A systematic review examining nutrition support interventions in patients with incurable cancer.

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Abstract

Purpose: Recent guidelines by the European Society for Clinical Nutrition and Metabolism (ESPEN) have advocated increased attention to nutritional support in all patients with cancer: however, little is known about the optimal type of nutritional intervention. The aim of this review was to assess the current evidence for nutrition support in patients with incurable cancer. **Methods:** This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. EMBASE, Medline and CINAHL were searched from 1990-2018. Evidence was appraised using a modified risk of bias table, based on guidance from the Cochrane Handbook for Systematic Reviews of Interventions. **Results:** Sixty studies were assessed of which twelve met the eligibility criteria. Eleven studies examined body composition, with six studies reporting improvements in weight. Six studies examined nutritional status with three studies reporting an improvement. Nine studies examined nutritional intake with six showing improvements including significant improvements in dietary and protein intake. Ten studies examined quality of life, with six studies reporting improvements following intervention. The most common nutritional interventions examined were nutrition counselling and dietary supplementation. **Conclusions:** There is moderate quality evidence to support the need for increased attention to nutrition support in patients with incurable cancer; however, despite some statistically significant results being reported the clinical effects of them were small. Key questions remain as to the optimal timing for these interventions to be implemented (e.g. cachexia stage, illness stage, timing with anticancer therapy) and the most appropriate endpoint measures.

Key words: Weight, supplements, cancer, nutritional interventions, cachexia, nutrition support

Introduction

Since the time of Hippocrates, cachexia has been associated with a poor outcome in patients with cancer.[1] Indeed, cancer cachexia results in increased mortality rates, with up to 20% of cancer deaths related to malnutrition.[2, 3]

Cachexia is not simply due to lack of adequate oral intake; rather, it's pathophysiology is complex and includes a combination of systemic inflammation and hyper-metabolism.[4] This, in combination with decreased oral intake and reduced physical function means that anabolism is impaired, resulting in loss of skeletal muscle.

With such a complex genesis it may at first seem daunting to address these multiple components however there is a plausible argument that multimodal therapies targeting each of these elements; inflammation, decreased oral intake and reduced physical function, is necessary to optimally treat cachexia.[5-7]

Appropriate nutritional intake is a key component of any intervention and this has recently been emphasized by the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on cancer-related malnutrition and cachexia. It is now advocated that increased attention is paid to nutritional interventions for all patients with cancer. [8]

Several key recommendations were subsequently made: nutritional intake should be screened regularly from the onset of cancer diagnosis, including those with advanced cancer; patients identified as having nutritional disturbance should undertake regular nutritional assessment including dietary intake, weight loss and body mass intake. [9]

In patients with cancer the nutritional aim is often about maintaining or improving nutritional status, function and survival. [10] However, in patients with incurable cancer the aim is often focused on improving quality of life and minimising symptoms such as nausea and vomiting which may impact on their nutritional intake. [11]

However, the evidence to support regular nutritional assessment in patients with incurable cancer is not clear. [9] There is a need to collate and evaluate the evidence concerning the clinical consequences of nutrition support via dietary interventions including nutrition counselling with or without the use of oral nutritional interventions.

The aim of this systematic review was to assess the current evidence for nutrition support via nutritional interventions implemented in patients with incurable cancer.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[12] Ethical approval was not required.

Search strategy and selection criteria

Original Studies with adult patients (>18 years) with incurable cancer (defined as not curable but might receive antineoplastic treatment aiming to prolong life and/or alleviate symptoms), evaluating the effect of oral dietary interventions were included. Eligible studies also had to have defined outcome measures such as, body composition; including weight (measured in kg, pound or percent change in lean body mass (LBM), total body mass (TBM) or fat mass (FM), nutritional intake; including energy intake (measured as kcal, kJ or MJ, absolute intake and/or energy balance), nutritional status; which were measured using validated tools such as the Patient Generated Subjective Global Assessment (PG-SGA) [13] and measurement of QoL using patient reported outcome measures such as the European Organisation for Research and Treatment of Cancer – Quality of Life - C30 (EORTC QLQ-C30) [14]. Both quantitative and qualitative trial designs were included.

Studies were excluded that evaluated the effect of either parental or enteral nutrition (including papers that evaluated mixed interventions that included enteral/parental nutrition). Studies were also excluded if the intervention was selected nutritional compounds such as certain vitamins, fatty acids, proteins or amino acids. Case reports, conference abstracts, systematic reviews or studies with ten or less participants were not included. Language was limited to English only.

The literature search was conducted in the following electronic databases; MEDLINE, Embase and CINAHL, with all databases being searched from 1990-2018. The last search date was the 25th October 2018. The search was performed by an experienced librarian. The search strategy for all databases is reported in appendix 1 (supplementary material). Appropriate strategies were developed for each database.

