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

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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.

Keywords: Palliative care; Intravenous nutrition; performance status; weight loss; cachexia; supportive care

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 [1, 2]. 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 [2]. The treatment goals of parenteral nutrition (PN) administration should be to maintain HRQoL and performance status [2]. 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 [2]. 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 [3]. 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 [3]. As a consequence of this conclusion, no randomized controlled trials (RCTs) involving patients with advanced cancer 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 administration 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 [4]. A Cochrane technology platform was used to manage the review process [5]. 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 practice is defined in this review as normocaloric infusion (not hypercaloric), 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.

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148 *2.3 Assessment of risk of bias*

149 The content of each of the included RCTs was analysed using methodological risk of bias
150 domains from the Cochrane Handbook for Systematic Reviews of Interventions at the study
151 level [6]. All reviewers assessed the risk of bias (RoB), and any discrepancies were resolved
152 through discussion. There is no single recommended instrument for assessing the RoB when
153 the systematic review also includes non-randomized trials [6]. Therefore, the Institute of Health
154 Economics (IHE) Quality Appraisal Checklist for Case Series Studies was opted for the
155 observational studies [7]. The quality appraisal checklist consists of 20 criteria, of which 16
156 criteria were considered important. Pre-defined aspects considered important were determined
157 for the study population (age, sex, cancer diagnosis, tumour stage, anti-neoplastic treatment,
158 nutritional status and physical function, and the quality of the description of the intervention
159 (composition of the PN solution, administration, rate, dosage, duration and indications). When
160 assessing the overall quality of the observational studies, the studies were categorized as good
161 or poor quality based on pre-defined cut-off scores. A total score was calculated by
162 summarizing scores from each of the 16 predefined criteria (3 points for yes, 2 points for
163 partially and 1 point for no/unclear reporting) and categorized as good (score of 40-48) or poor
164 quality (score of 16-39). A study was classified as good quality if at least 4 out of 6 reviewers
165 scored the study at 40-48 points. RoB and confounders were assessed.

166 **3. Results**

167 *3.1 Search results and selection of studies*

168 The literature review retrieved 1039 papers (Figure 1). Three additional studies were identified
169 by hand searching. After excluding duplicates and studies that did not meet the inclusion
170 criteria based on title and abstract screening, 85 papers were selected for full-text examination.
171 Full-text screening resulted in the exclusion of 64 papers (for reasons, see Figure 1).

Additionally, 13 studies were excluded based on critically high RoB [8-20] (Appendices 2 and 3). The present review is based on the results from eight articles: two RCTs [21, 22], five prospective observational studies [23-27] and one retrospective study [28].

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 [22] and 31 of the planned 116 patients were enrolled [21]. 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 (range, 16 – 90 years). Six of eight studies included different cancer diagnoses [21, 23-25, 27, 28]. 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 [22, 24, 25, 27], and 639 patients (71%) did not [21, 23-25, 28] (Table 4). One study (n=32, 4%) did not report the use of concurrent anti-neoplastic treatment [26].

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) [25], Nutritional Risk Screening 2002 (NRS2002) [22], Subjective Global Assessment (SGA) [27] or Patient-Generated Subjective Global Assessment (PG-SGA) [24]). Body mass index (BMI) was reported by two RCTs [21, 22] and by five observational studies [23, 24, 26-28]. Weight loss was reported in various ways: weight loss over the last three months [24], weight loss over the last six months [27, 28], percent weight loss of usual weight (usual not specified) [23] and weight loss without a specified time frame [22]. Oral food intake was reported by one RCT [22] and one observational study [24].

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 [22] and one observational study used a weight loss of ≥5% over the previous four weeks or a BMI (kg/m^2) < 19 [26]. Additionally, three studies used nil/negligible intake per os or enteral feeding as inclusion criteria [21, 23, 24].

Baseline performance status was reported in seven of eight studies using either the Karnofsky Performance Score (KPS) [23, 24, 27, 28] or Eastern Cooperative Oncology Group (ECOG) performance status [21, 22, 25] (Table 3 and 4). The two RCTs had performance status as an inclusion criterion: ECOG performance status of 0-2 [22] or ECOG performance status of 3 or 4 [21]. The mean performance status at baseline reported in the observational studies was a KPS of 60 (range, 20-100) [23, 24, 27, 28] and ECOG performance status of 1.5 (standard deviation (SD), 0.5) [25].

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) [21, 23-28] (Table 4). No or negligible food intake/enteral nutrition was the primary PN indication in 16% of the patients [21, 23, 24, 26]. 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) [22].

