Critical Reviews in Oncology / Hematology 139 (2019) 96–107

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Effects of current parenteral nutrition treatment on health-related quality of life, physical function, nutritional status, survival and adverse events exclusively in patients with advanced cancer: A systematic literature review

Randi Tobberup[a,b,*], Lene Thoresen[c,d], Ursula G. Falkmer[b,e], Mette K. Yilmaz[e], Tora S. Solheim[c,f], Trude R. Balstad[c,f]

[a] Center for Nutrition and Bowel Disease, Department of Gastroenterology, Aalborg University Hospital, Hobrovej 18-22, 9000, Aalborg, Denmark
[b] Department of Clinical Medicine, Aalborg University, Fredrik Bajers Vej 5, 9100, Aalborg, Denmark
[c] Cancer Clinic, St. Olavs hospital, Trondheim University hospital, Postboks 3250 Torgarden, NO-7006, Trondheim, Norway
[d] National Advisory Unit on Disease-Related Malnutrition, Oslo University Hospital, Sognsvannsveien 9, 0372, Oslo, Norway
[e] Department of Oncology, Clinical Cancer Research Center, Aalborg University Hospital, Hobrovej 18-22, 9000, Aalborg, Denmark
[f] Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology, PO Box 8905, NO-7491, Trondheim, Norway

ARTICLE INFO

Keywords:
Palliative care
Intravenous nutrition
Performance status
Weight loss
Cachexia
Supportive care

ABSTRACT

Background: The aim was to evaluate the effects of current parenteral nutrition (PN) treatment on clinical outcomes in patients with advanced cancer.
Methods: This review was conducted according to the PRISMA guidelines (PROSPERO ID: 4201707915).
Results: Two underpowered randomized controlled trials and six observational studies were retrieved (n = 894 patients). Health-related quality of life and physical function may improve during anti-neoplastic treatment in who PN treatment is the only feeding opportunity, but not necessarily in patients able to feed enterally. Nutritional status may improve in patients regardless of anti-neoplastic treatment and gastrointestinal function. PN treatment was neither superior to fluid in terminal patients nor to dietary counselling in patients able to feed enterally in regards to survival. The total incidence of adverse events was low.
Conclusion: Current PN treatment in patients with advanced cancer is understudied and the level of evidence is weak.

1. Introduction

Patients with advanced cancer frequently experience weight loss. High symptom burden in combination with side effects from anti-neoplastic treatments and metabolic derangement syndromes, such as cachexia, lead to inadequate food intake, inactivity and/or functional decline, which promotes anorexia, fatigue and catabolism (Cederholm et al., 2017; Arends et al., 2017). Moreover, patients in a palliative care setting may have a life expectancy of several months to years, and some still receive anti-neoplastic treatment, making them a heterogeneous population regarding decisions for medical nutritional therapy.

Nutritional guidelines for patients with advanced cancer recommend nutritional interventions only after carefully considering the prognosis and expected benefit on health-related quality of life (HRQoL) and potential survival (Arends et al., 2017). The treatment goals of parenteral nutrition (PN) administration should be to maintain HRQoL and performance status (Arends et al., 2017). The guidelines recommend PN in patients with chronic insufficient dietary intake if enteral nutrition is not sufficient or feasible and/or if patients have uncontrollable malabsorption. However, the level of evidence supporting the beneficial effects of PN is weak (Arends et al., 2017). Health care professionals are often challenged when selecting which patients with advanced cancer should receive PN and deciding when to terminate PN due to the uncertainties of expected individual benefits.

A meta-analysis from 1990 demonstrated a net harm of PN administration with trends in reduced survival and tumour response and an increased incidence of infectious complications in patients receiving PN during chemotherapy (McGeer et al., 1990). The authors concluded that routine use of PN should be strongly discouraged and that trials involving specific groups of patients should be undertaken with caution (McGeer et al., 1990). As a consequence of this conclusion, no randomized controlled trials (RCTs) involving patients with advanced cancer

* Corresponding author at: Aalborg University Hospital, Hobrovej 18-22, 9000, Aalborg, Denmark.
E-mail address: r.tobberup@rn.dk (R. Tobberup).

https://doi.org/10.1016/j.critrevonc.2019.04.014
Received 15 February 2019; Received in revised form 22 March 2019; Accepted 13 April 2019

were conducted during the next several decades. Administration techniques have improved, and considerable changes have been made to the dosage, composition and distribution of PN macronutrients. Thus, there is a need for an updated systematic review investigating the effect of current PN administration in patients with advanced cancer. The primary aims of this systematic review are to evaluate the effect of PN treatment on HRQoL and physical function (self-reported, performance status or physical performance testing). The secondary outcomes evaluated were nutritional status, survival, tolerance and dose-limiting toxicity to anti-neoplastic treatment and adverse events.

2. Methods

This systematic review was conducted according to the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009). A Cochrane technology platform was used to manage the review process (Covidence systematic review software, 2019). The review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD4201707915).

2.1. Search strategy and selection criteria

A systematic literature search was conducted by a research librarian using the Ovid MEDLINE, EMBASE, CINAHL EBSCOhost and The Cochrane Library databases on the 13th of September 2017 (Appendix 1). An updated search was conducted the 18th of May 2018. A hand search for additional relevant articles from references of key articles was also performed. Screening and eligibility assessments were conducted by two independent reviewers (RT and TRB) using the following criteria: prospective clinical trials or retrospective studies involving adults (≥ 16 years) diagnosed with any incurable/advanced cancers (defined as not curable but might respond to cancer treatment or disease-directed therapy to prolong life and reduce symptoms) who received any type or regimen of PN treatment compatible with current practices (at home or in a hospital/institution) that reported HRQoL outcomes, physical function (self-reported, performance status or physical performance testing), nutritional status (nutritional assessments, body weight or fat free mass), survival, tolerance or dose-limiting toxicity to anti-neoplastic treatment and adverse events associated with PN administration. PN treatment compatible with current practise is defined in this review as normocaloric infusion (not hypercaloric) and PN solution containing fatty acids, amino acids and glucose, preferably in all-in-one bags. Any uncertainties in assessing the eligibility of the studies were discussed among the authors until a consensus was reached. Studies were excluded if patients received treatment with curative intent, PN was administered pre-operatively, peri-operatively and/or post-operatively to assess complications related to surgery, patients were < 16 years old, patients had mixed malignant and benign diseases or the evaluated populations of cancer patients had different stages of disease (in which no subgroup analysis of an advanced cancer population was possible to retrieve), populations of less than 10 patients or less than 20 patients with more than three different cancer diagnoses, the intervention consisted of dietary counselling, enteral feeding, intravenous hydration, or the initiation of PN was not defined in studies using combined treatment with enteral nutrition strategies. Non-English articles were excluded.

2.2. Data collection process and data items

A data extraction table was developed, pilot tested and refined within the review group. Data were extracted by two review authors (RT and TRB) and evaluated independently by a third author (LT). Overall survival was assumed to be calculated from the time of initiation of PN administration, unless otherwise stated in the article.

2.3. Assessment of risk of bias

The content of each of the included RCTs was analysed using methodological risk of bias domains from the Cochrane Handbook for Systematic Reviews of Interventions at the study level (Higgins and Green, 2011). All reviewers assessed the risk of bias (RoB), and any discrepancies were resolved through discussion. There is no single recommended instrument for assessing the RoB when the systematic review also includes non-randomized trials (Higgins and Green, 2011). Therefore, the Institute of Health Economics (IHE) Quality Appraisal Checklist for Case Series Studies was opted for the observational studies (IHE IoHE, 2014). The quality appraisal checklist consists of 20 criteria, of which 16 criteria were considered important. Pre-defined aspects considered important were determined for the study population (age, sex, cancer diagnosis, tumour stage, anti-neoplastic treatment, nutritional status and physical function, and the quality of the description of the intervention (composition of the PN solution, administration, rate, dosage, duration and indications). When assessing the overall quality of the observational studies, the studies were categorized as good or poor quality based on pre-defined cut-off scores. A total score was calculated by summarizing scores from each of the 16 predefined criteria (3 points for yes, 2 points for partially and 1 point for no/unclear reporting) and categorized as good (score of 40–48) or poor quality (score of 16–39). A study was classified as good quality if at least 4 out of 6 reviewers scored the study at 40–48 points. RoB and confounders were assessed.

3. Results

3.1. Search results and selection of studies

The literature review retrieved 1039 papers (Fig. 1). Three additional studies were identified by hand searching. After excluding duplicates and studies that did not meet the inclusion criteria based on title and abstract screening, 85 papers were selected for full-text examination. Full-text screening resulted in the exclusion of 64 papers (for reasons, see Fig. 1). Additionally, 13 studies were excluded based on critically high RoB (Chouhan et al., 2016; Girke et al., 2016; Chen et al., 2013; Diver et al., 2013; Chermesh et al., 2011; Madhok et al., 2011; Soo and Gramlich, 2008; Fan, 2007; Finocchiaro et al., 2007; Brard et al., 2006; Bozzetti et al., 2002; Pasanisi et al., 2001; Pironi et al., 1997) (Appendices 2 and 3). The present review is based on the results from eight articles: two RCTs (Oh et al., 2014; Obling et al., 2017), five prospective observational studies (Bozzetti et al., 2014; Cotogni et al., 2017; Guerra et al., 2015; Pelzer et al., 2010; Vashi et al., 2014) and one retrospective study (Santarpia et al., 2006).