Appraisal process

All titles retrieved from the literature search were reviewed (HB) and if potentially eligible, studies were retrieved in full and appraised independently (HB, BL and EH). If all three authors agreed that the studies met the eligibility criteria these were then included in the review. Any disagreements regarding a trial were discussed between the three authors and a consensus agreed. The PRISMA statement for reporting systematic reviews was used [12].

Eligible studies are summarised (table 1) including risk of bias for each trial. Quality of studies was assessed by HB and CH using a modified risk of bias table, based on guidance from the Cochrane Handbook for Systematic Reviews of Interventions [15], and a summary table was developed (see table 2). The risk of bias for each patient-important outcome was evaluated and is presented in a modified summary of findings table (table 3).

Results

Search results and selection of studies

The literature search retrieved a total of 1139 papers (see Fig. 1). After screening of the titles and identifying any duplicates, a total of 60 studies remained. One thousand and eighteen studies were removed at title. After reviewing each study against the eligibility criteria, 48 studies were excluded. Twelve studies were eligible, of which eight were RCTs [6, 16-22], three prospective observational studies [23-25] and one post hoc analysis study. [26]

Twelve studies assessing a total of 1266 patients investigated the effect of nutritional interventions in patients with incurable cancer. Predominant cancer types were gastrointestinal (including pancreatic and colorectal) and lung, with over 40% receiving chemotherapy treatment.

Nutrition counselling with or without oral dietary intervention

Three studies (n=438) examined nutrition counselling with or without oral dietary intervention, two randomised controlled trials [16, 20] and one prospective observational study. [25] The prospective observational study examined nutrition counselling alone and the two RCT's examined nutrition counselling alongside an oral dietary intervention. One RCT compared the effects of nutrition counselling alone, the effect of ONS alone, the effect of

nutrition counselling and ONS in combination or no intervention. [16] The other RCT compared nutrition counselling and IAtta with nutrition counselling alone. [20]

Findings by Kapoor et al (2016) [20] reported that patients within the control arm had significantly decreased body weight (p=0.003), mid upper arm circumference (p=0.002) and body fat (p=0.002) by the end of the intervention. Although not significant, body weight gain was seen in the intervention group (p=0.08) as well as a significant increase of body fat (BF) (p=0.002) being observed. Patients in the intervention group also reported a significant improvement in fatigue (p=0.002) and appetite (p=0.006).

Baldwin et al's (2011) [16] RCT was stopped early on advice of the independent data monitoring committee due to lack of efficacy. There was no significant difference in survival or QoL between the groups. Patients in the intervention group weighed more at one year than those in control group, but no difference was seen between those receiving oral nutritional supplements (ONS) alone or the combination of ONS and dietary advice. There was no statistical difference between weight changes of non-survivors and survivors, however less weight loss was seen in the those who survived beyond 26 weeks.

Multimodal therapies alongside chemotherapy

Multimodal therapy e.g. dietary intervention and physical exercise, delivered alongside chemotherapy was examined in five studies (n=216) [6, 17, 21, 22, 24]; Four were RCT's [6, 17, 21, 22] while the other was a prospective observational study.[24]

Findings from Read et al (2006) [24] saw improvements in body composition including significant increase in mean weight at three weeks (p=0.03) with this remaining stable up to week nine. LBM also maintained throughout the nine weeks. Significant improvements were also seen in energy levels (p=0.03) between weeks three and nine, with all other QoL measures maintained. Dietary intake of n-3 fatty acids increased at week three and maintained up to week nine, this coincided with the commencement of the n-3 PUFA (polyunsaturated fatty acid) enriched ONS, this saw both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) improve significantly at week three and remaining high up to week nine. Significant decreases in nutritional intake including protein (p = 0.003) and energy (p =0.02) were seen following commencement of chemotherapy at the end of week three and nine.

Sanchez-Lara et al (2014) [21] also saw improvements in body composition. Significant differences were noted between groups ($p = 0.01$) for LBM which increased in the intervention group but decreased in the control group. The intervention group also had significantly greater energy and protein intakes ($p<0.001$) compared to those in the control group. No overall difference was seen in the response rate or survival between either group, but fatigue, neuropathy and loss of appetite decreased significantly in the intervention group ($p = \leq 0.05$ for all).

Breitkreutz et al (2005) [17] saw improvements in body composition including Fat Free Mass (FFM) increase in the intervention group compared to the control group. Body Cell Mass (BCM) decreased in the control group but was maintained within the intervention group, with significant intergroup differences between groups ($p<0.05$). QoL was also seen to improve more in the intervention group compared to the control group, but was not statistically significant.

Oral dietary interventions

Four studies examined the effect of oral dietary interventions alone (n=611). Two were RCT's, [18, 19] one exploratory prospective observational study, [23] and one post hoc analysis study. [26]

Fearon et al (2003) [18] showed that although consumption was below the recommended dose, the intervention group still showed a significant correlation between ONS intake and improved body composition, including weight gain ($p<0.001$) and an increase in LBM ($p<0.036$). Weight gain was also associated with improved QoL in the intervention group ($p<0.01$). However, no significant correlation was seen between intake and change in LBM between the two groups ($p<0.043$). Increased plasma EPA levels were also associated with weight and LBM gain ($p<0.01$).

