and took place twice monthly from start of chemotherapy. Length of intervention: 5 months
Persson et al., 2002	Comparison details: Dietary advice by phone and in writing to meet the Nordic recommended allowances using supplements if required vs. routine care. Length of intervention: 24 months.
Ravasco et al., 2005	Comparison details: Dietary counseling to achieve calculated energy and protein requirements vs. 400 kcal of supplement vs. no advice and no supplement (Patients with colorectal cancer).

	Length of intervention: 3 months
Ravasco et al. 2005	<p>Comparison details:</p> <p>Dietary counseling to achieve calculated energy and protein requirements vs. 400 kcal of supplement vs. no advice and no supplement (Patients with head and neck cancer).</p> <p>Length of intervention: 3 months</p>

Population:

Adults with cancer (all sites and stages) who were clearly malnourished or judged to be at risk of malnutrition on the basis of their clinical condition, receiving active treatments or palliative care, and were comparing oral nutritional interventions with usual care.

Primary outcomes:

Survival

QOL

Primary outcomes as defined by us:

ECOG / QoL

Survival

Complications /LOS

Does it appear in the SR and meta-analysis? YES.

Years included in the search:

The search undertaken to identify the studies was conducted between 1998 and February 2010.

Were additional RCTs on the subject published since then? NO

Methodological rigor:

Data extraction by more than one researcher: YES

Search strategy detailed: YES

Untoward restriction of search parameters: NO

Was the methodological rigor of the individual studies appraised, and did it serve for analysis? YES

Were sub-group analyses of interest performed? YES

Was heterogeneity tested? YES

Was an attempt to explain heterogeneity made? YES

Was the meta-analysis conducted according to the degree of heterogeneity? YES

No of included studies: **13**

No of included patients: **1414**

Mean number of patients per study: **108**

Main outcomes:

Survival: There were no statistically significant differences in mortality between the intervention and control groups. Relative risk, using a fixed effects model, and heterogeneity were low (relative risk = 1.06, 95% CI = 0.92 to 1.22, $P = .43$; $I^2 = 0\%$; $P_{\text{heterogeneity}} = .56$).

QOL: After removing the studies that accounted for the heterogeneity, meta-analysis indicated that oral nutritional interventions were associated with statistically significant improvements in the “emotional functioning” and “global QOL” function scales and the “dyspnea” and “loss of appetite” symptom scales. However, changes in other scales did not reach statistical significance.

Secondary outcomes:

Nutritional Status: Oral nutritional intervention was associated with statistically significant improvements to weight (mean difference in weight = 1.86 kg, 95% CI = 0.25 to 3.47, $P = .02$), but there was statistically significant heterogeneity.

Groups receiving nutritional interventions had a statistically significantly greater energy intake than groups receiving routine care: The mean change in energy intake from baseline to the end of the intervention period (assessed by a random effects model) was 432 kcal/d (95% CI = 172 to 693; $P = .001$). However, heterogeneity was high ($I^2 = 97.0\%$, $P < .001$) and could not be reduced by removing any one study.

GRADE: moderate quality (the systematic review is of high methodological quality)

Study limitation: negligible

Inconsistency: serious

Imprecision: moderate

Publication bias: probably

Effect size: low

Conclusions:

Despite the weaknesses in the meta-analyses, the data suggest that there are differences in the way patients with cancer respond to oral nutritional interventions. Studies are required to determine the factors, which contribute to the effectiveness of nutritional interventions in patients with cancer who are malnourished or at risk of malnutrition, to strengthen the evidence base for nutritional management in this patient group.

E3. Artificial nutrition and hydration in the last week of life in cancer patients. A systematic literature review of practices and effects

[PMID: 21199887](#)

Reference: Raijmakers, N. J. H., van Zuylen, L., Costantini, M., Caraceni, A., Clark, J., Lundquist, G., & van der Heide, A. (2011). Artificial nutrition and hydration in the last week of life in cancer patients. A systematic literature review of practices and effects. *Annals of Oncology*, 22(7), 1478-1486.

Objectives:

To give a comprehensive overview of currently available evidence on practices and effects concerning artificial nutrition (AN) and artificial hydration (AH) in the last week of life of cancer patients.

Studies Inclusion criteria:

Include cancer patients

Describe original empirical research, thus excluding case reports, reviews, discussion papers and ethical papers.

Include data on the last week of life.

Describe frequencies of practices or effects of AN or AH.

At least 25% of included patients had to be cancer patients.

Interventional/observational studies.

Intervention:

Artificial nutrition (AN) and artificial hydration (AH).

Population:

Cancer patients in the last days of life.

Primary outcomes:

Quality of life

Symptoms

Survival

Primary outcomes as defined by us:

Quality of life

Performance

Complications

Does it appear in the SR and meta-analysis? YES.

Years included in the search:

Databases such as PubMed, CINAHL, PsychInfo and EMBASE for papers that were published: between January 1998 and May 2009.

Hand search the most recent issues of 10 relevant peer-reviewed journals:
January 2008–February 2009

Were additional RCTs on the subject published since then? NO.

Methodological rigor:

Data extraction by more than one researcher: YES.

Search strategy detailed: YES.

Untoward restriction of search parameters: NO.

Was the methodological rigor of the individual studies appraised, and did it serve for analysis? NO.

Were sub-group analyses of interest performed? NO.

No of included studies: **10 (1 RCT, 9 observational)**

No of included patients: **1969**

Mean number of patients per study: **196**

This systematic review included one randomized controlled trial:

RCT1: Cerchietti, L., Navigante, A., Sauri, A., & Palazzo, F. (2000). Hypodermoclysis for control of dehydration in terminal-stage cancer. International Journal of Palliative Nursing, 6(8), 370-374.

Objectives:

To assess the usefulness of hypodermoclysis hydration in the relief of thirst, chronic nausea and delirium.

Inclusion criteria:

All patients presented one or more of the following symptoms: thirst; chronic nausea or delirium; dehydration diagnosed on physical examination, with or without renal failure; and inability to maintain an adequate water intake (less than 50 ml/day fluid).

Exclusion criteria:

The presence of other uncontrolled symptoms (pain in two of the patients, severe dyspnoea in another two), bowel obstruction syndrome requiring surgery (one patient) and severe constipation (three patients).

Study population:

50 patients in terminal-stage advanced cancer were consecutively evaluated. Forty-two patients were included in the trial (after the exclusion of 8 patients).

Study design:

Randomized controlled trial.

The main end points were assessment of thirst, chronic nausea and delirium. Additional end points were assessment of anguish, mood and severe adverse reactions that required the interruption of hydrations (oedema, increase in respiratory secretions, congestive heart failure). Additionally, local adverse reactions) discomfort, pain, infection, oedema, erythema, bleeding at the puncture site) and adverse drug reactions were quantified. Time from recruitment to death was recorded.

Methodological rigor:

Randomization method: Unclear

Allocation concealment: Unclear

Intention to treat analysis: Yes

Intervention:

Patients were randomly assigned to one of two groups. Both groups received drugs subcutaneously (haloperidol 2.5 mg every 4 hours to control delirium and/or metoclopramide 10 mg every 4 hours to control chronic nausea). The study group also received 1000 ml 5% dextrose in water infusion plus 140 milliequivalent per litre (mEq/L) sodium chloride, at a rate of 42 ml/hour per day.

Outcomes:

Twenty of the 42 patients included in the study received subcutaneous hydration.

Thirst, chronic nausea and delirium: Both groups showed significant improvements in relation to relief of thirst and chronic nausea after 24 hours, but no difference for delirium. There were no significant differences between the two groups for these symptoms ($p=0.864$ and 9.864 , respectively).

After 48 hours, improvement was only maintained in the group that received hypodermoclysis hydration, and only in relief from chronic nausea (an improvement of 1 unit on a scale of 10, $p=0.027$). Delirium did not improve significantly in either group during the trial period.

Mental status: The mental status of the patients who did not present delirium was maintained during the study period, showing no significant differences compared with the basal values in both groups.

Adverse effects: There were no significant differences between the groups regarding the incidence of local adverse reactions or adverse drug reactions, anguish and mood. Only one patient in the hypodermoclysis group presented a local adverse reaction (erythema and pain at the puncture site) 36 hours after the start of the treatment. This required a relocation of the hypodermopuncture site. No patient from the hydration group presented a severe adverse reaction.

Conclusions:

Current data suggest that decisions concerning rehydration of patients with terminal-stage cancer should be based on the patient's comfort rather than on providing optimal hydration. Rehydration in some cases would lead to unnecessary intrusion and could distract the doctors and nurses from the more human aspects of care.

GRADE: very low quality

Study limitation: major

Inconsistency: large

Imprecision: large

Systematic review, including observational studies:

Main outcomes:

Effect of AN in the last week of life on quality of life: No studies of the effect of AN in the last week of life on quality of life were found. However, a prospective observational study reported the combined effect of ANH. In this study, medical staff assessed the comfort level of 196 terminal cancer patients who received ANH. Two days before death, 145 patients still received ANH: 75% of them did not perceive any changes in comfort compared with an earlier assessment, 6% perceived more discomfort and 18% perceived more comfort

Effect of AH in the last week of life on quality of life: None of the studies used quality-of-life assessments to measure effects of AH compared with no AH.

Effects of AH on symptoms during the last week of life: Five papers reported on this outcome. Four studies had a prospective design, one of which used randomization for the allocation of AH; one study had a retrospective design. The prospective randomized trial found no significant effects in controlling several symptoms, except for chronic nausea that had improved significantly more after 48 h in the AH group. When comparing patients receiving or not receiving AH, two prospective studies found respectively significantly more ascites and more intestinal drainage in the AH group. The latter study found no differences in ascites and pleural drainage. It is not

clear was the authors meant by intestinal drainage. Secondary analyses of data from a large, prospective observational study revealed a significant association between AH 24 h before death and the absence of physical signs of dehydration (dry mouth, axillary moisture and sunkenness of eyes). Another prospective study only reported the feasibility and side-effects of rectal AH and a retrospective study compared two different protocols for preventing delirium by opioids and AH; no difference in delirium was found.

Effect of ANH on survival: only one study reported on the effect of ANH in the last week of life on survival of terminal cancer patients. The study did not distinguish AN and AH. Providing ANH in advanced cancer patients at either the time of admission or 2 days before death was found not to be a significant determinant of survival.

GRADE: low quality

Study limitation: negligible

Inconsistency: serious

Imprecision: moderate

Publication bias: no

Effect size: low (RCT); not applicable (all systematic review)

Conclusions:

When a patient is recognized as having entered the dying phase, medical treatment should primarily contribute to the patient's comfort. Issues concerning nutrition and hydration are an important and significant aspect of cancer patient care in the last days of life. Current literature suggests that the benefits of providing AH are limited and do not clearly outweigh the burdens, although some effects on specific symptoms may be present in some patients. Evidence concerning the effects of continuing or withdrawing AN in the last days of life is lacking and little is known concerning the life-shortening or prolonging effect of either AN or AH.

E4: Enteral feeding methods for nutritional management in patients with head and neck cancers being treated with radiotherapy and/or chemotherapy

PMID: 19270730

Reference: Nugent B, Lewis S, O'Sullivan JM. Enteral feeding methods for nutritional management in patients with head and neck cancers being treated with radiotherapy and/or chemotherapy. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD007904. DOI: 10.1002/14651858.CD007904.pub3.

Objectives:

To compare the effectiveness of different enteral feeding methods used in the nutritional management of patients with head and neck cancer receiving radiotherapy or chemoradiotherapy using the clinical outcomes, nutritional status, quality of life and rates of complications.

Studies Inclusion criteria:

Randomised controlled trials

Intervention:

Trials had to compare one method of enteral feeding with another. Combination of the methods of enteral feeding was acceptable provided one of the interventions was included in both of the arms of the study. Trials which were designed to look at a treatment intervention but include feeding methods were to be included. Intervention comparisons could include the following:

- Prophylactic percutaneous endoscopic gastrostomy (PEG) versus nasogastric tube (NG).
- Prophylactic PEG versus PEG.
- Prophylactic PEG versus radiological inserted gastrostomy (RIG).

- Prophylactic RIG versus NG.
- Prophylactic RIG versus PEG.
- Prophylactic RIG versus RIG.
- PEG versus NG.
- PEG versus RIG.
- RIG versus NG.

Corry 2008: PEG feeding during treatment or NG feeding during treatment; both devices placed during treatment period

Population:

Adult patients with a diagnosis of head and neck cancer receiving radiotherapy and/or chemoradiotherapy.

Corry 2008: 33 participants (15 received a PEG and 18 a NG); 24 male; all participants aged > 18 years.

Primary outcomes:

Nutritional status – change/maintenance. measured by percentage body weight difference and/or anthropometry measurement changes such as triceps skin fold thickness, mid arm muscle circumference or by hand grip strength difference, during and post-treatment period.

Primary outcomes as defined by us:

Survival

Quality of life

Performance

Completion of therapy

Complications /LOS

Does it appear in the SR and meta-analysis? YES, partly (secondary outcomes).

Years included in the search:

The date of the most recent search was 13 February 2012

Were additional RCTs on the subject published since then? NO.

Methodological rigor:

Data extraction by more than one researcher: YES.

Search strategy detailed: YES.

Untoward restriction of search parameters: NO.

Was the methodological rigor of the individual studies appraised, and did it serve for analysis? YES.

Were sub-group analyses of interest performed? NA.

Was heterogeneity tested? This was not required as there was only one study eligible for this systematic review.

No of included studies: 1

No of included patients: 33

Mean number of patients per study: 33

Main outcomes:

- **PEG versus NG**

Primary outcome:

Nutritional status: at six weeks post-treatment the PEG fed patients had a significant beneficial weight gain compared to the NG fed patients ($P = 0.001$). However, the NG fed patients had lower tricep skin-fold thickness suggesting that NG fed patients' loss of weight was predominantly due to loss of fat. By six months post-treatment the difference in weight was no longer statistically significant.

Secondary outcomes:

Complications arising from the enteral feeding device: There was no difference in chest infection rates between the two groups (27% in PEG group and 33% in NG group). Twelve NG patients experienced feeding tube dislodgement, with no tube dislodgement in the PEG group. Four of the PEG group had site infections.

User satisfaction of feeding device: Patient satisfaction was measured using a questionnaire and there was no significant difference in patient satisfaction between the two groups.

Length of time (in days) enteral feeding is required: The duration of PEG feeding (range 56 to 488 days) was significantly longer than for the NG group (range 23 to 136 days) ($P = 0.0006$).

NNT for main outcome: not applicable.

GRADE: low quality

Study limitation: negligible

Inconsistency: serious

Imprecision: serious

Publication bias: impossible to address

Conclusions:

There is no sufficient evidence to determine the optimal method of enteral feeding for patients with head and neck cancer receiving radiotherapy and/or chemoradiotherapy. Further trials of the two methods of enteral feeding, incorporating larger sample sizes, are required.

E5 - Nutrition support for bone marrow transplant patients (systematic review)

[PMID: 19160213](#)

Reference: Murray SM, Pindoria S. Nutrition support for bone marrow transplant patients. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD002920. DOI: 10.1002/14651858.CD002920.pub3.

Objectives:

To determine the efficacy of any form of enteral or parenteral nutrition support given to patients receiving bone marrow transplantation.

Studies: Inclusion criteria:

Randomized controlled trials

Quasi-randomized controlled trials.

Intervention:

RCTs comparing one type or mode of nutrition support (enteral or parenteral) with another or with an intravenous solution of glucose/saline.

Aldamiz 1996: 12- Continuous PN, 12- Cyclical PN. Start criteria: Day +1 after BMT, Stop criteria: not clear.

Anderson 1998: 98- Oral mouth rinse glutamine 1 g/m²x4/day, 95- Oral mouth rinse glycine 1g/m²x4/day. Start criteria: 7 days before BMT. Stop criteria: 28 days after BMT.

Aquino 2005: 57- Oral glutamine, 63- Oral glycine 2g/m² (max 4g/day) dissolved in 500 ml solution administered twice daily.

Brown 1998: 18- PN + Glutamine (50 g glutamine/day). 16- Standard PN (no glutamine).

Start criteria: day -7 before BMT. Stop criteria: on day discharge.

Charuhas 1997: 128- PN. 130- IV Hydration. Start criteria: at discharge. Stop criteria: oral intake >85% energy requirements, for 3 consecutive days.

Coghlin Dickson 2000: 29- Oral Glutamine (10 g x 3 doses/day). 29- Placebo (Sucrose, 10 g x 3/day).

Cope 1997: 23- EN 40- PN. Start/Stop criteria: not stated.

