Original Article

Enteral and parenteral nutrition in cancer patients: a systematic review and meta-analysis

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Background: In cancer patients, weight loss is an ominous sign suggesting disease progression and shortened survival time. As a result, providing nutrition support for cancer patients has been proposed as a logical approach for improving clinical outcomes. Nutrition support can be given to patients through enteral nutrition (EN) or parenteral nutrition (PN). The purpose of the review was to compare the outcomes of PN and EN in cancer patients.

Methods: A literature search was conducted in Ovid MEDLINE and OLDMEDLINE, Embase Classic and Embase, and Cochrane Central Register of Controlled Trials. Studies were included if over half of the patient population had cancer and reported on any of the following endpoints: the percentage of patients that experienced no infection, nutrition support complications, major complications or mortality. Risk ratios (RR) and 95% confidence intervals (CIs) using Review Manager Version 5.3 were calculated. Primary endpoints were stratified according to type of EN for subgroup analysis, grouping studies into either tube feeding (TF) or standard care (SC). Additionally, another subgroup analysis was conducted comparing studies with protein-energy malnutrition (PEM) patients and studies without PEM patients.

Results: The literature search yielded 674 articles of which 36 were included for the meta-analysis. There were no difference in the endpoints between the two study interventions except that PN resulted in more infection when compared with EN (RR =1.09, 95% CI: 1.01–1.18; P=0.03).

Conclusions: Other than increased incidence of infection, PN has not resulted in prolonging the survival, increasing nutrition support complications, or major complications when compared with EN in cancer patients.

Keywords: Parenteral nutrition (PN); enteral nutrition (EN); cancer patients; malnutrition; tube feeding (TF); standard care (SC)

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Background

Energy imbalance, typically caused by a decrease in food intake, is responsible for weight loss as body tissues are consumed for fuel (1). In cancer patients, weight loss is an ominous sign predicting disease progression and shortened survival time (2,3). As a result, providing nutrition support for cancer patients has been proposed as a logical approach for improving clinical outcomes (1). However, some studies have reported increased complications and costs (4,5). However the readers are cautioned that the world of clinical nutrition is markedly changed in the last 3 decades, i.e., many technological innovations have significantly increased the cost effectiveness of nutrition support (commercial 'all-in-one bags', new enteral and parenteral formulas, peripheral insertion, new materials for venous and enteral accesses, etc.), whereas new strategies have successfully minimized the risk of complications (standardized "bundles" of evidence-based interventions, strict policies of antisepsis, education of healthcare operators, etc.).

Nutrition support can be given to patients through enteral nutrition (EN) or parenteral nutrition (PN) (6). EN may be the preferred method of nutrition support, not only because of lower costs and fewer complications, but also due to the perceived better outcomes (6). Previously, meta-analyses by Heyland *et al.* and Braunschweig *et al.* conducted in 1998 and 2001, respectively, have evaluated the outcomes of EN, in both standard care (SC) and tube feeding (TF), compared to PN (7,8). Braunschweig *et al.* reported a trend for a lower risk of infection in the EN study population, while Heyland *et al.* claimed lower rates of complications in the PN study population (7,8). Both studies also disagreed on the mortality rates in response to the different treatment options (7,8).

The potential adverse consequences of PN and EN make it important to establish the therapeutic benefits of both nutrition support options before recommending their routine use in cancer patients (1). To date, a meta-analysis focusing primarily on the outcomes of EN and PN in the cancer setting has not been conducted. The purpose of the following review was to compare the outcomes of PN and EN in cancer patients.

Materials and methods

Search strategy

A literature search was conducted in Ovid MEDLINE and OLDMEDLINE from 1946 to July Week 2 2015, Embase Classic and Embase from 1947 to 2015 Week 29, and Cochrane Central Register of Controlled Trials up until June 2015. Search terms included "PN", "comparative study", and "EN". The search was limited to English-language studies and randomized controlled trials (RCTs). The complete search strategy is displayed in *Figure 1*. Reference lists from studies identified by the search were examined as well. Titles and abstracts were screened to identify references that were relevant for full-text review, based on pre-specified selection criteria for full-text review. Articles were identified for full-text review if the title or abstract included mentioning of parenteral and EN as two separate nutrition support treatment arms. Duplicates of articles found in each database were excluded.

Selection criteria for meta-analysis

Studies were included if over 50% of the study population had some type of cancer. Non-original research and small-sized trials (<5 patients) were excluded. Studies that did specify the medical procedure but not the medical diagnoses of the patient population were also excluded.

Endpoints

The primary endpoints were the percentage of patients that experienced no infection, nutrition support complications, major complications and mortality. The outcomes of thirteen studies (9-21) as reported by Braunschweig *et al.* (8) were recorded, except for the "Other Complications" heading in their table.

"Minor infections" as reported by studies were recorded under infection. For studies that reported the breakdown of infection complications, we simply recorded the number of patients that experienced wound infection, pneumonia and sepsis. Nutrition support complications were recorded as reported in the study or the summation of nausea and vomiting events were recorded. Major complications or morbidity, as reported in studies, were noted as major complications. Mortality rates were noted as mentioned in the literature.