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 [22, 24, 27, 28], three studies partially reported the composition of PN macronutrient solution [21, 25, 26], while one study failed to describe the composition of PN [23]. The method of PN administration was reported by four studies and included via a central venous catheter (CVC) [22, 23, 25, 28], transthoracic venous port [22] or peripherally inserted central catheter (PICC) line [22]. The administration rate was described by five studies [22, 24-27]; in four studies PN was preferably delivered during the night [22, 24-26], and one study reported using daily cyclic infusions [27]. 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 [23-25, 27, 28] and 25 kcal/kg/day in five out of seven days [26]. The planned protein dose ranged between 1.0 and 2.5 g/kg/d [23-28]. 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 [22]. 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) [21]. Additionally, three studies reported the calories administered but

did not confirm whether patients reached target goals [22, 24, 27]. The duration of PN administration varied among the studies, ranging from a median of 9 days [21] to 6 months [22]. Two studies reported administering PN until death or close to death in all patients [21, 28] and until death in approximately 66% of the patients in one study [23]. The median duration of PN administration was < 1 month in one study [21], 1-3 months in three studies [23, 25, 28] and > 3 months in four studies [22, 24, 26, 27].

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) [24, 27] and EORTC QLQ-C15-PAL [22]) and measured at different time points (monthly [24, 27] and every 6 weeks [22]), with various lengths of follow-up (3 months [27], 4 months [24] or 24 weeks [22]). 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 [22]. 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, $p=0.02$) [27]. 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 [24]. 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) [22, 24, 27] (Table 5). An RCT found no difference between patients receiving PN and control subjects at any time during the 24 weeks of intervention [22]. 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) [24] and after two (+14 points, $p=0.02$) and three months (+16 points, $p=0.005$) but not after one month (+3 points, $p=0.39$) [27]).

One RCT [22], one prospective study [27] and one retrospective study [28] 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 [22]. 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, $p=0.002$) [27]. In the retrospective study, there was no change in KPS after one month in subgroups of survivors after >60 and >90 days [28], 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) [22, 26-28] (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), $p<0.01$) [22]. No differences between the two arms on any nutritional status outcomes were observed at the other time points (week 6, 18 or 24) [22]. 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 [28] and 1.6 kg after one month [27], 2.4 kg after 2 months [27] and 4.6 kg after 3 months [27] ($p<0.05$). 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 ($p=0.0001$) [28]. No data were presented for survivors after <60 days [28]. Another observational study reported a median increase in BMI of 0.7 kg/m^2 (no effect per time unit or p value reported) [26]. 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 [27].

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) [21-25, 27, 28] (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 [21]. 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 [22]. The difference in mOS between patients receiving PN compared to subjects in the control groups in both RCTs was not statistically significant [21, 22]. In the three of the observational studies, the mOS in months was 3 (95% CI: 2.7-3.3) [23], 5.1 (95% CI: 2.8-7.3) [27] and 4.7 (range, 1-42) months [24]. In the two observational studies reporting survival in days, the mOS (range) was 40 (2-702) [25] and 45 (6-1269) days [28]. 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) [22, 24-26] (Table 5). One observational study reported no adverse events [26]. One RCT reported catheter-related infections in two patients but no episodes of severe catheter-related blood stream infection [22]. One observational study reported catheter-related infections in 3.6% of the patients [25], while another observational study reported an incidence of catheter-related bloodstream infection of 0.33 per 1000 catheter-days [24]. Two additional studies reported discontinuation of PN due to PN-related complications (n=466) [23, 27]: catheter-related complications in nine of 414 patients (incidence: 2.2%) [23], sepsis in two of 52 patients [27] and elevated liver function tests in two of 52 patients [27]. Death due to PN/CVC complications was reported in five of 414 patients (incidence: 1.2%) [23] and liver dysfunction in one patient after nine months on PN [27]. 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 [21, 23, 25]. 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 [28]. No patients were lost to follow-up in one study [26], while the remaining three studies reported losses to follow-up by stating the number of patients included at each time point of assessment [22, 24, 27]. The cumulative losses to follow-up were 27 of 163 patients at one month (17%) [24, 27], 11 of 47 patients at six weeks (23%) [22], 65 of 163 patients at two months (40%) [24, 27], 116 of 210 patients at three months (55%) [22, 24, 27], 57 of 111 patients at four months (51%) [24], 25 of 47 at 18 weeks (53%) [22] and 30 of 47 patients at

six months (64%) [22]. The main reason for loss to follow-up was death or worsening of the clinical state (98 of 210 patients (47%) [22, 24, 27]). Other reasons included weaning from PN to oral feeding or enteral nutrition, change in home care company, refusal to continue PN or adverse events [23, 24, 27].

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 [1]), 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 [29]. Earlier practices of hypercaloric PN aimed to reverse catabolism, particularly by use of high doses of glucose [3]. 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 [30, 31]. Cachexia cannot be reversed by nutritional support alone [29]; 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 [29, 32]. Following the meta-analysis on survival and adverse events from 1990 evaluating RCTs using hypercaloric and glucose-rich PN solutions [3], two previous systematic reviews have assessed the clinical effects of PN in patients with inoperable malignant bowel obstruction [33, 34]. 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 [33, 34]. 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 [22].