3.2. Risk of bias

A summary of the qualitative RoB assessment for the included studies can be seen in Tables 1 and 2. Both RCTs were underpowered, as only 47 of the planned 100 patients (Obling et al., 2017) and 31 of the planned 116 patients were enrolled (Oh et al., 2014). Most of the observational studies had a high risk of attrition bias as well as performance bias due to poor reporting of PN administration and lack of systematic reporting of adverse events associated with PN administration.

3.3. Study and patient characteristics

Detailed study characteristics of the included trials can be seen in Table 3 and some major study characteristics are listed in Table 4. Two RCTs (n = 78), five prospective studies (n = 664) and one retrospective study (n = 152) yielded a total of 894 patients, of who 857 received PN. The population size in the individual studies ranged from 31 to 414 and included 435 females (46%), 414 males (49%) and 45 patients (5%) whose sex was not reported. The patients' mean age was 60.8 years

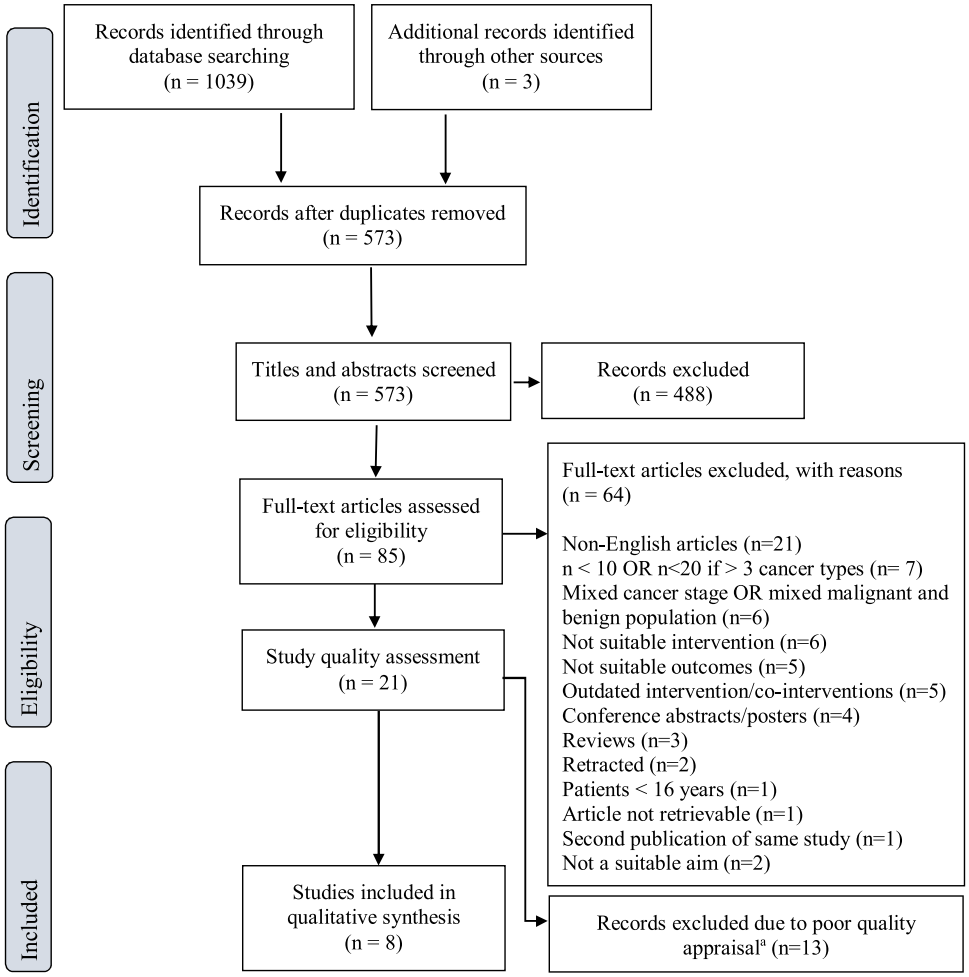

Fig. 1. Flow chart for the study selection process.
The figure provides details of reasons for exclusion of full text articles.
[a]Studies excluded based on poor quality appraisal, as assessed by a total score < 40 on the IHE Quality Appraisal Checklist for case series studies.

(range, 16–90 years). Six of eight studies included different cancer diagnoses (Oh et al., 2014; Bozzetti et al., 2014; Cotogni et al., 2017; Guerra et al., 2015; Vashi et al., 2014; Santarpia et al., 2006). A total of 28 cancer diagnoses were counted, of which gastric, colorectal, pancreatic and gynaecological cancers were the most common. In total, 223 patients (25%) received concurrent anti-neoplastic treatment (Obling et al., 2017; Cotogni et al., 2017; Guerra et al., 2015; Vashi et al., 2014), and 639 patients (71%) did not (Oh et al., 2014; Bozzetti et al., 2014; Cotogni et al., 2017; Guerra et al., 2015; Santarpia et al., 2006) (Table 4). One study (n = 32, 4%) did not report the use of concurrent anti-neoplastic treatment (Pelzer et al., 2010).

A wide range of methods were used to assess nutritional status at baseline. Four studies used validated screening or assessment tools for (risk of) undernutrition (Malnutrition Universal Screening Tool (MUST) (Guerra et al., 2015), Nutritional Risk Screening 2002 (NRS2002) (Obling et al., 2017), Subjective Global Assessment (SGA) (Vashi et al., 2014) or Patient-Generated Subjective Global Assessment (PG-SGA) (Cotogni et al., 2017)). Body mass index (BMI) was reported by two RCTs (Oh et al., 2014; Obling et al., 2017) and by five observational studies (Bozzetti et al., 2014; Cotogni et al., 2017; Pelzer et al., 2010; Vashi et al., 2014; Santarpia et al., 2006). Weight loss was reported in various ways: weight loss over the last three months (Cotogni et al., 2017), weight loss over the last six months (Vashi et al., 2014; Santarpia et al., 2006), percent weight loss of usual weight (usual not specified) (Bozzetti et al., 2014) and weight loss without a specified time frame (Obling et al., 2017). Oral food intake was reported by one RCT (Obling et al., 2017) and one observational study (Cotogni et al., 2017).

All patients were either considered at risk of undernutrition or malnourished at inclusion. Two studies used patients' (risk of) undernutrition specifically as an inclusion criterion, of which one RCT used the score of ≥2 on the NRS2002 (Obling et al., 2017) and one observational study used a weight loss of ≥5% over the previous four weeks or a BMI (kg/m^2) < 19 (Pelzer et al., 2010). Additionally, three studies used nil/negligible intake per os or enteral feeding as inclusion criteria (Oh et al., 2014; Bozzetti et al., 2014; Cotogni et al., 2017).

Baseline performance status was reported in seven of eight studies using either the Karnofsky Performance Score (KPS) (Bozzetti et al., 2014; Cotogni et al., 2017; Vashi et al., 2014; Santarpia et al., 2006) or Eastern Cooperative Oncology Group (ECOG) performance status (Oh et al., 2014; Obling et al., 2017; Guerra et al., 2015) (Tables 3 and 4). The two RCTs had performance status as an inclusion criterion: ECOG performance status of 0–2 (Obling et al., 2017) or ECOG performance status of 3 or 4 (Oh et al., 2014). The mean performance status at baseline reported in the observational studies was a KPS of 60 (range, 20–100) (Bozzetti et al., 2014; Cotogni et al., 2017; Vashi et al., 2014; Santarpia et al., 2006) and ECOG performance status of 1.5 (standard deviation (SD), 0.5) (Guerra et al., 2015).

All studies reported the indications for initiating PN (Table 3). In 79% of the patients, the primary PN indication was compromised gastrointestinal function (obstruction, short bowel syndrome or fistula formation) (Oh et al., 2014; Bozzetti et al., 2014; Cotogni et al., 2017;

Table 1
Summary of risk of bias of randomized controlled trials.

Author Year	Types of bias					
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Other bias
Obling et al. (2017)	**Low Risk** Restricted randomization method minimization by use of MinimPy web-based program	**Low risk** Web-based	**High risk** No blinding of patients or personnel	**High risk** No blinding of outcome assessment	**Low risk** Number of patients reported for each outcome at all time points	**High risk** Underpowered
Oh et al. (2014)	**Unclear risk** Patients were randomized, but the method explaining the randomization procedure was unknown	**Low risk** Allocation concealment performed by research staff of Seoul Medical Center Research Institute and was judged as a central allocation	**Low risk** Lack of blinding is unlikely to influence survival outcome	**Low risk** Lack of blinding is unlikely to influence survival outcome	**Low risk** All patients accounted for in survival analysis	**High risk** Underpowered

Table 2
Summary of risk of bias of observational studies.