The type of EN, TF or SC, was also noted. Additionally, we noted if there were members of the study population that were malnourished, or deemed protein-energy malnutrition (PEM), via binary options of yes or no. For studies that did not mention PEM, we assumed there were no patients malnourished as we postulated that such demographics would certainly be reported if they existed.

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to July Week 2 2015> Search Strategy:

1 exp Parenteral Nutrition/ (21825)
2 exp Enteral Nutrition/ (16400)
3 Comparative Study/ (1727639)
4 (comparison or comparative or compare* or versus or vs or match or rival* or oppose or "side by side" or alone).mp. (4648391)
5 1 and 2 and (3 or 4) (1096)
6 limit 5 to (english language and randomized controlled trial) (186)

Database: Embase Classic+Embase <1947 to 2015 Week 29> Search Strategy:

1 exp parenteral nutrition/ (40909)
2 exp enteric feeding/ (22362)
3 exp comparative study/ (1087676)
4 (comparison or comparative or compare* or versus or vs or match or rival* or oppose or "side by side" or alone).mp. (6029569)
5 1 and 2 and (3 or 4) (1875)
6 limit 5 to randomized controlled trial (293)
7 limit 6 to (english language) (277)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <June 2015> Search Strategy:

1 exp parenteral nutrition/ (1402)
2 (parenteral adj2 (nutrition or feeding)).mp. (3256)
3 exp enteral nutrition/ (1314)
4 ((enteral or enteric) adj2 (nutrition or feeding)).mp. (3058)
5 exp comparative study/ (7)
6 (comparison or comparative or compare* or versus or vs or match or rival* or oppose or "side by side" or alone).mp. (431463)
7 (1 or 2) and (3 or 4) and (5 or 6) (520)
8 limit 7 to (randomized controlled trial and english language) (211)

Figure 1 Complete search strategy.

Subgroup analysis

We stratified primary endpoints according to type of EN for subgroup analysis, grouping studies into either TF or SC as defined in the publications. Additionally, subgroup analysis was conducted on whether studies were composed of PEM patients or not.

Statistical analysis

Statistical analyses were conducted using Review Manager (RevMan 5.3) for Cochrane IMS. The Mantel-Haenszel method was applied and a random effect analysis model was used to generate risk ratios (RR), and their accompanying 95% confidence intervals (CIs). A P value of less than 0.05 was considered statistically significant in the test for overall effect and a heterogeneity test with p-value greater than 0.05 was considered suitable. For all endpoints in the forest plots, we used the number of patients that did not experience the outcomes as the event numbers. This allowed for all endpoints to be greater than 0, thus allowing for calculable RR for all studies.

Results

The literature search yielded 674 articles, with 186 from MEDLINE, 277 from EMBASE, and 211 from Cochrane. An additional 68 were identified from the references of the papers. Of the 661 titles and abstracts screened (9-33), 36 were included for the meta-analysis (*Figure 2*) (34-44).

Infection

EN was statistically superior to PN, with a point estimate of RR as 1.09, and 95% CI from 1.01 to 1.18 (P=0.03)

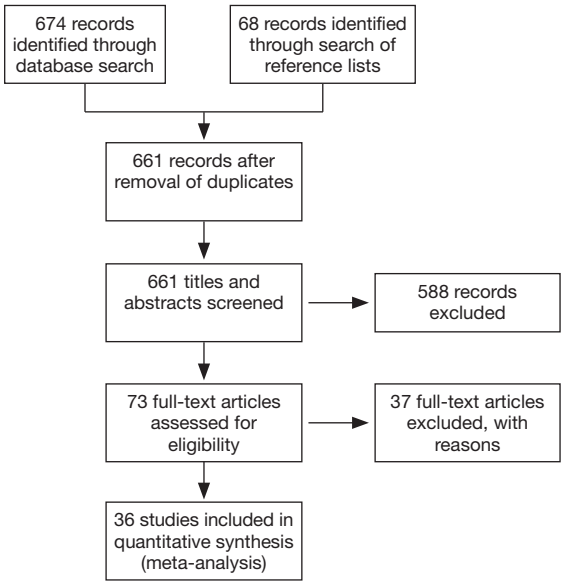

Figure 2 Flow of information diagram for RCTs included in the systematic review. RCTs, randomized controlled trials.

(*Figures 3*,*4*). However, neither EN nor PN were superior in subgroup analysis of TF (RR =1.04; 95% CI: 0.96–1.12; P=0.32) and SC (RR =1.22; 95% CI: 1.00–1.50; P=0.05) (*Figure 3*). Subgroup analysis of studies with (RR =1.12; 95% CI: 0.98–1.12; P=0.09) and without (RR =1.06; 95% CI: 0.97–1.17; P=0.19) PEM patients showed no difference, with respect to infection, between EN and PN (*Figure 4*).