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 [2]. Patients in one study were terminally ill with days or a few weeks of expected survival [21], 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 [22]. 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 [2]. A multicentre phase III RCT involving patients with advanced cancer aimed at study the effect of PN on HRQoL was recently completed [35]. 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 [36].

4. 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.

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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.

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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. 2016	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;	Administration route and dose given not described	Statistical method unknown	No comment	Large drop out	**High**

	performance status at baseline not reported					
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	**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.	**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

Republic of Korea	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		**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)	**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)

	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, 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),	**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

	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		**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)	**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)

	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		
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)	**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

	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

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

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,	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.

	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).			
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).	**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:	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)	1 of 9 patients on PN > 9 months developed hepatic dysfunction

	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).	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).	n=25 survived < 6 months, n=27 survived > 6 months, n=12 survived > 1 year (of those 5 patients survived > 2 years)	Early PN discontinuation due to sepsis: n=2, elevated liver function tests: n=2
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

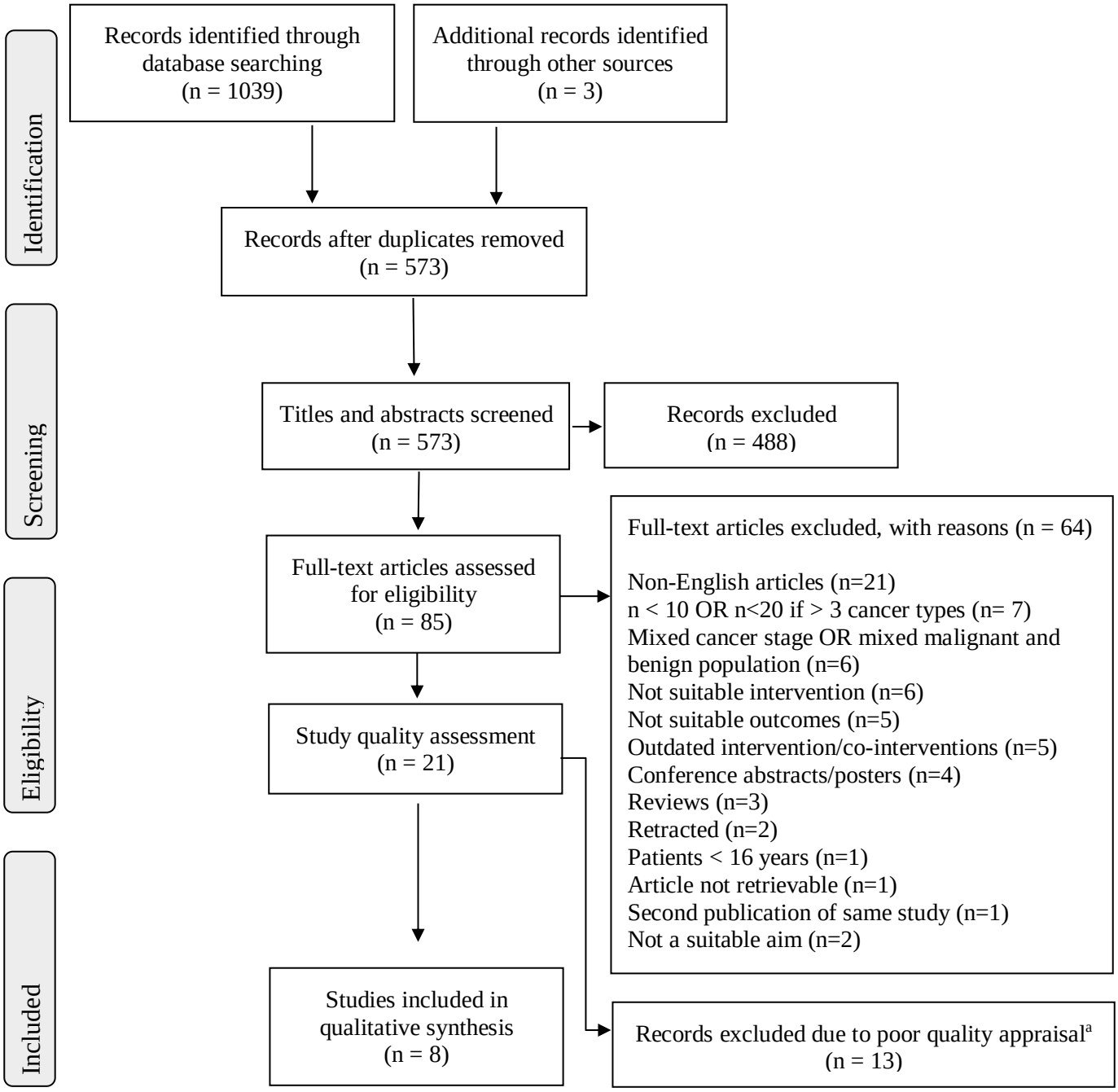

Figure 1. Flow chart for the study selection process.
The figure provides details of reasons for exclusion of full text articles

[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.

