Supportive Care in Cancer (2020) 28:1877–1889
https://doi.org/10.1007/s00520-019-04999-4

ORIGINAL ARTICLE

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

Honor A. Blackwood[1] · Charlie C. Hall[1,2] · Trude R. Balstad[3,4] · Tora S. Solheim[3,4] · Marie Fallon[2] · Erna Haraldsdottir[1,5,6] · Barry J. Laird[1,2]

Received: 14 March 2019 / Accepted: 16 July 2019 / Published online: 29 July 2019

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 to 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 and timing with anticancer therapy) and the most appropriate endpoint measures.

Keywords Weight · Supplements · Cancer · Nutritional interventions · Cachexia · Nutrition support

This has been presented in poster format at the 11th International SCWD Conference on Cachexia, Sarcopenia and Muscle Wasting.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00520-019-04999-4) contains supplementary material, which is available to authorized users.

✉ Honor A. Blackwood
hblackwood@stcolumbashospice.org.uk

Barry J. Laird
barry.laird@ed.ac.uk

[1] St Columba's Hospice, Centre for Education and Research, Edinburgh, UK

[2] Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

[3] Cancer Clinic, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

[4] Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, NTNU–Norwegian University of Science and Technology, Trondheim, Norway

[5] Queen Margaret University, Edinburgh, UK

[6] School of Health Sciences, University of Iceland, Reykjavík, Iceland

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, its 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, are necessary to optimally treat cachexia [5–7].

Appropriate nutritional intake is a key component of any intervention, and this has recently been emphasised 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 index [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 aimed at prolonging life and/or alleviate symptoms) and 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); and nutritional status, which were measured using validated tools such as the Patient Generated Subjective Global Assessment (PG-SGA) [13], and quality of life (QoL) was measured 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 (via feeding tube) nutrition (including papers that evaluated mixed interventions that included enteral/parental nutrition). Studies were also excluded if the intervention 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 to 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 was agreed upon. The PRISMA statement for reporting systematic reviews was used [12].

Eligible studies are summarised (Table 1) including risk of bias for each trial. Study quality 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 (Table 2). The risk of bias for each patient-important outcome was evaluated and is presented in the table of modified summary of findings (Table 3).

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 [18]	Randomised controlled trial	$N = 23$ Histologically proven GI adenocarcinoma. Stage T2–T4—all metastatic. All diseases are advanced or non-resectable; therefore, patients received chemotherapy Outpatients	Combined therapy alongside chemotherapy	Group B—usual care + ONS (providing 20 non-protein kcal/kg per day; 100 ml contained 9.3 g of fat) + nutrition counselling every 14 days Nutritional target for both groups was 35 non-protein kcal/kg per day + 1.1 g 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 with group A ($p < 0.05$) after 8 weeks BCM significantly decreased in group A compared with maintaining in group B (not statistically significant) QoL improved more in group B compared with 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
Bauer et al. 2005 [17]	Post hoc analysis	$N = 200$ Unresectable pancreatic adenocarcinoma Outpatients	ONS	Consumption of 2 energy + protein dense, n-3 PUFA enriched (1.1 g 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 QLQ-C30)	Significant differences in energy + protein intake + weight in compliant pts compared with 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	300 mg celecoxib once daily, two × 220 ml 1 g n-3 PUFA-enriched ONS daily + 30 min nutrition counselling, 60 min of home-based aerobic exercises weekly + 3 days of 20-min 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 the intervention group compared with wt. loss in the 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 [20]	Randomised double-blind controlled trial	$N = 200$ Advanced unresectable pancreatic ca. Outpatients	ONS	2 × n-3 PUFA-enriched (1.1 g EPA each) + antioxidant-enriched ONS daily + usual diet	2 × ONS (without n-3 + antioxidants) + usual diet	Body composition (Wt., BIA, TBW, LBM), dietary intake (3-day diet diaries) + QoL	Mean rate wt. loss at enrolment 3.3 kg/month. Consumption of ONS	High

Table 1 (continued)