Nutrition support complications

Overall, EN and PN achieved the same nutrition support complications (RR =1.00; 95% CI: 0.96–1.05; P=0.83) (*Figures 5*,*6*). Subgroup analysis of EN types showed TF (RR =0.99; 95% CI: 0.91–1.08; P=0.81) and SC (RR =1.02; 95% CI: 1.00–1.05; P=0.10) to produce similar outcomes to PN (*Figure 5*). Subgroup analysis of PEM patients revealed indifference as well between EN and PN, with PEM patients (RR =0.98, 95% CI: 0.92–1.05, P=0.62) and no PEM patients (RR =1.03, 95% CI: 0.99–1.08, P=0.19)

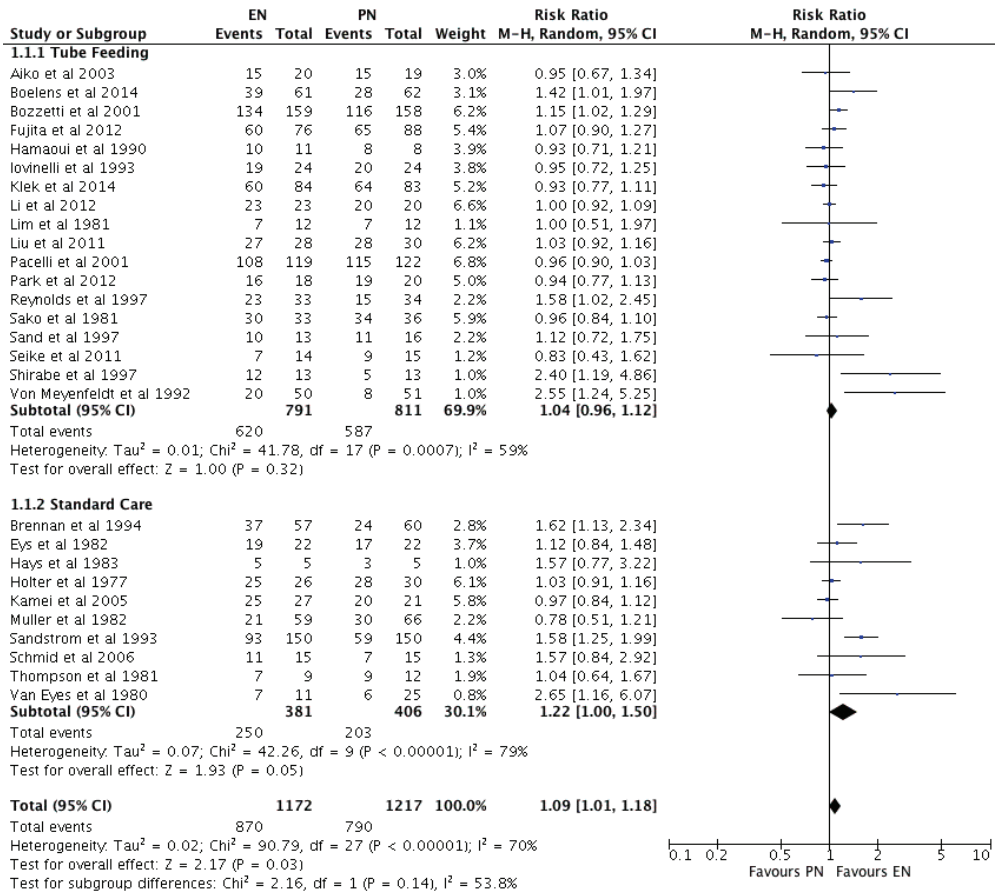

Figure 3 No infection for enteral nutrition (EN) and parenteral nutrition (PN) patients—tube feeding and standard care (SC).