Appendix 2. Study characteristics and results of excluded studies

Publication	**Population**	**PN indication**	**PN intervention**	**Results**	
Authors (year published), study period, country	N, sex, age, cancer diagnosis, tumour stage, anti-neoplastic treatment, performance status, nutritional status	Medical related, Food/nutrition related	Composition of PN solution, administration, rate, dose planned, dose given and duration of PN	Primary outcomes	Secondary outcomes
Chouhan J. et al. (2016) Study period: 2005-2013 USA Retrospective study	**N**= 82 **Sex**: female (n= 51), male (n=31) **Age** (years), median (range): 55 (17-85) **Cancer diagnosis**: gastrointestinal (n=49), gynaecological (n=18) and other (n=15) **Tumour stage**: metastatic disease **Anti-neoplastic treatment**: CT (all patients) **Performance status**: NR **Nutritional status**: NR	**Medical related:** Malignant small bowel obstruction **Food/nutrition related:** NR	**Composition:** NR **Administration:** NR **Rate:** NR **Dose planned**: NR **Dose given:** NR **Duration**, median (range): 45 days (9-639)	**QoL:** NA **Physical function:** NA	**Nutritional status:** NA **Survival**: mOS (range) 3.1 months (0.03-69.4) **Adverse events:** Line infections or hyperbilirubinemia (n=27)
Girke J. et al. (2016) Study period: 2010-2013 Germany Prospective study	**N**= 36 **Sex**: female (n=13), male (n=23) **Age** (years), mean (range): 60 (37-76) **Cancer diagnosis**: mixed cancer patients, mainly gastrointestinal and ovarian cancers. **Tumour stage**: Advanced progressive, mainly end-stage disease **Anti-neoplastic treatment**: Palliative treatment (not further specified)	**Medical related**: PN indication according to ESPEN guideline **Food/nutrition related**: > 25% of daily energy requirement from food and drinks (n=17), < 25% of daily energy requirement	NR	**QoL**: NR in subgroup of malignant patients **Physical function:** Performance testing: Handgrip strength unchanged at 4 weeks (n=17). Physical activity: unchanged (n=10)	**Nutritional status:** BMI unchanged at 4 weeks (n= NR, NS). Arm circumference: unchanged at 4 weeks (n= NR, NS) **Survival**: Mean OS (range): 76 days (8-330) **Adverse events**: NR

	Performance status: KPS ≤50 (n=11) **Nutritional status**: WL: < 5% (n=5), 5-10% (n=10), >10% (n=18); SGA B: (n=5) and SGA C: (n=31)	from food and drinks (n=10), no oral intake (n=9)			
Chen CJ. et al. (2013) Study period: 2005-2009 Taiwan Retrospecti ve study	**N**=46 **Sex**: female (n= 22), male (n= 24) **Age** (years), mean (SD): 56.5 ± 13.7 **Cancer diagnosis**: stomach (n=18), colorectum (n=15), ovary (n=7), pancreas (n=1), lung (n=1), unknown (n=2), small bowel (n=1), head and neck (n=1) **Tumour stage**: metastatic disease (unresponsive to any oncological treatment) **Anti-neoplastic treatment:** none **Performance status**: NR **Nutritional status**: BMI (kg/m^2), mean (SD): 18.6 ± 3.3	**Medical related:** Mechanical bowel (sub)obstruction secondary to peritoneal carcinomatosis **Food/nutrition related:** no significant food intake possible	**Composition:** Amino acids, lipids, glucose, minerals and trace elements **Administration:** CVC **Rate:** NR **Dose planned**: Based on individual requirements (not further specified) **Dose given:** NR **Duration**, mean (SD): 24.1 days (27.4)	**QoL:** NA **Physical function:** NA	**Nutritional status:** NA **Survival**: mOS (range): 40 days (4-148) in the 31 patients who died during their hospital stay **Adverse events:** Fluid overload (n=5), severe infection (n=5)
Diver E. et al.(2013) Study period: 2000-2008 USA Retrospecti ve study	**N**=41 PN vs. 74 no PN **Sex**: female (all patients) **Age** (years), median (range): 57 (26-88) **Cancer diagnosis**: ovarian (n=96), cervical (n=6), uterine (n=13) **Tumour stage**: NR, patients had malignant bowel obstruction requiring palliative gastrostomy tube placement	**Medical related:** patients had malignant bowel obstruction, however PN indication neither reported nor standardized but based on individual preferences and goals for care.	NR	**QoL:** NA **Physical function:** NA	**Nutritional status:** NA **Survival**: mOS (range) following gastrostomy tube placement: 5.57 weeks (1 day - 5.5 years) (all patients). mOS PN group: 9.6 weeks (4 days to 4.7 years) vs. mOS no PN group: 4.3 weeks (1

