# 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, metaanalyses 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 smallsized 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.

#### Chow et al. Enteral and parenteral nutrition in cancer patients: a systematic review and meta-analysis

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)
  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)
  (comparison or comparative or compare* or versus or vs or match or rival* or oppose or "side by side" or
4
alone).mp. (6029569)
5 1 and 2 and (3 or 4) (1875)
  limit 5 to randomized controlled trial (293)
  limit 6 to (english language) (277)
7
.....
Database: EBM Reviews - Cochrane Central Register of Controlled Trials <June 2015> Search Strategy:
  exp parenteral nutrition/ (1402)
2 (parenteral adj2 (nutrition or feeding)).mp. (3256)
  exp enteral nutrition/ (1314)
3
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)
   (1 or 2) and (3 or 4) and (5 or 6) (520)
  limit 7 to (randomized controlled trial and english language) (211)
8
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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).

	EN		PN			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2.1.1 PEM						, ,	
Bozzetti et al 2001	134	159	116	158	6.2%	1.15 [1.02, 1.29]	-
Evs et al 1982	19	22	17	22	3.7%	1.12 [0.84, 1.48]	
Holter et al 1977	25	26	28	30	6.1%	1.03 [0.91, 1.16]	+
Klek et al 2014	60	84	64	83	5.2%	0.93 [0.77, 1.11]	
lim et al 1981	7	12	7	12	1.1%	1 00 [0 51 1 97]	
Muller et al 1982	21	59	30	66	2.2%	0.78 [0.51, 1.21]	
Park et al 2012	16	18	19	20	5.0%	0.94 [0.77, 1.13]	
Revnolds et al 1997	23	33	15	34	2.2%	1.58 [1.02, 2.45]	
Sako et al 1981	30	33	34	36	5.9%	0.96 [0.84, 1.10]	
Sandstrom et al 1993	93	150	59	150	4 4%	158[125 199]	
Thompson et al 1981	7	9	9	12	1.9%	1.04 [0.64, 1.67]	
Van Eves et al 1980	. 7	11	6	25	0.8%	2.65 [1.16. 6.07]	
Von Mevenfeldt et al 1992	20	50	8	51	1.0%	2.55 [1.24, 5.25]	
Subtotal (95% CI)		666	-	699	45.9%	1.12 [0.98, 1.28]	•
Total events	462		412				•
Heterogeneity: $Tau^2 = 0.03$	$Chi^2 = 4$	3.97. c	if = 12 (F	< 0.0	$0011:  ^2 =$	73%	
Test for overall effect: Z = 1	.68 (P =	0.09)					
2.1.2 No. PEM							
Alke et al 2002	15	20	15	10	2 09/	0.05 (0.67, 1.34)	
Aiku et al 2003	10	20	20	13	3.0%	0.95 [0.67, 1.34]	
Buelens et al 2014	39	51	28	62	3.1%	1.42 [1.01, 1.97]	
Brennan et al 1994	37	27	24	60	2.8%	1.62 [1.13, 2.34]	
Fujita et al 2012	60	/6		88	5.4%	1.07 [0.90, 1.27]	
Hamabul et al 1990	10	11		0	3.9%	0.93 [0.71, 1.21]	
Hays et al 1983	2	2	5	2	1.0%	1.57 [0.77, 3.22]	
Iovinelli et al 1993	19	24	20	24	5.8%	0.95 [0.72, 1.25]	
Kamel et al 2005	20	27	20	21	2.8%	0.97 [0.84, 1.12]	Т
Li et al 2012	23	23	20	20	0.0%	1.00 [0.92, 1.09]	T
Liu et al 2011	27	28	28	30	6.2%	1.03 [0.92, 1.16]	T
Fatelli et al 2001	108	119	115	122	0.8%	0.96 [0.90, 1.03]	
Sand et al 1997	10	15	11	10	2.2%	1.12 [0.72, 1.75]	
Schmid et al 2006	11	15		15	1.5%	1.57 [0.84, 2.92]	
Seike et al 2011 Shiraha at al 1007	17	14	9	12	1.2%	0.85 [0.45, 1.62]	
Shirabe et al 1997 Subtotal (95% CI)	12	506	5	518	1.0% 54.1%	2.40 [1.19, 4.86] 1.06 [0.97, 1.17]	•
Total events	402	200	379		- 112/0	2.00 [0.57, 2.27]	•
Heterogeneity Tau <sup>2</sup> – 0.011	Chi <sup>2</sup> = 2	878 -	570 If = 1470	2 = 0.0	005) <sup>,</sup> 1 <sup>2</sup> -	63%	
Test for overall effect: $Z = 1$	.30 (P = 1	0.19)	0 – T4 (L	- 0.0	000), i =	. 05/0	
Total (95% CI)		1172		1217	100.0%	1.09 [1.01, 1.18]	•
Total events	870		790		/*	,,,	*
Heterogeneity Tau <sup>2</sup> - 0.021	Chi <sup>2</sup> – 9	0.79 c	,	2200	00011:12	- 70%	
Test for overall effect: 7 - 7	17 (P - )	0.72,0 0.03)	27 ()	× v.v	0001), 1	- 1 9/9	0.1 0.2 0.5 1 2 5 10
Test for subgroup difference	r = r = r as: Chi <sup>2</sup> =	037 0	Hf = 1 (P	- 0.54	1 1 <sup>2</sup> − 09	·	Favours PN Favours EN
rescron subgroup unterence	5. CHI =	V.27,1	ы — т (г	- 0.54	-5, 1 = 0.4	,	