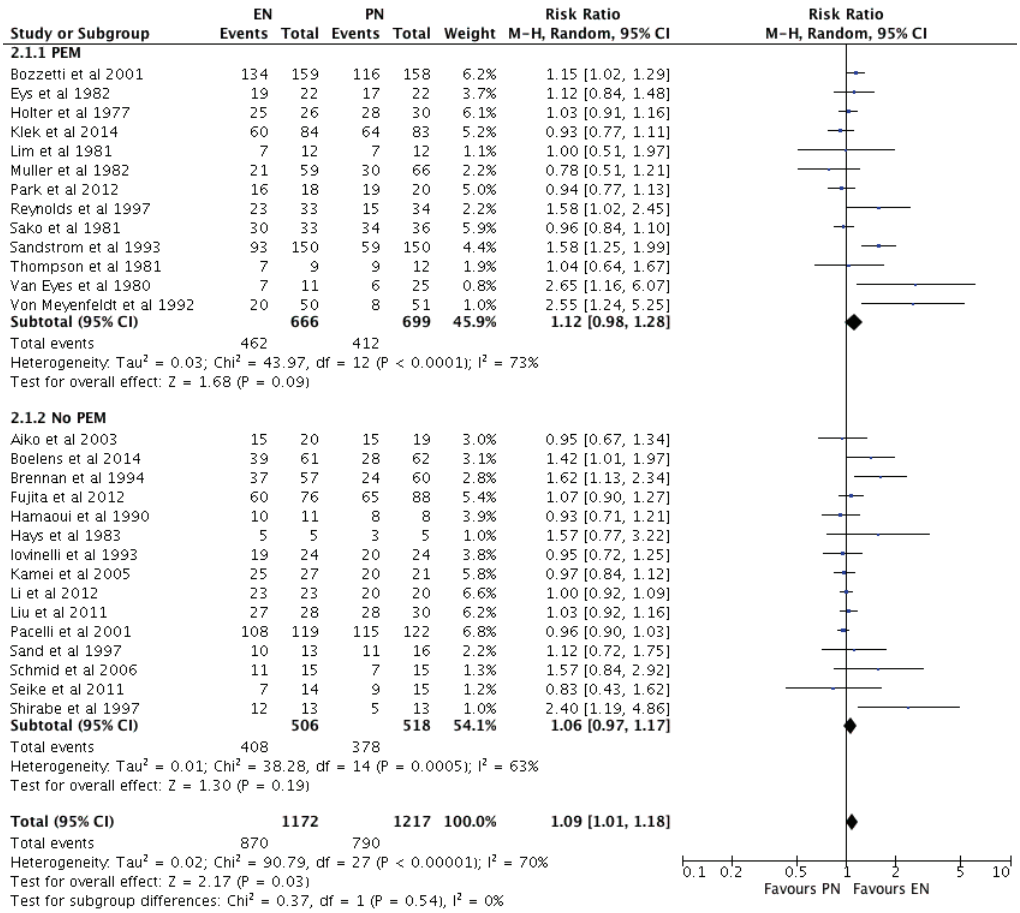

Figure 4 No infection for enteral nutrition (EN) and parenteral nutrition (PN) patients—protein-energy malnutrition (PEM).

achieving similar outcomes (*Figure 6*).

Major complications

There was no difference between EN and PN, with respect to major complications (RR =1.03; 95% CI: 0.98–1.08; P=0.31) (*Figures 7,8*). Analysis by types of EN also showed no superiority of either treatment, TF (RR =1.04; 95% CI: 0.99–1.09; P=0.13) and SC (RR =1.02; 95% CI: 0.80–1.30; P=87), in comparison to PN (*Figure 7*). Furthermore, subgroup analysis of studies containing no PEM (RR =1.06; 95% CI: 0.98–1.15; P=0.13) and PEM (RR =0.99; 95% CI: 0.91–1.07; P=0.73) patients showed indifference (*Figure 8*).

Mortality

In terms of survival, neither EN nor PN were found to be superior (RR =1.00; 95% CI: 0.97–1.04; P=0.60) (*Figures 9,10*). Subgroup analysis of TF (RR =1.00; 95% CI: 0.98–1.01; P=0.52) and SC (RR =1.00; 95% CI: 0.97–1.04; P=0.83) (*Figure 9*) showed no survival differences between EN and PN, as did subgroup analysis of studies that contained (RR =0.99; 95% CI: 0.97–1.02; P=0.47) and did not contain (RR =1.00; 95% CI: 0.98–1.02; P=0.88) PEM patients (*Figure 10*).

Heterogeneity

Two of four primary analyses between EN and PN had unsuitable levels of heterogeneity (Infection: P<0.00001; Nutrition support complications: P=0.0003) (*Figures 3-6*). Seven of sixteen subgroup analyses of EN and PN also had unsuitable levels of heterogeneity, namely infections of the TF (P=0.0007), SC (P<0.00001), PEM (P<0.0001), and no PEM (P=0.0005) cohorts, nutrition support complications

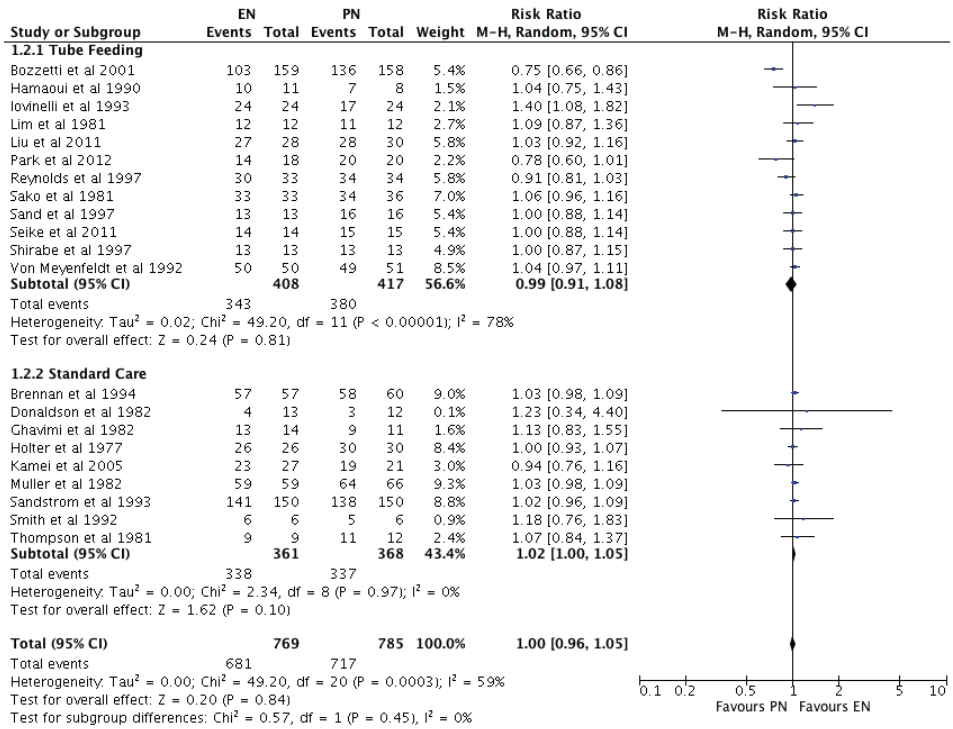

Figure 5 No nutrition support complications for enteral nutrition (EN) and parenteral nutrition (PN) patients—tube feeding and standard care (SC).