Casas et al (2011) [23] showed significant differences in the intervention group for anxiety ($p =0.023$) and depression ($p = 0.011$), with QoL showing significant differences from baseline measurements between groups ($p = 0.017$). Significant differences were also seen between the groups in the global scale ($p = 0.016$) and fatigue scale ($p = 0.007$).

Summary of Findings

Twelve studies were identified, all from the outpatient setting. Following assessment of study quality using a modified risk of bias table, based on guidance from the Cochrane Handbook for Systematic Reviews of Interventions, [15] we have shown that there is moderate quality evidence to support the need for increased attention to nutrition support in patients with incurable cancer; however, despite some statistically significant results being reported the clinical effects of them were small.

Body composition

Eleven studies examined body composition as an outcome measure. Six reported an increase in weight [6, 17, 20, 22, 24, 26] of which one, looking at a combination of nutrition counselling and ONS alongside chemotherapy, reported an increase in FFM ($p<0.05$) and maintenance in BCM compared to the control group [17]. One study, examining the effects of IAtta, reported an increase in body weight gain ($p=0.08$) with significant increase in body fat ($p=0.002$) [20]. Only one study, examining nutrition counselling with the emphasis on restricting carbohydrates, reported significant weight loss following intervention. [25] Four studies reported weight stability [16, 18, 19, 21], although one of those studies, examining nutrition counselling and consumption of an n-3 PUFA enriched ONS alongside chemotherapy, reported an increase in LBM.[21] Of the six studies reporting an improvement in body composition, one study examined nutrition counselling alongside dietary intervention of IAtta [20], one study examined the effect of an n-3 PUFA enriched ONS [26] and four studies examined multimodal therapies alongside chemotherapy. [6, 17, 22, 24]. Of the six studies which saw improvements, all examined an oral dietary intervention, five of which were ONS, [6, 17, 22, 24, 26] with three of those being an n-3 PUFA enriched ONS and one examined IAtta. [20]

QoL

Eleven studies examined QoL as an outcome measure with eight studies reporting an improvement in QoL, measured on various subscales (three studies saw significant improvements, [20, 21, 23] and five studies saw non-significant improvements), [17, 18, 22, 25, 26] compared to the control group and three studies reporting no difference between groups [16, 19, 24]. Of the eight studies reporting an improvement in QoL, two were examining the effect of nutrition counselling alongside a dietary intervention [20, 25], three examined an oral nutritional intervention, [18, 23, 26] including one examining ice cream as a dietary intervention compared to ONS. [23] Three studies examined multimodal therapies alongside chemotherapy. [17, 21, 22] Of

the eight studies which saw improvements in QoL, seven examined an oral dietary interventions, of which six were ONS, [17, 18, 21-23, 26] with four of those being an n-3 PUFA enriched ONS, and one study examined IAtta as a dietary intervention. [20] The remaining study was examining nutrition counselling aimed at restricting carbohydrates. [25]

Nutritional intake

Nine studies examined nutritional intake as an outcome measure, with six studies reporting an improvement in nutritional intake [17-21, 26] including protein and energy intake ($p<0.01$), and three studies reporting a reduction in appetite loss [19-21]. Only one of these studies, examining nutrition counselling and consumption of an n-3 PUFA enriched ONS alongside chemotherapy, reported a decrease in intake following commencement of chemotherapy. [24] One study, examining nutrition counselling alongside an oral dietary intervention, failed to analyse nutritional intake due to compliance issues with the outcome tool used, [16] and one study, examining nutrition counselling and consumption of an n-3 PUFA enriched ONS alongside chemotherapy, showed no difference between groups. [22] Of the six studies reporting an improvement in nutritional status, one examined nutrition counselling alongside dietary intervention, [20] and three examined an oral dietary intervention, [18, 19, 26] and two examined multimodal therapies alongside chemotherapy. [17, 21] Of the six studies which saw improvements, all examined an oral dietary intervention, four were examining ONS, [17, 18, 21, 26], including 3 of those examining n-3 PUFA enriched ONS, one study examined IAtta as a dietary intervention [20] and the final study examined ice cream as a dietary intervention. [23] Of the six studies which saw improvements in nutritional intake, three of these also saw improved QoL [17, 20, 21], with three studies seeing improvements in body composition including weight [17, 20, 26], free fat mass (FFM) [17] and body fat (BF).[20]

Nutritional status

Six studies examined nutritional status as an outcome measure with three studies seeing improvement in nutritional status [20, 21, 23]. Three studies reported no differences between groups.[6, 22, 24] Of the three studies that reported improvements in nutritional status, one study examined ice cream as a dietary interventions compared to ONS [23], one study was examining nutrition counselling alongside the addition of IAtta [20] and one study examined nutrition counselling and the consumption of an n-3 PUFA enriched ONS alongside chemotherapy. [21] Of the three studies which saw improvements, all examined an oral dietary intervention, one

examined an n-3 PUFA enriched ONS, [21], one examined IAtta [20] and the last one examined ice cream as a dietary intervention, compared to ONS. [23]

Discussion

There is limited evidence as to the most effective nutrition intervention for patients with incurable cancer, despite various guidelines.[8, 27] This review examined the effects of nutrition support in patients with incurable cancer.