Author year	Type of bias					
	Selection bias and confounding	Performance bias	Detection bias	Attrition bias	Reporting bias	Overall bias
Cotogni et al. (2017)	No comment	Authors did not report administration route	No comment	No comment	Large drop out	**Moderate**
Guerra et al. (2015)	Tumour stage not reported, but patients not considered candidates for further chemotherapy were excluded	Authors did not describe dose given	No comment	Unknown whether all patients died, as this was not explicitly reported; Kaplan-Meier curve suggested that some patients are still alive	No comment	**High**
Bozzetti et al. (2014)	Missing information of indication for PN in one-third of the population	Dose administered and composition of PN not described	Large range of performance status at baseline makes interpretation of results difficult	No comment	No comment	**High**
Vashi et al. (2014)	Unknown whether patients were recruited consecutively	Administration route not described	No comment	No comment	Large drop out	**Moderate**
Pelzer et al. (2010)	Unsure whether patients were recruited consecutively and whether patients received concurrent oncologic therapy; performance status at baseline not reported	Administration route and dose given not described	Statistical method unknown	No comment	Large drop out	**High**
Santarpia et al. (2006)	No comment	Dose administered and administration rate not described	Definitions of “improvement”, “stable” and “decreased” KPS not described	No comment	No comment	**High**

Table 3
Study characteristics.

Publication Authors (year published), study period, country	Population N, sex, age, cancer diagnosis, tumour stage, anti-neoplastic treatment, PS, NS, inclusion and exclusion criteria	PN indication Medical related, Food/nutrition related	PN intervention Composition of PN solution, administration, rate, dose planned, dose administered and duration of PN
Randomized controlled trials			
Obling et al. (2017) 2014-2016 Denmark	**N** = 47 (22 PN vs. 25 control) **Sex**: Female (n = 7 vs. 10), male (n = 15 vs. 15) **Age**, mean (range): 67.4 (41.5-81.6) vs. 65.9 (43.3-88.2) **Cancer diagnosis**: GI cancer **Tumour stage**: locally advanced or metastatic **Anti-neoplastic treatment**: CT (n = 20 vs. n = 23) **PS**: KPS 0 (n = 1 vs. 5), 1 (n = 12 vs. 13), 2 (n = 9 vs. 7) **NS**: WL < 5% (n = 1 vs. 7), 5-10% (n = 6 vs. 4), > 10% (n = 15 vs. 14). Sarcopenia assessed by BIA (n = 2 vs. 1), sarcopenia assessed by handgrip strength (n = 9 vs. 9). NRS2002: score ≥2 (all patients) **Inclusion criteria:** Incurable GI cancer, age > 18, PS 0-2, NRS2002 > 2 **Exclusion criteria:** functional or actual short bowel syndrome	**Medical related**: to prevent and treat functional decline accompanying cachexia in patients at nutritional risk (≥ 2 by NRS2002) **Food/nutrition intake**: > 75% of energy requirement (n = 20 vs. 23), > 75% of protein requirement (n = 10 vs. 12)	**PN arm**: supplemental PN + nutritional counselling **Composition**: 3-chamber bag (Olimel N9E., Baxter); 56.9 g protein, 1070 kcal and 40 g fat/L **Administration**: tunnelled CVC (n = 15), transthoracic venous port (n = 3), PICC line (n = 3) **Rate**: NR **Dose planned**: supplemental PN to reach 30 kcal/kg/d and 1.5 g protein/kg/d **Dose given**: typically 25-35% of daily nutritional requirement **Duration**: 24 weeks **Control arm**: Dietetic counselling to ensure intake > 75% of nutritional requirement (advice to address eating difficulties and stimulate intake, supplemental ONS when protein and calorie intake was unmet by food; EN offered if nutrient intake was below 75% of nutritional needs)
Oh et al. (2014) June-December 2011 Republic of Korea	**N** = 31 (15 PN vs. 16 control) **Sex**: Female (n = 6 vs. 6), male (n = 10 vs. 9) **Age**, mean (SD): 60.4 ± 12.6 vs. 59.1 ± 9.6 **Cancer diagnosis**: Hepatobiliary/pancreas (n = 8 vs. 2), colon (n = 3 vs. 4), stomach (n = 0 vs. 4), breast (n = 2 vs. 1), neuroendocrine (n = 0 vs. 2), lung (n = 0 vs. 1), prostate (n = 0 vs. 1), melanoma (n = 1 vs. 0), salivary gland (n = 0 vs. 1), leukaemia (n = 1 vs. 0) **Tumour stage**: advanced terminal cancer, no further plans of active treatment **Anti-neoplastic treatment**: None **PS**: ECOG 3 (n = 11 vs. 6), ECOG 4 (n = 5 vs. 9) **NS**: BMI < 18.5 (n = 4 vs. 1) **Inclusion criteria:** advanced cancer with no further plans for anti-neoplastic treatment, inability to feed via an enteral route, age > 19, life expectancy ≤ 12 weeks, PS 3-4, presence venous access, admission to hospital for a minimum of 1 day **Exclusion criteria:** cardiac or renal disease that restricted administration of fluid, electrolyte imbalance, poorly controlled diabetes, indication of unsuitability	**Medical related**: Feeding via enteral route not possible **Food/nutrition related**: no feeding per os	**PN arm**: **Composition**: any type of marketed amino acid and fat emulsion allowed, including ready to use products **Administration**: NR **Rate**: NR **Dose planned**, mean (SD): 1286.6 kcal/d (108.3) and 59.6 g protein/d **Dose given,** average: 1286 kcal/day **Duration**: until death or withdrawal of consent, not further specified **Control arm**: Intravenous fluid therapy with a maximum of 30 ml/kg/d (fluid consisted of saline, half saline or dextrose water). Maximum calories administered limited to under 20 kcal/kg/d (physician decision) **Dose**, mean: 374.7 ± 71.7 kcal/d
Prospective observational studies			
Cotogni et al. (2017) 2011-2013 Italy	**N** = 111 **Sex**: female (n = 54), male (n = 57) **Age**, median (range): 62 (32-79) **Cancer diagnosis**: stomach (n = 38), colorectal (n = 21), pancreas/biliary (n = 20), oesophagus (n = 10), lung (n = 10), ovary (n = 2), other (n = 10) **Tumour stage**: stage III (n = 25), stage IV (n = 86) **Anti-neoplastic treatment**: CT (n = 61), RT (n = 2), CRT (n = 9) **PS**: KPS, median (range): 70 (60-80) **NS**: PG-SGA B (n = 41) or PG-SGA C (n = 70); WL, median (range): 11.7% (0-38.3%); BMI, median (range): 20.7 (13.5-29.5) **Inclusion criteria**: adult cancer patients candidates for PN according to ESPEN guidelines, proven and prolonged failure to meet nutrition requirements by oral/enteral route with impending risk of death due to malnutrition, life expectancy > 2 months,	**Medical related**: Intestinal (sub)obstruction (n = 90), short bowel syndrome (high output ileostomy/ fistula) (n = 14), EN not tolerated or feasible (n = 7) **Food/nutrition related**: inadequate oral/enteral intake (oral intake (kcal/d), median (range): 500 (200-1300)	**Composition**: all-in-one bag **Administration route**: NR **Rate:** 10-14 hours overnight **Dose planned**: 20-25 kcal/kg/d (bedridden), 25-30 kcal/kg/d (outpatients) + 1.0-1.5 g amino acids/kg/d **Dose given**, median: 1000-1250 kcal/d **Duration**, median (range): 137 days (21-576)

(*continued on next page*)

Table 3 (*continued*)