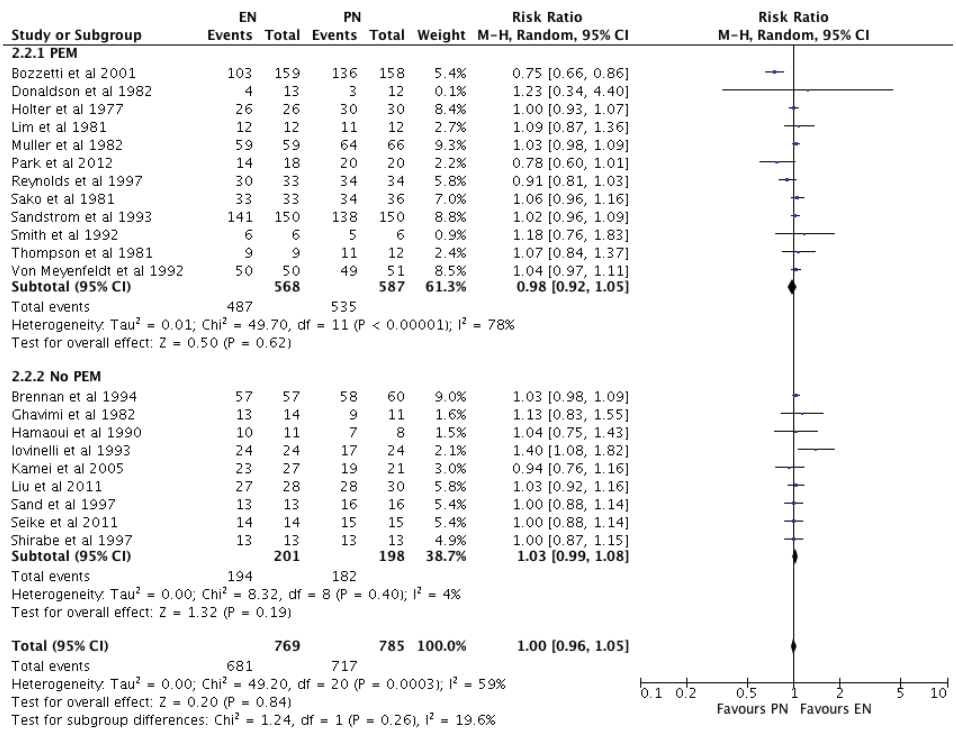

Figure 6 No nutrition support complications for enteral nutrition (EN) and parenteral nutrition (PN) patients—protein-energy malnutrition (PEM).

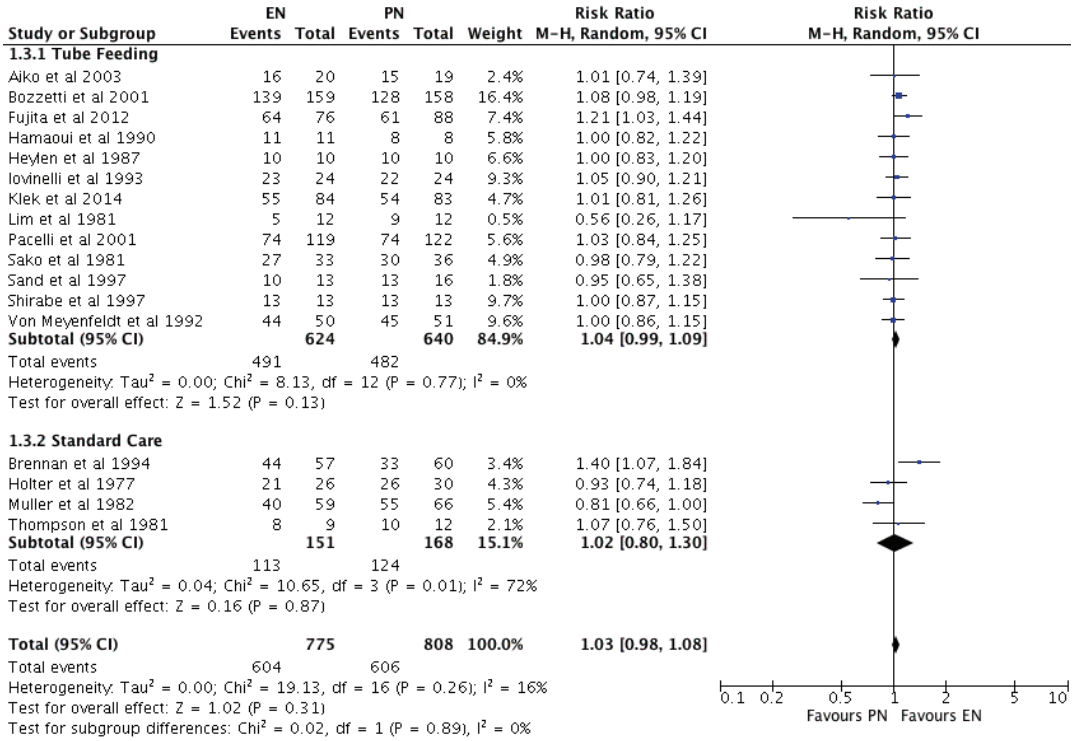

Figure 7 No major complications in enteral nutrition (EN) and parenteral nutrition (PN) patients—tube feeding and standard care (SC).