The National Institute for Clinical Excellence (NICE) [27] guidelines and the ESPEN guidelines [8] highlight the need for early nutritional screening in order to identify patients who are malnourished. Diagnostic criteria for cachexia have been developed and used to classify patient's degree of cachexia, these consider; food intake, catabolic drivers, muscle mass/strength and effect of cachexia on the patient.[4] Cachexia classifications highlight that if cachexia is present, it can develop progressively from pre-cachexia to cachexia and on to refractory cachexia which cannot be fully reversed by conventional nutrition support and leads to progressive functional impairment. The studies included in this review did not classify the stage of cancer cachexia in which interventions were delivered. It would be interesting in future work to assess optimal timings of delivery of nutritional interventions. Should the cachexia classification criteria be used routinely for cancer patients, alongside nutritional assessments in order to identify as early as possible, those who are not only malnourished but at risk of cachexia and to what degree? This should be considered for patients when they are initially diagnosed with cancer and regularly screened throughout their cancer journey to minimise the risk of developing malnutrition/cachexia complications and/or prevent further deterioration which may impact on their functional status.[28]

Nutrition counselling is considered the most appropriate first line nutritional intervention [8, 27] and the findings herein support this. Further aspects however need to be considered including; who is the best person to conduct the nutritional intervention, when should this take place, and should advice be standardised.[29] Patients are often provided with nutritional advice at varying time points of their journey from different health professionals and advice can often be conflicting or incorrect. Symptoms as a result of deteriorating status or from cancer treatment also need to be taken into consideration when providing nutritional advice as these can often have a negative effect on oral intake.[30] The type of interventions within studies should therefore be clearly described for both the control and the intervention group as well as timeframes undertaken.

High attrition rates are common in studies involving palliative care patients, and this was also evident in the studies examined in this review, with attrition rates over 40% recorded in three studies [18, 20, 26], this is often due to the frail nature of this patient group leading to withdrawal and high dropout rates. [31]

Appropriate outcome measures also need to be considered and it is imperative in palliative care that these are relevant to assess appropriate palliative goals of care. Various tools have been developed such as the PG-SGA [13] to measure nutritional outcomes but there is no defined consensus on which tools are most appropriate. Due to the nature of this patient group, patients can often be too unwell, frail or fatigued to complete self-completed measurements. This can lead to reporting bias whereby frailer patient data is not included or missing. [32, 33]

Limitations

Relevant studies may have been missed in this review, despite a thorough search strategy being implemented, however we believe we identified all appropriate studies. Meta-analysis of studies was not possible due to the differences in trial designs. Multiple assessors assessed study quality to limit any risk of bias, and any discrepancies were discussed in detail, then agreed upon. Baldwin et al [16] highlights that although RCT's are the gold standard these are difficult to undertake for nutritional intervention studies. They argue it is often impossible to blind both the participants and the person undertaking the intervention or to have a placebo for the control group which can often then lead to bias [29]: indeed this was the case for most of the studies included in this review. This study also reviewed observational studies, which are often seen as inferior to RCT's due to high risk of confounding factors and selection bias of patients. [34]

Conclusion

This review demonstrates moderate evidence for nutrition support in patients with incurable cancer, which supports the recommendations by ESPEN for increased attention to nutritional support in this patient group. Further high-quality studies are needed in order to identify the most appropriate types of nutritional interventions.

Conflict of interest

None declared. This has been presented in poster format at the 11th International SCWD conference on cachexia, sarcopenia and muscle wasting.