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

	EN		PN			Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI			
1.2.1 Tube Feeding										
Bozzetti et al 2001	103	159	136	158	5.4%	0.75 [0.66, 0.86]	-			
Hamaoui et al 1990	10	11	7	8	1.5%	1.04 [0.75, 1.43]				
lovinelli et al 1993	24	24	17	24	2.1%	1.40 [1.08, 1.82]				
Lim et al 1981	12	12	11	12	2.7%	1.09 [0.87, 1.36]	<u>+</u>			
Liu et al 2011	27	28	28	30	5.8%	1.03 [0.92, 1.16]	+			
Park et al 2012	14	18	20	20	2.2%	0.78 [0.60, 1.01]				
Reynolds et al 1997	30	33	34	34	5.8%	0.91 [0.81, 1.03]				
Sako et al 1981	33	33	34	36	7.0%	1.06 [0.96, 1.16]	-			
Sand et al 1997	13	13	16	16	5.4%	1.00 [0.88, 1.14]	+			
Seike et al 2011	14	14	15	15	5.4%	1.00 [0.88, 1.14]	+			
Shirabe et al 1997	13	13	13	13	4.9%	1.00 [0.87, 1.15]	+			
Von Meyenfeldt et al 1992	50	50	49	51	8.5%	1.04 [0.97, 1.11]	+			
Subtotal (95% CI)		408		417	56.6%	0.99 [0.91, 1.08]	•			
Total events	343		380							
Heterogeneity: Tau <sup>2</sup> = 0.02;	$Chi^2 = 4$	9.20, d	f = 11 (F)	P < 0.0	0001); I <sup>2</sup>	= 78%				
Test for overall effect: Z = 0.	24 (P =	0.81)								
122 Standard Care										
Bronnon et al 1994	57	57	50	60	0.0%	1 02 10 08 1 001				
Denoldson et al 1997	1	12	20	17	9.0%	1.03 [0.96, 1.09]				
Chavimi at al 1982	12	14	د م	11	1.6%	1 12 [0.37, 4.40]				
Holter et al 1977	26	26	20	30	9.4%	1.00 [0.03, 1.00]	1			
Kamei et al 2005	20	20	19	21	3.0%	0.94 [0.76, 1.16]				
Muller et al 1987	59	59	64	66	9.3%	1 03 10 98 1 091	L .			
Sandstrom et al 1993	141	150	138	150	8.8%	1.02 [0.96, 1.09]	L			
Smith et al 1992	6	6	5	6	0.9%	1 18 [0 76 1 83]				
Thompson et al 1981	9	å	11	12	2.4%	1 07 [0 84 1 37]				
Subtotal (95% CI)	-	361		368	43.4%	1.02 [1.00, 1.05]				
Total events	338		337							
Heterogeneity $Tau^2 = 0.00^{\circ}$	$Chi^2 = 2$	34 df	= 8 (P =	0.971	$ ^2 = 0\%$					
Test for overall effect: $Z = 1.62$ (P = 0.10)										
Total (95% CI)		769		785	100.0%	1.00 [0.96, 1.05]	L .			
Total events	681	.05	717		100.0/0	1.00 [0.50, 1.05]	ľ			
Heterogeneity $T_{2}u^{2} = 0.00$	Chi <sup>2</sup> - 4	9.20 8	/ 1/ If = 20 /F	2 - 0.0	1031: I <sup>2</sup> -	50%				
Test for overall effect: 7 = 0	20 (P = 1	0.20,0 0.84)	n – 20 (r	- 0.0			0.1 0.2 0.5 1 2 5 10			
Test for subgroup difference	20 (r = -	0.57 0	4f = 1 (P	- 0.45	$1   l^2 = 0.9$	(	Favours PN Favours EN			
Test for subgroup differences: Chi <sup>2</sup> = 0.57, df = 1 (P = 0.45), l <sup>2</sup> = 0%										