Author/year	Study type	Participants	Intervention	Intervention specifics	Control	Main outcomes (measures)	Main findings	Risk of bias
				8 weeks		(EuroQol EQ-5D and EORTC QLQ-C30)	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 the control group. Significant correlation between intake and change in LBM between groups ($p < 0.043$). Wt. gain was associated with improved QoL in the intervention group ($p < 0.01$). Increased plasma levels associated with wt. + LBM gain ($p < 0.01$)	
Casas et al. 2011 [19]	Exploratory prospective observational study	$N = 70$ Mixed stage III and IV cancers Outpatients	Ice cream	Group 1: 2 × 90 g ice cream servings daily Duration not stated	Group 2: 200 ml 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 the global scale ($p = 0.016$) + fatigue scale ($p = 0.007$)	Low
Jatoi et al. 2016 [21]	Randomised controlled trial	$N = 141$ Advanced cancer patients including lung + gastrointestinal. Patients were permitted to receive chemotherapy or radiation while participating in the 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 the wine arm + 37% pts in the ONS arm reported improvements in appetite (not significantly improved) Wt. stability was achieved in ~ 9% pts in both arms (not significantly improved)	High
Kapoor et al. 2017 [22]	Randomised controlled trial	$N = 63$		30-min nutrition counselling + 100 g of improved atta		Anthropometric status (body wt. MUAC, SFT,	Pts in the control group had significantly	Unclear

Table 1 (continued)

Author/year	Study type	Participants	Intervention	Intervention specifics	Control	Main outcomes (measures)	Main findings	Risk of bias
		Free-living cachectic female advanced ca pts Various cancer types Outpatients	Nutrition counselling ± oral dietary intervention	(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	BF%) + QoL (EORTC QLQ-C30)	decreased body weight ($p = 0.003$), mid-upper arm circumference ($p = 0.002$) + body fat ($p = 0.002$) by the end of the intervention. Body weight gain in the intervention group (not statistically significant $p = 0.08$) + significant increase in 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 the end of the intervention	
Read et al. 2016 [23]	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 × 1.09 g n-3 PUFA-enriched ONS. Chemotherapy commenced at wk. 4 + repeated every 2 weeks 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 3 weeks. Mean CRP increased over the first 3 wks. ($p = 0.004$) but decreased to baseline	High

Table 1 (continued)

Author/year	Study type	Participants	Intervention	Intervention specifics	Control	Main outcomes (measures)	Main findings	Risk of bias
							levels by the end of the trial. There was a significant correlation between plasma IL-6 and IL-10 concentrations + survival + between IL-12 + toxicity	
Sanchez-Lara et al. 2014 [24]	Randomised controlled trial	$N = 112$ Stage IIIb + IV histologically confirmed NSCLC Outpatients	Combined therapy alongside chemotherapy	Standardised menus +2 × n-3 PUFA enriched ONS Both groups had isocaloric diets All patients received paclitaxel (175 mg/m^2) + cisplatin (75 mg/m^2)/ carboplatin (AUC6) every 3 weeks for at least 2 cycles (with max 6 cycles) Duration not stated	Standardised menus of 1400, 1600, 1800, 2000 or 2200 kcal All patients received paclitaxel (175 mg/m^2) + cisplatin (75 mg/m^2)/carboplatin (AUC6) every 3 weeks 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 with the control group. LBM increased in the intervention group but decreased in the 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 the 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 was 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
Trabal et al. 2010 [26]	Randomised controlled trial	$N = 13$		2 n-3 PUFA-enriched ONS/day + nutrition	Nutrition counselling + chemotherapy	Nutritional status (PG-SGA), dietary intake (food diary),	Intervention group significantly	Low

Table 1 (continued)

Author/year	Study type	Participants	Intervention	Intervention specifics	Control	Main outcomes (measures)	Main findings	Risk of bias
		Stage IV colorectal cancer included Chemotherapy regimens administered were 5-fluorouracil + oxaliplatin + folinic acid or capecitabine Outpatients	Combined therapy alongside chemotherapy	counselling + chemotherapy 12 weeks		tolerability (EORTC QLQ-C30) + chemotherapy compliance	increased wt. after intervention + better scores in important domains of HRQoL, compared with controls (not statistically significant). Supplemented group did not experience interruptions in chemo treatment compared with the control group, with more interruptions due to toxicity	