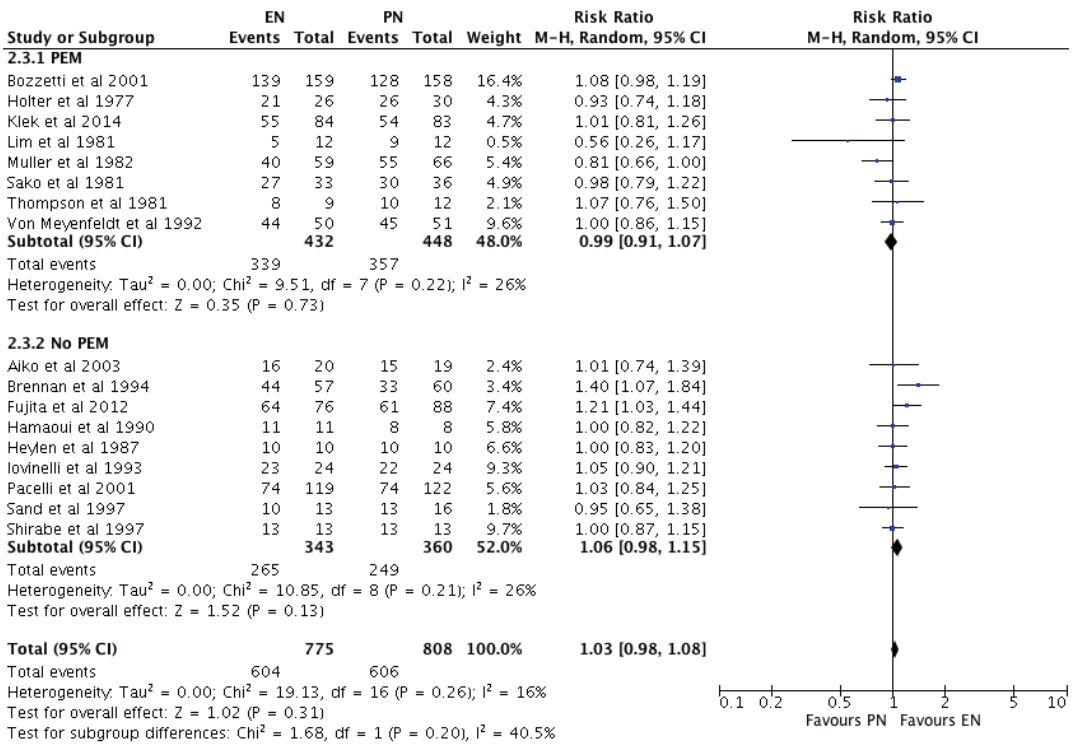

Figure 8 No major complications in enteral nutrition (EN) and parenteral nutrition (PN) patients—protein-energy malnutrition (PEM).