Publication Authors (year published), study period, country	Population N, sex, age, cancer diagnosis, tumour stage, anti-neoplastic treatment, PS, NS, inclusion and exclusion criteria	PN indication Medical related, Food/nutrition related	PN intervention Composition of PN solution, administration, rate, dose planned, dose administered and duration of PN
	KPS > 50, control of pain, absence of severe organ dysfunction, presence of environmental conditions compatible with PN **Exclusion criteria**: Not specified		
Guerra et al. (2015) 2007-2012 Spain	**N** = 55 **Sex**: not reported **Age**, mean (SD): 60 (4.3) **Cancer diagnosis**: gastrointestinal (n = 38), gynaecological (n = 10), other (n = 37, urinary, unknown and pelvic) **Tumour stage**: NR, stated as advanced cancer **Anti-neoplastic treatment**: CT (n = 26) **PS**: ECOG, mean (SD): 1.5 (0.5) **NS**: BMI, mean (SD): 21.6 (4.3); malnourished (assessed by MUST) (n = 43) **Inclusion criteria**: advanced cancer and intestinal occlusion with peritoneal carcinomatosis, considered candidates for active chemotherapy **Exclusion criteria**: patients not considered candidates for ongoing chemotherapy	**Medical related**: SBO with peritoneal carcinomatosis **Food/nutrition related**: NR	**Composition**: glucose 3-6 g/kg/d, amino acids 1.0 g/kg/d, lipids < 1 g/kg/d, EAA 7-10 g/d + vitamins/trace elements added if needed **Administration**: Peripherally CVC **Rate**: Intermittent infusion, primarily at night-time **Dose planned**: 20-35 kcal/kg/d **Dose given:** NR **Duration**, mean (SD): 54.13 days (114.99) (GI), 60.7 days (44.49) (gynaecological), 34.29 days (57.53) (other cancers)
Bozzetti et al. (2014) 2004-2011 International	**N** = 414 **Sex**: female (n = 190), male (n = 224) **Age**, median (range): 62 (16-90) **Cancer diagnosis**: head & neck (n = 50), stomach (n = 92), small bowel-biliary (n = 10), colorectal (n = 84), ovary (n = 51), pancreas (n = 46), other (n = 81) **Tumour stage**: metastatic (n = 276), vital organ metastasis (n = 170), locoregional disease (n = 105) **Anti-neoplastic treatment**: None **PS**: KPS, median (range): 60 (20-100) **NS**: WL (habitual weight), median (range): 24% (-8 to -56); WL (previous 6 months), median (range): 16% (-44 to -50); BMI, median (range): 19.5 (12.8-30.0) **Inclusion criteria**: adults with no/negible oral/enteral nutrition, incurable malignancy without major organ failure or major involvement of a vital organ or severe metabolic derangement **Exclusion criteria**: patients with ascites or pleural effusion, uncontrolled symptoms, receiving PN in the perspective to become candidates for future oncologic treatment	**Medical related**: SBO/sub-obstruction (approx. 2/3 of patients) **Food/nutrition related**: no/negligible oral/EN	**Composition:** NR **Administration:** CVC **Rate:** daily infusion **Dose planned**: at least 25 kcal/kg/d and 1 g amino acid/kg/d **Dose given**: NR **Duration:** until death (n = 273); Premature PN discontinuation, median (range): 2 month (1-126) (n = 139)
Vashi et al. (2014) 2009-2014 USA	**N** = 52 **Sex**: female (n = 31), male (n = 21) **Age**, mean (SD): 53.2 (9.4) **Cancer diagnosis**: pancreas (n = 14), colorectal (n = 11), ovarian (n = 6), appendix (n = 5), stomach (n = 4), other cancers (n = 12) **Tumour stage**: stage IV, with multiple organ involvement **Anti-neoplastic treatment**: all patients received either CT, RT or hormonal therapy **PS**: KPS, mean (SD): 60.1 (10.8) **NS**: PG-SGA B (n = 19), PG-SGA C (n = 33); WL previous 6 months, mean (SD): 16.9% (9.3) **Inclusion criteria**: cancer, expected survival > 90 days, no PN prior to hospital admission, no associated liver or kidney problems, cancer cachexia with tumor burden involving multiple organs and compromised GI function **Exclusion criteria**: patients who did not give informed consent	**Medical related**: Compromised GI function **Food/nutrition related**: Poor oral intake, PN only nutritional option	**Composition**: Total Nutrient Admixture solution (lipids < 30E%), amino acids and dextrose) + Multivitamin Infusion-13 & Multitrace 5. **Administration:** NR **Rate:** daily cycled infusion **Dose planned**: 25-30 kcal/kg (BMI < 30), 22-25 kcal/kg of ideal body weight (BMI ≥ 30). Protein 1.5 to 2.5 g/kg depending on BMI. **Dose given**, mean (SD): 1468 kcal/d (328), 81.1 g protein/d (16.4) (PN less than 3 months) vs. 1273 kcal/d (238), 70.0 g protein/d (14.6) (PN more than 3 months) **Duration**, mean (range): 3.4 months (0.4-11.7)

(*continued on next page*)

Table 3 (*continued*)

Publication Authors (year published), study period, country	Population N, sex, age, cancer diagnosis, tumour stage, anti-neoplastic treatment, PS, NS, inclusion and exclusion criteria	PN indication Medical related, Food/nutrition related	PN intervention Composition of PN solution, administration, rate, dose planned, dose administered and duration of PN
Pelzer et al. (2010) 2002-2004 Germany	**N** = 32 **Sex**: female (n = 14), male (n = 18) **Age**, median (range): 62 (47-75) **Cancer diagnosis**: inoperable pancreatic cancer **Tumour stage**: IV **Anti-neoplastic treatment**: Not reported **PS**: NR **NS**: > 5% WL previous 4 weeks OR BMI < 19 **Inclusion criteria:** ambulant patients with stage IV pancreatic cancer, weight loss > 5 % in four weeks or BMI < 19 in spite of enteral and drug support **Exclusion criteria:** not specified	**Medical related**: Gastrointestinal stenosis, gastro-paresis, and loss of appetite (most of the patients) **Food/nutrition related**: WL > 5% in previous four weeks or BMI < 19 (despite caloric supplement 200-400 ml, 1.5 kcal/ml combined drug support)	**Composition**: Amino acids 1.2-1.5 g/kg, lipids at least 35 E%, additional vitamins or electrolyte if indicated. No additional glutamine or omega 3 **Administration**: NR **Rate**: overnight infusion to reach targeted calorie intake in 5 of 7 days **Dose planned**: 25 kcal/kg/d in 5 of 7 days: amino acids 1.2-1.5 g/kg, lipids at least 35 E%, additional vitamin or electrolyte if indicated. (given dose not reported) **Dose given**: NR **Duration**, median (range): 18 weeks (8-35)
Retrospective observational study			
Santarpia et al. (2006) 1996-2003 Italy	**N** = 152 **Sex**: female (n = 107), male (n = 45) **Age**: median (range): 59.5 (22-88) **Cancer diagnosis**: stomach (n = 48), ovaries (n = 42), colorectal (n = 30), endometrium (n = 7), breast (n = 6), ileum (n = 5), gallbladder (n = 4), pancreas (n = 3), kidney (n = 2), skin (n = 1), prostate (n = 1), abdominal sarcoma (n = 1), unknown (n = 2) **Tumour stage**: Considered terminal (unresponsive to oncologic treatment) **Anti-neoplastic treatment**: None **PS**: 90 patients had KPS ≤ 40, 40 had KPS ≥ 50, 18 had a KPS = 60 and 4 had a KPS = 70 **NS**: Mean (SD) WL (kg) previous 6 months: 9.5 (4.7), range WL: 2-26 kg. BMI, mean (SD): 20.1 (3.6) **Inclusion/exclusion criteria**: not specified	**Medical related**: Bowel obstruction due to peritoneal carcinomatosis **Food/nutrition related**: Food intake not possible	**Composition**: All-in-one bags containing amino acids, glucose, lipids, minerals, trace elements and vitamins **Administration**: CVC **Rate:** NR **Dose**: 20- 30 kcal/kg/d, 3-4 gram/kg body weight of carbohydrates, 1-1.5 gram/kg body weight protein and 1 gram/kg body weight of lipids **Duration**: Given until 1 to 3 days before death

BIA: Bioimpedance; BMI: body mass index; CRT: concurrent chemo-radiation; CT: chemotherapy; CVC: central venous catheter; E%: energy percent; ECOG: Eastern Cooperative Oncology Group; EN; enteral nutrition; kcal: kilocalories; KPS: Karnofsky Performance Status; NR: not reported; NRS2002: Nutritional Risk Screening 2002; NS: nutritional status; ONS: oral nutritional support; PG-SGA: Patient-Generated Subjective Global Assessment; PN: parenteral nutrition; PS: performance status; QoL: quality of life, RT: radiotherapy; WL: weight loss; EAA: essential amino acids; SBO: short bowel obstruction; GI: gastrointestinal.

Guerra et al., 2015; Pelzer et al., 2010; Vashi et al., 2014; Santarpia et al., 2006) (Table 4). No or negligible food intake/enteral nutrition was the primary PN indication in 16% of the patients (Oh et al., 2014; Bozzetti et al., 2014; Cotogni et al., 2017; Pelzer et al., 2010). Lastly, in the remaining 5% of the patients, PN was provided to patients in an attempt to prevent functional decline in malnourished patients not otherwise indicated for PN (functional gastrointestinal tract and food intake above 75% of the energy and protein requirement in most of the patients) (Obling et al., 2017).

3.4. Intervention

The composition of PN solutions was reported in most studies, albeit the degree of reported details varied (Table 3). Four studies reported using all-in-one bags (Obling et al., 2017; Cotogni et al., 2017; Vashi et al., 2014; Santarpia et al., 2006), three studies partially reported the composition of PN macronutrient solution (Oh et al., 2014; Guerra et al., 2015; Pelzer et al., 2010), while one study failed to describe the composition of PN (Bozzetti et al., 2014). The method of PN administration was reported by

Table 4
Major baseline characteristics of the included trials.

Publication	Gastrointestinal function	Anti-neoplastic treatment (%)	Performance status
Obling et al. (2017)	Good	91 %	Good
Oh et al. (2014)	Dysfunctional	0 %	Poor
Cotogni et al. (2017)	Dysfunctional	65 %	Good
Guerra et al. (2015)	Dysfunctional	47 %	Good
Bozzetti et al. (2014)	Dysfunctional	0 %	Any
Vashi et al. (2014)	Dysfunctional	100 %	Any
Pelzer et al. (2010)	Dysfunctional	Unknown	Unknown
Santarpia et al. (2006)	Dysfunctional	0 %	Any

Good performance status defined as Eastern Cooperative Oncology Group performance status 0–2 or Karnofsky Performance Score 60-100.