BCM body cell mass, *BF%* body fat percentage, *BIA* bioelectrical impedance analysis, *BW* body weight, *Ca* cancer, *CHO* Carbohydrate, *DATA* disease and treatment assessment form, *ECM* Extracellular mass, *EORTC QLQ-C30* European Organisation for Research and Treatment of Cancer Quality of Life, *EPA* eicosapentaenoic acid, *EQ-5D* EuroQoL, *FAACT* Functional Assessment of Anorexia/Cachexia Treatment, *FFM* free fat mass, *FM* fat mass, *HADS* Hospital Anxiety and Depression Scale, *HRQoL* Health-related quality of life, *LASA* Linear Analog Scale Assessment scale of quality of life, *LBM* lean body mass, *MM* muscle mass, *MUAC* Mid-Upper Arm Circumference, *NCCTG* North Central Cancer Treatment Group, *NCICTC* National Cancer Institute Common Toxicity Criteria, *NCTCAE* National Cancer Institute Common Toxicity Criteria for Adverse Event, *ONS* oral nutritional supplement, *PG-SGA* Patient Generated Subjective Global Assessment, *Pt* Patient, *PUFA* polyunsaturated fatty acid, *SFT* skin fold thickness, *SGA* subjective global assessment, *TBF* total body fat, *TBW* total body water, *Wt*. weight

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. [17]	Post hoc analysis	N/A	N/A	N/A	N	Y		Unclear
Breitkreutz et al. [18]	RCT	U/C	U/C	U/C	Y	Y	N	Unclear
Casas et al. [19]	Prospective observational study	N/A	N/A	N/A	N	Y	N	High
Fearon et al [20]	RCT	Y	Y	Y	Y	Y		Low
Jatoi et al. [21]	RCT	Y	U/C	Y	Y	Y		Low
Kapoor et al [22]	RCT	U/C	U/C	U/C	Y	Y		Unclear
Read et al. [23]	Prospective observational study	N/A	N/A	N/A	Y	Y		Low
Sanchez-Lara et al. [24]	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. [26]	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 = High, Low, Unclear

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

Results

Search results and selection of studies

The literature search retrieved a total of 1139 papers (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 randomised controlled trials (RCTs) [6, 16, 18, 20–22, 24, 26], three prospective observational studies [19, 23, 25] and one post hoc analysis study [17].

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 cancer, 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 RCTs [16, 22] and one prospective observational study [25]. The prospective observational study examined nutrition counselling alone, and the two RCTs examined nutrition counselling alongside an oral dietary intervention. One RCT compared the effects of nutrition counselling alone, the effect of oral nutritional supplements (ONS) alone, the effect of nutrition counselling and ONS in combination or the effect of no intervention [16]. The other RCT compared nutrition counselling and improved atta (IAtta) with nutrition counselling alone [22].

Findings by Kapoor et al. [22] 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 ($p = 0.08$); also, a significant increase in body fat (BF) ($p = 0.002$) was 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 [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 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 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, 18, 23, 24, 26]; four were RCTs [6, 18, 24, 26] while the other was a prospective observational study [23].

Findings from Read et al. [23] saw improvements in body composition including a significant increase in mean weight at

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) EuroQoL 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, 16–18, 20–26]	*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 in 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, 19, 22–24, 26]	*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 [16–18, 20–24, 26]	*n* = 658 Food diaries (424) 24-h dietary recall (32) IMS-FFQ (32) NCCTG (118) SNUT (food frequency questionnaire) (84)	Low	Improvements in nutritional intake were seen in six studies. Three studies were of high-quality evidence with three studies, and 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 and 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 into each trial. † Some studies used more than 1 tool to assess an outcome