Jebb 1995: 12- Oral mouth rinse glutamine, 4g x 4/d. 12- Oral mouth rinse polycal, 4g x 4/d.

Start criteria: day +1 after BMT. Stop criteria: until mucositis resolved or discharge.

Jimenez 1999: 19 - 22.5% BCAA* + 20%LCT. 26 - 45% BCAA* + 20%LCT* 17- 45% BCAA*+ 20%MCT*/ LCT*.

Lenssen 1987: 20 - 23%BCAA* (PN). 20 - 45% BCAA*(PN). Start criteria: pre BMT (day not specified). Stop criteria: oral protein >10g/day.

Lenssen 1998: 253- Standard PN Lipid. 259- Low dose PN Lipid. Start criteria: oral energy intake < basal requirements. Stop criteria: oral energy intake >10kcal/kg/day.

Lough 1990: 14- PN. 15- IV Hydration. Start criteria: day+1 after BMT. Stop criteria: 15 days after BMT.

MacBurney 1994: 22- PN+ Glutamine (0.57 g/kg/day). 21- Standard PN (no glutamine). Start criteria: day+1 after BMT. Stop criteria: oral intake > 50% energy requirements for 3 days.

Malhotra 1996: Elemental diet Vs. Normal ad lib diet. Start criteria: 72 hours pre high dose therapy. Stop criteria: not stated.

Mulder 1989: 11- PN. 11- PN+EN. Start criteria: day + 4 after BMT. Stop criteria: leukocyte count > 1x 10⁹.

Muscaritoli 1998: 35- PN Glucose. 31- PN Lipid. Start criteria: day +1 after BMT.

Stop criteria: day + 16 after BMT.

Pytlik 2002: 21- PN + glutamine. 19- PN + placebo. Start criteria: day +1 after BMT. Stop criteria: day +14 or to discharge.

Roberts 2003a: 27- PN. 28- Oral diet (also given IV fluids). PN started day -1 were also allowed ad lib oral diet.

Santos 2001: group 1: PN with lipid for 4 days and then PN without lipids for 4 days. group 2: PN without lipids for 4 days and then PN with lipids for 4 days. The composition of the PN lipid solution was given as 0.8 g/kg/d of 50:50 mixture of medium and long chain triglycerides.

Scheltinga 1991: 10- PN+Glutamine (0.57g/kg/day), 10- Standard PN (no glutamine). Start criteria: day+1 after BMT. Stop criteria: oral intake > 50% energy requirements for 3 days.

Schloerb 1993: 16- PN+ Glutamine (2830 mg glutamine/100 ml), 13- Standard PN (no glutamine). Start criteria: unclear, Stop criteria: oral intake >50% energy requirements.

Schloerb 1999: 35- Oral Glutamine, 10g x 3 /day, 33- Oral/PN Glycine, 10g x 3/day. Start criteria: unclear. Stop criteria: oral intake >50% energy requirement.

Szeluga 1987: 31- PN, 30- EN. Start criteria: day before BMT. Stop criteria: 28 days after BMT.

Takatsuka 2002: 8- eicosapentaenoic acid (EPA) from day -21 to day 180 post BMT. 9- received nil.

Weisdorf 1987: 71- PN, 66- IV Hydration. Start criteria: 7 days before BMT.

Stop criteria: 4 weeks post BMT.

Young 1993: 13- PN + Glutamine (0.57g glutamine/kg/day), 10- Standard PN. Start criteria: Day + 1 after BMT. Stop criteria: oral intake >50% energy requirements.

Young 1997: 10- PN, 10- EN. Start criteria: weight loss >10% nutritional requirements inadequate. Stop criteria: not stated.

Ziegler 1992: 24- PN+ Glutamine (0.57g/kg/day) 21 Standard PN (no glutamine). Start criteria: day+1 after BMT. Stop criteria: oral intake > 50% energy requirements for 3 days.

Ziegler 1998: 9- PN+ Glutamine (0.57 g/kg/day), 11- Standard PN (no glutamine). Start criteria: day+1 after BMT, Stop criteria: not stated.

Population:

Participants of all ages receiving any type of bone marrow transplant.

Aldamiz 1996: 24 recruited patients. BMT type: 6 Allogeneic and 18 Autologous. Disease type not specified. Age mean(\pm SD) years: Continuous PN = 37(\pm 9.3) Cyclical PN = 35.4(\pm 11.1).

Anderson 1998: 195 recruited patients. BMT type: 106 Allogeneic and 87 Autologous. Disease type: Haem malignancy: 106, Haem disorders: 8, Solid tumour: 62, Inherited disorders: 17. Age (yrs) - mean (range): Oral Glutamine = 29 (1-62) Oral Placebo = 27 (1-62).

Aquino 2005: 120 children recruited. BMT type: 54 Allogeneic and 66 Autologous.

Disease type: Haem malignancy: 64, Solid tumour: 48, Haem abnormalities: 10. Age (yrs) – mean: Oral Glutamine = 8.9 Oral Glycine = 10.5.

Brown 1998: 34 recruited patients. BMT type: 7 Allogeneic and 27 Autologous. Disease type: 34 Haem malignancy. Age- years, median (range): Glutamine = 41(19-62) Control = 32 (16-55).

Charuhas 1997: 265 BMT outpatients recruited. BMT type: 212 Allogeneic and 53 Autologous. Disease type: 241 Haem malignancy, 2 Haem disorders, 12 solid tumour, 3 Inherited disorders. Age (range) years: PN group = 2.7 - 64.2 yrs, IV hydration = 2.1 - 63.1 yrs.

Coghlin Dickson 2000: 58 recruited patients. BMT type: 24 Allogeneic and 34 Autologous. Disease type: 59 Haem malignancy. Age (range) years: Glutamine group: 17-58 yrs. Control: 21-59 yrs.

Cope 1997: 63 recruited patients. BMT type: not specified. Disease type: not specified. Age range not specified.

Jebb 1995: 24 recruited patients. BMT type: 24 Autologous. Disease type: 24 Haem malignancy. Age range not specified.

Jimenez 1999: 62 recruited patients.

Lenssen 1987: 40 recruited patients. BMT type: 40 Allogeneic. Disease type: 40 Haem malignancy. Age median(range) years: 23% BCAA*, PN = 28.5 (18-48). 45% BCAA*, PN = 28.5 (18-49).

Lenssen 1998: 512 recruited patients. BMT type: 419 Allogeneic and 93 Autologous. Disease type: 512 Haem malignancy. Age mean + (range) years: Standard PN Lipid group = 35 (0.5-65). PN+ low dose lipid group = 35 (0.4 -67).

Lough 1990: 29 recruited patients. BMT type: 17 Allogeneic and 12 Autologous. Disease type: 29 Haem malignancy. Age range: 14-44 yrs.

MacBurney 1994: 43 recruited patients. BMT type: 43 Allogeneic. Disease type: not specified. Age range: not specified.

Malhotra 1996: 45 recruited patients. BMT type: not specified. Disease type: not specified. Age range: not specified.

Mulder 1989: 22 recruited patients. BMT type: 22 Autologous. Disease type: 22 solid tumour. Age (range) years: PN group = 28- 54 yrs. EN group = 21- 56 yrs.

Muscaritoli 1998: 66 recruited patients. BMT type: 66 Allogeneic. Disease type: 66 Haem malignancy. Age mean(range) years: Glucose based PN = 30.5 (15-47). Lipid based PN = 29.1 (16-44).

Pytlik 2002: 40 recruited patients. BMT type: 40 Autologous. Disease type: Haem malignancy -32, Solid tumour – 4, Other inherited conditions -4. Age range (mean +/-sd): PN and Glutamine= 49 +/- 12. Control: Placebo= 42+/-14.

Roberts 2003a: 55 recruited patients. BMT type: 55 Autologous. Disease type: Solid tumours (Breast cancer)- 55. Mean Age: PN group:41.6 yrs, Oral diet group:45.6.

Santos 2001: 10 recruited patients. BMT type: 10 allogeneic. Disease type: all had haematological malignancies. Mean age: 36.7 years (sd 12.0).

Scheltinga 1991: 20 recruited patients. BMT type: 20 Allogeneic. Disease type: 20 Haem malignancy. Age(years)- mean(SEM): PN + Glutamine: 36+/-3, Standard PN: 33+/-3.

Schloerb 1993: 29 recruited patients. BMT type: 13 Allogeneic and 16 Autologous. Disease type: 26- Haem malignancy, 3- Solid tumour. Age (years) - mean (range): PN + Glutamine: 35.6(19-55), Standard PN - 37.6 (19-55).

Schloerb 1999: 66 recruited patients. BMT type:19 Allogeneic and 47 Autologous. Disease type: 43- Haem malignancy, 23- Solid tumour. Age: all > 17 yrs.

Szeluga 1987: 65 recruited patients. BMT type: 46 Allogeneic and 15 Autologous. Disease type: 45- Haem malignancy, 16- other miscellany of disorders. Age (years): PN = 21 > 19 yrs, 10 < 19 yrs. EN group = 21 > 19 yrs, 9 < 19 yrs.

Takatsuka 2002: 17 recruited patients. BMT type: 17 Allogeneic. Disease type: 17- haematological malignancy. Age: 1- < 17yrs, 16- >= 17yrs.

Weisdorf 1987: 137 recruited patients. BMT type: 104 Allogeneic and 32 Autologous. Disease type: 118- Haem malignancy, 8- Solid tumour, 3- Inherited disorder, 50- Haem abnormalities, 1- other malignancy, 2- unaccounted. Age - years, mean (+/-SD): PN group = 20 (+/- 12.9), IV hydration = 18.3 (+/- 12.9).

Young 1993: 23 recruited patients. BMT type: 23 Allogeneic. Disease type: 23- Haem malignancy. Age (yrs) (mean range): PN + Glutamine = 36 (20-49), Standard PN = 30 (22-44).

Young 1997: 20 recruited patients. BMT type: 20 Allogeneic. Disease type: not specified. Age: not specified.

Ziegler 1992: 45 recruited patients. BMT type: 45 Allogeneic. Disease type: 45 Haem malignancy. Age (years) - mean (range): PN + Glutamine = 32.1(20-48), Standard PN: 35.5(20-49).

Ziegler 1998: 20 recruited patients. BMT type: 20 Allogeneic. Disease type: 20 Haem malignancy. Age (years) - mean (+/- SE): PN + Glutamine: 36 (+/- 3), Standard PN- 35 (+/-3).

Primary outcomes:

- Hospital duration- e.g. mean duration admission to discharge or from day 0 to discharge home.
Mucositis- mean number of days patient groups had some degree of mucositis from start to end of study.
GVHD- number of patients who developed > grade 2 graft versus host disease (GVHD).
Nutritional status- difference in mean % change in body weight from start to end of study between the trial groups.

Duration of nutritional intervention/time to resume adequate oral intake.

Neutropaenia- mean number of days to achieve normal neutrophil level after day of BMT, day 0.

Line infection- number of patients who developed line infections from start to the end of the study.

Number of patients with positive blood cultures.

Survival up to 100 days post BMT.

Survival beyond 100 days or two years post BMT

Primary outcomes as defined by us:

Survival

Quality of life

Performance

Completion of therapy

Complications /LOS

Does it appear in the SR and meta-analysis? Partially.

Years included in the search:

The Cochrane Library: Issue 4, 2000, subsequent search Issue 2, 2006.

MEDLINE: 1966 to 2000, subsequent search June 2006.

EMBASE: 1988 to 2000, subsequent search June 2006.

CINAHL: 1982 to 2000, subsequent search June 2006.

Were additional RCTs on the subject published since then? YES – but included in other systematic reviews (PMID: 18317456 Efficacy of glutamine-supplemented parenteral nutrition on short-term survival following allo-SCT: a randomized study, PMID: 19497646 Olive oil-based intravenous lipid emulsion in pediatric patients undergoing bone marrow transplantation: a short-term prospective controlled trial).

Methodological rigor:

Data extraction by more than one researcher: YES

Search strategy detailed: YES

Untoward restriction of search parameters: NO

Was the methodological rigor of the individual studies appraised, and did it serve for analysis? YES

Were sub-group analyses of interest performed? YES

Was heterogeneity tested? YES

Was an attempt to explain heterogeneity made? YES

Was the meta-analysis conducted according to the degree of heterogeneity? A systematic review.

No of included studies: **29**

No of included patients: **2149**

Mean number of patients per study: **74**

Main outcomes:

Oral glutamine versus oral placebo studies:

Hospital duration: Mean Difference (IV, Fixed, 95% CI): -2.39 days [-6.11, 1.34].

Nutritional status: Mean Difference (IV, Fixed, 95% CI): 5.73% of change in body weight [-7.09, 18.55].

Duration of nutritional intervention/time to resume adequate oral intake: Mean Difference (IV, Fixed, 95% CI): 1.00 day [-4.42, 2.43].

Neutropaenia: Mean Difference (IV, Fixed, 95% CI): 6.82 days [1.67, 11.98].

Number of patients with positive blood cultures: Peto Odds Ratio (Peto, Fixed, 95% CI): 1.18 [0.39, 3.62].

Survival up to 100 days post BMT: Peto Odds Ratio (Peto, Fixed, 95% CI): 1.51 [0.88, 2.60].

PN + glutamine versus standard PN:

Hospital duration: Mean Difference (IV, Fixed, 95% CI): 0.22 days [-1.29, 1.72].

Mucositis: Mean Difference (IV, Fixed, 95% CI): -0.02 days [-0.48, 0.45].

Nutritional status: Mean Difference (IV, Fixed, 95% CI): -0.34% of change in body weight [-1.40, 0.72].

Duration of nutritional intervention/time to resume adequate oral intake: Mean Difference (IV, Fixed, 95% CI): 0.36 days [-1.63, 2.35].

GVHD: Peto Odds Ratio (Peto, Fixed, 95% CI): 0.57 [0.18, 1.83].

Neutropaenia: Mean Difference (IV, Fixed, 95% CI): 0.57 days [-1.63, 2.76].

Survival up to 100 days post BMT: Peto Odds Ratio (Peto, Fixed, 95% CI): 0.69 [0.16, 2.97].

Number of patients with positive blood cultures: Peto Odds Ratio (Peto, Fixed, 95% CI): 0.46 [0.20, 1.04].

PN versus IV hydration:

Hospital duration: Mean Difference (IV, Fixed, 95% CI): 3.30 days [-0.38, 6.98].

Line infection: Peto Odds Ratio (Peto, Fixed, 95% CI): 21.23 [4.15, 108.73].

Nutritional status: Difference (IV, Fixed, 95% CI): 2.81% of change in body weight [1.34, 4.29].

Duration of nutritional intervention/time to resume adequate oral intake: Mean Difference (IV, Fixed, 95% CI): 12.2 days [8.66, 15.74].

Survival up to 200 days post BMT: Peto Odds Ratio (Peto, Fixed, 95% CI): 2.10 [0.48, 9.18].

Oral eicosapentaenoic acid supplementation versus nil:

GVHD: Odds Ratio (M-H, Fixed, 95% CI): 12.09 [0.52, 280.40].

GRADE: good quality

Study limitation: negligible

Inconsistency: medium

Imprecision: medium

Publication bias: no

Conclusions:

Routine use of parenteral nutrition and glutamine for bone marrow patients predicted to have prolonged gastrointestinal failure could be considered.

Caution in the routine use of PN is still required because of the increased risk of line infection.

Use of intravenous fluids and oral diet should be considered as a preference to parenteral nutrition, however, in the event of a patient suffering severe gastrointestinal failure even with a trial of enteral feeding, PN with the addition of glutamine could be considered.

E6: Glutamine for chemotherapy induced diarrhea: a meta-analysis

PMID: 22705427

Reference: Sun J, Wang H, Hu H. Glutamine for chemotherapy induced diarrhea: a meta-analysis. Asia Pac J Clin Nutr. 2012; 21(3):380-5.

Objectives:

To clarify the effectiveness of prophylactic glutamine in patients requiring chemotherapy comparing the effects of glutamine and placebo on chemotherapy-induced diarrhea. Bone marrow transplant (BMT) patients were also included in this protocol.

Studies Inclusion criteria:

Randomized controlled trials.

Intervention:

Prophylactic glutamine, IV or oral. The dosages ranged from 16 gr/day to 40 gr/day, the higher doses given IV.

Population:

Patients requiring chemotherapy.

Primary outcomes:

Duration of diarrhea.

Severity of diarrhea.

Primary outcomes as defined by us:

Survival

Quality of life

Performance

Completion of therapy

Complications /LOS

Does it appear in the SR and meta-analysis? NO.

Years included in the search: Not mentioned.

Methodological rigor:

Data extraction by more than one researcher: YES.

Search strategy detailed: Partially.