	Anti-neoplastic treatment: CT in 22 of the 41 PN patients vs. 23 of the 74 no PN patients **Performance status**: NR **Nutritional status**: NR	**Food/nutrition related:** NR			day to 5.5 years), ($p<0.01$) **Adverse events:** NR
Cheremesh I. et al. (2011) Study period: 2003-2009 Israel Prospective study	**N**= 28 **Sex**: female (n=13), male (n=15) **Age** (years), mean (SD): 59.9 (12.7) **Cancer diagnosis**: ovary (n=9), stomach (n=8), colon (n=4), pancreas (n=3), breast (n=2), larynx (n=1, carcinoid (n=1) **Tumour stage**: NR, but stated as incurable **Anti-neoplastic treatment**: NR **Performance status**: NR **Nutritional status**: BMI, mean (SD): 20.4 (4.6)	**Medical related**: Small bowel obstruction **Food/nutrition related**: inability to eat orally or enterally	**Composition:** NR **Administration:** NR **Rate:** NR **Dose planned**: NR **Dose given:** NR **Duration:** until death, except for 3 patients (refused to continue PN (n=1), enteral/oral feeding possible (n=3)	**QoL:** NA **Physical function:** NA	**Nutritional status**: NR **Survival**: mOS (range): 140 days (20-783). **Adverse events:** In all, n=8 experienced 9 PN-related complications: bone pain (n=1) (resolved after withdrawal of an MCT/LCT lipid from solution); hyperkalaemia (n=1), line sepsis (n=6)
Madhok BM. et al. (2010) Study period: 2002-2008 UK Prospective study	**N**=65 **Sex**: female (all patients) **Age** (years), median (range): 67 (24-92) **Cancer diagnosis**: ovarian carcinoma **Tumour stage**: IIIc or IV **Anti-neoplastic treatment**: CT (n=16) **Performance status**: WHO≤1 (n=43), WHO≥2 (n=22) **Nutritional status**: Poor (n=27), moderate (n= 21), good (n=17) (method not reported)	**Medical related:** Protracted post-operative ileus (n=30), intestinal obstruction (n=23), enterocutaneous fistulae (n=4), short bowel syndrome (n=4), symptom alleviation (n=4) **Food/nutrition related:** NR	**Composition:** Precompounded bags or custom formulations to tailor each prescription **Administration:** non-tunnelled CVC (n=47), tunnelled CVC (n=13), peripheral long line (n=4), peripherally inserted central catheter (n=1) **Rate:** NR	**QoL:** NA **Physical function:** NA	**Nutritional status:** NA **Survival**: mOS (IQR): 112 days (30-365 days) **Adverse events:** Line sepsis (n=11), hyperglycaemia (n=3), pneumothorax (n=2), electrolyte disturbances (n=2), venous thrombosis (n=1)

			Dose planned: individually calculated (Schofield equation), adjusted for stress, activity factor and diet-induced thermogenesis. **Dose given:** NR **Duration,** median (IQR): 10 days (5-19 days)		
Soo I. and Gramlich L. (2008) Study period: 1999-2006 Canada Retrospecti ve study	**N**=38 **Sex**: female (n= 27), male (n=11) **Age** (years), mean (SD): 48.76 (13.8) **Cancer diagnosis**: ovarian (n=13), colonic (n=6), gastric (n=6), peritoneal (n=3), unknown (n=2), oesophageal (n=2), carcinoid (n=1), cervical (n=1) ampullary (n=1), gastrointestinal stromal tumour (n=1), anaplastic large cell lymphoma (n=1) and rectal (n=1) **Tumour stage**: Advanced cancer **Anti-neoplastic treatment**: CT (n=14), CRT (n=1), none (n=23) **Performance status**: Mean (SD) KPS: 62.7 (18.53) **Nutritional status**: NR	**Medical related:** Non-functional gastrointestinal tract (n=32), short bowl syndrome (n=2), gastroesophageal obstruction (n=2), enterocutaneous fistula (n=1) and intractable pain (n=1) **Food/nutrition related:** Not able to tolerate enteral feeding	**Composition:** all macronutrients, electrolytes, trace elements, vitamins and minerals. **Administration:** NR **Rate:** NR **Dose planned**: 25 kcal per kg per day, 1 g protein per kg per day **Dose given:** NR **Duration:** until death (n=20), until 1 week (n=7), 2 weeks (n=6), 3 weeks (n=1), 4 weeks (n=1) prior to death, still ongoing (n=3).	**QoL:** NA **Physical function:** NA	**Nutritional status:** NA **Survival**: Mean OS (range): 5.4 months (0.25-33). **Adverse events:** Line infections (n=5), elevated liver enzymes (n=1), hyperglycaemia (n=1), bacteraemia (n=1) Complications of PN did not contribute to the death of any of the patients
Fan GB et al. (2007)	**N**=115 **Sex**: female (n= 62), male (n=53) **Age** (years), median (range): 51 years (31-74)	**Medical related:** malignant bowel obstruction	**Composition:** All-in-one bag **Administration:** Central venous port	**QoL:** NA **Physical function:** NA	**Nutritional status:** NA **Survival**: Mean OS: 6.5 months