BCM body cell mass, *DATA* disease and treatment assessment form, *ECM* Extracellular mass, *EORTC QLQ-C30* European Organisation for Research and Treatment of Cancer Quality of Life, *EQ-5D* EuroQoL, *FAACT* Functional Assessment of Anorexia/Cachexia Treatment, *FFM* Free Fat Mass, *FM* fat mass, *HADS* Hospital Anxiety and Depression Scale, *HRQoL* Health-related quality of life, *LASA* Linear Analog Scale Assessment scale of quality of life, *LBM* lean body mass, *MM* muscle mass, *MUAC* Mid-Upper Arm Circumference, *NCCTG* North Central Cancer Treatment Group, *PG-SGA* Patient Generated Subjective Global Assessment, *SFT* skin fold thickness, *SGA* subjective global assessment, *TBW* total body water, *TBF* total body fat

three weeks ($p = 0.03$) with this remaining stable up to week nine. Lean body mass (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. Significant improvement was seen in both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) at week three and remained 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 weeks three and nine.

Sanchez-Lara et al. [24] 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

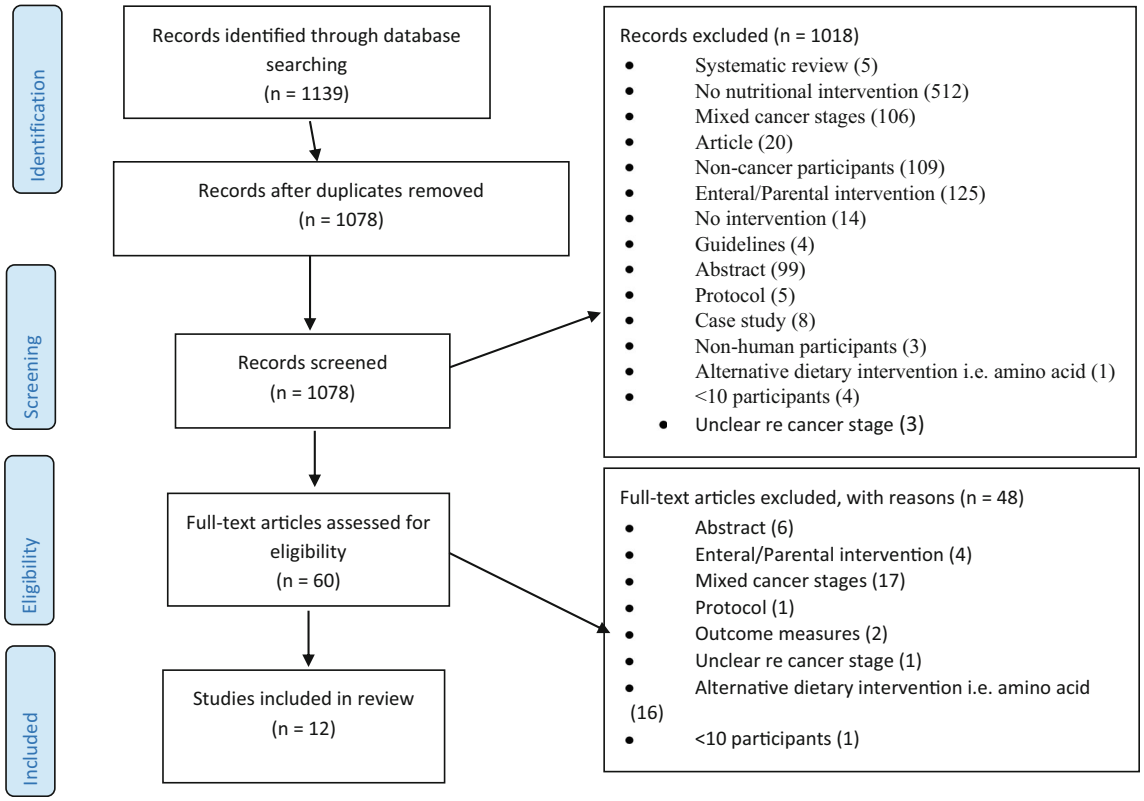

Fig. 1 Literature search process

had significantly greater energy and protein intakes ($p < 0.001$) compared with those in the control group. No overall difference was seen in the response rate or survival between groups, but fatigue, neuropathy and loss of appetite decreased significantly in the intervention group ($p = \leq 0.05$ for all).