Untoward restriction of search parameters: YES: Only studies written English or Chinese were searched.

Was the methodological rigor of the individual studies appraised YES, and did it serve for analysis? NO.

Were sub-group analyses of interest performed? YES.

Was heterogeneity tested? YES.

Was an attempt to explain heterogeneity made? NO.

Was the meta-analysis conducted according to the degree of heterogeneity? YES.

No of included studies: 8

No of included patients: 298

Mean number of patients per study: 37

Main outcomes:

Duration of diarrhea: glutamine significantly reduced the duration of diarrhea compared with placebo (WMD, -1 days; 95% confidence interval (CI), -1.73, -0.26). In the subgroup analysis, the authors found that oral glutamine significantly reduced the duration of diarrhea (WMD, -1.06 days; 95% CI, -2.01, -0.11), but intravenous glutamine was ineffective in this regard (WMD, -0.89; 95% CI, -2.07, 0.28).

Severity of diarrhea: glutamine did not improve the severity of diarrhea (WMD, -0.49; 95% CI, -1.36, 0.39).

NNT for main outcome:

GRADE: low quality

Study limitation: major

Inconsistency: serious (discrepancy between duration and severity)

Imprecision: negligible

Publication bias: impossible to address

Conclusions:

The authors concluded that glutamine could reduce the duration of diarrhea, but it could not improve its severity.

E7: Systematic review and meta-analyses of studies of glutamine supplementation in haematopoietic stem cell transplantation

PMID: 19270730

Reference: Crowther M, Avenell A, Culligan DJ. Systematic review and meta-analyses of studies of glutamine supplementation in haematopoietic stem cell transplantation. Bone Marrow Transplant. 2009 Oct; 44(7):413-25. doi: 10.1038/bmt.2009.41. Epub 2009 Mar 9.

Objectives:

The purpose of this study was to perform an up-to-date systematic review with the aim of clarifying the function of glutamine supplementation in haematopoietic stem cell transplantation (HSCT).

Studies Inclusion criteria:

Randomized controlled trials (RCTs) (the intention was to include non-randomised trials as well but they were excluded once it was clear that enough RCT are available).

Intervention:

Studies that compared interventions with glutamine and interventions with no-glutamine (control). Glutamine was administered either orally or i.v.

Population:

Patients undergoing haematopoietic stem cell transplantation (HSCT).

Primary outcomes:

Mortality- mortality was reported as deaths up to and including D100 and deaths after D100.

Infections- infections were reported in several ways either as direct measures (number of clinical infections (a clinical diagnosis of infection not necessarily requiring a positive culture) or number of positive cultures) or surrogate measures (days of fever, days of antibiotics or mean maximum daily temperature).

Mucositis- there were several different outcomes measuring mucositis: average mucositis score, days of mucositis, presence of severe mucositis, maximum mucositis score and days of opioids (as a surrogate marker).

GVHD.

Time to neutrophil recovery.

Length of hospital stay.

Time to platelet recovery.

Relapse after 6 months.

Weight change.

Days of TPN.

Blood transfusions.

Primary outcomes as defined by us:

ECOG / QoL

Survival

Complications /LOS

Does it appear in the SR and meta-analysis? YES.

Years included in the search:

Medline, Embase, Cinahl, CAB abstracts and the Cochrane Controlled Trials Register: From January 1970 until July 2008.

Hand searching: January 1990–February 2008.

Conference abstracts: January 1997–February 2008.

The European Society of Blood and Marrow Transplantation: January 1999–February 2008.

The European Haematology Society: January 2003–February 2008.

Ongoing studies were identified through the National Institute of Health website¹² and the Current Controlled Studies website

Were additional RCTs on the subject published since then? NO

Methodological rigor:

Data extraction by more than one researcher: YES

Search strategy detailed: YES

Untoward restriction of search parameters: NO

Was the methodological rigor of the individual studies appraised, and did it serve for analysis? YES

Were sub-group analyses of interest performed? YES

Was heterogeneity tested? YES

Was an attempt to explain heterogeneity made? YES

Was the meta-analysis conducted according to the degree of heterogeneity? YES

No of included studies: 22

No of included patients: 2331

Mean number of patients per study: 122

Main outcomes:

Mortality: Three studies (379 patients) reported mortality up to D100 with oral glutamine and found no statistically significant effect (RR=0.94, 95% CI 0.58–1.51, $I^2=36\%$). Five studies reported mortality up to D100 (193 patients) with i.v. glutamine and similarly demonstrated no effect (RR=0.78, 95% CI 0.43–1.43, $I^2=0\%$). When oral and i.v. studies were combined, glutamine had no effect on mortality up to D100 (RR=0.88, 95% CI 0.60–1.27, $I^2=0\%$). One study reported mortality after D100 with oral glutamine. Three studies (137 patients) reported mortality after D100 with i.v. glutamine; there appears to be no statistically significant effect of glutamine (RR=1.12, 95% CI 0.65–1.92) but with considerable heterogeneity ($I^2=78\%$).

Two studies of autologous transplants only suggested an increased mortality with glutamine (combined effect RR=3.21, 95% CI 1.17–8.79, $I^2=0\%$) whereas the single study that suggested decreased mortality investigated allogeneic transplants only and the excess deaths in the control arm all occurred in the first 100 days.

Infections: Two studies reported number of clinical infections with oral glutamine (75 patients) and demonstrated no statistically significant effect (RR=0.85, 95% CI 0.44–1.64, $I^2=0\%$). Glutamine (i.v.) was investigated in five studies (199 patients), which demonstrated a reduction in the number of clinical infections with glutamine (RR 0.75, 95% CI 0.58–0.97, $I^2=26\%$). The overall effect of i.v. and oral glutamine combined was a reduction in clinical infections (RR 0.77, 95% CI 0.60–0.98, $I^2=0\%$). Sensitivity analysis revealed that removing studies that either did not have adequate allocation concealment, did not perform intention-to-treat analysis or were commercially sponsored meant that the results were no longer statistically significant although in each case only three studies were left.

The number of positive cultures was reported by two studies using oral glutamine (172 patients) and demonstrated no statistically significant effect of glutamine (RR=1.09, 95% CI 0.69–1.57, $I^2=0\%$). Four studies reported a number of positive cultures with i.v. glutamine and demonstrated a reduction (RR=0.72, 95% CI 0.57–0.91, $I^2=0\%$). Overall, the effect of i.v. and oral glutamine combined was a trend towards fewer positive cultures (RR=0.83, 95% CI 0.67–1.02, $I^2=28\%$).

Three studies of i.v. glutamine reported days of fever in 116 patients. One study only reported 'no statistical difference' and therefore the data could not be used. The two studies when combined demonstrated an MD of 0.92 days (95% CI -0.20 to 2.04, $I^2=0\%$). Five studies (182 patients) reported days of antibiotics, all using i.v. glutamine. One only reported 'no statistical difference'. Combining the results revealed no statistically significant effect on days of antibiotics with glutamine (MD -0.31 days, 95% CI -1.88 to 1.27, $I^2=0\%$).

Mean maximum daily temperature was reported in two studies of i.v. glutamine (74 patients). The overall effect was no difference in the temperature between the two groups (MD -0.05 C, 95% CI -0.25, 0.15, $I^2=0\%$).

Mucositis: Three studies compared oral glutamine with placebo (329 patients) and reported average mucositis score. The overall effect was a reduction in the average mucositis score (SMD -0.38, 95% CI -0.59 to -0.16, $I^2=27\%$). Glutamine (i.v.) was studied in four studies (145 patients) and demonstrated no statistically significant effect of glutamine (SMD 0.08, 95% CI -0.25, 0.41, $I^2=40\%$). The overall effect of oral and i.v. glutamine was a reduced average mucositis score (SMD -0.24, 95% CI -0.42 to -0.05, $I^2=48\%$). Subgroup analyses revealed a trend towards a lower average score if the glutamine was started before D0 compared to after ($P=0.09$). Four studies (131 patients) reported days of mucositis as an outcome with oral glutamine (SMD -0.26 days, 95% CI -1.02–0.50, $I^2=59\%$). Adding the only i.v. glutamine study gave an overall effect of an SMD of -0.31 days (95% CI -0.82 to 0.20, $I^2=45\%$). Two studies with 52 patients on oral glutamine reported the presence of severe mucositis. Meta-analysis found an RR of 0.81 (95% CI 0.58–1.14, $I^2=46\%$). Two studies reported maximum mucositis score for i.v. glutamine (87 patients) SMD -0.09 (95% CI -1.15 to 0.96, $I^2=83\%$). When these three studies are combined the overall result was SMD -0.09 (95% CI -0.61 to 0.43, $I^2=67\%$). Four studies of oral glutamine (352 patients) reported days of opioids. The combined effect was fewer days of opioids with oral glutamine (MD -1.95 days, 95% CI -3.66 to -0.25, $I^2=82\%$). When the i.v. and oral studies were combined, overall there was no

statistically significant effect on days of opioids with glutamine (MD -0.21 days, 95% CI -1.52 to 1.10, $I^2=84\%$). Subgroup analysis found that a greater reduction in days of opioids was seen if the glutamine was given before D0 ($P=0.03$). Both removal of non-blinded assessors and commercially sponsored studies reduced the effect.

GVHD: Two studies investigating oral glutamine (75 patients) reported GVHD and found a reduction in GVHD with glutamine (RR=0.42, 95% CI 0.21–0.85, $I^2=13\%$). GVHD was reported in four studies of i.v. glutamine (164 patients) and these found no statistically significant effect of glutamine (RR=0.85, 95% CI 0.60–1.22, $I^2=39\%$).

The overall effect of i.v. and oral glutamine on GVHD was a reduction in GVHD (RR=0.73, 95% CI 0.53–0.99, $I^2=47\%$).

Subgroup analysis suggested a benefit for starting glutamine before D0 with a greater overall reduction in GVHD ($P=0.012$).

Time to neutrophil recovery: Five studies (160 patients) investigated oral glutamine and time to neutrophil recovery, two studies reported data in an unusable format, 'no statistical difference' and no spread of data was given. Oral glutamine demonstrated no statistically significant effect (MD -0.39 days, 95% CI -1.79 to 1.01, $I^2=0\%$). Time to neutrophil recovery was reported in seven studies with i.v. glutamine (276 patients), one study reported spread of data as range and hence could not be used. When the studies were combined the result was MD -0.76 days (95% CI -1.85 to 0.34, $I^2=28\%$). Overall the result of oral and i.v. glutamine was MD -0.62 days (95% CI -1.48 to 0.25, $I^2=0\%$). Subgroup and sensitivity analysis demonstrated a reduced effect of glutamine when non-assessor blinded studies were removed but an increased effect when studies without intention to treat were removed.

Length of hospital stay: Four studies reported length of stay with oral glutamine (246 patients). The overall effect of oral glutamine was a trend towards a reduced length of stay (MD -2.59 days, 95% CI -5.21 to 0.02, $I^2=0\%$). Length of stay was an outcome in eight studies with i.v. glutamine and the overall effect was not statistically significant, MD 0.41 days (95% CI -0.89 to 1.71, $I^2=42\%$). Overall, when oral and i.v. glutamine were combined, there was no effect of glutamine on length of stay (MD 0.41 days, 95% CI -0.89 to 1.71, $I^2=36\%$). Subgroup analysis suggested that the effect of increased length of stay is mainly from one study and is therefore limited to autologous transplants and to studies published after 2000. The addition of missing data reduces the effect of glutamine.

Time to platelet recovery: One study using oral glutamine reported time to platelet recovery. Four studies with i.v. glutamine (148 patients) reported time to platelet recovery, although only two had usable data, they demonstrated no statistically significant effect of glutamine (MD 0.33 days, 95% CI -2.29 to 2.93, $I^2=0\%$). When oral and i.v. glutamine were combined the result was MD 0.41 days (95% CI -2.18 to 2.99, $I^2=0\%$).

Relapses after 6 months: Two studies (74 patients) using oral glutamine reported patients with relapses (RR 1.00, 95% CI 0.55–1.82, $I^2=75\%$). Two studies (70 patients) found increased number of patients with relapses with i.v. glutamine (RR

2.91, 95% CI 1.34–6.29, $I^2=0\%$). When oral and i.v. were combined, glutamine appeared to increase the number of patients with relapses (RR 1.61, 95% CI 1.01–2.55, $I^2=64\%$). There were too few studies to investigate heterogeneity further but the two i.v. studies included autologous transplants only. When random effect measures were used the overall RR was not significant, RR 1.50 (95% CI 0.64–3.50).

Weight change: Change in weight was reported as either percentage weight change or actual weight change. Hence, SMDs were used. One study reported weight change with oral glutamine. Three studies reported weight change with i.v. glutamine (100 patients) and when combined the SMD was 0.17 (95% CI -0.43 to 0.78, $I^2=56\%$). Overall there was a trend towards weight gain with oral and i.v. glutamine (SMD 0.58, 95% CI -0.08 to 1.24, $I^2=71\%$).

Days of TPN: Five studies reported days of TPN with oral glutamine (246 patients), the combined effect was no statistically significant difference in the days of TPN with oral glutamine (MD -0.69 days, 95% CI -3.79 to 2.41, $I^2=70\%$). On investigation, the heterogeneity seemed to be coming from one study. There was no obvious reason for this, the MD with this study excluded was -5.44 days (95% CI -9.69 to -1.19, $I^2=0\%$). Five studies reported days of TPN with i.v. glutamine (195 patients) and the combined effect was MD -0.89 days (95% CI -2.61 to 0.82, $I^2=20\%$). The overall effect of i.v. and oral glutamine on days of TPN was MD -0.84 days (95% CI -2.35 to 0.66, $I^2=53\%$).

Blood transfusions: Three studies (114 patients) reported the number of red cell transfusions with i.v. glutamine and the combined effect was a trend towards more transfusions in the glutamine arm (MD 1.05 transfusions, 95% CI -0.35 to 2.44, $I^2=0\%$). Four studies (142 patients) reported number of platelet transfusions, although one study's data could not be used as the investigators stated that there was 'no statistically significant

difference'. Overall there was no effect of glutamine on platelet transfusions (MD 0.22 transfusions, 95% CI -1.00 to 1.44, $I^2=0\%$).

NNT for main outcome: Not applicable

GRADE: moderate quality

Study limitation: minor

Inconsistency: minor

Imprecision: major

Publication bias: impossible to perform

Conclusions: glutamine may have beneficial effects in HSCT. Oral glutamine may reduce mucositis and GVHD whereas i.v. glutamine may reduce infections. However, these findings are based on mainly small, poorly reported studies. Although a relatively cheap intervention, with the possibility of increased relapse, the authors feel that the routine use of glutamine cannot be recommended at present. For definitive answers larger well-designed RCTs are required, which report detail according to the CONSORT statement.

E8: Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia

[PMID: 17253515](#)

Reference: Dewey A, Baughan C, Dean T, Higgins B, Johnson I. Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD004597

Objectives:

The objective of this review was to determine the effectiveness and safety of the omega-3 fatty acid eicosapentaenoic acid (EPA) to alleviate cachexia and related symptoms in patients with incurable or advanced cancer.

Studies Inclusion criteria:

Randomised controlled trials (RCTs)

Intervention:

This review focuses on the following treatment comparisons:

Oral fish oil supplementation (containing EPA) regardless of type (i.e., capsules or liquid supplementation) or dosage (in terms of level of EPA) versus placebo;

Oral fish oil supplementation (containing EPA) regardless of type and at any dose versus active matched control (without EPA).

Bruera 2003: 60 patients with mixed cancer tumour types were randomised to receive 18 gelatin capsules of 1000 mgs of fish oil (each containing: 180 mg EPA, 120 DHA (docosahexaenoic acid) with the addition of 1mg of Vitamin E); or 1000 mgs of a placebo

capsule (olive oil). After random assignment of 19 patients (nine fish oil and ten placebo) high level of complaints of vomiting in approximately ten patients (in both arms) suggested that these patients were unable to tolerate 18 capsules/day. The trial protocol was amended to six capsules/day with encouragement

to take up to 18 capsules/day. The trial lasted two weeks with assessments (subjective and objective measurements) performed at baseline and on day 14.

Gogos 1998: 64 patients with mixed cancer tumour types were randomised to receive either 18 g of fish oil capsules (each containing: 170 mg EPA and 115 mg DHA) or placebo (sugar tablets). The supplements were taken as six capsules three times daily. Patients in the fish oil arm also received 200 mgs of Vitamin E daily. The trial lasted for 40 days. Assessment took place at the end of the 40 days study period.