Study period: 2000-2006 China Retrospective study	**Cancer diagnosis**: gastric (n=24), colorectal (n=23), oesophageal (n=20), jejunal (n=14), breast (n=10), sarcoma (n=9), cholangiocarcinoma (n=9), pancreatic (n=3), lymphoma (n=3) **Tumour stage**: metastatic disease with estimated life expectancy longer than a few months **Anti-neoplastic treatment**: NR **Performance status**: NR **Nutritional status**: average weight loss before start PN 9 kg (no range or SD reported)	**Food/nutrition intake:** Cessation of food intake	**Rate:** 12-18 hour infusion daily **Dose planned**: NR **Dose given:** typically 30 kcal±2 kcal/kg/d with 0.3±0.05 g nitrogen/kg/d. **Duration:** until death		11 patients lived > 1 year (range: 14-20 months) after cessation of food intake. Censored survival data in 2 patients (still alive when article was published, excluded from survival analysis) **Adverse events:** Patients with adverse events to PN were excluded from the study (n=17 of 132). Adverse events among these 17 patients were as follows: line sepsis (n=14), death due to PN-related liver disease (n=3)
Finocchiaro E. et al. (2007) Study period: 2000-2005 Italy, multicentre Prospective study	**N**=730 **Sex**: female (n=347), male (n=383) **Age** (years), median (range): 62 (30-87) **Cancer diagnosis**: gastric (33%), pancreatic/biliary (22%), colorectal (18%), ovary (12%), other (15%) **Tumour stage**: NR, stated as advanced and incurable cancer **Anti-neoplastic treatment**: NR **Performance status**: KPS, median (range): 60 (50-90)	**Medical related**: SBO/sub-obstruction (50%) Malnutrition (44%) Other reasons (6%) **Food/nutrition related**: Oral intake < 500 kcal/d (64%), no feeding per mouth possible (36%)	**Composition:** standard formula preferred. Specialized formula in n=2 diabetic patients. **Administration:** CVC port (44%), tunnelled (Groshong, 37%), the Hohn type (19%) **Rate:** NR **Dose planned,** median (range): 24 (9-	**QoL** (Therapy Impact Questionnaire), improved in n=29, unchanged in n=91 and worsened in n=40 at 2 months (of total n=160). **Physical function,** (KPS) median (range): 60 (50-90) at baseline to 60 (40-90) at 2 months (n=160).	**Nutritional status:** Body weight, median (range): 54 kg (29-90) at baseline to 53 kg (32-91) at 2 months (n=160). BMI: unchanged (n=160). PG-SGA: B 42% at baseline to 60% at 2 months (no p value reported); C: 56% at baseline to 40% at 2 months (no p value

	Nutritional status: BMI, median (range): 20 (13-35) (n=160); PG-SGA A: 0%, PG-SGA B: 42%, PG-SGA C: 56% (n=160); WL (% of usual body weight), median (range): 17% (2-32) (n=160).		40) non-protein kcal/kg/d + 1.1 (0.8-1.3) g AA/kg/d, liquids 28 (13-53) mL/kg/d **Dose given:** NR **Duration,** median (range)**:** 80 days (20-766) (data based on 76% of patients who died)		reported). Overall PG-SGA improved in 16% of the 160 patients. **Survival**: A total of n=555 (76%) deceased: alive at 1 month (82%), 2 months (54%), 3 months (34%) and > 6 months (10%) **Adverse events:** Data collected from one centre (n=302): a total of 25 catheter-related complications episodes in 22 patients (7%); sepsis (n=18), venous thrombosis (n=2), catheter dislocation (n=4), metabolic complications: hyperglycaemia (n=4). Incidence of adverse events per PN year: sepsis 0.2; thrombosis 0.02; dislocation 0.06.
Brard L. et al. (2006) Study period: 1994-2002 USA	**N**=55 (PN=28, no PN=27) **Sex**: female (n=55) **Age** (years), mean (SD): 56.4 (11.7) **Cancer diagnosis**: epithelial ovarian cancer **Tumour stage**: IIIc-IV with inoperable intestinal obstruction	**Medical related:** Terminal intestinal obstruction **Food/nutrition related:** enteral feeds not possible	NR	**QoL:** NA **Physical function:** NA	**Survival**: mOS from terminal intestinal obstruction to death: 72 days in PN group vs. 41 days in no PN group, p=0.01 Difference not significant when adjusting for