Table 5
Study results.

Publication Authors (year)	Results			
	HRQoL and physical function	Nutritional status	Survival	Adverse events
Randomized controlled trials				
Obling et al. (2017)	**HRQoL** (EORTC QLQ-C15 PAL): Mean Δ +16.0 score in favour of PN at week 12 ($p < 0.05$). NS at week 6, 18 or 24 (end-point) **Physical function:** Self-reported physical function (EORTC QLQ-C15): NS at any time point Performance testing: HGS and 6MWT NS at any time point	**Fat free mass** (BIA): Mean Δ fat free mass 6.44 kg (SD 2.9-10.0), $p < 0.05$ at week 12, in favour of PN arm. NS difference at week 6, 18 or 24. **BMI**: mean Δ 1.65 kg/m^2 (SD 0.4-2.9), $p < 0.05$ at week 12, in favour of PN arm. NS at week 6, 18 or 24	mOS NS different between groups (mOS 168 days (95% CI 80-268) PN vs. 169 days (88-295) in control group) n = 11 in PN arm vs. n = 11 in control arm still alive at week 24, n = 3 in PN arm vs. n = 5 in control arm alive at 1 year (NS)	Catheter-related infection (n = 2), no severe catheter-related bloodstream infection
Oh et al. (2014)	NA	NA	mOS in the PN group 13 (95% CI 3.1-22.9) days vs. 8 (95% CI 5.7-10.3) days in the control group. NS difference between groups.	NA
Prospective observational studies				
Cotogni et al. (2017)	**HRQoL** (EORTC QLQ C-30): improvement over time in global HRQoL, mean (SD) 52 (17) at baseline, 58 (17) at 1 month, 66 (17) at 2 months, 71 (14) at 3 months and 66 (16) at 4 months ($p < 0.001$). **Physical function:** Self-reported physical function (EORTC QLQ C-30) improved at all time points, mean (SD) 38 (22) at baseline, 42 (22) at 1 month, 46 (21) at 2 months, 55 (16) at 3 months, 52 (17) at 4 months ($p < 0.001$).	NA	mOS (range): 4.7 months(1-42) (n = 47). n = 74 alive at 3 months n = 38 alive at 6 months 24 of 72 patients on concurrent oncologic treatment died vs. 23 of 39 patients without concurrent oncologic treatment.	Incidence of catheter-related blood stream infection: 0.33 per 1000 catheter-days. No PN-related mortality.
Guerra et al. (2015)	NA	NA	mOS (range): 40 days (2-702). Outpatients survived longer than inpatients (log rank: 7.090, p = 0.008). Patients who started concurrent oncologic treatment during or after PN (n = 28) lived longer than those who did not (log rank: 17.316, $p < 0.001$). Patients who started chemotherapy during or after start of PN survived longer than those who did not (log rank: 17.316, $p < 0.001$). Twenty-eight could receive chemotherapy after PN due to improved status.	Catheter-related blood stream infection (n = 2) without affecting survival (log rank: 0.061, p = 0.804)
Bozzetti et al. (2014)	NA	NA	mOS (95% CI): 3.0 months (2.7-3.3). In cachectic patients (n = 143): 3- and 6-month survival was n = 42 and n = 12	PN stopped prematurely due to catheter- related complications (n = 9, 2.2%), central venous catheter complications resulting in death n = 5 (1.2%)
Vashi et al. (2014)	**HRQoL** (EORTC QLQ-C30): Unchanged at 1 month, improved score at 2 months (mean Δ +12, $p < 0.02$) and at 3 months (mean Δ +16, $p < 0.02$). Every month on PN associated with improved global HRQoL by 6.3 points ($p < 0.001$). **Physical function**: Self-reported physical function (EORTC QLQ-C30) improved at 2 months (mean Δ score +14, $p < 0.02$) and at 3 months (mean Δ +24, $p < 0.02$). Every month on PN associated with improved physical HRQoL domain by 6 points ($p < 0.005$).	**SGA global rating**: Improved at all time points ($p < 0.05$). At baseline: A (n = 0), B (19), C (33). At 1 month on PN: A (n = 2), B (n = 20), C (n = 17); at 2 months on PN: A (n = 3), B (n = 13), C (n = 6); at 3 months on PN: A (n = 2), B (n = 12), C (n = 1). **Body weight**: Improved at 1 month: mean Δ 1.6, $p < 0.03$, at 2 months: mean Δ 2.4, $p < 0.04$, at 3 months: mean Δ 4.8, $p < 0.04$. Every month on PN associated with improved weight by 1.3 kg ($p = 0.009$).	mOS: 5.1 months (95% CI: 2.8-7.3) mOS: 6.4 months (KPS ≤ 50) vs. 4.6 months (KPS > 50) mOS: 3.2 months (SGA-B) vs. 6.5 months (SGA-C) n = 25 survived < 6 months, n = 27 survived > 6 months, n = 12 survived > 1 year (of those 5 patients survived > 2 years)	1 of 9 patients on PN > 9 months developed hepatic dysfunction Early PN discontinuation due to sepsis: n = 2, elevated liver function tests: n = 2

(*continued on next page*)

Table 5 (*continued*)

Publication Authors (year)	Results			
	HRQoL and physical function	Nutritional status	Survival	Adverse events
Pelzer et al. (2010)	NA	**BMI**, median (range): increased from 19.7 (14.4-25.9) to 20.5 (15.4-25.0) during treatment (no p value or effect per time given)	NA	No severe side effects observed
Retrospective observational study				
Santarpia et al. (2006)	**HRQoL**: NA **Physical function**: Subgroup analysis in patients alive at > 60 and > 90 days: NS change in KPS from baseline to 1 month	**Body weight and BMI:** Subgroup analysis in survivors > 60 days (n = 64) and > 90 days (n = 39): Increased from 51.7 kg ± 10.3 (baseline) to 53.2 kg ± 10.3 (1 month) ($p < 0.0001$) and 50.5 kg ± 10.2 (baseline) to 52.0 kg ± 10.1 (1 month) ($p < 0.0001$). Mean BMI increased from 19.6 kg/m^2 ± 3.1 (baseline) to 20.1 kg/m^2 ± 03.1 (1 month) ($p < 0.0001$) and 19.2 kg/m^2 ± 3.2 (baseline) to 20.0 kg/m^2 ± 3.2 (1 month) ($p < 0.0001$). No results presented in survivors < 60 days.	mOS (range): 45 days (6-1269) n = 56 survived > 30 days, n = 34 survived 31-60 days, n = 25 survived 61-90 days, n = 37 survived > 90 days	Not reported

Δ: difference; 6MWD: six-minute walk distance; BIA: Bioimpedance; BMI: body mass index; CI: confidence interval; HGS: hand grip strength; HRQoL: health-related quality of life; KPS: Karnofsky Performance Status; m: metre; mOS: median overall survival; NA: not applicable; NS: not significant; SGA: Subjective Global Assessment; SGA-A: well nourished; SGA-B: moderately malnourished; SGA-C: severely malnourished; PN: parenteral nutrition; SD: standard deviation; vs: versus.

four studies and included via a central venous catheter (CVC) (Obling et al., 2017; Bozzetti et al., 2014; Guerra et al., 2015; Santarpia et al., 2006), transthoracic venous port (Obling et al., 2017) or peripherally inserted central catheter (PICC) line (Obling et al., 2017). The administration rate was described by five studies (Obling et al., 2017; Cotogni et al., 2017; Guerra et al., 2015; Pelzer et al., 2010; Vashi et al., 2014), in four studies PN was preferably delivered during the night (Obling et al., 2017; Cotogni et al., 2017; Guerra et al., 2015; Pelzer et al., 2010), and one study reported using daily cyclic infusions (Vashi et al., 2014). None of the studies reported the infusion rate (e.g., continuous infusion or ml/min). The planned energy dose ranged between 20–35 kcal/kg/day (Bozzetti et al., 2014; Guerra et al., 2015; Vashi et al., 2014; Santarpia et al., 2006) and 25 kcal/kg/day in five out of seven days (Pelzer et al., 2010). The planned protein dose ranged between 1.0 and 2.5 g/kg/d (Bozzetti et al., 2014; Santarpia et al., 2006). In one RCT, PN contributed 25–35% of the planned intake (30 kcal/kg/day and 1.5 g protein/kg/day), as the patients had a substantial oral intake (Obling et al., 2017). One study did not report a planned dose of either calories or protein and reported only the amount of calories administered (average 1286 kcal/day) (Oh et al., 2014). Additionally, three studies reported the calories administered but did not confirm whether patients reached target goals (Obling et al., 2017; Cotogni et al., 2017; Vashi et al., 2014). The duration of PN administration varied among the studies, ranging from a median of 9 days (Oh et al., 2014) to 6 months (Obling et al., 2017). Two studies reported administering PN until death or close to death in all patients (Oh et al., 2014; Santarpia et al., 2006) and until death in approximately 66% of the patients in one study (Bozzetti et al., 2014). The median duration of PN administration was < 1 month in one study (Oh et al., 2014), 1–3 months in three studies (Bozzetti et al., 2014; Guerra et al., 2015; Santarpia et al., 2006) and > 3 months in four studies (Obling et al., 2017; Cotogni et al., 2017; Pelzer et al., 2010; Vashi et al., 2014).