Zuijdgeest 2000: 17 patients with mixed cancer tumour types and 16 healthy subjects were randomised to receive either 6 g of EPA ethyl ester capsules or placebo capsules (containing 6 g of oleic acid ethyl ester capsules). The supplements were provided in 0.5 capsules and taken as four capsules three times daily. The trial lasted for one week with assessment (subjective and objective measurements) performed at baseline, day two and seven.

Fearon 2003: 200 patients with pancreatic cancer were randomised to receive either two cans of an oral nutritional supplement which provided 2.2 g EPA (each can providing 1.1 g EPA, plus antioxidants Vitamin A, E, C and selenium, 310 kcal, 16 g protein and 6 g fat) or two cans of an identical supplement, but without the addition of EPA and enhanced antioxidants. The trial lasted for eight weeks with assessment (both subjective and objective measurements) performed at baseline, four and eight weeks.

Jatoi 2004: 421 patients with mixed cancer tumour types were randomised to one of three arms as follows:

- Arm one - received a twice daily EPA supplement (providing 1.09 g per can) plus placebo liquid suspension (instead of Megestrol Acetate liquid suspension);
- Arm two - received Megestrol acetate (MA) liquid suspension (600 mg/day) plus twice daily a matched nutritional supplement (without EPA);

- Arm three - received a combination of MA plus the same twice daily EPA supplement as Arm one.

The median number of days on the study was slightly more than three months for the arms as a whole. All patients were assessed weekly for four weeks and then monthly with patients continuing treatment as long as both the patient and treating oncologist considered it beneficial, or acceptable, to the patient.

Population:

Trials of patients with a confirmed diagnosis of incurable or advanced cancer and either a reported weight loss of 5% and above or a clinical diagnosis of cachexia (independent of gender, age or race) were included:

Bruera 2003: randomised 91 patients (46 to fish oil and 45 to placebo) with the following characteristics: advanced cancer (defined by locally recurrent or metastatic disease) more than 5% pre-illness weight loss (time period of weight loss not specified), presence of anorexia but the ability to maintain oral food intake over the two-week study period) as well as normal cognitive status. Cancer types included: genitourinary, breast, gastrointestinal, lung, hematologic, head and neck and sarcoma tumours. At baseline, there was no significant difference between arms.

Gogos 1998: randomised 64 patients with generalised solid tumour of the following cancer types: breast, gastrointestinal, lung, liver and pancreas. Each arm was then sub-divided into the following two subgroups, those considered to be in a good nutritional state or well nourished (WN) and malnourished (MN). Patients in the well-nourished (WN) subgroups in both arms included patients who had a less than 10% weight loss over the previous six months, serum albumin of more than 30 g/L, serum transferrin of more than 2.0 g/L and a Karnofsky Performance status of more than 60. Patients in the malnourished (MN) subgroups of both arms included patients that had a weight loss of more than 10% during the previous six months, serum albumin of less than 30 g/L, serum transferrin of less than 2.0 g/L and Karnofsky Performance status of less than 60. In addition a group of 15 healthy individuals served as controls.

Zuijdgeest 2000: randomised 17 patients with different cancer tumour types including: gastrointestinal tract, pancreatic, rectal, renal, breast, oesophageal, lung, mesothelioma, cervical, carcinoid and adenocarcinoma of unknown primary site. All but one patient in the fish oil arm had metastatic disease or locoregional relapse, or both. Weight loss ranged from 5.3% to 18.1% in the preceding six months. Baseline characteristics appear to be similar although despite randomisation, energy intake at baseline was significantly higher in the EPA arm compared to the placebo arm. Sixteen healthy subjects acted as controls.

Fearon 2003: randomised 200 unresectable pancreatic cancer patients who had lost more than 5% of pre-illness weight over the previous six months. The trial was included with patients having a Karnofsky performance score of 60 or more and a life expectancy of greater than two months. The average pre-illness weight loss was 17%. At baseline there was no significant difference between the treatment arms in terms of sex, performance status and quality of life characteristics. In the EPA arm there was a greater proportion of stage IV disease patients (52%) than in the placebo arm (41%).

Jatoi 2004: randomised 421 patients with incurable cancer; lung, gastrointestinal and others. All patients had associated weight loss defined as a self-reported two-month weight loss of at least 2.3 kgs or physician estimated calorific intake of less than 20 calories/ kg of body weight/day, or both. At baseline, there was no significant difference found between the three treatment arms of patient groups in terms of Eastern Cooperative oncology group performance status, Karnofsky score physician estimate of survival, patient reported appetite or medical centre of enrolment. In addition, there were no significant difference on the basis of stratification factors:

- a) cancer type (gastrointestinal versus thoracic versus other,
- b) severity of weight loss: less than 4.6 kg versus more than 4.6 kg in the preceding two-months,
- c) planned concurrent chemotherapy versus none, and
- d) age: less than 50 years versus more than 50 years.

The stratification process used was a minimization algorithm that balanced the marginal distributions.

Primary outcomes:

Weight gain

Body composition

Median survival

Primary outcomes as defined by us:

Survival

Quality of life

Performance

Completion of therapy

Complications /LOS

Does it appear in the SR and meta-analysis? Yes, partially

Years included in the search:

The Cochrane Central Registers of Controlled Trials (CENTRAL), The Cochrane Database of Systematic Reviews, Issue 4, 2003;

MEDLINE (1966 to 28/08/2004);

EMBASE (1986 to 28/07/2004);

CINAHL (1986 to 23/07/2004);

SIGLE (1980 to 22/02/2005);

Dissertations Abstracts On Line (1980 to 10/11/2004);

National Research Trials Register (20/10/2003).

Were additional RCTs on the subject published since then? No relevant trial.

Methodological rigor:

Data extraction by more than one researcher: YES.

Search strategy detailed: YES.

Untoward restriction of search parameters: NO.

Was the methodological rigor of the individual studies appraised, and did it serve for analysis? YES.

Were sub-group analyses of interest performed? YES.

Was heterogeneity tested? YES.

Was an attempt to explain heterogeneity made? Not applicable

Was the meta-analysis conducted according to the degree of heterogeneity? Not applicable

No of included studies: **5**

No of included patients: **587**

Mean number of patients per study: **117**

Main outcomes:

EPA versus placebo

Weight gain: Only one of the three included studies, Bruera 2003 (Assessment based on 60 patients) reported weight gain. In this trial, although there was a slight increase in weight gain for patients in the EPA arm the results were not significant.

Body composition: Of the three included studies, only one study (Bruera 2003) reported body composition. Using anthropometry, lean body mass was estimated using anthropometric measurements carried out on days one and 14, but were not statistically significant difference for patients in the EPA treatment arm compared with those in the placebo arm.

Survival: Of the three included studies, only the Gogos 1998 provided survival data. Actual numbers for survival days were not provided and the authors were unable to confirm these figures. Survival days have been estimated from the published diagram. This data suggests that all patients in the EPA arm ($n = 30$) had a statistically significant ($P = < 0.025$) increase in survival compared with the placebo arm. In the EPA arm, well-nourished (WN) patients survived 870 days and malnourished (MN) patients survived 600 days compared to all patients ($n = 30$) in the placebo arm (WN = 480 days, MN = 242 days).

Quality of life: Only one of the three included studies (Bruera 2003) reported the patient's overall sensation of well being which was measured using a Visual Analogue Scale (VAS) (zero to 100 mm where 0 mm = best and 100 mm worst). This study reported that there was no significant improvement in the treatment arm compared to that of the placebo arm.

Functional or performance status: Although two studies reported performance status (Bruera 2003; Gogos 1998) there were insufficient data available to be combined in a meta-analysis; In the Bruera 2003, performance status was measured using both the Karnofsky Performance Scale and the Edmonton Functional Assessment Test, but there was no significant difference in the functioning status for patients in the treatment arm compared with placebo; In the Gogos 1998 study performance status was measured using the Karnofsky performance scale. This study reported a statistically significant increase ($P = 0.01$) in performance status 51 ± 3 to 72 ± 4 (expressed as Mean with SD) in the group of malnourished cancer patients' treatment arm, compared to the control arm. However, there were no published or unpublished details available on the Karnofsky performance status for either the well nourished cancer patients of the treatment group or both malnourished and well nourished cancer patients in the control arm.

Nutritional status: Two studies (Bruera 2003; Zuijdgeest 2000) measured total energy intake as calorific intake per day (Bruera 2003) and kilo joules/ day (Zuijdgeest 2000). Combination of the results from these two studies provided no evidence to suggest that total energy intake was significantly improved compared to that of the control arm ($P = 0.55$).

EPA versus matched active treatment control:

Weight gain: In Fearon 2003 study patients in both arms receiving either nutritional supplements (with or without EPA) had a statistically significant increase in overall weight gain. In addition, Fearon et al. conducted post-hoc analysis using Pearson's parametric test of correlation to examine possible dose-response relationships in either arm of the study over the eight week period. Fearon 2003 found there was a significant positive correlation in the EPA arm between daily supplement intake and increase in body weight (expressed as Pearson's correlation coefficient $r = 0.50$, $P < 0.001$). Maximum weight was achieved in the EPA arm with an intake which provided 1.5 to 2.2 g of EPA. There was no such correlation in the control arm. However, although interesting, it should be noted that this was exploratory analysis using post-hoc data analysis which is fraught with hazard. In the Jatoi 2004 study, the primary end point was a 10% weight gain above baseline. When weight gain was evaluated with increments of more than 10% weight increase, patient reported weight gained showed 5%, 13% and 7% in the EPA treated, MA treated and combined treatment arms respectively, but the results were not statistically significant ($P = 0.08$). Clarification was requested from the authors and to obtain actual weight gain figures (rather than percentage). Combining data from these two included studies (Fearon 2003 and Jatoi 2004) showed there was no significant benefit of EPA for weight gain ($P = 0.63$). Indeed, the combination of EPA with MA (versus MA alone) resulted in the combined therapy being worse.

Body composition: Of the two included studies, only the Fearon 2003 study measured lean body mass which was measured using bioelectrical impedance analysis. When compared to rate of loss at baseline there was a significant attenuation of lean body mass in both of the study arms (EPA and Control) at four and eight weeks ($P < 0.001$ for all within group comparisons). However, there was no significant difference between groups ($P = 0.88$). Again, although not the primary outcome of the study, Fearon 2003 conducted post-hoc analysis to examine for a potential dose-response relationship in either arm (EPA or Control). This post-hoc analysis showed a significant positive increase in the EPA arm between daily

supplement intake and increase in lean body mass ($r = 0.33$, $P = 0.036$). The correlation between intake and lean body mass gain was significantly greater in the EPA arm than in the control arm ($P = 0.0043$).

Survival: Although both included studies (Fearon 2003; Jatoi 2004) reported some data on survival there were insufficient data available to combine in a meta-analysis. In the Fearon 2003 study there was no significant difference in median duration of survival between the two arms: EPA arm (Median 142 days) compared to Control arm (Median 128 days). In the Jatoi 2004 study there was no significant difference ($P = 0.82$) in median duration of survival across the three arms: EPA arm (Median 147 days), Megestrol arm (Median 128 days) and Combined EPA/Megestrol arm (Median 151 days).

Quality of life: There were two studies (Fearon 2003 and Jatoi 2004) that reported quality of life measures using different validated questionnaires: A meta-analysis was performed on the quality of life outcomes for these two studies (Fearon 2003; Jatoi 2004) which provided no evidence to suggest that quality of life in the treatment arm was significantly improved compared with that of the control arm ($P = 0.45$).

Functional or performance status: Only one of the two included studies (Fearon 2003) assessed functional or performance status using the Karnofsky Performance Scale and reported that there was no significant differences between the arms, but there were no published data given.

Nutritional status: Of the two included studies, one study (Fearon 2003) assessed nutritional status by measuring total calorific and protein intake per day. At baseline, patients in both arms of the study were consuming insufficient intakes of energy and protein to maintain body weight. Although spontaneous intake was partially reduced, when patients in both the EPA Control arm consumed an average 1.4 cans of oral supplement (equivalent to 420 kcal and 21 g protein/ day) oral supplementation in both arms provided a net gain in total energy and protein intake.

NNT for main outcome: not relevant.

GRADE: low quality

Study limitation: minor

Inconsistency: major

Imprecision: major

Publication bias: impossible to perform

Conclusions:

The conduct of this systematic review did not enable the authors to confirm or refute previous literature on the use of EPA and it was not possible to recommend its use in clinical practice. Whilst the results from this systematic review suggests that there is little evidence of harm from using EPA it may not be reasonable to suggest its use in people who are very ill or if palatability is low and problems of compliance occur. There appears to be no significant improvement in management of symptoms by the addition of EPA to that gained from patients taking a high calorie, high protein nutritional supplement with or without the addition of the appetite stimulant, Megestrol Acetate (MA). Indeed it may be that combining EPA with MA may have a slight inhibitory action on MA.

E-9: A systematic review on the role of fish oil for the treatment of cachexia in advanced cancer: an EPCRC cachexia guidelines project

[PMID: 21865295](#)

Reference: Ries, A., Trottenberg, P., Elsner, F., Stiel, S., Haugen, D., Kaasa, S., & Radbruch, L. (2012). A systematic review on the role of fish oil for the treatment of cachexia in advanced cancer: An EPCRC cachexia guidelines project. *Palliative Medicine*, 26(4), 294-304.

Objectives:

To evaluate whether there is a net benefit from therapy with n-3-FA in patients with advanced cancer and cachexia.

Studies Inclusion criteria:

Only clinical studies and systematic reviews evaluating clinical studies were included.

The review focussed on clinical studies comparing treatment with n-3-FA in patients with advanced cancer and suffering from cachexia with standard therapy that did not include this enriched supplement.

Studies comparing n-3-FA with melatonin, megestrol acetate, or drug combinations were also included, but were evaluated separately, as were studies comparing different dosages of n-3-FA.

Preoperative treatment of cachectic patients with advanced cancer with n-3-FA were included, regardless of whether surgery was performed with curative or palliative intent, but were evaluated separately.

This summery will focus on RCT's.

Intervention:

Treatment with EPA, fish oil, or n-3-FA.

- **n-3-FA compared to standard therapy without n-3-FA:**

Fearon 2003: patients were asked to consume two cans of supplement (each with 1.1 g EPA) for 8 weeks, and control group patients received identical cans with a supplement that was without n-3-FA and enhanced antioxidants for 8 weeks.

Fearon 2006: 175 patients took capsules with 2 g EPA, 172 patients received capsules with 4 g EPA and 171 patients were treated with placebos for 8 weeks.

Bruera 2003: half of the group was treated with fish oil capsules and the other half with placebo for 2 weeks.

Gogos 1998: well nourished with EPA/DHA (WNA), well nourished placebo (WNB), malnourished with EPA/DHA (MNA) and malnourished placebo (MNB).

Moses 2004: 15 patients received supplement and nine patients EPA enriched supplement for a treatment period of 8 weeks.

Zuijdgeest-Van Leeuwen 2000: 17 patients received EPA enriched supplement and 16 patients received oleic acid enriched supplement in a control group of for 1 week.

n-3-FA versus other substance/mix versus both/mix:

Jatoi 2004: the trial compared an eicosapentaenoic acid supplement with megestrol acetate (MA) and with a combination of both substances.

Persson 2005: the trial compared fish oil (FO) containing EPA and DHA with melatonin (MLT) and with the combination of both. In a cross-over design patients were treated with either FO or MLT for 4 weeks then switched over to the combination of both for another 4 weeks.

Mantovani 2008: Patients were randomized to one of following five arms for a treatment duration of four months: (1) medroxy progesterone acetate/megestrol acetate, (2) pharmacological nutritional support containing eicosapentaenoic acid, (3) L-carnitine, (4) thalidomide, or (5) 1234.

De Luis 2008: two groups received a high omega-3/omega-6 ratio and a low ratio, respectively

Bauer 2005: half of the patients were asked to consume two cans per day of EPA supplement and the other half received control supplement for a period of 8 weeks.³⁶ However, the study focussed on compliance only, differentiating a compliant and a non-compliant group, and a comparison of EPA and placebo groups was not provided.

Population:

Adult subjects with cancer cachexia.

- **n-3-FA compared to standard therapy without n-3-FA:**

Fearon 2003: 185 patients with advanced cancer and full cachexia.

Fearon 2006: 518 patients with advanced cancer and full cachexia.

Bruera 2003: 91 patients with advanced cancer and full cachexia.

Gogos 1998: 60 patients with advanced cancer and full cachexia, well-nourished and malnourished patients.

Moses 2004: 24 patients with advanced cancer and full cachexia.

Zuijdgheest-Van Leeuwen 2000: 33 patients with advanced cancer and full cachexia.

n-3-FA versus other substance/mix versus both/mix:

Jatoi 2004: 412 patients with advanced cancer and full cachexia.