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Table 1: Study summaries

Author/year	Study type	Participants	Intervention	Intervention specifics	Control	Main outcomes (measures)	Main findings	Risk of bias
Breitkreutz et al 2005 [17]	Randomised controlled trial	N = 23 Histologically proven GI adenocarcinoma. Stage T2-T4 – all metastatic. All advanced or non resectable disease, therefore patients received chemotherapy. Outpatients	Combined therapy alongside chemotherapy	Group B - Usual care + ONS (providing 20 non-protein kcal/kg per day; 100ml contained 9.3g of fat) + nutrition counselling every 14 days. Nutritional target for both groups was 35 non-protein kcal/kg per day + 1.1g of protein/kg per day. 8 weeks.	Group A - Usual care + nutrition counselling every 14 days	Changes in body composition (BW, BIA, TBW, FFM, TBF, BCM, ECM) QoL (LASA scale)	FFM increased significantly in Group B compared to Group A ($P<0.05$) after 8 weeks. BCM significantly decreased in group A compared to maintaining in group B (not statistically significant) QoL improved more in Group B compared to group A (not statistically significant).	Unclear
Baldwin et al. 2011 [16]	Prospective randomised controlled trial	N = 358 Metastatic or locally advanced cancer of the GI tract, non-small cell lung or mesothelioma all agreeing to undergo palliative chemotherapy. Outpatients	Nutrition counselling +/- oral dietary intervention	Randomly allocated to receive nutrition counselling via dietitian, ONS or nutrition counselling via dietitian plus ONS + followed up weekly over a 6-week period.	No intervention	Mortality	Trial stopped early due to lack of efficacy. No significant differences seen.	High

Author/year	Study type	Participants	Intervention	Intervention specifics	Control	Main outcomes (measures)	Main findings	Risk of bias
Bauer et al 2005 [26]	Post hoc analysis	N = 200 Unresectable pancreatic adenocarcinoma Outpatients	ONS	Consumption of 2 energy + protein dense, n-3 PUFA enriched (1.1g EPA each) ONS. 8 weeks.	Consumption of 2 isocaloric ONS without n-3 fatty acid enrichment.	Body composition (Wt., LBM, BIA, TBW), intake (3-day food diary) + QoL (EORTC-QLQC30)	Significant differences in energy + protein intake + weight in compliant pts compared to non-compliant pts. (P<0.050).	Unclear
Solheim et al 2017 [6]	Randomised controlled trial	N = 46 Stage 3/4 non-small cell lung and pancreatic cancer due to start chemotherapy Outpatients	Combined therapy alongside chemotherapy	300mg Celecoxib once daily, two x 220ml 1g n-3 PUFA enriched ONS daily + 30min nutrition counselling, 60minutes of home-based aerobic exercises weekly + 3 days of 20min resistance exercises weekly + chemotherapy 6 weeks	Standard care + chemotherapy	Feasibility (recruitment, attrition, compliance with intervention and contamination of the control arm)	Compliance acceptable in all components other than the ONS (48%). Plasma EPA levels increased in both groups significantly higher in treatment arm. Mean weight increase (1.29%) seen in intervention group compared to wt. loss in control group (P = 0.001). No statistical differences were seen in muscle mass, physical activity, nutritional status or intake between groups.	High
Fearon et al 2003 [18]	Randomised double blind controlled trial	N = 200 Advanced unresectable pancreatic ca. Outpatients	ONS	2 x n-3 PUFA enriched (1.1g EPA each) + antioxidant enriched ONS daily + usual diet. 8 weeks.	2 x ONS (without n-3 + antioxidants) + usual diet.	Body composition (Wt., BIA, TBW, LBM), dietary intake (3-day diet diaries) + QoL (EuroQol EQ-5D and EORTC QLQ-C30)	Mean rate wt. loss at enrolment 3.3kg/month. Consumption of ONS below recommended dose. Intervention group showed significant correlation between ONS intake + wt. gain (P<0.001) + increase in LBM (P<0.036). No significant correlations in control group. Significant correlation between intake and change in LBM between groups (P<0.043). Wt. gain was associated with improved QoL in intervention group (P<0.01). Increased plasma levels associated with wt. + LBM gain (P<0.01)	High

Author/year	Study type	Participants	Intervention	Intervention specifics	Control	Main outcomes (measures)	Main findings	Risk of bias
Casas et al 2011 [23]	Exploratory prospective observational study	N = 70 Mixed stage III and IV cancers. Outpatients	Ice cream	Group 1: 2 x 90g ice cream servings daily. Duration not stated	Group 2: 200ml ONS of 2-3 daily shots	QoL (HADS and EORTC QLQ C30)	Significant differences seen in group 1 for anxiety ($p = 0.023$) + depression ($p = 0.011$). QoL significantly different from baseline between groups ($p = 0.017$). Significant differences between groups in global scale ($p = 0.016$) + fatigue scale ($p = 0.007$).	Low
Jatoi et al 2016 [19]	Randomised controlled trial	N = 141 Advanced cancer patients including lung + gastrointestinal. Patients were permitted to receive chemotherapy or radiation whilst participating in study (with 50% planned to undertake this) Outpatients	Wine	Patients randomly assigned to one of two treatment arms. Treatment arm 1 – white wine with <15% alcohol content twice daily + ONS. 3-4 weeks.	Treatment arm 2 – ONS (+ no alcohol)	Appetite improvement (NCCTG, FAACT, food diary, adherence questionnaire)	48% pts in wine arm + 37% pts in ONS arm reported improvements in appetite (not significantly improved). Wt. stability was achieved in ~9% pts in both arms (not significantly improved).	High