3.5. Effects of PN on HRQoL

Three studies provided data on HRQoL (n = 210) (Table 5). HRQoL was assessed by different methods (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) (Cotogni et al., 2017; Vashi et al., 2014) and EORTC QLQ-C15-PAL (Obling et al., 2017)) and measured at different time points (monthly (Cotogni et al., 2017; Vashi et al., 2014) and every 6 weeks (Obling et al., 2017)), with various lengths of follow-up (3 months (Vashi et al., 2014), 4 months (Cotogni et al., 2017) or 24 weeks (Obling et al., 2017)). In one RCT, a significantly higher mean (95% confidence interval (CI)) score of +16 (0.6, 31) points in HRQoL at 12 weeks was reported in favour of PN compared to control treatment ($p < 0.05$), but not at week 6, 18 or 24 (Obling et al., 2017). In one observational study, HRQoL was unchanged after one month but significantly improved after two (+12 points, $p = 0.02$) and three months (+24 points, $p = 0.02$) (Vashi et al., 2014). Another observational study reported significant improvement over time during four months using analysis of repeated measures ($p < 0.001$), with +6 points at one month, +14 points at two months, +19 points at three months and +14 points at four months (Cotogni et al., 2017). In summary, the effect of current PN treatment on HRQoL in patients with advanced cancer is poorly investigated. PN was superior in a transient manner to dietetic counselling in patients with functional gastrointestinal tract while undergoing anti-neoplastic treatment. In patients where PN is the only viable feeding option, HRQoL may improve after a minimum of two months on PN in malnourished patients while undergoing anti-neoplastic treatment. Although statistical significance was reached, the reported effect sizes does not necessarily reach clinical relevant improvements in HRQoL (< 20%).

3.6. Effects of PN on physical function

Three studies provided data on self-reported physical function from subscales of HRQoL questionnaires (n = 210) (Obling et al., 2017;

Cotogni et al., 2017; Vashi et al., 2014) (Table 5). An RCT found no difference between patients receiving PN and control subjects at any time during the 24 weeks of intervention (Obling et al., 2017). The two observational studies reported improved self-reported physical function over time ((+4 points at one month, +8 points at two months, +17 points at three months and +14 points at four months; $p < 0.001$ for repeated measures) (Cotogni et al., 2017) and after two (+14 points, $p = 0.02$) and three months (+16 points, $p = 0.005$) but not after one month (+3 points, $p = 0.39$) (Vashi et al., 2014)).

One RCT (Obling et al., 2017), one prospective study (Vashi et al., 2014) and one retrospective study (Santarpia et al., 2006) reported a change in performance status as assessed by health providers' perception of patients' function (KPS) or physical performance tests (strength or endurance) (n = 251) (Table 3). Patients randomized to receive PN or control treatment both improved on the 6-minute walk test and in terms of hand grip strength from baseline to week 24 in the RCT, although no significant difference between the two arms was found (Obling et al., 2017). In the prospective study, there was a significant increase in KPS after one (+6 points, $p = 0.01$), two (+10 points, $p = 0.01$) and three months (+15 points, $p = 0.002$) (Vashi et al., 2014). In the retrospective study, there was no change in KPS after one month in subgroups of survivors after > 60 and > 90 days (Santarpia et al., 2006), but no data from patients who survived less than 60 or 30 days were reported.

In summary, the effect of current PN treatment on physical function in patients with advanced cancer is poorly investigated. PN was not superior to dietetic counselling in malnourished patients with functional gastrointestinal tract undergoing active anti-neoplastic treatment. However, PN may be beneficial in malnourished patients when PN is the only feeding opportunity and who still receive anti-neoplastic treatment, but not in patients not undergoing anti-neoplastic treatment.

3.7. Effects of PN on nutritional status

Nutritional status was reported in 4 of 8 studies (n = 283) (Obling et al., 2017; Pelzer et al., 2010; Vashi et al., 2014; Santarpia et al., 2006) (Table 5). In one RCT, the mean (95% CI) BMI and fat free mass was significantly increased at week 12 in favour of the supplementary PN arm compared to the control arm (mean (95% CI): +1.65 (0.4, 2.9) BMI (kg/h^2), $p < 0.05$; + 6.44 kg (2.9, 10.0) FFM (kg), $p < 0.01$) (Obling et al., 2017). No differences between the two arms on any nutritional status outcomes were observed at the other time points (week 6, 18 or 24) (Obling et al., 2017). Two observational studies (n = 251) reported an increase in mean body weight (kg) by 1.5 kg in subgroups of survivors after > 60 and > 90 days (Santarpia et al., 2006) and 1.6 kg after one month (Vashi et al., 2014), 2.4 kg after 2 months (Vashi et al., 2014) and 4.6 kg after 3 months (Vashi et al., 2014) ($p < 0.05$). One observational study reported a mean increase in BMI of 0.5 kg/m^2 at one month in subgroups of survivors after > 60 and > 90 days ($p = 0.0001$) (Santarpia et al., 2006). No data were presented for survivors after < 60 days (Santarpia et al., 2006). Another observational study reported a median increase in BMI of 0.7 kg/m^2 (no effect per time unit or p value reported) (Pelzer et al., 2010). One observational study reported nutritional status using the SGA global rating, and the of patients in category SGA-A (well nourished) changed from zero patients at baseline, to two patients at 1 month and three patients at 2 months, SGA-B (moderately malnourished) changed from 19 patients at baseline to 20 patients at 1 month, 13 patients at 2 months, and 12 patients at 3 months, while the number of patients in category SGA-C (severely malnourished) decreased from 33 patients at baseline to 17 patients at 1 month, 6 patients at 2 months and one patient at 3 months (Vashi et al., 2014).

In summary, current PN treatment seems to be superior to dietetic counselling in a transient manner in regards to BMI and fat free mass in malnourished patients with functional gastrointestinal tract, while undergoing anti-neoplastic treatment. When PN is the only feeding opportunity, PN may improve nutritional status in malnourished patients regardless of anti-neoplastic treatment after 2–3 months of PN treatment.

3.8. Effects of PN on survival

Data on survival were available from seven studies (n = 862) (Oh et al., 2014; Obling et al., 2017; Bozzetti et al., 2014; Cotogni et al., 2017; Guerra et al., 2015; Vashi et al., 2014; Santarpia et al., 2006) (Table 5). In the RCT involving terminal patients, the median overall survival (mOS) was 8 days (95% CI: 5.7–10.3) in the control group compared to 13 days (95% CI: 3.1–22.9) in the PN group (Oh et al., 2014). In the other RCT, the mOS was 169 (95% CI: 88–295) days in the control group versus 168 (95% CI: 88–268) days in the supplemental PN group (Obling et al., 2017). The difference in mOS between patients receiving PN compared to subjects in the control groups in both RCTs was not statistically significant (Oh et al., 2014; Obling et al., 2017). In the three of the observational studies, the mOS in months was 3 (95% CI: 2.7–3.3) (Bozzetti et al., 2014), 5.1 (95% CI: 2.8–7.3) (Vashi et al., 2014) and 4.7 (range, 1–42) months (Cotogni et al., 2017). In the two observational studies reporting survival in days, the mOS (range) was 40 (2–702) (Guerra et al., 2015) and 45 (6–1269) days (Santarpia et al., 2006). In summary, survival between patients receiving and not receiving current PN treatment is poorly investigated and both RCTs were underpowered. PN is neither superior to dietetic counselling in patients with functional gastrointestinal tract undergoing anti-neoplastic treatment, nor superior to fluid administration in terminal patients.

3.9. Effects of PN on tolerance and dose-limiting toxicity of anti-neoplastic treatment

No studies reported outcomes on tolerance or dose-limiting toxicity of anti-neoplastic treatment.

3.10. Effects of PN on adverse events

Adverse events were systematically reported in four of eight studies (n = 245) (Obling et al., 2017; Cotogni et al., 2017; Guerra et al., 2015; Pelzer et al., 2010) (Table 5). One observational study reported no adverse events (Pelzer et al., 2010). One RCT reported catheter-related infections in two patients but no episodes of severe catheter-related blood stream infection (Obling et al., 2017). One observational study reported catheter-related infections in 3.6% of the patients (Guerra et al., 2015), while another observational study reported an incidence of catheter-related bloodstream infection of 0.33 per 1000 catheter-days (Cotogni et al., 2017). Two additional studies reported discontinuation of PN due to PN-related complications (n = 466) (Bozzetti et al., 2014; Vashi et al., 2014): catheter-related complications in nine of 414 patients (incidence: 2.2%) (Bozzetti et al., 2014), sepsis in two of 52 patients (Vashi et al., 2014) and elevated liver function tests in two of 52 patients (Vashi et al., 2014). Death due to PN/CVC complications was reported in five of 414 patients (incidence: 1.2%) (Bozzetti et al., 2014) and liver dysfunction in one patient after nine months on PN (Vashi et al., 2014). In summary, the incidence of adverse events of current PN treatment were acceptable, but lack of systematic reporting was observed.