Persson 2005: 24 patients with advanced cancer and full cachexia.

Mantovani 2008: 110 patients with advanced cancer and full cachexia.

De Luis 2008: 65 patients with advanced cancer and full cachexia.

Bauer 2005: 185 patients with advanced cancer and full cachexia.

Primary outcomes:

Weight

Lean body mass

Karnofsky performance status

Survival

Primary outcomes as defined by us:

Survival

Quality of life

Performance

Completion of therapy

Complications /LOS

Does it appear in the SR and meta-analysis? YES.

Years included in the search: from 1966 to June 2010.

Methodological rigor:

Data extraction by more than one researcher: Not mentioned.

Search strategy detailed: YES.

Untoward restriction of search parameters: YES. The search was restricted to publications in English language.

Was the methodological rigor of the individual studies appraised, and did it serve for analysis? YES.

Were sub-group analyses of interest performed? NO.

Was heterogeneity tested? No, systematic review.

No of included studies: **11**

No of included patients: **1707**

Mean number of patients per study: **155**

Main outcomes:

- **n-3-FA compared to standard therapy without n-3-FA:**

Four of the six high-quality randomized controlled trials found no significant benefit from the administration of n-3-FA

Fearon 2003+Fearon 2006: In both studies the results indicated no statistically significant benefit of the EPA enriched supplement. Intention-to-treat analyses did not provide a therapeutic advantage nor a statistically significant improvement in weight, lean body mass, Karnofsky performance status, or survival.

Fearon 2003: further analysis reported significant correlations between the amount of supplement intake and weight gain and increase in lean body mass for the patients on EPA supplement. Increased plasma EPA levels in the EPA group were correlated with weight gain and lean body mass gain. Weight gain was related to improved quality of life in the EPA group.

Bruera 2003: fish oil did not significantly influence appetite, tiredness, nausea, wellbeing, caloric intake, nutritional status, or function within this short treatment period.

Gogos 1998: The ratio of T-helper cells to T-suppressor cells was significantly lower in malnourished patients. n-3-FA had a considerable immunomodulating effect by

increasing this ratio in the subgroup of malnourished patients. There were no significant differences in cytokine production among the four groups, except for an increase in tumour necrosis factor production in malnourished cancer patients which was reduced by n-3-FA. The mean survival was significantly higher for the well-nourished patients in both groups, whereas n-3-FA prolonged the survival of all the patients. No data on weight changes were reported.

Moses 2004: After 8 weeks TEE and PAL increased significantly in those who received the EPA enriched supplement, but not in control group patients. No significant changes were reported for REE and weight.

Zuijdgeest-Van Leeuwen 2000: there were no significant effects of the EPA Treatment on energy intake, whole body lipolysis (rate of appearance of H5-labelled glycerol in plasma), palmitic acid release (rate of appearance of ¹³C-labelled palmitic acid in plasma), palmitate oxidation rate, free fatty acid concentration in plasma and plasma triacylglycerol concentrations, but found no significant effects of the EPA treatment.

n-3-FA versus other substance/mix versus both/mix:

Jatoi 2004: EPA supplement, either alone or in combination with MA, did not improve weight, appetite, survival or quality of life more than MA alone

Persson 2005: No statistically significant changes in weight and KPS were reported after 4 weeks, but statistically significant lower KPS was found in the fish oil group after 8 weeks. The authors concluded that FO, MLT or their combination did not induce malnutrition or biochemical changes indicative of a strong anticachectic effect. Nonetheless, the interventions used may have had a weight-stabilizing effect

Mantovani 2008: Concentrating on the results of treatment groups with EPA, there was a significant increase in MFSI-SF score (fatigue symptoms) and REE, a decrease in EQ-5D index as well as improvement in ECOG PS score in arm 2. In arm 5 total body weight and appetite increased significantly and MFSI-SF, REE, and ECOG performance status score were improved.

De Luis 2008: No significant differences in plasma proteins (albumin, prealbumin, transferrin) nor in other variables were reported after 12 weeks of treatment. Both groups

experienced weight stabilization and good gastrointestinal tolerance. The study did not allow any conclusion whether n-3-FA attenuated cachexia.

Bauer 2005: a comparison of EPA and placebo groups was not provided.

Adverse effects: Adverse effects of EPA and other n-3-FA were reported in only a few studies. Most often gastrointestinal effects such as mild abdominal discomfort, flatulence, nausea or vomiting, transient diarrhoea or steatorrhoea were reported. Some studies reported abnormal taste of food, sometimes with a fish aftertaste, or fish belching. Toxicity of the central nervous system and severe paraesthesia were reported in one patient each in a randomized study.

GRADE: low quality

Study limitation: negligible

Inconsistency: high

Imprecision: medium

Publication bias: not assessed

Conclusions:

This review found evidence of a net benefit of n-3-FA on cachexia in advanced cancer only in trials with lack of methodological stringency, and no evidence of a clear benefit in studies with higher methodological quality.

E-10: n-3 PUFAs in cancer, surgery, and critical care: a systematic review on clinical effects, incorporation, and washout of oral or enteral compared with parenteral supplementation

[PMID: 21940600](#)

Reference: van der Meij BS, van Bokhorst-de van der Schueren MA, Langius JA, Brouwer IA, van Leeuwen PA. n-3 PUFAs in cancer, surgery, and critical care: a systematic review on clinical effects, incorporation, and washout of oral or enteral compared with parenteral supplementation. Am J Clin Nutr. 2011 Nov; 94(5):1248-65. doi: 10.3945/ajcn.110.007377. Epub 2011 Sep 21.

Objectives:

To systematically review effects of oral or enteral and parenteral n-3 FA supplementation on clinical outcomes in patients with cancer who underwent surgery or critical care.

To review the knowledge on the incorporation into phospholipids of plasma, blood cells, and mucosal tissue and the subsequent washout after oral or enteral and parenteral n-3 FA supplementation in these patient populations.

This summary will focus on the first objective.

Studies Inclusion criteria:

Randomized controlled trials.

Intervention:

For the primary research objective, the investigators included studies that compared supplementation of n-3 FAs to a control or placebo intervention. The means of n-3 FAs were fish-oil capsules, ONSs, and enteral or parenteral nutrition. The investigators excluded studies with dietary interventions of multiple immune-enhancing compounds (eg, arginine, glutamine, nucleotides, and n-3 FAs) or studies with concurrent use of appetite stimulants.

Study	Intervention
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Guarcello, 2007	<p>Duration: 60 days</p> <p>n=26: n-3 FA ONSs (2.2 g EPA and 1.0 g DHA; Prosure, Abbott Laboratories)</p> <p>n=20: isonitrogenous control ONSs</p>
Takatsuka, 2001	<p>Duration: 21 days</p> <p>before BMT to 180 d after BMT</p> <p>n= 7: 3 capsules (1.8 g EPA/d)</p> <p>n= 9: no capsules</p>
Gogos, 1998	<p>Duration: 40 days</p> <p>n= 30: 18 fish-oil capsules (3.1 g EPA and 2.0 g DHA)</p> <p>n= 30: control (sugar) tablets</p>
Fearon, 2006	<p>Duration: 8 weeks</p> <p>n= 175: 2 g EPA (95% diester capsules)</p> <p>n= 172: 4 g EPA (95% diester capsules)</p> <p>n= 171: control capsules</p>
Bruera, 2003	<p>Duration: 14 days</p> <p>n= 30: 18 fish-oil capsules (3.2 g EPA and 2.2 g DHA)</p> <p>n= 30: 18 control (olive oil) capsules</p>
Fearon, 2003	<p>Duration: 8 weeks</p> <p>n= 95: n23 FA ONSs (2.2 g EPA and 1.0 g DHA)</p> <p>n= 105: isonitrogenous control ONSs</p>
De Luis, 2008	<p>Duration: 12 weeks</p> <p>postoperative (starting at hospital discharge)</p> <p>n= 31: ONSs with a high ratio (3.7) of n-3:n-6 FAs (2.0 g EPA and 0.9 g DHA) n= 34: control ONSs with a low ratio (0.99) of n-3:n-6 FAs (1.8 g EPA and 1.2 g DHA)</p>
van der Meij, 2010	<p>Duration: 5 weeks</p> <p>n= 20: n23 FA ONSs (2.02 g EPA and 0.92 g DHA; Prosure)</p>

	n= 20: isocaloric control ONSs (Ensure; Abbott Laboratories)
Kenler, 1996	Duration: 7 days postoperative n= 17: n-3 FA enteral nutrition (4.0 g EPA and 1.9 g DHA) n= 18: isocaloric, isonitrogenous control enteral nutrition (Osmolite HN; Abbott Laboratories)
Swails, 1997	Duration: 7 days postoperative n= 8: n-3 FA enteral nutrition (2.8 g EPA and 1.4 g DHA) n= 10: isocaloric, isonitrogenous control enteral nutrition (Osmolite HN)
Ryan, 2009	Duration: 5 days preoperative (ONSs) to 21 days postoperative (enteral nutrition) n= 28: n-3 FA enteral nutrition (2.3 g EPA and 1.0 g DHA; Prosure, Abbott Laboratories) n = 25: isocaloric, isonitrogenous control enteral nutrition (Ensure Plus; Abbott Laboratories)
Heller, 2004	Duration: 5 days postoperative (parenteral) n= 24: soybean oil and fish oil (0.2 g/kg body weight) n-3:n-6 FA ratio of 1:4 (eg, body weight of 70 kg, 2.8 g EPA, and 3.2 g DHA) n= 20: soybean oil
Liang, 2008	Duration: 7 days postoperative (parenteral) n= 21: n-3 lipid emulsion (0.2 g/kg body weight) and soybean oil emulsion (1.0 g/kg body weight) n-3:n-6 FA ratio of 1:3 (eg, body weight of 70 kg, 2.8 g EPA, and 3.2 g DHA) n= 21: soybean oil emulsion (1.2 g/kg body weight)

Jiang, 2010	Duration: 7 days postoperative (parenteral) n= 100: soybean-oil plus n-3 FA emulsion (1.0 and 0.2 g/kg body weight, respectively) n= 103: soybean-oil emulsion (1.2 g/kg body weight)
Wachtler, 1997	Duration: 5 days postoperatively (parenteral) n= 19: 20% n23 FA lipid emulsion (Lipoplus; B Braun) n= 21: 20% isocaloric MCT and LCT lipid emulsion Daily dose: not specified
Badia-Tahull, 2010	Duration: 5 days (parenteral) n= 13: olive oil emulsion, partially replaced with FO (16.6%, w/w) n= 14: olive oil emulsion

Population:

Adult human subjects with any type of cancer who received chemotherapy and/or radiotherapy/palliative care/underwent elective surgery (abdominal, head and neck, or gastrointestinal).

Primary outcomes:

Nutritional status- body weight, LBM, midupper arm circumference, and appetite.

Morbidity

Mortality

Length of hospital stay and length of ICU stay.

Quality of life- included symptoms (eg, fatigue), physical function, and performance status, which were measured by validated self-administered questionnaires or classification methods for clinicians.

Primary outcomes as defined by us:

Survival

Quality of life

Performance

Completion of therapy

Complications /LOS

Does it appear in the SR and meta-analysis? YES.

Years included in the search:

Studies published from the start date of the electronic databases (1948 for PubMed and 1986 for EMBASE) until 1 April 2011.

Methodological rigor:

Data extraction by more than one researcher: NO. Both reviewers read the selected articles; One reviewer extracted the data; a second reviewer checked the extracted data to minimize the possibility of errors.

Search strategy detailed: YES.

Untoward restriction of search parameters: YES. Limited to publications in English.

Was the methodological rigor of the individual studies appraised, and did it serve for analysis? YES.

Were sub-group analyses of interest performed? NO.

Was heterogeneity tested? NO.

Was an attempt to explain heterogeneity made? NO.

Was the meta-analysis conducted according to the degree of heterogeneity? NO.

No of included studies: **28**

No of included patients: **2665**

Mean number of patients per study: **95**

Main outcomes:

Nonsurgical oncology

Oral or enteral supplementation of n-3 FAs

Quality of life: Quality of life was an endpoint in 4 studies. In lung cancer patients, improvements of quality of life variables in the n-3 FA group were shown in time. In a large-scale, double-blinded RCT, patients who received n-3 FAs showed a tendency for a better maintenance of physical functioning than did control patients: Physical function improved by 7% in 2-g EPA group ($P= 0.04$) and decreased by ~5% in the 4-g EPA group. Weakness tended to decrease in the 2-g EPA group at 4 and 8 wk, whereas there was little change in the 4-g EPA group. In a post hoc analysis of this study, weight gain was associated with an improved quality of life in the n-3 FA group. One trial of a 2-wk supplementation of n-3 FAs via fish-oil capsules did not find improvements in well-being, but there was a trend for a reduction of tiredness in the n-3 FA group. With regard to Karnofsky Performance Status, no differences between n-3 FAs and control patients were observed in one large excellent-quality trial and one small average-quality trial of 2 wk. One

small poor-quality trial showed an increase of Karnofsky Performance Status in a subgroup of malnourished patients who received n-3 FAs.

Morbidity: Morbidity was studied in 2 trials; one study observed less GVHD in patients who received n-3 FAs around bone marrow transplants: GVHD; n= 2 grade III in the EPA group; n= 3 grade III or IV) (P value not reported), and a study in patients with head and neck cancer did not observe differences for complications between n-3 FAs and the control group.

Mortality: Mortality was reported in 5 studies: 2 small RCTs (of poor and average quality) showed beneficial effects on survival in bone marrow–transplant patients (P= 0.01) and in patients with various types of cancer, whereas 2 high-quality RCTs and one small study did not show such beneficial effects.

- **Nutritional status:** Seven studies reported on body-weight changes. One study showed a beneficial effect: after 4 wk, the n-3 FA group showed higher energy and protein intakes [2456 kJ (P= 0.03) and 25.0 g (P= 0.01), respectively], whereas 4 studies did not show a beneficial effect. A trend for a beneficial effect was observed in one study: a supplementation of 2g EPA showed positive trend for body weight after 8 wk (weight change 11.2 kg; P= 0.66). Mean weight change in 4g EPA group was 10.3 kg. Finally, one study reported weight maintenance in the intervention group, whereas body weights in the control group decreased: Body weight at 0, 30, and 60 d—n-3 FAs: 57.7, 58.6, and 58.6 kg, respectively (P<0.05 compared with 0 d); control: 59.1, 57.0, and 59.1 kg, respectively. However, this study failed to report changes compared with those with the placebo.
- Five studies measured the effects of n-3 FA supplemented by ONSs on LBM. One small study observed a significant maintenance of LBM: there was a smaller decrease in LBM in the study group compared to the control group [1.5 kg (P= 0.05) and 1.9 kg (P= 0.02) after 3 and 5 wk, respectively]. 2 studies showed a nonsignificant maintenance compared with that of a control

intervention; 2 studies showed no effects on LBM after supplementation of n-3 FAs during 2 and 12 wk.

Parenteral supplementation of n-3 FAs:

The systematic review found no RCTs that investigated the effects of parenteral supplementation of n-3 FAs in nonsurgical oncology.

Surgical oncology:

Oral or enteral supplementation of n-3 FAs:

Morbidity: Three studies measured morbidity in terms of postoperative complications; the number of complications between n-3 FAs and control enteral feedings was not significantly different. Two studies reported a tendency for fewer infectious complications per patient in the n-3 FA group who received enteral nutrition during 7 d after gastrointestinal surgery [50% reduction in the total number of infections in the n-3 FA group ($P= 0.037$), lower number of infected patients with more than one infection in the n-3 FA group ($P= 0.09$); trend for fewer infections per infected patient (P values not reported)].

Length of stay and mortality: no significant differences were observed between patients who received postoperative n-3 FAs as enteral nutrition and controls.

Nutritional status: One study reported on perioperative body weight (lower number of patients with 5% weight loss at 1 mo postoperative) and LBM changes in esophageal cancer patients and showed a postoperative maintenance of body weight and LBM (n-3 FAs: 10.3 kg, $P= 0.8$), whereas this effect decreased in the control group (21.9 kg, $P= 0.03$).

Parenteral supplementation of n-3 FAs:

Morbidity: In 3 studies, no differences in complications or infections were observed between n-3 FAs and control groups after gastrointestinal cancer surgery. One small study showed a lower incidence of infections in the n-3 FA group than in the control group (23.1% compared with 78.6%; $P=0.007$). One excellent-quality study observed a tendency for a lower incidence of infections (4 compared with 12 on day 8; $P=0.066$) and a significant lower incidence of systemic inflammatory response syndrome in the group that received parenteral n-3 FAs and SIRS (4 compared with 13; $P=0.039$).