Breitkreutz et al. [18] saw improvements in body composition including a fat free mass (FFM) increase in the intervention group compared with 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 with the control group, but the difference was not statistically significant.

Oral dietary interventions

Four studies examined the effect of oral dietary interventions alone ($n = 611$). Two were RCTs [20, 21], one exploratory prospective observational study [19] and one post hoc analysis study [17].

Fearon et al. [20] 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. [19] 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, 18, 22, 23, 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 with the control group [18]. One study, examining the effects of IAtta, reported an increase in body weight gain ($p = 0.08$) with a significant increase in body fat ($p = 0.002$) [22]. 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, 20, 21, 24], although one of those studies, examining nutrition counselling and consumption of an n-3 PUFA-enriched ONS alongside chemotherapy, reported an increase in LBM [24]. Of the six studies reporting an improvement in body composition, one study examined nutrition counselling alongside dietary intervention of IAtta [22], one study examined the effect of an n-3 PUFA-enriched ONS [17] and four studies examined multimodal therapies alongside chemotherapy [6, 18, 23, 26]. Of the six studies which saw improvements, all examined an oral dietary intervention, of which five examined ONS [6, 17, 18, 23, 26], with three of those being an n-3 PUFA-enriched ONS, and one examined IAtta [22].

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 [19, 22, 24], and five studies saw non-significant improvements) [17, 18, 20, 25, 26], compared with the control group and three studies reporting no difference between groups [16, 21, 23]. Of the eight studies reporting an improvement in QoL, two were examining the effect of nutrition counselling alongside a dietary intervention [22, 25], three examined an oral nutritional intervention [17, 19, 20], including one examining ice cream as a dietary intervention compared with ONS [19]. Three studies examined multimodal therapies alongside chemotherapy [18, 24, 26]. Of the eight studies which saw improvements in QoL, seven examined oral dietary interventions, of which six examined ONS [17–20, 24, 26], with four of those being an n-3 PUFA-enriched ONS, and one study examined IAtta as a dietary intervention [22]. 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, 18, 20–22, 24] including protein and energy intake ($p < 0.01$) and three studies reporting a reduction in appetite loss [21, 22, 24]. 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 [23]. 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 [26]. Of the six studies reporting an improvement in nutritional status, one examined nutrition counselling alongside dietary intervention [22], three examined an oral dietary intervention [17, 20, 21] and two examined multimodal therapies alongside chemotherapy [18, 24]. Of the six studies which saw improvements, all examined an oral dietary intervention: four were examining ONS [17, 18, 20, 24], including three of those examining n-3 PUFA-enriched ONS, one study examined IAtta as a dietary intervention [22] and the final study examined ice cream as a dietary intervention [19]. Of the six studies which saw improvements in nutritional intake, three of these also saw improved QoL [18, 22, 24], with three studies seeing improvements in body composition including weight [17, 18, 22], free fat mass [18] and body fat [22].

Nutritional status

Six studies examined nutritional status as an outcome measure with three studies seeing improvements in nutritional status [19, 22, 24]. Three studies reported no differences between groups [6, 23, 26]. Of the three studies that reported improvements in nutritional status, one study examined ice cream as a dietary intervention compared with ONS [19], one study examined nutrition counselling alongside the addition of IAtta [22] and one study examined nutrition counselling and the consumption of an n-3 PUFA-enriched ONS alongside chemotherapy [24]. Of the three studies which saw improvements, all examined an oral dietary intervention: one examined an n-3 PUFA-enriched ONS [24], one examined IAtta [22] and the last one examined ice cream as a dietary intervention, compared with ONS [19].

Discussion

This systematic review has found only limited evidence as to the most effective nutrition intervention for patients with incurable cancer, despite various guidelines [8, 27].