Retrospective study	**Anti-neoplastic treatment**: Platinum-based CT (n=18 PN group vs. 7 no PN group) **Performance status**: 1 (n=1), 2 (n=47), 3 (n=4)) (method for PS not reported) **Nutritional status**: NR				concurrent use of chemotherapy. **Adverse events:** Line sepsis (n=1)
Bozzetti F. et al. (2002) Study period: 3 year registry Italy, multicentre Prospective study	**N**=69 **Sex**: female (n=41), male (n= 28) **Age** (years), median (range): 54 (29-82) **Cancer diagnosis**: colon-rectum (n=21), stomach (n=16), uterus, ovary (n=13), breast (n=2), other (n=17)) **Tumour stage**: NR, stated as advanced cancer **Anti-neoplastic treatment**: CT (n=36) **Performance status**: KPS, median (range): 69 (40-90) **Nutritional status**: weight loss: < 10% (n=13), 10-14% (n=11), 15-19% (n=13), > 20% (n=32)	**Medical related** Intestinal obstruction (n=58), malnutrition (n=7), other reasons (n=4) **Food/nutrition related**: NR	**Composition:** glucose, lipids and nitrogen **Administration:** port-a-cath (n=18), external tunnelled central venous catheter (n=51) **Rate:** daily infusion **Dose planned**: 30 non-protein kcal/kg/d + amino acids **Dose given,** median (range): glucose 300 g/d (160-500), lipids 60 g/d (42-100), nitrogen 12 g/d (6.2-13.7) **Duration,** median (range): 4 months (1-14). PN given until death (n=52), oral feeding possible (n=7), complication (n=6), refused continuation (n=4)	**QoL** (Rotterdam Symptom Checklist): Not significantly different after 1 month or after end of PN compared to baseline (n=64) **Physical function**: Self-reported physical function (Rotterdam Symptom Checklist): a transient benefit in the initial months on PN. KPS seems stable, until 2-3 months prior to death	**Nutritional status:** Body weight, median (range): 52.5 kg (35.5-77.5) at baseline to 54.0 kg (36-78) at death **Survival**: mOS (range): 3 months (1-14). Censored for survival analysis (n=21) **Adverse events:** NR

Pasanisi F. et al. (2001) Study period: 1995-1999 Italy Prospective study	**N**= 76 **Sex**: female (n=54), male (n=22) **Age** (years), mean (SD): 56.8 (14.0) **Cancer diagnosis**: stomach (n=28), ovary (n=18), colon and/or rectum (n=16), other (n=14). **Tumour stage**: Terminal cancer patients (unresponsive to further treatment) **Anti-neoplastic treatment**: none **Performance status**: KPS, median (range): 50 (40-70) **Nutritional status**: BMI, mean (SD): 20.8±3.7; n=31 BMI <19	**Medical related**: mechanical bowel obstruction (n=76) **Food/nutrition related**: Chronic underfeeding	**Composition:** all-in-one bag 1-1.2 g amino acids/kg/d, glucose 50-65E%, lipids 25-30 E%, minerals and vitamins. **Administration:** CVC **Rate:** daily infusion **Dose planned**: NR **Dose given:** NR **Duration**: until 2-3 days before dying	**QoL**: NA **Physical function:** NA	**Nutritional status:** NA **Survival**: mOS (range): 74 days (6-301). N=11 died < 1 month of starting PN. Survival ≤ or > 3 months: significant difference in KPS: 46 vs. 30. **Adverse events:** NR
Pironi L. et al. (1997) Study period: 1990-1996 Italy Prospective study	**N**= 29 **Sex**: NR **Age**: NR **Cancer diagnosis**: Head & neck (n=3), gastrointestinal (n=18), lung (n=1), genitourinary (n=4), other (n=3). **Tumour stage**: Disseminated cancer (stage IV): n=26 **Anti-neoplastic treatment**: NR, palliative care (not further specified) **Performance status**: KPS, median (range): 50-60 (30-80) **Nutritional status**: Low BMI or WL ≥10%: n=24	**Medical related**: Dysphagia (n=3), upper gastrointestinal obstruction (n=9), lower gastrointestinal obstruction (n=17) **Food/nutrition related**: Hypophagia (all patients) (defined as oral caloric intake < 50% of basal energy expenditure)	**Composition:** bags containing standard formula, prepared by hospital pharmacy **Administration:** non-tunnelled percutaneous catheters (79%), tunnelled percutaneous catheters (14%), totally implanted ports (7%) **Rate:** 24 h infusion (69%), cyclical (31%) **Dose planned**: NR **Dose given:** NR **Duration:** NR	**QoL:** NA **Physical function**: KPS increased (n=2), decreased (n=5), unchanged (n=22) at 1 month	**Nutritional status:** NA **Survival**: Mean OS (SD): 12.2 weeks (8.0) All, but one patient died **Adverse events:** PN-related hospital readmission (n=3). Frequency of complications per year PN: 0.67 for catheter sepsis, 0.16 for deep vein thrombosis and 0.50 for metabolic instability.