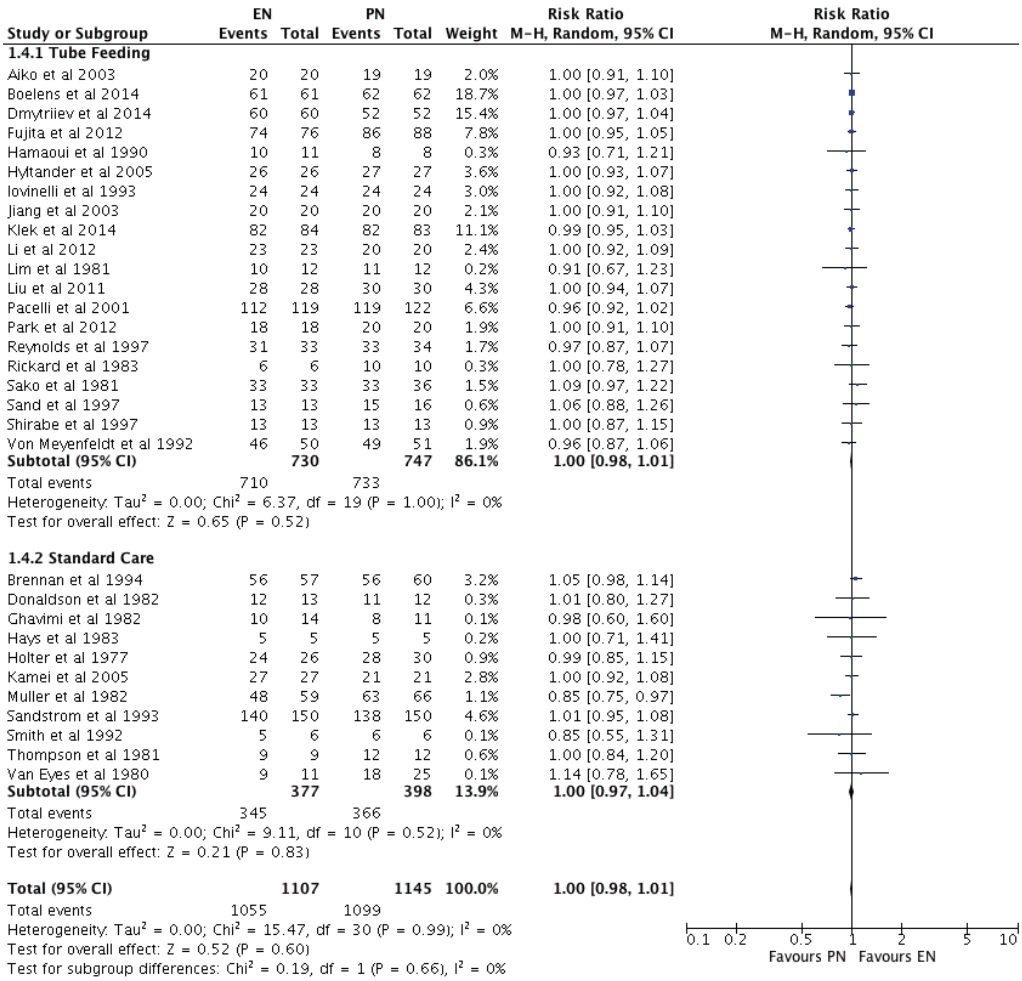

Figure 9 No mortality in enteral nutrition (EN) and parenteral nutrition (PN) patients—tube feeding and standard care (SC).

of the TF (P<0.00001) and PEM (P<0.00001) cohorts, and major complications with respect to SC (P=0.01) (*Figures 3-7*). The remaining two primary analyses and eleven subgroup analyses had satisfactory levels of heterogeneity (P values from 0.21 to 1.00) (*Figures 5-10*).

Discussion

During the last 15 years, conflicting meta-analysis results regarding the benefits of EN *vs.* PN in different ICU, surgical or cancer populations were published. A common reason a cancer patient may need nutrition support is due to negative side effects of the anticancer treatments (surgery, chemotherapy, and radiation therapy). In such patients, the European guidelines recommend 'EN if oral nutrition remains inadequate despite nutritional interventions, and PN if EN is not sufficient or feasible' (45). Moreover, independently regardless of whether receiving or not receiving anticancer therapies, the administration of PN depends on the oncological diagnosis. The most frequent diagnoses among patients with PN were tumors of the gastrointestinal tract, i.e., gastric carcinoma, colorectal carcinoma, and pancreatic carcinoma. Besides, the work of Orrevall *et al.* (46) showed that nausea, vomiting, and obstructions were the most common indications for PN in palliative patients. As in many other papers of this type, any conclusion is hardly generalizable to the overall cancer patient population. EN and PN are competitors in the choice of way to deliver nutrition support in cancer patients but have specific indications and contraindications.

This is the first study to our knowledge to review and compare the outcomes of EN and PN in cancer patients.