Length of hospital stay: Patients who received parenteral n-3 FAs had a significant shorter length of hospital stay (mean \pm SD: 15 ± 5 compared with 17 ± 8 d; $P=0.041$) or a tendency for a shorter length of stay (mean \pm SD: 17.45 ± 4.80 compared with 19.62 ± 5.59 d; $P=0.19$). A study in patients with gastrointestinal or pancreatic cancer observed a tendency for a shorter ICU stay in a post hoc analysis in which only patients with an increased risk of sepsis were selected. One study did not observe differences for a hospital or ICU stay after major intestinal surgery. A small study in major gastrointestinal surgery did not show any differences in the length of hospital stay between n-3 FAs and control parenteral nutrition.

Mortality: In 3 studies, effects on mortality were investigated; none of the studies showed any differences on mortality between parenteral n-3 FAs or controls.

Nutritional status: One study reported on body-weight changes after gastrointestinal or pancreatic cancer surgery and showed no significant difference between groups that received n-3 FAs or control parenteral nutrition (mean \pm SD: fish oil, 0.0 ± 2.9 kg; soybean oil, 21.1 ± 2.2 kg; NS).

GRADE: very low quality

Study limitation: high

Inconsistency: high

Imprecision: high

Publication bias: not assessed

Conclusions: The investigators showed some evidence for beneficial effects of oral supplementation of n-3 FAs for 5–8 wk on body weight (but not on LBM) during chemo(radio)therapy and in palliative care. Effects on Karnofsky Performance Status and survival were inconsistent. There was no evidence for beneficial effects of postoperative enteral supplementation of n-3 FAs on nutritional status, length of stay, infectious complications, and mortality in surgical oncology. Short-term (5–7 d) perioperative parenteral supplementation of n-3 FAs might have shortened the length of an ICU or hospital stay but did not improve other clinical outcome variables in surgical oncology.

Although studies were heterogeneous with regard to the n-3 FA dose, supplementation method, endpoints, and quality, the investigators believe there is enough evidence to advise the oral or enteral supplementation of n-3 FA supplementation in cancer patients with a high risk of weight loss and in critical care patients (provided that the digestive tract is functioning and platelet and coagulation function are adequate). Supplementation of the optimal dose should be continued as long as the initial indication for n-3 FA supplementation exists, taking the incorporation period (which is a few days longer for enteral than parenteral supplementation) and the relative short washout period into account. During the washout period, clinical beneficial effects of n-3 FAs probably extinguish.

E11: Is there a benefit from lycopene supplementation in men with prostate cancer? A systematic review.

[PMID: 19901932](#)

Reference: Haseen, F., Cantwell, M. M., O'Sullivan, J. M., & Murray, L. J. (2009). Is there a benefit from lycopene supplementation in men with prostate cancer & quest; A systematic review. *Prostate cancer and prostatic diseases*, 12(4), 325-332.

Objectives:

A systematic review of all available experimental evidence relating to lycopene supplementation and prostate cancer progression to provide evidence-based recommendations for patients with prostate cancer.

Studies Inclusion criteria:

Intervention studies (RCTs, nonrandomized controlled trials or before-after studies).

Studies examining mixed supplementation with lycopene and other nutrient/supplements were excluded.

This summary will focus on the RCT's.

Intervention:

Lycopene supplementation in any form (for example, tablet/capsule, whole tomato, tomato sauce or tomato juice).

Population:

Prostate cancer patients, regardless of their disease duration, stage and treatment modalities.

Primary outcomes:

Disease progression- measured by changes in the PSA level.

Primary outcomes as defined by us:

Survival

Quality of life

Performance

Completion of therapy

Complications /LOS

Does it appear in the SR and meta-analysis? NO.

Years included in the search:

Studies published till January 2009

Were additional RCTs on the subject published since then? NO.

Methodological rigor:

Data extraction by more than one researcher: YES.

Search strategy detailed: YES.

Untoward restriction of search parameters: NO.

Was the methodological rigor of the individual studies appraised, and did it serve for analysis? YES.

Were sub-group analyses of interest performed? NO.

Was heterogeneity tested? YES

Was an attempt to explain heterogeneity made? NO

Was the meta-analysis conducted according to the degree of heterogeneity? A meta analysis was no performed due to high heterogeneity.

No of included studies: 8 met the inclusion criteria, only **two** RCTs.

No of included patients: **89**

Mean number of patients per study: **44**

Main outcomes:

Two studies were RCTs, but one was very small and included 35 patients with data available for analysis from only 26 patients. The other study, an RCT of lycopene supplementation for 2 years in addition to orchidectomy, was also small (54 patients), and neither RCT achieved a Jadad score of 3 or higher.

Change in PSA levels: There was no significant difference in the percentage change in mean PSA between the intervention and non-intervention arms in the RCT undertaken by Kucuk (2001) in which men received lycopene supplementation (30mg per day) by capsule for a short period (3 weeks) before radical prostatectomy. In the larger RCT (Ansari 2003) involving men with metastatic prostate cancer treated by orchidectomy, lycopene supplementation (4mg per day for 2 years) was associated with a lower mean PSA after treatment (3.0 ng ml⁻¹ in the intervention and 9.0 ng ml⁻¹ in the nonintervention arms,

$P < 0.001$). Furthermore, 11 (40%) patients in the orchidectomy arm and 21 (78%) in the orchidectomy and lycopene group had a complete PSA response (reduced to $< 4 \text{ ng ml}^{-1}$), $P < 0.05$.

Cancer-related symptoms: Lycopene was shown to be potentially effective in ameliorating cancer-related symptoms (pain, urinary tract symptoms) in one RCT (Kucuk 2001). Moreover, 62% of patients managed to cut down their dose of analgesics. Analgesic use for body pain was also less evident in the supplemented group as opposed to the control group in the larger RCT (Ansari 2003) as well (15 vs 25%). A significant improvement in urinary peak flow rate was observed in the lycopene-supplemented group compared with the control arm. After intervention, the urinary peak flow rate was 12.2 ml s^{-1} in the lycopene group compared with 11.0 ml s^{-1} in the control group ($P < 0.04$), although they were comparable at baseline. Moreover, a subjective improvement in voiding symptoms (frequency, urgency and dysuria) was reported more in the supplemented group (80 vs 50%).

Evidence of progression from bone scans: A significantly higher proportion of patients had a complete response (normal bone scan) in the intervention group compared with control group at the end of the trial (25 vs 15%, $P < 0.02$). Moreover, progressive disease (development of any new 'hot spot' on bone scans) was significantly less common in the intervention group ($P < 0.02$). Bone pain and use of analgesics showed a direct relationship with bone scan response, and patients with a complete response required no analgesic.

Survival: Longer overall survival was observed in the supplemented group than in the control group in the trial by Ansari (2003) after a mean follow-up period of 25.5 months, 19 patients (35%) died, 12 (22%) in the control group and 7 (13%) in the supplemented group ($P < 0.001$). Follow-up in this study was brief, hence no information was provided on long-term survival.

Toxicity/side effects: no adverse effects or reactions were reported during and after supplementation in the intervention arm.

GRADE: very low quality

Study limitation: major

Inconsistency: major

Imprecision: major

Publication bias: impossible to perform

Conclusions:

The trials summarized in this systematic review do not provide sufficient evidence to recommend the use of lycopene supplements in routine clinical practice for patients diagnosed with prostate cancer, although the studies do indicate that lycopene is unlikely to be harmful to such patients. However, no study has been conducted with an adequately sound methodology.

Many questions remain unanswered, including which patient group may be most likely to benefit from lycopene supplementation, and what are the most appropriate dose, duration and methods of supplementation.

Large robust randomized controlled trials in broader patient groups with clinically relevant end points are required to answer these questions. A double-blinded RCT to assess the ability of lycopene to slow down the progression of prostate cancer or to increase survival is required; however, the role of other carotenoids and phytochemical compounds in tomatoes also needs to be addressed. Research focused on the effects of lycopene should also consider the effects of other active components in tomato products.

E-12: Impact of antioxidant supplementation on chemotherapeutic efficacy: A systematic review of the evidence from randomized controlled trials

[PMID: 17367938](#)

Reference: Block, K. I., Koch, A. C., Mead, M. N., Tothy, P. K., Newman, R. A., & Gyllenhaal, C. (2007). Impact of antioxidant supplementation on chemotherapeutic efficacy: a systematic review of the evidence from randomized controlled trials. *Cancer treatment reviews*, 33(5), 407-418.

Objectives:

This systematic review evaluated randomized controlled trials which measured survival and/or treatment response levels of patients given antioxidants concurrently with chemotherapy in order to determine if the antioxidants enhanced or interfered with the efficacy of the chemotherapy.

Studies Inclusion criteria:

randomized controlled trials

Studies included provided survival data and/or tumour response data.

Intervention:

Patients took antioxidants (orally or intravenously) concurrently with chemotherapy. ROS-generating chemotherapy (doxorubicin, epirubicin, daunorubicin, idarubicin, cisplatin, carboplatin, oxaliplatin, bleomycin, carmustine, cyclophosphamide, melphalan, etoposide, mitomycin, vinblastine, vinorelbine, paclitaxel, docetaxel) together with an antioxidant compound (vitamin C, vitamin E, vitamin A, melatonin, glutathione, N-acetylcysteine, polyphenols, green tea catechins, carotenoids, carnitine, selenium, ellagic acid, curcumin, coenzyme Q10, lycopene, flavonoids, and isoflavones, including chemical names and synonyms of vitamin names. Whole herbs and multicomponent herbal formulas that

contained phytochemical antioxidants were not included in the study because of the potential for confounding of results by non-antioxidant activities of complex herbs and mixtures, which is avoided to some extent by the use of antioxidant phytochemical extracts.

Population:

Only cancer patients who were currently undergoing chemotherapy were included. All types of cancer were included, as well as various chemotherapies that utilized the reactive oxygen species mechanism.

Primary outcomes:

Survival

Tumour response

Primary outcomes as defined by us:

Survival

Quality of life

Performance

Completion of therapy

Complications /LOS

Does it appear in the SR and meta-analysis? YES.

Years included in the search: From inception to the last week of December, 2006.

Were additional RCTs on the subject published since then? no

Methodological rigor:

Data extraction by more than one researcher: YES.

Search strategy detailed: YES.

Untoward restriction of search parameters: NO.

Was the methodological rigor of the individual studies appraised, and did it serve for analysis? YES.

Were sub-group analyses of interest performed? Systematic review.

Was heterogeneity tested? Systematic review.

No of included studies: **19**

No of included patients: **1554**

Mean number of patients per study: **81**

Main outcomes:

Glutathione and chemotherapy:

In a large study (Smyth 1997), 58% of patients taking GSH were able to receive the full six cycles of chemotherapy, versus only 39% of the placebo group ($P = .04$). Specifically, significantly fewer patients in the GSH group experienced nephrotoxicity that kept them from receiving six cycles of treatment than the control group ($P = .012$).

Of six studies that reported on neurotoxicity, all of them observed similar or greater reductions in neurotoxicity for the GSH group versus the control group, and two showed

statistically significant reductions. In one study with 50 patients, a significant difference in the occurrence of neurotoxicity was seen between patients on GSH (17%) and the control group (89%) ($P = .0001$). In another study with 52 patients, 26% of the control group experienced grade three or four neurotoxicity, while none (0%) of the GSH group experienced grade three or four neurotoxicity ($P = .01$).

Survival and/or treatment response: For the six studies that reported overall response rates (complete response + partial response), none reported significantly lower response or survival in antioxidant supplemented groups versus control groups (one study did not report any statistical analysis). One study reported a significant advantage in complete response rates for patients taking GSH within a subgroup of patients who were surgically restaged. Based on 'pathological' response, the GSH group reported a complete response in six of 13 patients versus only one of 11 patients in the control group ($P = .014$). In a study by Colombo 1995, a non-significant advantage was shown by GSH supplemented patients who had both higher overall response rates than those patients receiving placebo (75% versus 60%, respectively), as well as higher complete response rates (44% versus 27%, respectively). Of note is that the GSH group achieved a superior response rate despite having a larger average tumor burden. Only one study compared the effects of a non-platinum based chemotherapy (mitomycin C and FT-207 (a 5-FU prodrug)) plus placebo with chemotherapy plus supplementation of both phenobarbital and GSH. While the overall results were essentially the same between the two groups (only a slightly better treatment response was seen in the GSH supplemented group), when patients were grouped by gastric cancer stages, stage III patients had statistically significant higher survival rates for years 3–5 than the control group; the finding of statistical significance in this subgroup may have been more likely due to a larger number of subjects ($n = 72$ versus $n = 38, 48$ and 44 in other stages).

Melatonin and chemotherapy:

Of four studies that compared melatonin supplementation to placebo, all reported better overall outcomes in those patients taking MLT than those taking placebo. Three of the studies reported statistically significant increases in survival rates for those taking melatonin supplements. Response rates were also significantly higher in patients taking melatonin in two of the three studies (35% versus 18%, $P < 0.05$ and 34% versus 15%, $P < .001$).

Additionally, the number of patients with progressive disease was significantly lower in the MLT group than in the control group (12% versus 39%, $P < .01$). In the study by Cerea 2003

no survival rates were reported, however, disease stabilization rates (partial response plus stable disease) were significantly higher in patients taking MLT than those taking placebo (86% versus 44%, $P < .05$).

N-acetylcysteine (NAC) and chemotherapy:

Only one study that evaluated NAC with chemotherapy met the inclusion criteria. The study evaluated the potential cardioprotective effect of adjuvant NAC on 24 patients who had failed to respond to their previous chemotherapy regimens. While no cardioprotective effect was seen, 50% of the NAC-supplemented patients had stable disease or partial remissions versus 33% of the placebo group. However, no statistical analysis of these results was performed due to the diverse tumor types involved.

Vitamin C, mixed supplements, and chemotherapy:

Only one RCT was found that evaluated vitamin C treatment concurrently with chemotherapy. In this study, a non-significant advantage was shown in objective response (complete response + partial response), which was higher in the vitamin C supplemented group (60%) than the placebo arm (33%). Additionally, while both the vitamin C group and the control group had significant reductions in the sizes of the average lump diameter before and after treatment, the mean change was $3.53 \pm .73$ in the vitamin C group versus $1.93 \pm .77$ in the control group. Two recently published studies have included vitamin C as part of an antioxidant mixture given concurrently with chemotherapy. Pathak et al. (2005) evaluated vitamins C, E and beta carotene, while Weijl et al. (2004) evaluated vitamins C, E and selenium. Weijl reported poor adherence to the supplemental regimen: 46% of all patients did not drink the beverage (placebo or antioxidant) throughout the entire study. While the overall response rates were similar between the two groups (48% antioxidant group versus 44% control group), nine patients had a complete response in the antioxidant group, versus six patients in the placebo arm. A statistically significant correlation regarding improvement in toxicities was found between patients with the highest serum levels of the antioxidant supplements and the lowest loss of high-tone hearing after three cycles of chemotherapy ($P = .019$).

In the study by Pathak et al., while none of the results achieved statistical significance, an advantage in overall response rates (37% versus 33%) and median survival (11 months versus 9 months) was seen for patients taking the antioxidant supplements.

Vitamin E and chemotherapy:

Pace et al. (2003) evaluated oral vitamin E supplements for a neuroprotective effect when combined with platinum-based chemotherapy. A significant difference was seen between the incidence of neurotoxicity in the vitamin E supplemented group (31%) versus the placebo arm (86%) ($P < .01$). While not statistically significant, objective response (complete response plus partial response) was higher in the placebo group (73%) than in the supplemented patients (62%).

Ellagic acid and chemotherapy:

Falsaperla et al. (2005) found prostate cancer patients taking ellagic acid had significantly decreased neutropenia over patients taking a placebo (33% versus 75%, $P < .05$) (Table 3). The ellagic acid group also showed slight, non-significantly higher survival times (ellagic acid group 5.85 months versus placebo 4.55 months), more complete responses (25% versus 0%), and greater reductions in serum PSA levels (>75% reduction: 58.3% versus 33.3%) than the control group in this high-risk subject population.

Vitamin A and chemotherapy:

Two studies evaluated supplementation with vitamin A, a weaker antioxidant. Israel et al. (1985) observed that patients supplemented with vitamin A showed a greater than twofold increase in the complete response rate (38% versus 15% for controls, $P < .02$). Among chemotherapy responders in both groups, the projected 43-month survival rate, based on a life table analysis using the Kaplan–Meier method and logrank test, was 93% in vitamin A supplemented responders versus 30% in non-supplemented responders ($P < .02$).