Author/year	Study type	Participants	Intervention	Intervention specifics	Control	Main outcomes (measures)	Main findings	Risk of bias
Kapoor et al 2017 [20]	Randomized Controlled Trial	N = 63 Free living cachectic female advanced ca pts. Various cancer types. Outpatients	Nutrition counselling +/- oral dietary intervention	30 min nutrition counselling + 100g of Improved Atta (IAtta - nutritious flour mix) - consumed in addition to normal dietary intake. Appointments every fortnight. Physical activity also encouraged in pts. 6 months	30 min nutrition counselling with twice monthly appointments.	Anthropometric status (Body wt. MUAC, SFT, BF%) + QoL (EORTC QLQ C30)	Pts in control group had significantly decreased body weight (P = 0.003), mid–upper-arm circumference (P = 0.002) + body fat (P = 0.002) by end of intervention. Body weight gain in intervention group (not statistically significant P = 0.08) + significant increase of body fat (P = 0.002) was observed. Pts reported a significant improvement in fatigue (P = 0.002) + appetite scores (P = 0.006) under quality-of-life domains at end of intervention.	Unclear
Read et al 2016 [24]	Prospective observational study	N = 23 Histologically confirmed diagnosis of stage IV CRC receiving irinotecan Outpatients	Combined therapy alongside chemotherapy	Pts were instructed to consume 2 x 1.09g n-3 PUFA enriched ONS. Chemotherapy commenced at wk. 4 + repeated every 2 wks. 9 weeks.	No control	Nutritional status PG-SGA), body composition (BIA, FFM, FM, TBW), QoL (DATA), plasma phospholipids (PPL), CRP, cytokines + chemotherapy toxicity (NCICTC)	Significant increase in mean weight at 3 weeks (p=0.03). LBM was maintained (not statistically significant). Protein + energy intake significantly decreased after commencement of chemo (protein p=0.003, energy p=0.02). Significant increase in energy levels (p=0.03) and overall wellbeing (P=0.05). All other QOL measures were maintained (not significantly significant). PPL EPA levels increased significantly over the 1st 3wks. Mean CRP increased over the first 3 wks. (p=0.004) but decreased to baseline levels by end of trial. There was a significant correlation between plasma IL-6 and IL-10 concentrations + survival + between IL-12 + toxicity.	High

Author/year	Study type	Participants	Intervention	Intervention specifics	Control	Main outcomes (measures)	Main findings	Risk of bias
Sanchez-Lara et al 2014 [21]	Randomised controlled trial	N = 112 Stage IIIb + IV histologically confirmed NSCLC Outpatients	Combined therapy alongside chemotherapy	Standardised menus + 2 x n-3 PUFA enriched ONS. Both groups had isocaloric diets. All patients received paclitaxel (175mg/m_2) + cisplatin (75mg/m_2)/carboplatin (AUC6) every 3 wks. for at least 2 cycles (with max 6 cycles) Duration not stated	Standardised menus of 1400, 1600, 1800, 2000 or 2200kcal. All patients received paclitaxel (175mg/m_2) + cisplatin (75mg/m_2)/carboplatin (AUC6) every 3 wks. for at least 2 cycles (with max 6 cycles)	Effect on body composition (Wt. BIA, FM, LBM), nutritional intake (food frequency questionnaire, intake diaries), inflammatory parameters, HRQoL (EORTC QLQ C30 + QLQ LC13), response + toxicity to chemo (CTCAE) + survival.	Intervention group had significantly greater energy ($P<0.001$) + protein ($P<0.001$) intakes compared to control group. LBM increased in intervention group but decreased in control group with significant differences seen between groups ($p = 0.01$). No difference in response rate or overall survival between groups. Fatigue, neuropathy + loss appetite significantly decreased in intervention group with a significant difference seen between groups.	High
Tan-Shalaby et al 2016 [25]	Prospective observational study	N = 17 Advanced, metastatic, and unresectable malignancies of various types. Outpatients	Nutrition counselling	Pts were allowed 20-40 g CHO/day during a 2-day screening period. Pts were advised on grocery shopping, + menu planning. Consumption of high carbohydrate foods were restricted. Calories and protein not restricted. 16 weeks	No control	Safety + feasibility (EORTC QLQ C30)	All lost significant wt. with hematologic, biochemical + lipid tests remaining stable. QoL scores remained stable (not statistically significant). No significant correlations between serum glucose, ketones or lipids. Responders (stable disease or partial responders) lost statistically more wt. than non-responders. Dietary compliance was difficult.	High

Author/year	Study type	Participants	Intervention	Intervention specifics	Control	Main outcomes (measures)	Main findings	Risk of bias
Trabal et al 2010 [22]	Randomised controlled trial	N = 13 Stage IV colorectal cancer included. Chemotherapy regimens administered were 5-Fluorouracil + Oxaliplatin + Folinic acid or Capecitabine. Outpatients	Combined therapy alongside chemotherapy	2 n-3 PUFA enriched ONS/day + nutrition counselling + chemotherapy 12 weeks	Nutrition counselling + chemotherapy	Nutritional status (PG-SGA), dietary intake (food diary), tolerability (EORTC QLQ C30) + chemotherapy compliance.	Intervention group significantly increased wt. after intervention + better scores in important domains of HRQoL, compared to controls (not statistically significant). Supplemented group did not experience interruptions in chemo treatment compared to control group, with more interruptions due to toxicity.	Low