3.11. Losses to follow-up

Losses to follow-up were reported in or could be retrieved from all studies. Three studies assessed survival as the only outcome, and all patients were included in the survival analysis (Oh et al., 2014; Bozzetti et al., 2014; Guerra et al., 2015). One study performed an analysis in survivors over the previous 60 and 90 days; however, they presented conflicting numbers of losses to follow-up between the text and tables (Santarpia et al., 2006). No patients were lost to follow-up in one study (Pelzer et al., 2010), while the remaining three studies reported losses

to follow-up by stating the number of patients included at each time point of assessment (Obling et al., 2017; Cotogni et al., 2017; Vashi et al., 2014). The cumulative losses to follow-up were 27 of 163 patients at one month (17%) (Cotogni et al., 2017; Vashi et al., 2014), 11 of 47 patients at six weeks (23%) (Obling et al., 2017), 65 of 163 patients at two months (40%) (Cotogni et al., 2017; Vashi et al., 2014), 116 of 210 patients at three months (55%) (Obling et al., 2017; Cotogni et al., 2017; Vashi et al., 2014), 57 of 111 patients at four months (51%) (Cotogni et al., 2017), 25 of 47 at 18 weeks (53%) (Obling et al., 2017) and 30 of 47 patients at six months (64%) (Obling et al., 2017). The main reason for loss to follow-up was death or worsening of the clinical state (98 of 210 patients (47%) (Obling et al., 2017; Cotogni et al., 2017; Vashi et al., 2014)). Other reasons included weaning from PN to oral feeding or enteral nutrition, change in home care company, refusal to continue PN or adverse events (Bozzetti et al., 2014; Cotogni et al., 2017; Vashi et al., 2014).

4. Discussion

This systematic review selectively assessed the effect of current PN treatment exclusively in patients with advanced cancer. Since the launch of PN treatment, the most important advancement in this therapy is the reduction of the glucose load by implementing fatty acids in the PN solution and reducing the caloric load to match the caloric demand, as well as improving the hygiene protocols. Trials using outdated PN strategies (hypercaloric, glucose rich PN therapies) were thus excluded in order to assess the effects of PN treatment more compatible with today's practice. The evidence level of all outcomes is weak, due to the few high quality trials. Effects on HRQoL and physical function are based on the findings from one RCT and three observational studies. The RCT was conducted in malnourished patients with functional gastrointestinal tract during anti-neoplastic treatment. Two of the observational studies were conducted in malnourished patients in who PN was the only viable feeding option and received concurrent anti-neoplastic treatment. One retrospective study that assessed physical function was conducted in malnourished patients in who PN was the only viable feeding option without concurrent anti-neoplastic treatment. In malnourished patients receiving anti-neoplastic treatment and in who PN was the only available feeding route, PN may improve HRQoL, physical function and nutritional status after two months of PN treatment. On the contrary, malnourished patients receiving anti-neoplastic treatment, with a moderate spontaneous food intake and who could be fed via enteral route, PN was not superior to dietary counselling in regards to HRQoL, physical function, nutritional status or survival during a six month intervention, apart from a transient effect on HRQoL and nutritional status at three months. In malnourished patients, no longer candidates to receive anti-neoplastic treatment, current PN treatment can improve nutritional status, but not physical function.

Unlike simple undernutrition (non-disease-related malnutrition (Cederholm et al., 2017)), a negative energy balance and muscle loss in patients with cancer cachexia is characterized by a combination of reduced food intake and catabolism driven by systemic inflammation (Fearon et al., 2011). Earlier practices of hypercaloric PN aimed to reverse catabolism, particularly by use of high doses of glucose (McGeer et al., 1990). High energy-dense lipid emulsions have later been integrated into PN solutions, thus reducing the glucose load and high volume infusion. Furthermore, the use of soybean oil rich in pro-inflammatory n-6 polyunsaturated fatty acids (PUFAs) has been replaced with olive oil and fish oil, which are rich in anti-inflammatory n-3 PUFAs (Jones and Calder, 2018; Wanten and Calder, 2007). Cachexia cannot be reversed by nutritional support alone (Fearon et al., 2011); thus, hypercaloric PN is no longer the standard of care. Nevertheless, the optimal PN treatment for these patients is still questioned as the energy requirement, and whether these patients have an anabolic potential in response to energy balance is uncertain (Fearon et al., 2011; Prado et al., 2013). Following the meta-analysis on survival and adverse events from 1990 evaluating RCTs using hypercaloric and glucose-rich PN solutions (McGeer et al., 1990), two previous systematic reviews have assessed the clinical effects of PN in patients with inoperable malignant bowel obstruction (Naghibi et al., 2015; Sowerbutts et al., 2018). Both reviews failed to provide a conclusion on HRQoL due to the use of non-validated QoL tools used by the majority of the individual studies (Naghibi et al., 2015; Sowerbutts et al., 2018). Furthermore, these reviews included studies using outdated PN treatment, such as hypercaloric PN, and consequently cannot be used to evaluate the efficacy of current PN treatment.

The studies conducted in recent years have predominantly been observational, and these studies can provide important information about prevalence and adverse events. Nevertheless, observational studies cannot provide reliant effect sizes for key questions regarding the effects of PN on clinically relevant outcomes due to bias and confounding factors. The observed effects could, for instance, be a response to anti-neoplastic treatment, symptom alleviation and loss of patients with initially poor nutritional/clinical status ("survivalism") and underpin the importance of a control group when the effects of an intervention are evaluated. The importance of an actual control group is exemplified by one RCT in which both arms showed increased physical performance and a transient increase in muscle mass in 40% of the patients in the control arm (Obling et al., 2017).

The major limitations of this review were the lack of well-designed RCTs. Both RCTs were underpowered and did not comply with indications for PN treatment according to guidelines (Arends et al., 2017). Patients in one study were terminally ill with days or a few weeks of expected survival (Oh et al., 2014), while the majority of patients in the other RCT had a nutritional intake above 75% of the estimated requirement and a functional gastrointestinal (GI) tract (Obling et al., 2017). PN administration is neither indicated in terminally ill patients nor the first choice of nutritional support in patients with ≥75% of recommended nutritional intake and a functional GI tract (Arends et al., 2017). A multicentre phase III RCT involving patients with advanced cancer aimed at study the effect of PN on HRQoL was recently completed (Pazart et al., 2014). The inclusion criteria comply with indications for PN administration according to guidelines and will, if positive, identify causal effects of PN on HRQoL and other important outcomes in patients with advanced cancer. Future studies must provide detailed descriptions regarding PN administration, including planned and administered dosages, sufficiency of caloric intake compared to nutritional requirements, composition, infusion rate, and duration, to gather information on the optimal PN treatment. For better reporting of nutritional interventions, investigators can find guidance using a checklist (Hoffmann et al., 2014).

5. Conclusion

This systematic review is the first to evaluate the effects of current PN treatment exclusively in patients with advanced cancer. The evidence is weak for all outcomes and is predominantly based on observational studies. During anti-neoplastic treatment, PN seems to improve HRQoL and physical function in patients who PN is the only viable feeding option, but not necessarily in patients able to be fed enterally. Regardless of anti-neoplastic treatment and GI function, nutritional status seems to be improved by current PN treatment in malnourished patients. No benefit on survival of PN in terminal patients or patients able to feed enterally were reported. The frequency of adverse effects was low; however, a lack of systematic reporting was observed. Further RCTs with sufficient number of patients of clinically homogenous subgroups are urgently needed.

Conflict of interest

All authors have contributed to the review and writing process, and none have conflicts of interest to declare. No funding was granted or associated with this review/manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Contributors

All authors contributed to the planning process, risk of bias assessment, analysis and interpretation of data. RT and TRB acquired the data and drafted the article, which was critically revised for important intellectual content by the remaining authors. All authors have approved the final article.

Acknowledgements

The authors thank Conni Skrubbeltrang, research advisor at the Medical library, Aalborg University Hospital for help with the systematic searches and valuable input on the process and Henrik Højgaard Rasmussen, Professor at Centre for Nutrition and Bowel Disease, Department of Gastroenterology, Faculty of Medicine, Aalborg University Hospital, Aalborg University, for valuable criticism.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2019.04.014.