Classification of patients by menopausal status indicated that serum retinol levels were significantly elevated only in postmenopausal patients supplemented with vitamin A ($P < .001$). For this subgroup, the response rates, duration of response and projected survival were significantly elevated. Postmenopausal patients on vitamin A ($n = 25$) had a 78% chance of surviving 43 months, compared to 19% for non-supplemented ($n = 30$) postmenopausal women ($P < .02$). In the study by Meyskens et al. (1995), patients in the control group experienced less grade 2 + toxicities (4%) than the vitamin A group (23%) ($P = .002$). This was the only study to report a statistically significant reduction of toxicity in the control group versus the antioxidant group, which was not unexpected for vitamin A supplementation. Patients in the vitamin A group had longer durations of clinical

progression- free survival (median 46 months) and overall survival (51 months) compared to those in the chemotherapy-alone group (38 and 44 months, respectively); however, the differences were not statistically significant.

GRADE: very_low quality

Study limitation: medium

Inconsistency: high

Imprecision: high

Publication bias: not assessed

Conclusions:

This systematic review, the first to consider the impact of antioxidant supplementation in combination with chemotherapy, provides suggestive evidence that antioxidant supplementation helps reduce some adverse reactions including neurotoxicity, thrombocytopenia, diarrhea, thus enabling increased or uninterrupted dosing in patients who otherwise may discontinue treatment due to side effects.

While many of the trials summarized in this review found survival and/or treatment response rates to be similar or higher in the antioxidant groups than placebo, the number of small, underpowered studies and diversity of tumor and treatment type limits any clear conclusions about potential additive effects of antioxidant supplementation during chemotherapy. However, this review did not detect diminished chemotherapeutic efficacy in patients receiving antioxidant supplementation in randomized trials. The lack of negative impact of antioxidant supplementation on efficacy of ROSgenerating chemotherapy in the studies reviewed, and the potential to diminish dose-limiting toxicity suggest that the clinical application of antioxidant supplementation during chemotherapy should be further explored. Future research on concurrent use of antioxidants and chemotherapy should employ larger sample sizes and better research designs.

E-13: Prognostic role of vitamin d status and efficacy of vitamin D supplementation in cancer patients: a systematic review.

[PMID: 21835895](#)

Reference: Buttigliero C, Monagheddu C, Petroni P, Saini A, Dogliotti L, Ciccone G, Berruti A. Prognostic role of vitamin D status and efficacy of vitamin D supplementation in cancer patients: a systematic review. *Oncologist*. 2011; 16(9):1215-27. doi: 10.1634/theoncologist.2011-0098. Epub 2011 Aug 11.

Objectives: To systematically review observational studies on cancer patients in which the predictive role of vitD or the VDR status was analyzed in relation to major clinical outcomes, as well as randomized controlled trials (RCTs) in which vitD was administered to improve prognosis. The key questions concern whether or not hypovitaminosis D is associated with a poor prognosis and whether or not vitD repletion improves the prognosis of cancer patients. This summary will focus on the systematic review and meta-analysis of randomized controlled trials.

Studies Inclusion criteria:

Articles reporting directly or indirectly on the prognostic role of vitD status or VDR in cancer patients were included if they reported data from RCTs, cohort studies, or case– control studies.

Intervention:

Vitamin D administration.

Population:

Patients during cancer treatment.

Primary outcomes:

Overall Survival (OS)

Primary outcomes as defined by us:

ECOG / QoL

Survival

Complications /LOS

Does it appear in the SR and meta-analysis? YES.

Years included in the search:

Through June 2010.

Methodological rigor:

Data extraction by more than one researcher: YES.

Search strategy detailed: YES.

Untoward restriction of search parameters: YES. Searches were limited to English language studies.

Was the methodological rigor of the individual studies appraised, and did it serve for analysis? YES.

Were sub-group analyses of interest performed? NO.

Was heterogeneity tested? YES.

Was an attempt to explain heterogeneity made? NO.

Was the meta-analysis conducted according to the degree of heterogeneity? NA.

No of included studies: **3**

No of included patients: 1273

Mean number of patients per study: 424

Main outcomes:

Overall Survival (OS): A randomized, placebo-controlled, double-blinded phase II study explored whether or not the activity of docetaxel in terms of PSA response was enhanced with the concomitant administration of doxercalciferol an inactive prohormone that undergoes hepatic conversion to its active metabolites 1,25-dihydroxyvitamin D2 and 1,24-dihydroxyvitamin D2. Seventy castration-resistant, chemotherapy-naïve prostate cancer patients were randomized to treatment. The median progression-free survival interval in the doxercalciferol arm was 6.17 months (95% CI, 4.20 –10.7 months) versus 6.20 months (95% CI, 4.83–9.07 months) in the placebo arm ($p=.764$). The median OS time in the doxercalciferol arm was 17.8 months (95% CI, 14.9 –23.6 months) versus 16.4 months (95% CI, 11.9 –23.8 months) in the placebo arm ($p=.383$).

In a double-blinded, randomized phase II study, the antineoplastic activity of the combination of DN-101, a high-dose oral formulation of calcitriol, and docetaxel was tested against docetaxel alone in 250 patients with advanced castration resistant prostate cancer. The administration of DN-101 failed to be associated with a significantly higher PSA response rate—58% for DN-101 patients and 49% for placebo patients ($p=0.16$)—or a significantly longer skeletal morbidity-free survival duration (HR, 0.78; 95% CI, 0.57– 1.074; $p = .13$).

Despite this, patients in the DN-101 group had a longer survival time than their counterparts not treated with DN-101 (HR, 0.67; 95% CI, 0.45– 0.97; $p = .04$) on multivariate analysis.

An open-label, phase III trial with the same design was subsequently planned to enroll 900 patients with advanced castration resistant prostate cancer (ASCENT-II trial). However, that trial was prematurely interrupted after an interim analysis showed an unexpectedly greater mortality rate in the DN- 101 arm. At the last available analysis, with a median follow- up of 11.7 months, 174 of 477 men in the calcitriol arm had died (36.5%), compared with 138 of the 476 docetaxel- treated patients (29%).

A meta-analysis of these three randomized trials, based on the number of deaths reported or extrapolated from the original papers, confirms a strong heterogeneity among studies (p for heterogeneity test = .001), without any pooled effect of vitD supplementation on survival, both with a fixed-effects model (RR, 1.07; 95% CI, 0.93–1.23) and with a random-effects model (RR, 1.00; 95% CI, 0.71– 1.40).

GRADE: low quality

Study limitation: minor

Inconsistency: major

Imprecision: major

Publication bias: impossible to perform

Conclusions: the three RCTs evaluating the potential benefit of vitD administration in advanced prostate cancer patients suffered from some limitations. Two of them were phase II studies with biochemical response as the primary endpoint and the third used different schedules of docetaxel in the two arms. Moreover, these clinical trials used either a synthetic vitD analog (Hectoral) or activated vitD (DN-101), which are not the standard replacement therapy for low vitD. Overall no effect was shown.

E-14: Immunoenhanced enteral nutrition formulas in head and neck cancer surgery: a systematic review
PMID: 23114931

Reference: de Luis, D. A., and J. M. Culebras. Immunoenhanced enteral nutrition formulas in head and neck cancer surgery: a systematic review. *Nutricion hospitalaria: organo oficial de la Sociedad Espanola de Nutricion Parenteral y Enteral* 27.3 (2011): 681-690.

Objectives:

To determine whether preoperative immunonutrition has a role in the treatment of head and neck cancer.

Studies Inclusion criteria:

Clinical trials were eligible if patients undergoing head and neck surgery for cancer had been randomly allocated to be in a control group receiving either traditional care (i.v. fluids) or polymeric nutritional supplements and an interventional group receiving polymeric nutritional supplements with immunonutritional additives.

Intervention:

Trials that compare polymeric feeds with immunonutrition.

Trials that compare two types of immunonutrition started at hospital discharge.

All studies used isocaloric and isonitrogenous feed regimens.

Population:

Patients undergoing surgery for head and neck cancer.

Primary outcomes:

Long-term survival and locoregional recurrence

Immunological parameters

Wound infections and fistula formation

Length of hospital stay

Primary outcomes as defined by us:

Survival

Quality of life

Performance

Completion of therapy

Complications /LOS

Does it appear in the SR and meta-analysis? YES.

Years included in the search: between 1999 and 2010

Methodological rigor:

Data extraction by more than one researcher: YES.

Search strategy detailed: YES.

Untoward restriction of search parameters: NO.

Was the methodological rigor of the individual studies appraised, and did it serve for analysis? YES.

Were sub-group analyses of interest performed? NO.

Was heterogeneity tested? NO. Systematic review.

No of included studies: 14

No of included patients: 836

Mean number of patients per study: 59

Main outcomes:

Wound infections and fistula formation: Occurrence of wound infection was reported in five trials. The risk of wound infection ranged from 0% (0/45) to 4.8% (4/82) in immunonutrition fed groups and from 0% (0/45) to 12.5% (3/24) in control groups. The effects of immunonutrition in malnourished patients could only be ascertained from the study by RISO et al., where 13 patients were considered malnourished. These patients had reduced wound infections when given immunonutrition ($p < 0.05$). Occurrence of fistula formation was reported in nine trials and ranged from 0% (0/23) to 5% (4/82) in immunonutrition fed groups and from 0% (0/38) to 18.9% (7/37) in control groups.

Hospital stay: Mean postoperative hospital stays were long with broad standard deviations. De Luis et al. reported a significant ($p < 0.05$) reduction in postoperative stay, 25.8 days versus 35 days in intervention and control groups, respectively. RISO et al. reported a reduced hospital stay in the intervention group ($p < 0.05$).

Immunological parameters: The trials examined reported on a broad range of biochemical and immunological parameters including interleukin-6, tumour necrosis factor- α , C-reactive protein, T-cell subsets and total lymphocyte counts. Riso et al. demonstrated an increase in total lymphocytes, CD4 and CD4/CD8 ratio on postoperative day 4 ($p < 0.05$). Malnourished patients ($n = 13$) in the study by Riso et al. showed reduced preoperative immune status in some variables (CD4, CD4/CD8, IgA, IgG), with some parameters (CD4, CD4/CD8) increasing postoperatively compared with baseline but not between the two groups. Casas-Rodera et

al. showed no significant intergroup differences in the trend of the two plasma proteins, lymphocytes and weight. In the three groups that were compared there was a significant decrease of the transferrin at the seventh postoperative day, in relation to preoperative levels, with a significant increase only in the enriched diet groups, at the fourteenth postoperative day. The control group showed the lower levels of lymphocytes at the seventh and fourteenth postoperative day. The control group showed the highest levels of TNF α at the fourteenth postoperative day.

Long-term survival and locoregional recurrence: Buijs et al. showed that the median overall long-term survival was 34.8 months in the arginine-supplemented group and 20.7 months in the control group (P = 0.019). Disease-specific survival was 94.4 months in the arginine-supplemented group and 20.8 months in the control group (P = 0.022). Locoregional recurrence occurred in 4 of the 17 patients in the arginine group and in 9 of the 15 patients in the control group.

GRADE: very low quality

Study limitation: serious

Inconsistency: serious

Imprecision: serious

Publication bias: impossible to address

Conclusions:

There is little evidence from the randomised controlled trials reviewed here to guide the choice of intervention, patient groups or the value of preoperative supplementation. Clinically important end-points such as fistula formation, wound infection and pneumonia should be addressed. Any reduction in length of hospital stay needs to be explained. A suitable powered clinical trial is required before firm recommendations can be made on the use of immunonutrition in head and neck cancer patients postoperatively.

E15: Perioperative immunonutrition for gastrointestinal cancer: A systematic review of randomized controlled trials

PMID: 22317969

Reference: Zhang, Y., Gu, Y., Guo, T., Li, Y., & Cai, H. (2012). Perioperative immunonutrition for gastrointestinal cancer: A systematic review of randomized controlled trials. *Surgical Oncology*, 21(2), e87-95. doi: <http://dx.doi.org/10.1016/j.suronc.2012.01.002>.

Objectives:

The purpose of this study was to assess the effects of IN (immunonutrition) on postoperative complications and length of hospital stay through a meta-analysis based on randomized controlled trials (RCTs).

Studies Inclusion criteria:

Randomized controlled trials (RCTs) with or without blinding method.

Intervention:

The trials compared perioperative IN diet with standard diet. IN diet included at least two of following nutrients: arginine, glutamine, u-3 PUFA or RNA. IN administration was performed at three periods, including pre-operation period, both pre- and post-operation period, or post-operation regardless of the method of delivery e.g. orally or via a tube.

Population:

Patients with digestive system malignancy and undergoing elective surgery were considered.

Primary outcomes:

Postoperative complications (including infectious and non-infectious complications).

Length of hospital stay.

Primary outcomes as defined by us:

ECOG / QoL

Survival

Complications /LOS

Does it appear in the SR and meta-analysis? YES.

Years included in the search:

PubMed: 1995-2011.4

The Cochrane Library: 1995-2011.4

EMBASE: 1995-2011.4

Were additional RCTs on the subject published since then? NO

Methodological rigor:

Data extraction by more than one researcher: YES

Search strategy detailed: YES

Untoward restriction of search parameters: YES, Only articles written in English were considered to be eligible.

Was the methodological rigor of the individual studies appraised, and did it serve for analysis? YES

Were sub-group analyses of interest performed? YES

Was heterogeneity tested? YES

Was an attempt to explain heterogeneity made? NO

Was the meta-analysis conducted according to the degree of heterogeneity? YES

No of included studies: 19

No of included patients: 2331

Mean number of patients per study: 122

Study characteristics:

Characteristics of included randomized trials.

Trials	Yr	Patient (groups analyzed)	Group		Immunonutrition		
			Study	Control	Contents	Dose (4 days after operation)	Preop./postop duration (days)
Daly	1995	60 (30/30)	Postop.	ICN	Arg, n-3FA, RNA	25 kcal/kg/day	-/open
Schilling	1996	45 (14/14/13)	post	IC, IV	Arg, n-3FA, RNA	25 kcal/kg/day	-/open
Heslin	1997	195 (81/83)	Postop	IVF	Arg, n-3FA, RNA	25 kcal/kg/day	-/open
Senkal	1997	164(77/77)	Postop	IC	Arg, n-3FA, RNA	25 kcal/kg/day	-/5
Gianotti	1997	260(87/87/86)	postop	ICN, TPN	Arg, n-3FA, RNA	25 kcal/kg/day	-/7
Braga	1998	166(55/55/56)	postop	ICN, TPN	Arg, n-3FA, RNA	25 kcal/kg/day	-/8
Braga	1999	206(85/86)	periop	ICN	Arg, n-3FA, RNA	1 l/1.5 l	7/7
Di Carlo	1999	100(33/35/32)	postop	ICN, TPN	Arg, n-3FA, RNA	25 kcal/kg/day	-/open
Senkal	1999	178 (78/76)	Periop	ICN	Arg, n-3FA, RNA	1 l/(25 kcal/kg/day)	5/5
Braga	2002	150(50/50/50)	peri, pre	ICN	Arg, n-3FA, RNA	1 l/(28 kcal/kg/day)	7/7
Braga-2	2002	200(50/50/50/50)	peri, pre	ICN, RD	Arg, n-3FA, RNA	1 l/1.5 l	5/open
Gianotti	2002	305(101/102/102)	peri, pre	IV + RD	Arg, n-3FA, RNA	1 l/1.5 l	5/open
Farreras	2005	66(30/30)	Post	ICN	Arg, n-3FA, RNA	Harris-Benedict formula	-/7
Xu	2006	60(30/30)	pre	ICN	Arg, n-3FA, RNA	25 kcal/kg/day	7/-
Klek	2008	205(52/51/53/49)	Post	ICN	Arg, n-3FA, Glu,	75 ml/h	-/7
Gunerhan	2009	56 (13/11/9)	pre	IC, RD	Arg, n-3FA, RNA	Harris-Benedict formula	7/-
Okamoto	2009	60 (30/30)	pre	IC	Arg, n-3FA, RNA	750 ml/d	7/-
Suzuki	2010	30(10/10/10)	peri, post	TPN	Arg, n-3FA, RNA	750 ml/(25 kcal/kg/day)	5/7
Klek	2010	305(152/153)	Post	ICN	Arg, n-3FA, Glu	75 ml/h	-/7

preop, preoperative IN; postop, postoperative IN; periop, preoperative IN and postoperative IN combined; ICN, isocaloric and isonitrogenous; IC, isocaloric; TPN, total parenteral nutrition; IV, intravenous glucose or saline solution; RD, regular diet; Arg, arginine; n-3 FA, omega-3 fatty acids (unsaturated); Glu, glutamine.