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 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 also 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 groups 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 [17, 20, 22]; 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 and then a consensus was agreed upon. Baldwin et al. [16] highlights that although RCTs 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 RCTs 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.

Acknowledgements The authors thank Marie Smith, Library and Knowledge Service Co-ordinator of NHS Fife, for undertaking the systematic search.

Funding information This work was financially supported by the Nancie Massey Charitable Trust, Miss M B Reekie's Charitable Trust and the P F Charitable Trust.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Katz AM, Katz PB (1962) Diseases of the heart in the works of Hippocrates. Br Heart J 24:257–264
2. Argiles JM et al (2014) Cancer cachexia: understanding the molecular basis. Nat Rev Cancer 14(11):754–762
3. Ross PJ, Ashley S, Norton A, Priest K, Waters JS, Eisen T, Smith IE, O'Brien MER (2004) Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers? Br J Cancer 90(10):1905–1911
4. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S, Baracos VE (2011) Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 12(5): 489–495
5. Fearon KC (2008) Cancer cachexia: developing multimodal therapy for a multidimensional problem. Eur J Cancer 44(8):1124–1132
6. Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, Pettersen CH, Fallon M, Fayers P, Fearon K, Kaasa S (2017) A randomized phase II feasibility trial of a multimodal intervention

for the management of cachexia in lung and pancreatic cancer. J Cachexia Sarcopenia Muscle 8(5):778–788
7. Solheim TS, Laird BJA, Balstad TR, Bye A, Stene G, Baracos V, Strasser F, Griffiths G, Maddocks M, Fallon M, Kaasa S, Fearon K (2018) Cancer cachexia: rationale for the MENAC (Multimodal-Exercise, Nutrition and Anti-inflammatory medication for Cachexia) trial. BMJ Support Palliat Care 8:258–265
8. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, Fearon K, Hütterer E, Isenring E, Kaasa S, Krznaric Z, Laird B, Larsson M, Laviano A, Mühlebach S, Muscaritoli M, Oldervoll L, Ravasco P, Solheim T, Strasser F, de van der Schueren M, Preiser JC (2017) ESPEN guidelines on nutrition in cancer patients. Clin Nutr 36(1):11–48
9. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, Erickson N, Laviano A, Lisanti MP, Lobo DN, McMillan DC, Muscaritoli M, Ockenga J, Pirlich M, Strasser F, de van der Schueren M, van Gossum A, Vaupel P, Weimann A (2017) ESPEN expert group recommendations for action against cancer-related malnutrition. Clin Nutr 36(5):1187–1196
10. Acreman S (2009) Nutrition in palliative care. Br J Community Nurs 14(10):427–428 430-1
11. Nourissat A, Vasson MP, Merrouche Y, Bouteloup C, Goutte M, Mille D, Jacquin JP, Collard O, Michaud P, Chauvin F (2008) Relationship between nutritional status and quality of life in patients with cancer. Eur J Cancer 44(9):1238–1242
12. Moher D, Liberati A, Tetzlaff J, Altman DG, for the PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339:b2535
13. Bauer J, Capra S, Ferguson M (2002) Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. Eur J Clin Nutr 56(8):779–785
14. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, Haes JCJM, Kaasa S, Klee M, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw K, Sullivan M, Takeda F (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85(5):365–376
15. The cochrane collaboration, The Cochrane handbook for systematic reviews of interventions. 2008
16. Baldwin C, Spiro A, McGough C, Norman AR, Gillbanks A, Thomas K, Cunningham D, O'Brien M, Andreyev HJN (2011) Simple nutritional intervention in patients with advanced cancers of the gastrointestinal tract, non-small cell lung cancers or mesothelioma and weight loss receiving chemotherapy: a randomised controlled trial. J Hum Nutr Diet 24(5):431–440