BMI: body mass index; CT: chemotherapy; CRT: chemo/radiotherapy; CVC: central venous catheter; IQR: interquartile range; KPS: Karnofsky Performance Status; kcal/kg/d: kilocalories per kilo body weight per day; mOS: median overall survival; NA: not assessed; NR: not reported; NS: not statistically significant; OS: overall survival; PG-SGA: Patient-Generated Subjective Global Assessment; PN:

parenteral nutrition; SD: standard deviation; QoL: quality of life; RT: radiotherapy; SGA: Subjective Global Assessment; WHO: World Health Organization; WL: weight loss

Appendix 3. Summary of risk of bias of excluded studies

Author Year	Type of bias						Overall bias
	Selection bias and confounding	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	
Chouhan J. et al., 2016	No blinding. Survival likely confounded by concurrent chemotherapy.	Wide range in PN duration and missing information of PN composition, administration, rate or dose	No comment	No comment	No comment		Critically high
Girke J. et al., 2016	No blinding	No description of PN administration	No comment	Large drop out rate due to death	Survival data censored in 7 patients	Funding from Braun Trava Care	Critically high
Chen CJ. et al., 2013	No blinding. Missing information of patients' baseline performance status	Poor description of PN administration	No comment	No comment	Survival selectively reported in the 31 patients who died while in hospital. Adverse events only reported if PN was terminated.		Critically high
Diver E. et al., 2013	No blinding. Indications for PN not reported nor standardized, but based on individual patient characteristics and goals for care, a decision	No description of the PN administration	No comment	No comment	No comment		Critically high

	made between each patient and her provider. Survival likely confounded by concurrent anti-neoplastic treatment.						
Cheremesh I. et al., 2011	No blinding. Missing information of patients' baseline performance status.	Missing information of potential concurrent anti-neoplastic treatment. No information of PN administration therapy, apart from duration.	No comment	No comment	No comment		Critically high
Madhok BM. et al., 2010	No blinding. Outcomes likely confounded by enteral feeding and concurrent anti-neoplastic treatment.	PN duration short compared to survival time, why survival unlikely affected by PN as the majority of patients re-established enteral feeding.	No comment	No comment	No comment		Critically high
Soo I. & Gramlich L., 2008	No blinding. Outcomes likely confounded by concurrent anti-neoplastic treatment	No comment	No comment	No comment	No comment	Small study with many different diagnoses	Critically high
Fan GB., 2007	No blinding. Missing information of patients' baseline performance status and use of anti-	No comment	No comment	No comment	Survival reported in patients without adverse events to PN only		Critically high

	neoplastic treatment. Patients with adverse events to PN were excluded from the study.					
Finocchiaro E. et al., 2007	No blinding. Missing information of anti-neoplastic treatment.	No comment	Unclear what defines change in QoL	No comment	QoL, physical function and nutritional status assessed in a subgroup of 160 patients only, presenting patients from one centre. These results were reported as descriptive data and assessed as difference between baseline and at two months, without pre-defined time of assessment. Survival estimates based on the deceased patients only, even though some patients were still alive and receiving PN.	Critically high
Brard L. et al., 2006	No blinding. Allocation to PN and/or chemotherapy based on doctors' decision (or patient refusal), no additional information provided.	No description of the PN administration	No comment	No comment	No comment	Critically high

Bozzetti F. et al., 2002	No blinding. Outcomes likely confounded by concurrent anti-neoplastic treatment.	No comment	No comment	No comment	Survival censored in 21 patients: recovered ability to eat (n=7), admitted to hospital unrelated to PN (n=6), refused to continue HPN (n=4), died for other reasons than related to cancer or HPN (n=3), committed suicide (n=1)	Critically high
Pasanisi F. et al., 2001	No blinding	Missing information of planned or given PN dose. Given the date of data collection (1995-1999), hypercaloric PN cannot be ruled out.	No comment	No comment	No comment	Critically high
Pironi L. et al., 1997	No blinding. Missing information of concurrent anti-neoplastic treatment. Not specified when PN was chosen over EN.	Dose of PN unknown, and given the time of data collection (1990-1996), hypercaloric PN cannot be ruled out.	Unclear what defines change in performanc e status	No comment	Unclear whether survival data was censored in one patient	Critically high