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

	EN		PN			Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
2.2.1 PEM									
Bozzetti et al 2001	103	159	136	158	5.4%	0.75 [0.66, 0.86]			
Donaldson et al 1982	4	13	3	12	0.1%	1.23 [0.34, 4.40]			
Holter et al 1977	26	26	30	30	8.4%	1.00 [0.93, 1.07]	+		
Lim et al 1981	12	12	11	12	2.7%	1.09 [0.87, 1.36]	+		
Muller et al 1982	59	59	64	66	9.3%	1.03 [0.98, 1.09]	+		
Park et al 2012	14	18	20	20	2.2%	0.78 [0.60, 1.01]			
Reynolds et al 1997	30	33	34	34	5.8%	0.91 [0.81, 1.03]			
Sako et al 1981	33	33	34	36	7.0%	1.06 [0.96, 1.16]	+-		
Sandstrom et al 1993	141	150	138	150	8.8%	1.02 [0.96, 1.09]	+		
Smith et al 1992	6	6	5	6	0.9%	1.18 [0.76, 1.83]			
Thompson et al 1981	9	9	11	12	2.4%	1.07 [0.84, 1.37]			
Von Meyenfeldt et al 1992	50	50	49	51	8.5%	1.04 [0.97, 1.11]	+		
Subtotal (95% CI)		568		587	61.3%	0.98 [0.92, 1.05]	•		
Total events	487		535						
Heterogeneity: Tau <sup>2</sup> = 0.01;	$Chi^2 = 4$	9.70, d	lf = 11 (F	P < 0.0	0001); I <sup>2</sup>	= 78%			
Test for overall effect: Z = 0	50 (P = 1	0.62)							
2.2.2 No PEM									
Brennan et al 1994	57	57	58	60	9.0%	1.03 [0.98, 1.09]	t		
Ghavimi et al 1982	13	14	9	11	1.6%	1.13 [0.83, 1.55]			
Hamaoui et al 1990	10	11	7	8	1.5%	1.04 [0.75, 1.43]			
lovinelli et al 1993	24	24	17	24	2.1%	1.40 [1.08, 1.82]			
Kamei et al 2005	23	27	19	21	3.0%	0.94 [0.76, 1.16]			
Liu et al 2011	27	28	28	30	5.8%	1.03 [0.92, 1.16]	+		
Sand et al 1997	13	13	16	16	5.4%	1.00 [0.88, 1.14]	+		
Seike et al 2011	14	14	15	15	5.4%	1.00 [0.88, 1.14]	+		
Shirabe et al 1997	13	13	13	13	4.9%	1.00 [0.87, 1.15]			
Subtotal (95% CI)		201		198	38.7%	1.03 [0.99, 1.08]	•		
Total events	194		182						
Heterogeneity: Tau <sup>2</sup> = 0.00;	Chi² = 8	.32, df	= 8 (P =	0.40);	12 = 4%				
Test for overall effect: Z = 1.32 (P = 0.19)									
Total (95% CI)		769		785	100.0%	1 00 [0 96 1 05]			
Total operato	601	109	717	,05	100.0%	1.00 [0.90, 1.03]			
Hotorogonoity Tou <sup>2</sup> . 0.00:	001 Chi <sup>2</sup> - 4	0.20 4	/1/ F = 20.4		0.021:12	5.0%			
Test for everall effect: 7 = 0	20 /P = 1	9.20, U 0.94)	n = 20 (r	= 0.0	005), 1- =	. , 9/6	0.1 0.2 0.5 1 2 5 10		
Test for subgroup difference	.20 (F = 1 c: Chi2	V.04J	JF 1./D	0.76	N 12 1 C	. CW	Favours PN Favours EN		
Test for subgroup differences: $Ch^{\mu} = 1.24$ , df = 1 (P = 0.26), P = 19.6%									