17. Bauer J et al (2005) Compliance with nutrition prescription improves outcomes in patients with unresectable pancreatic cancer. Clin Nutr 24(6):998–1004
18. Breitkreutz R, Tesdal K, Jentschura D, Haas O, Leweling H, Holm E (2005) Effects of a high-fat diet on body composition in cancer patients receiving chemotherapy: a randomized controlled study. Wien Klin Wochenschr 117(19–20):685–692
19. Casas F, León C, Jovell E, Gómez J, Corvitto A, Blanco R, Alfaro J, Seguí MÁ, Saigí E, Massanés T, Sala C, Librán A, Arcusa A (2012) Adapted ice cream as a nutritional supplement in cancer patients: impact on quality of life and nutritional status. Clin Transl Oncol 14(1):66–72
20. Fearon KC, von Meyenfeldt M, Moses AG, van Geenen R, Roy A, Gouma DJ, Giacosa A, van Gossum A, Bauer J, Barber MD, Aaronson NK, Voss AC, Tisdale MJ (2003) Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. Gut 52(10):1479–1486
21. Jatoi A, Qin R, Satele D, Dakhil S, Kumar P, Johnson DB, Thomas SP, Stella PJ, Castillo J, Li M, Fernandez-Zapico M (2016) "Enjoy glass of wine before eating:" a randomized trial to test the orexigenic effects of this advice in advanced cancer patients. Support Care Cancer 24(9):3739–3746
22. Kapoor N, Naufahu J, Tewfik S, Bhatnagar S, Garg R, Tewfik I (2017) A prospective randomized controlled trial to study the impact of a nutrition-sensitive intervention on adult women with cancer cachexia undergoing palliative care in India. Integr Cancer Ther 16(1):74–84
23. Read JA, Beale PJ, Volker DH, Smith N, Childs A, Clarke SJ (2007) Nutrition intervention using an eicosapentaenoic acid (EPA)-containing supplement in patients with advanced colorectal cancer. Effects on nutritional and inflammatory status: a phase II trial. Support Care Cancer 15(3):301–307
24. Sanchez-Lara K et al (2014) Effects of an oral nutritional supplement containing eicosapentaenoic acid on nutritional and clinical outcomes in patients with advanced non-small cell lung cancer: randomised trial. Clin Nutr 33(6):1017–1023
25. Tan-Shalaby JL, Carrick J, Edinger K, Genovese D, Liman AD, Passero VA, Shah RB (2016) Modified Atkins diet in advanced malignancies - final results of a safety and feasibility trial within the Veterans Affairs Pittsburgh Healthcare System. Nutr Metab (Lond) 13:52
26. Trabal J, Leyes P, Forga M, Maurel J (2010) Potential usefulness of an EPA-enriched nutritional supplement on chemotherapy tolerability in cancer patients without overt malnutrition. Nutr Hosp 25(5):736–740
27. National Institute for Clinical Excellence (NICE). Nutrition support in adults: oral supplements, enteral tube feeding and parental nutrition. 2006 [cited 2018 August]. Available from: http://www.nice.org.uk
28. Davies M (2005) Nutritional screening and assessment in cancer-associated malnutrition. Eur J Oncol Nurs 9(Suppl 2):S64–S73
29. Baldwin C, Weekes CE, Campbell KL (2008) Measuring the effectiveness of dietetic interventions in nutritional support. J Hum Nutr Diet 21(4):303–305
30. Hickson, M, Smith S, Advanced nutrition and dietetics in nutrition support. 2018
31. Hui D, Glitza I, Chisholm G, Yennu S, Bruera E (2013) Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. Cancer 119(5):1098–1105
32. Hearn J, Higginson IJ (1997) Outcome measures in palliative care for advanced cancer patients: a review. J Public Health Med 19(2):193–199
33. Hearn J, Higginson IJ (1999) Development and validation of a core outcome measure for palliative care: the palliative care outcome scale. Palliative Care Core Audit Project Advisory Group. Qual Health Care 8(4):219–227
34. Horn SD, DeJong G, Deutscher D (2012) Practice-based evidence research in rehabilitation: an alternative to randomized controlled trials and traditional observational studies. Arch Phys Med Rehabil 93(8 Suppl):S127–S137