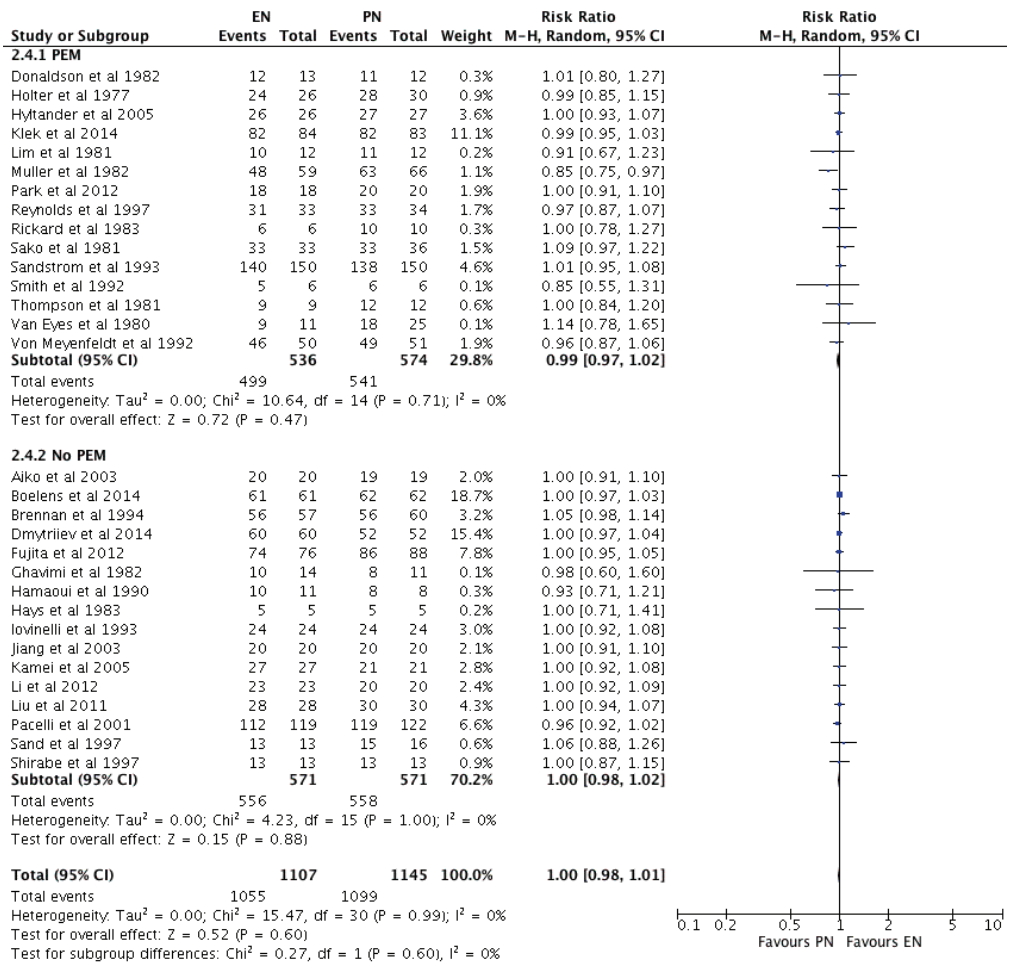

Figure 10 No mortality in enteral nutrition (EN) and parenteral nutrition (PN) patients—protein-energy malnutrition (PEM).

A meta-analysis conducted by Braunschweig *et al.* in 2001 reported in a subgroup analysis that EN was superior to PN in the cancer population with respect to less infection and other complications in the TF population (8), which was not shown in our meta-analysis. However, it should be noted that while Braunschweig *et al.*'s study only included eight studies in their subgroup analyses of cancer patients (8), our meta-analysis comprises of a total of 36 studies. The result of our study does confirm Braunschweig *et al.*'s finding that the infection of EN patients in general, regardless of type, are less likely to contract infections. The most feared and relevant complications of PN are catheter-related bloodstream infections. Indeed, nowadays all cancer patients have a CVC, independently regardless of whether receiving or not receiving PN.

Several studies have reported that PN patients receive more calories than EN patients (10,23,27,44). As PN has been shown to provide more calories for patients, it has been hypothesized that PN is more effective for malnourished patients when compared to EN. Accordingly, some institutions have made it common practice to assign malnourished patients to PN (26,27,44).

Although PN allows for easy administration of a predetermined amount of calories, micronutrients and substrates, it has been reported to also encourages gut atrophy and bacterial translocation due to the absence of enteral food elements (7,47-49), in addition to potentially stimulating tumor growth (50-54). In contrast, EN, specifically TF, is cheaper and has fewer complications, but has been reported to also be associated with higher mortality rates, specifically in the malnourished population (8). Our study finds that in the cancer population, EN does indeed result in fewer infection, but does not have higher mortality rates or major complications associated with it. Since 2009, the

European guidelines recommend that 'Although PN supplies nutrients to the tumor, there is no evidence that this has deleterious effects on the outcome. This consideration should therefore have no influence on the decision to feed a cancer patient when PN is clinically indicated' (55).

While the existing literature reveals that the additional calories provided by PN may not actually translate to better survival rates (56,57), there is no consensus on the practice. For instance, a study by Bozzetti *et al.* conducted a RCT of malnourished cancer patients comparing PN and EN treatments and found that 9% of EN cases required switchover to PN (24), as deemed necessary by physicians. Clinicians may still have a general perception that higher caloric intake will improve survival. In contrast, the study by Bozzetti *et al.* speculated that patients may actually have better survival rates with EN (24). Our meta-analysis shows no significant advantage in survival for patients receiving PN.

In comparison to EN, PN has also been reported to require less time in improving a patient's nutritional state and to be more beneficial in the cancer surgery setting (14,24). The shorter timeframe during preoperative and postoperative stay is beneficial for hospitals in aiming to keep hospital stay to a minimum due to limited hospital beds (24). However, PN has been reported to be over twice the cost of EN (10); thus, despite shorter hospital stays, patients receiving PN may incur greater financial costs (34). Evidence showed that nutrition support is a relatively cheap adjuvant therapy if compared to other anticancer therapies but a prolonged in-hospital length of stay may be more expensive than PN administration.

Of note, patients receiving EN may experience a decreased flexibility when compared to PN patients since oral feeding must be withheld for some preoperative diagnostic procedures (14). The ability to continue artificial nutrition uninterrupted via PN at all treatment stages may partially justify its higher overall price. Still, this meta-analysis shows that, with respect to complications (both in nutrition support and major complications) and mortality, there is no added benefit in receiving PN instead of EN.

This review was not without limitations. The text of two studies (17,19) was not found, and hence verification of the data supplied by Braunschweig *et al.* (8) was not possible. Additionally, one study (25) was in the form of an abstract. Furthermore, the reporting across studies was not standardized: there were different definitions and recording methods for the infections, nutrition support complications and major complications outcomes. Moreover, while some studies reported the number of episodes reported per outcome (32), other studies solely reported the number of patients who experienced the outcome (22,23). Additionally, some studies defined "Major Complications" differently, resulting in difficult cross-comparison among all studies included.

Conclusions

In conclusion, this systematic review highlights that neither PN nor EN are superior with respect to nutrition support complications, major complications and mortality. EN, the conglomerate of TF and SC, was favoured over PN with respect to less infection. The perceived advantages of PN in lower mortality rates and fewer complications due to higher and more efficient caloric intake are not confirmed in the cancer population.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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