Table 2. Quality of studies - Risk of bias summary

Reference	Trial design	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias*
Baldwin et al [16]	RCT	Y	Y	N	Y	Y	N	Low
Bauer et al [26]	Post hoc analysis	N/A	N/A	N/A	N	Y		Unclear
Breitkreutz et al [17]	RCT	U/C	U/C	U/C	Y	Y	N	Unclear
Casas et al [23]	Prospective observational study	N/A	N/A	N/A	N	Y	N	High
Fearon et al [18]	RCT	Y	Y	Y	Y	Y		Low
Jatoi et al [19]	RCT	Y	U/C	Y	Y	Y		Low
Kapoor et al [20]	RCT	U/C	U/C	U/C	Y	Y		Unclear
Read et al [24]	Prospective observational study	N/A	N/A	N/A	Y	Y		Low
Sanchez-Lara et al [21]	RCT	Y	Y	N	Y	Y		Low
Tan-Shalaby et al [25]	Prospective observational study	N/A	N/A	N/A	Y	Y	N	Low
Solheim et al [6]	RCT – open label	Y	U/C	X	Y	Y		Low
Trabal et al [22]	RCT – open label	U/C	U/C	N	N	Y	N	High

Y = low risk of bias, N = high risk of bias, U/C = risk of bias unclear

*Risk of bias	Definition (Cochrane Handbook for Systematic Reviews of Interventions) [15]
HIGH	Plausible bias that seriously weakens confidence in the results.
LOW	Plausible bias unlikely to seriously alter the results.
UNCLEAR	Plausible bias that raises some doubt about the results.

Table 3: Summary of Findings: (Modified due to study types)

Patient- Important Outcomes	Studies	N= Total Participants** † (Breakdown per outcome measure	Risk of bias	Comments
Quality of Life	**11** [16-26]	**n = 739** EORTC-QLQ-C30 (570) FAACT (271) HRQOL (13) Euro-QoL EQ-5D (110) QLQ-LC13 (84) DATA form (15) HADS (70) LASA scale (23)	**Low**	Improvements seen in two studies of high-quality evidence, two studies of low quality of evidence and two studies where quality of evidence was unclear. Four further high-quality evidence studies and one study where quality of evidence was unclear, reported no differences.
Body composition	**11** [6, 16-22, 24-26]	**n = 710** Weight (594) MM (41) MUAC (32) SFT (32) LBM (319) TBW (258) FM (99) FFM (38) TBF (23) BCM (23) ECM (23)	**Low**	Improvements seen two high-quality evidence studies, one low-quality evidence study and three studies which it was unclear regarding quality of evidence. Of the other studies reporting on body composition. Four high, quality evidence studies reported weight stability with one high quality study reporting weight loss following intervention. Limitations were seen in the studies.
Nutritional status	**6** [6, 20-24]	**n =255** PG-SGA (158) SGA (97) AveS (41)	**Low**	Improvements in nutritional status were seen in three studies, one high quality study, one low quality study and one study where quality of evidence was unclear. The remaining three studies reporting no differences between groups.

Nutritional intake	**9** [16-22, 24, 26]	**n = 658** Food diaries (424) 24 hr dietary recall (32) IMS-FFQ (32) NCCTG (118) SNUT (food frequency questionnaire) (84)	**Low**	Improvements in nutritional intake was seen in six studies. Three studies were of high-quality evidence with three studies, quality of evidence was unclear. Of the remaining studies to report on nutritional intake, one was unable to analyse the data due to compliance issues, one study showed no difference between groups. Only one study showed a reduction in intake following commencement of treatment.

** Total participants include final numbers analysed within studies for each outcome as opposed to table 1 showing 'n' as numbers enrolled in to each trial.

†Some studies used more than 1 tool to assess an outcome

Abbreviations

Patient generated subjective global assessment (PG-SGA)	Skin fold thickness (SFT)	Free fat mass (FFM)	Functional assessment of anorexia/cachexia treatment (FAACT)
Subjective global assessment (SGA)	Lean Body Mass (LBM)	Total body fat (TBF)	Health related quality of life (HRQoL)
Muscle mass (MM)	Total body water (TBW)	Body cell mass (BCM)	Hospital anxiety and depression scale (HADS)
Mid upper arm circumference (MUAC)	Fat Mass (FM)	Extra cellular mass (ECM)	Linear analog scale assessment scale of quality of life (LASA scale)
Patient (Pt.)	Cancer (Ca)	European organisation for research and treatment of cancer quality of life (EORTC-QLQ-C30)	North Central Cancer treatment group (NCCTG)
Body weight (BW)	Weight (Wt.)	Euro QoL EQ 5D	Eicosapentaenoic acid (EPA)
Body fat percentage (BF%)	Bioelectrical impedance analysis (BIA)	National Cancer Institute Common Toxicity Criteria (NCICTC)	
National Cancer Institute common toxicity criteria for adverse events (CTCAE)	Disease and treatment assessment form (DATA)		
	Oral nutritional supplement (ONS)		