References

Arends, J., Bachmann, P., Baracos, V., Barthelemy, N., Bertz, H., Bozzetti, F., et al., 2017. ESPEN guidelines on nutrition in cancer patients. Clin. Nutr. 36 (1), 11–48.
Bozzetti, F., Cozzaglio, L., Biganzoli, E., Chiavenna, G., De Cicco, M., Donati, D., et al., 2002. Quality of life and length of survival in advanced cancer patients on home parenteral nutrition. Clin. Nutr. 21 (4), 281–288.
Bozzetti, F., Santarpia, L., Pironi, L., Thul, P., Klek, S., Gavazzi, C., et al., 2014. The prognosis of incurable cachectic cancer patients on home parenteral nutrition: a multi-centre observational study with prospective follow-up of 414 patients. Ann. Oncol. 25 (2), 487–493.
Brard, L., Weitzen, S., Strubel-Lagan, S.L., Swamy, N., Gordinier, M.E., Moore, R.G., et al., 2006. The effect of total parenteral nutrition on the survival of terminally ill ovarian cancer patients. Gynecol. Oncol. 103 (1), 176–180.
Cederholm, T., Barazzoni, R., Austin, P., Ballmer, P., Biolo, G., Bischoff, S.C., et al., 2017. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin. Nutr. 36 (1), 49–64.
Chen, C.J., Shih, S.C., Wang, H.Y., Sun, F.J., Lu, S.C., Chu, C.H., et al., 2013. Clinical application of total parenteral nutrition in patients with peritoneal carcinomatosis. Eur. J. Cancer Care (Engl) 22 (4), 468–473.
Chermesh, I., Mashiach, T., Amit, A., Haim, N., Papier, I., Efergan, R., et al., 2011. Home parenteral nutrition (HTPN) for incurable patients with cancer with gastrointestinal obstruction: do the benefits outweigh the risks? Med. Oncol. 28 (1), 83–88.
Chouhan, J., Gupta, R., Ensor, J., Raghav, K., Fogelman, D., Wolff, R.A., et al., 2016. Retrospective analysis of systemic chemotherapy and total parenteral nutrition for the treatment of malignant small bowel obstruction. Cancer Med. 5 (2), 239–247.
Cotogni, P., De Carli, L., Passera, R., Amerio, M.L., Agnello, E., Fadda, M., et al., 2017. Longitudinal study of quality of life in advanced cancer patients on home parenteral nutrition. Cancer Med. 6 (7), 1799–1806.
Covidence systematic review software, 2019. Veritas Health Innovation, Melbourne, Australia. Available at. www.covidence.org.
Diver, E., O'Connor, O., Garrett, L., Boruta, D., Goodman, A., Del Carmen, M., et al., 2013. Modest benefit of total parenteral nutrition and chemotherapy after venting gastrostomy tube placement. Gynecol. Oncol. 129 (2), 332–335.
Fan, B.G., 2007. Parenteral nutrition prolongs the survival of patients associated with malignant gastrointestinal obstruction. JPEN J. Parenter. Enteral Nutr. 31 (6), 508–510.
Fearon, K., Strasser, F., Anker, S.D., Bosaeus, I., Bruera, E., Fainsinger, R.L., et al., 2011. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 12 (5), 489–495.
Finocchiaro, E., Rahimi, F., Angello, E., Monge, E., Scigliano, M., Fadda, M., et al., 2007. Home parenteral nutrition in advanced cancer patients: a four-years multicenter prospective observational study. Nutr. Ther. Metab. 25 (1), 31–39.
Girke, J., Seipt, C., Markowski, A., Luettig, B., Schettler, A., Momma, M., et al., 2016. Quality of life and nutrition condition of patients improve under home parenteral nutrition: an exploratory study. Nutr. Clin. Pract. 31 (5), 659–665.
Guerra, E.M., Cortes-Salgado, A., Mateo-Lobo, R., Nattero, L., Riveiro, J., Vega-Pinero, B., et al., 2015. Role of parenteral nutrition in oncologic patients with intestinal occlusion and peritoneal carcinomatosis. Nutr. Hosp. 32 (3), 1222–1227.
Higgins, J., Green, S., 2011. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011] ed. .
Hoffmann, T.C., Glasziou, P.P., Boutron, I., Milne, R., Perera, R., Moher, D., et al., 2014. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. Bmj. 348, g1687.
IHE IoHE, 2014. Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics.
Jones, C.J., Calder, P.C., 2018. Influence of different intravenous lipid emulsions on fatty acid status and laboratory and clinical outcomes in adult patients receiving home parenteral nutrition: a systematic review. Clin. Nutr. 37 (1), 285–291.
Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P., et al., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Bmj 339, b2700.
Madhok, B.M., Yeluri, S., Haigh, K., Burton, A., Broadhead, T., Jayne, D.G., 2011. Parenteral nutrition for patients with advanced ovarian malignancy. J. Hum. Nutr. Diet. 24 (2), 187–191.
McGeer, A.J., Detsky, A.S., O'Rourke, K., 1990. Parenteral nutrition in cancer patients undergoing chemotherapy: a meta-analysis. Nutrition 6 (3), 233–240.
Naghibi, M., Smith, T.R., Elia, M., 2015. A systematic review with meta-analysis of survival, quality of life and cost-effectiveness of home parenteral nutrition in patients with inoperable malignant bowel obstruction. Clin. Nutr. 34 (5), 825–837.
Obling, S.R., Wilson, B.V., Pfeiffer, P., Kjeldsen, J., 2017. Home parenteral nutrition increases fat free mass in patients with incurable gastrointestinal cancer. Results of a randomized controlled trial. Clin. Nutr.
Oh, S.Y., Jun, H.J., Park, S.J., Park, I.K., Lim, G.J., Yu, Y., et al., 2014. A randomized phase II study to assess the effectiveness of fluid therapy or intensive nutritional support on survival in patients with advanced cancer who cannot be nourished via enteral route. J. Palliat. Med. 17 (11), 1266–1270.
Pasanisi, F., Orban, A., Scalfi, L., Alfonsi, L., Santarpia, L., Zurlo, E., et al., 2001. Predictors of survival in terminal-cancer patients with irreversible bowel obstruction receiving home parenteral nutrition. Nutrition 17 (7-8), 581–584.
Pazart, L., Cretin, E., Grodard, G., Cornet, C., Mathieu-Nicot, F., Bonnetain, F., et al., 2014. Parenteral nutrition at the palliative phase of advanced cancer: the ALIM-K study protocol for a randomized controlled trial. Trials 15, 370.
Pelzer, U., Arnold, D., Govercin, M., Stieler, J., Doerken, B., Riess, H., et al., 2010. Parenteral nutrition support for patients with pancreatic cancer. Results of a phase II study. BMC Cancer 10 (86), 86.
Pironi, L., Ruggeri, E., Tanneberger, S., Giordani, S., Pannuti, F., Miglioli, M., 1997. Home artificial nutrition in advanced cancer. J. R. Soc. Med. 90 (11), 597–603.
Prado, C.M., Sawyer, M.B., Ghosh, S., Lieffers, J.R., Esfandiari, N., Antoun, S., et al., 2013. Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential? Am. J. Clin. Nutr. 98 (4), 1012–1019.
Santarpia, L., Alfonsi, L., Pasanisi, F., De Caprio, C., Scalfi, L., Contaldo, F., 2006. Predictive factors of survival in patients with peritoneal carcinomatosis on home parenteral nutrition. Nutrition 22 (4), 355–360.
Soo, I., Gramlich, L., 2008. Use of parenteral nutrition in patients with advanced cancer. Appl. Physiol. Nutr. Metab. = Physiologie appliquee, nutrition et metabolisme 33 (1), 102–106.
Sowerbutts, A.M., Lal, S., Sremanakova, J., Clamp, A., Todd, C., Jayson, G.C., et al., 2018. Home parenteral nutrition for people with inoperable malignant bowel obstruction. Cochrane Database Syst. Rev. 8, CD012812.
Vashi, P.G., Dahlk, S., Popiel, B., Lammersfeld, C.A., Ireton-Jones, C., Gupta, D., 2014. A longitudinal study investigating quality of life and nutritional outcomes in advanced cancer patients receiving home parenteral nutrition. BMC Cancer 14, 593.
Wanten, G.J., Calder, P.C., 2007. Immune modulation by parenteral lipid emulsions. Am. J. Clin. Nutr. 85 (5), 1171–1184.

Randi Tobberup, RD, PhD scholar, Dept. of Medicine, Dept. of Clinical Medicine, Aalborg University Hospital, Aalborg University, Denmark.

Lene Thoresen, RD, PhD, Cancer Clinic, St Olavs University hospital, Trondheim, and the National Advisory Unit on Disease-Related Malnutrition, Oslo University Hospital, Norway.

Ursula Falkmer, MD, PhD, Professor in Clinical Oncology, Dept. of Oncology, Clinical Cancer Research Center, Dept of Clinical Medicine, Aalborg University Hospital, Aalborg University, Denmark.

Mette Yilmas, MD, senior consultant, Dept of Oncology, Clinical Cancer Research Center, Aalborg University Hospital, Denmark.

Tora S. Solheim, MD, PhD, ass. Professor in Palliative Medicine, Cancer Clinic, St Olavs University hospital, Trondheim, Dept. of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, NTNU, Trondheim, Norway.

Trude R. Balstad, RD, PhD, researcher at Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, NTNU, Trondheim, Norway.