Main outcomes:

Comparison between postoperative IN and standard diet (meta-analysis):

Postoperative infectious: complication was lower in IN group than that in standard diet group. Through pooled analysis, statistically significant differences were present between

the two groups (RR, 0.69; 95% CI, 0.57 to 0.84; $P < 0.01$).

Postoperative non-infectious complication: no significant differences were observed through pooled analysis (RR, 0.81; 95% CI, 0.41 to 1.59; $P = 0.54$).

Length of hospital stay: postoperative IN also had positive effect on length of hospital stay than that of standard diet group (WMD, -2.95; 95% CI, -4.57 to -1.32; $P < 0.01$).

Comparison between preoperative IN and standard diet:

Postoperative infectious: the pooled result indicated there were significant differences in risks of postoperative infectious complications (RR, 0.45; 95% CI, 0.31 to 0.65; $P < 0.01$).

Postoperative non-infectious complication: there is no statistical difference in postoperative non-infectious complication between perioperative IN and standard diet. But pooled result favoured perioperative use of IN (RR, 0.72; 95% CI, 0.54 to 0.97; $P = 0.03$).

Length of hospital stay: there were significant differences of length of hospital stay between two groups (WMD, -2.62; 95% CI, -3.26 to -1.97; $P < 0.01$).

Comparison between preoperative IN and perioperative IN:

Postoperative infectious: The pooled results showed that there were no statistical differences of postoperative infectious complication between two groups (RR, 1.12; 95% CI, 0.64 to 1.97; $P = 0.68$).

Postoperative non-infectious complication: No benefit of postoperative non-infectious complication could be obtained for use of IN (RR, 1.10; 95% CI, 0.78 to 1.56; $P = 0.57$).

Length of hospital stay: there were no significant differences in the length of hospital stay in three trials (WMD, -0.02; 95% CI, -0.75 to 0.71; $P = 0.96$).

GRADE: low quality

Study limitation: serious

Inconsistency: low

Imprecision: low

Effect size: medium

Publication bias: not addressed

Conclusions: perioperative IN contributed to reducing postoperative morbidity of postoperative infectious and non-infection complication as well as length of hospital stay.

E16: Nutritional screening in cancer patients: a systematic review

Methods:

Types of studies: We intended to include randomized controlled trials, and if these were not found – cohort studies.

Types of participants: Cancer patients.

Types of interventions: Nutritional assessment/screening tools based on anthropometric measures or nutritional questioners or combined.

Types of outcome measures: survival, quality of life, outcomes of treatment (chemotherapy/radiotherapy).

Search phrase:

(Cancer OR carcinoma OR malignancy OR lymphoma OR leukemia OR myeloma OR melanoma OR metastas* OR bone marrow transplant) AND (nutrition* OR Malnutrition) AND (screening OR assessment OR "Mini-Nutritional Assessment-Short Form" OR "MNA-SF" OR "Malnutrition Screening Tool" OR "MST" OR "Malnutrition Universal Screening Tool" OR "MUST")

Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study? PMID: 16093275

Reference: Freyer, G., Geay, J. F., Touzet, S., Provencal, J., Weber, B., Jacquin, J. P. & Pujade-Lauraine, E. (2005). Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study. *Annals of oncology*, 16(11), 1795-1800.

Objectives:

The aim of this study, specifically performed in elderly patients with stage III/IV ovarian carcinoma, was to evaluate the ability of some Comprehensive Geriatric Assessment (CGA) parameters to predict efficacy and tolerance of the carboplatin + cyclophosphamide combination, in order to identify which subgroups of elderly patients should receive standard or dose-reduced therapy and for whom chemotherapy would not be beneficial.

Study population:

Inclusion criteria: patients >70 years old with stage III or IV ovarian epithelial carcinoma, who met the following criteria: cytologically or histologically proven epithelial carcinoma, initial laparotomy or not, normal blood counts with neutrophils >1.5 g/l and platelets >100 g/l, no prior irradiation, and absence of icterus. A patient was eligible, regardless of PS (ECOG), if her treating physician considered that she could receive chemotherapy.

Study design:

The study was an open multicenter prospective study to identify prognostic factors.

Comprehensive Geriatric Assessment: During the consultation immediately preceding inclusion and first chemotherapy cycle, each patient completed with the investigator the CGA evaluation. Patient autonomy was assessed, comorbidities, mainly heart and vascular diseases, respiratory disease, diabetes, liver and kidney function test results were recorded, and the number of different drugs taken daily at baseline. Nutritional status was assessed by body mass index (BMI), protidemia, albuminemia and total cholesterol. Cognitive function was evaluated with the Mini-Mental Status (MMS) test. The presence or absence of clinical symptoms of depression was assessed by the investigator.

Outcomes:

From July 1998 to October 2000, 83 patients >70 years old with advanced ovarian carcinoma were enrolled in 30 centers.

Nutritional status was assessed as part of the Comprehensive Geriatric Assessment.

Comprehensive Geriatric Assessment: The median BMI was 22.89 (SD 4.05). The median total protidemia and albuminemia were 64 g/l (SD 8.08) and 31.3 g/l (SD 12.46), respectively. The median Mini-Mental Status (MMS) score was 27 (SD 6.41).

Chemotherapy tolerance: Sixty out of the 83 patients [72%; 95% confidence interval (CI) 64.5% to 80.2%] completed treatment without severe toxicity (STox) or tumor progression. Concerning hematological toxicities, grade 3/4 neutropenia, anemia and thrombocytopenia were observed in 28.7%, 9% and 8.3% of the cycles, respectively. There was no statistically significant predictive factor for grade 3/4 thrombocytopenia, which was observed in 39.5% of patients. Twenty-three patients (27.7%; 95% CI 19.9% to 39.3%) experienced STox: six developed febrile neutropenia, six discontinued treatment because of hematological toxicity, one grade 3 mucositis, one grade 3 asthenia, one death consecutive to cranial trauma, and hospitalization lasting >7 days for one patient with hematological toxicity, four patients with grade 3 infection, one with grade 4 infection, one with femoral trauma and one with thrombophlebitis. According to univariate analysis, the covariates reaching statistical significance were: PS (performance status) ≥ 2 ($P = 0.007$), dependence ($P = 0.017$) and symptoms of depression at baseline ($P = 0.006$). FIGO stage IV tended towards significance ($P = 0.075$). The multivariate analysis retained the following independent factors as predictive of STox: depression ($P = 0.006$), PS ≥ 2 ($P = 0.026$) and dependence ($P = 0.048$).

Survival: Median progression-free survival for the entire population was 9.9 months (95% CI 7.2–12.6). The multivariate analysis retained the following independent prognostic factors as being independently associated with poorer progression-free survival: depression ($P < 0.003$), FIGO stage IV ($P < 0.04$) and initial non-optimal surgery ($P < 0.008$). Median overall survival for the entire population was 21.6 months (95% CI 13.4–29.8). The multivariate analysis retained the following prognostic factors as being independently associated with poorer overall survival: depression ($P = 0.003$), FIGO stage IV ($P = 0.007$) and more than six different comedication drugs per day ($P = 0.04$).

Conclusions:

Nutritional status did not affect chemotherapy tolerance or progression free survival or survival. Screening was done but not clear if acted upon.

Methodological strength: Good (7 points on the Newcastle-Ottawa scale).

Nutritional Status Affects Treatment Tolerability and Survival in Metastatic Colorectal Cancer Patients: Results of an AGEO Prospective Multicenter Study PMID: 22269999

Reference: Barret, M., Malka, D., Aparicio, T., Dalban, C., Locher, C., Sabate, J. M. & Taieb, J. (2012). Nutritional status affects treatment tolerability and survival in metastatic colorectal cancer patients: results of an AGEO Prospective Multicenter Study. *Oncology*, 81(5-6), 395-402.

Objectives:

To evaluate the nutritional status of metastatic colorectal cancer (mCRC) patients receiving chemotherapy as well as its impact on treatment tolerability and overall survival.

Study population:

Patients receiving chemotherapy for mCRC were screened, on an inpatient or outpatient basis, in eight French gastroenterology or GI oncology departments.

The inclusion criteria were age > 18 years and mCRC currently treated with chemotherapy.

The exclusion criteria were: hepatic metastases from an unknown primary adenocarcinoma; adjuvant chemotherapy; concomitant radiotherapy, and surgery within 2 months before the date of inclusion (owing to the risk of

impaired nutritional status attributable to postoperative complications). Patients with a follow-up < 2 months were also excluded from the study, because of an insufficient amount of data, jeopardizing treatment tolerability evaluation. All chemotherapy regimens were allowed.

Study design:

A multicenter prospective study.

The following information was recorded in order to assess nutritional status: age; sex; usual weight (6 months before cancer diagnosis) and current weight; height; WHO performance status; symptomatic GI stenosis, and serum albumin level. The body mass index and nutritional risk index ($\text{NRI} = 1.519 \times \text{serum albumin level} + 0.417 \times \text{current weight/basic weight} \times 100$) were calculated. Based on the NRI, patients were classified as having 'no malnutrition' ($\text{NRI} > 97.5$), 'moderate malnutrition' ($97.5 \geq \text{NRI} \geq 83.5$) or 'severe malnutrition' ($\text{NRI} < 83.5$), as previously described.

Outcomes:

Of the 313 patients screened, 114 patients met the inclusion criteria and were enrolled to the study. Nearly half of the patients had a primary tumor in the descending colon, and 79% underwent curative or palliative surgical resection. Only 8% of the patients had GI stenosis.

Nutritional Assessment: Median values of nutritional parameters were within the normal ranges. Malnutrition was diagnosed in 65% of the cases, which was moderate and severe in 46 and 19% of the patients, respectively; 32.5% had a weight loss > 10%, and 2.6% had a body mass index < 18.5. Furthermore, almost half of the patients were overweight according to the body mass index.

Treatment Tolerability: Taking only clinically relevant (grade ≥ 2) events into account, overall toxicity (all events; $p = 0.01$), GI toxicity (diarrhea, nausea/vomiting, and/or mucositis; $p = 0.04$), and hematological toxicity ($p < 0.001$) were all more frequent in severely malnourished

patients than in patients with no or moderate malnutrition. Overall toxicity grade ≥ 2 was also more frequent in patients with hypoalbuminemia (albumin level < 35 g/l): 72 versus 54%, $p = 0.04$, and in patients with a weight loss $> 10\%$: 78 versus 56%, $p = 0.02$.

Survival: Median follow-up from the date of nutritional evaluation was 38.2 months (95% CI, 28.9–58.3). Progressive disease was diagnosed in 107 patients and median progression-free survival was 8.6 months (95% CI, 7.2–10.3). Progression-free survival did not correlate with nutritional status. Sixty-two of the 114 patients died during the study period. Median overall survival was 33.2 months (95% CI, 21.0–37.5). Severe malnutrition was associated with significantly reduced overall survival in the severely malnourished patients [14 (95% CI, 7.7–37.2) vs. 36 months (95% CI, 23.3–39.1) in the non- or moderately malnourished group; log rank test, $p = 0.02$]. Overall survival was also decreased in patients with hypoalbuminemia [median survival = 23.5 months (95% CI, 13.9–38.3 months) for patients with a serum albumin level < 35 g/l vs. 36.8 months (95% CI, 21–41.6 months) for patients with a serum albumin level > 35 g/l, log rank test, $p = 0.29$] and significantly decreased in patients with an important weight loss [median survival = 37.2 months (95% CI, 30.2–42 months) for patients with $< 10\%$ weight loss vs. 17.3 months (95% CI, 11.4–36.24 months), log rank test, $p = 0.01$]. In univariate analysis, the hazard ratio for overall survival was 2.1 (95% CI, 1.1–4.0, $p = 0.02$) in case of severe malnutrition. In multivariate analysis, including age, WHO performance status, number of metastatic sites, carcinoembryonic antigen (CEA) value, treatment line, chemotherapy protocol, and nutritional status, the only parameter linked to overall survival was CEA > 100 $\mu\text{g/l}$ (hazard ratio = 3.3, 95% CI, 1.84–5.76, $p < 0.001$). Major prognostic factors for CRC, such as age > 70 years ($p = 0.4$), right colon cancer ($p = 0.9$), > 2 metastatic sites ($p = 0.9$), and baseline CEA > 100 ng/ml ($p = 0.15$), were well balanced between severely malnourished and non- or moderately malnourished patients.

Conclusions:

Severely malnourished patients with metastatic CRC, identified using the NRI, had more frequent and more severe chemotherapy-related toxicities, and survival was shorter. The data underlines the need for systematic nutritional evaluation of mCRC patients at baseline, in order to detect severe malnutrition and to consider early nutritional intervention in these patients.

Methodological strength: Good (6 points on the Newcastle-Ottawa scale).

Nutritional Risk Factors in Planned Oncologic Surgery: What Clinical and Biological Parameters Should Be Routinely Used? PMID: 19387725

Reference: Antoun, S., Rey, A., Béal, J., Montange, F., Pressoir, M., Vasson, M. P. & Bachmann, P. (2009). Nutritional risk factors in planned oncologic surgery: what clinical and biological parameters should be routinely used?. World journal of surgery, 33(8), 1633-1640.

Objectives:

The aim of the present study was to determine the most relevant nutritional parameters not only in terms of an association with surgical morbidity but also of practical routine feasibility for cancer patients undergoing planned major surgery of any type.

Study population:

Two hundred seventy-five Patients (167 women, 108 men) that were admitted to a hospital for planned major surgical procedures over a 3 month period were included during the initial anaesthesia consultation. The average age of the participants was 57 years (median = 58 years, range = 17–86 years).

Inclusion criteria: adult patients undergoing major cancer surgery, including complex surgery for head and neck cancer (resection of oropharyngolaryngeal airways with or without reconstruction), esophageal and gastrointestinal surgery (resection of a segment of the digestive tract, esophagectomy, partial or total gastrectomy, colonic and rectal resections, reconstruction of bladder using the Bricker technique), pancreatic surgery, extensive retroperitoneal surgery, invasive surgery for gynaecological cancers, and surgical resection of peritoneal carcinosis (excluding intraperitoneal hyperthermic chemotherapy).

Exclusion criteria: any colioscopic procedure, intraperitoneal hyperthermic chemotherapy for peritoneal carcinosis, partial hepatectomy, isolated bile duct surgery, isolated urinary tract surgery, minor head and neck surgery (cervical dissection, lymph node biopsy, thyroid surgery), surgery to other sites of malignancy: breast, lung, limbs (sarcomas), and any emergency surgery.

Study design:

A prospective, observational, multicenter study involving 9 of the 20 French cancer centers.

Each patient was followed for 1 month after surgery for mortality and complications.

The clinical parameters and biological data studied were collected during the pre-anaesthesia consultation.

Every center organized the collection of the Ottery subjective score or PG-SGA according to local conditions (document given to the patient in the waiting room and partly completed by the nurse before the consultation).

Outcomes:

With respect to clinical parameters, no statistical correlation was discovered between BMI and morbidity or between $WL > 10\%$ and major surgical complications of either infectious or non infectious origin ($p = NS$). The only clinical parameter found to be linked with major surgical complications was PG-SGA, but this score was available for only 71% of the patients. No significant correlation was detected between $WL > 10\%$ and the presence of major complications, provided that a $WL > 15\%$ of the normal weight was taken as the cut-off value ($p = 0.03$). With respect to biological parameters, no statistically significant correlation was

found between transthyretin and surgical morbidity. Conversely, a substantial statistical correlation was found between albumin<30 g/l and major surgical complications (either infectious or non infectious) ($p<0.001$); this level provided 96% specificity with only 18% sensitivity. Albumin>30 g/l was also strongly correlated with the duration of hospital stay ($p<0.001$). The correlation between major complications and blood albumin levels remained high ($p = 0.001$), provided that the albumin cut-off value was set at a higher level of 35 g/l (80% specificity, 42% sensitivity). Length of hospital stay was also significantly correlated with weight loss, NRI, and PG-SGA score. With respect to the three surgical parameters evaluated, a statistical correlation was recorded only between a duration of the procedure longer than 4 h ($p<0.001$), the amount of red blood cell units transfused ($p = 0.03$), and the presence of major complications. There was no correlation with the ASA score.

The only two persistent variables tested in multivariate analysis and found statistically linked to major complications were blood albumin<30 g/l and procedures lasting longer than 4 h.

Conclusions: the prediction of not only major infectious but also major non infectious complications seemed less accurate with anthropometric features and clinical score than with albumin levels<30 g/l. With albumin level being the only variable found statistically linked to major complications in the multivariable analysis, collecting these data before surgery is mandatory.

Methodological strength: Good (6 points on the Newcastle-Ottawa scale).