Identification

Records identified through database searching
(n = 1139)

Records excluded (n = 1018)

- Systematic review (5)
- No nutritional intervention (512)
- Mixed cancer stages (106)
- Article (20)
- Non-cancer participants (109)
- Enteral/Parental intervention (125)
- No intervention (14)

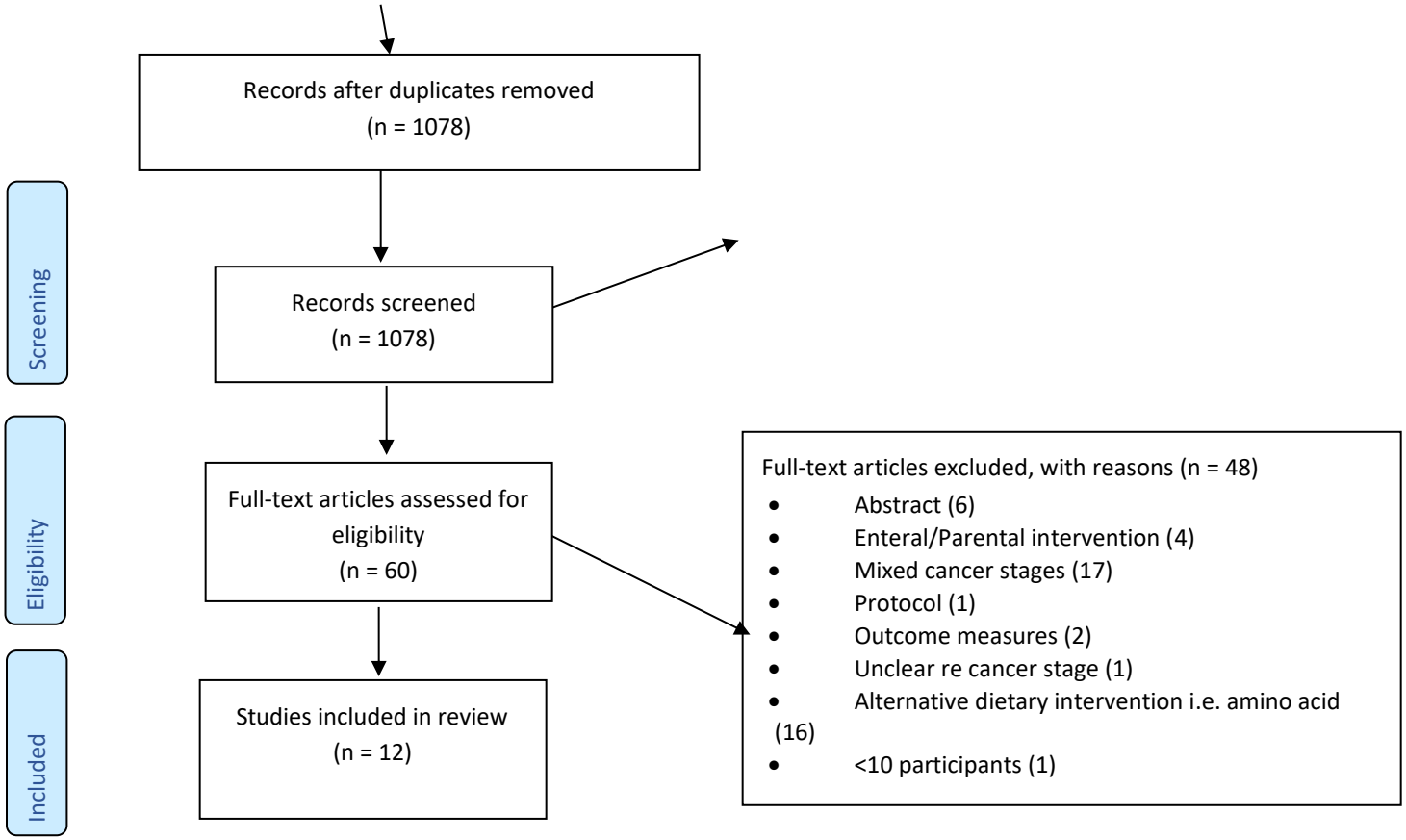

Fig 1. Literature search process

Appendices

Appendix 1: Search Strategy (supplementary material)

CINAHL strategy (librarian).docx

Embase strategy (librarian).docx

MEDLINE strategy (Librarian).docx