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

	EN		PN		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
1.3.1 Tube Feeding								
Aiko et al 2003	16	20	15	19	2.4%	1.01 [0.74, 1.39]		
Bozzetti et al 2001	139	159	128	158	16.4%	1.08 [0.98, 1.19]	-	
Fujita et al 2012	64	76	61	88	7.4%	1.21 [1.03, 1.44]	<b>_-</b> -	
Hamaoui et al 1990	11	11	8	8	5.8%	1.00 [0.82, 1.22]	_ <del></del>	
Heylen et al 1987	10	10	10	10	6.6%	1.00 [0.83, 1.20]	-	
lovinelli et al 1993	23	24	22	24	9.3%	1.05 [0.90, 1.21]	+	
Klek et al 2014	55	84	54	83	4.7%	1.01 [0.81, 1.26]	_ <del></del>	
Lim et al 1981	5	12	9	12	0.5%	0.56 [0.26, 1.17]		
Pacelli et al 2001	74	119	74	122	5.6%	1.03 [0.84, 1.25]	+	
Sako et al 1981	27	33	30	36	4.9%	0.98 [0.79, 1.22]		
Sand et al 1997	10	13	13	16	1.8%	0.95 [0.65, 1.38]	<del></del>	
Shirabe et al 1997	13	13	13	13	9.7%	1.00 [0.87, 1.15]	+	
Von Meyenfeldt et al 1992	44	50	45	51	9.6%	1.00 [0.86, 1.15]	+	
Subtotal (95% CI)		624		640	84.9%	1.04 [0.99, 1.09]	•	
Total events	491		482					
Heterogeneity: Tau <sup>2</sup> = 0.00;	$Chi^{2} = 8$	.13, df	= 12 (P	= 0.77	); $ ^2 = 0\%$			
Test for overall effect: Z = 1	52 (P =	0.13)						
1.3.2 Standard Care								
Brennan et al 1994	44	57	33	60	3.4%	1.40 [1.07, 1.84]		
Holter et al 1977	21	26	26	30	4.3%	0.93 [0.74, 1.18]		
Muller et al 1982	40	59	55	66	5.4%	0.81 [0.66, 1.00]		
Thompson et al 1981	8	9	10	12	2.1%	1.07 0.76. 1.50		
Subtotal (95% CI)		151		168	15.1%	1.02 [0.80, 1.30]	<b>•</b>	
Total events	113		124					
Heterogeneity, $Tau^2 = 0.04$ ;	$Chi^2 = 1$	0.65, d	f = 3 (P	= 0.01	); $1^2 = 723$	6		
Test for overall effect: Z = 0	16 (P =	0.87)						
Total (95% CI)		775		808	100.0%	1.03 [0.98, 1.08]		
Total events	604		606				ſ	
Heterogeneity, $Tau^2 = 0.00$ :	$Chi^2 = 1$	9.13. d	f = 16 (F	P = 0.2	$6):  ^2 = 10$	5%		
Test for overall effect: $7 = 1$	02 (P =	0.31)					0.1 0.2 0.5 1 2 5 10 <sup>°</sup>	
Test for subaroup difference	s: $Chi^2 =$	0.02. 0	df = 1 (P	= 0.89	$  _{1}^{2} = 0\%$		Favours PN Favours EN	
rest for subgroup dimensions. Chi = 0.02, di = 1 (r = 0.03), r = 0.8								

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

	EN		PN			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2.3.1 PEM							
Bozzetti et al 2001	139	159	128	158	16.4%	1.08 [0.98, 1.19]	-
Holter et al 1977	21	26	26	30	4.3%	0.93 [0.74, 1.18]	
Klek et al 2014	55	84	54	83	4.7%	1.01 [0.81, 1.26]	_ <del></del>
Lim et al 1981	5	12	9	12	0.5%	0.56 [0.26, 1.17]	
Muller et al 1982	40	59	55	66	5.4%	0.81 [0.66, 1.00]	
Sako et al 1981	27	33	30	36	4.9%	0.98 [0.79, 1.22]	
Thompson et al 1981	8	9	10	12	2.1%	1.07 [0.76, 1.50]	
Von Meyenfeldt et al 1992	44	50	45	51	9.6%	1.00 [0.86, 1.15]	+
Subtotal (95% CI)		432		448	48.0%	0.99 [0.91, 1.07]	<b>+</b>
Total events	339		357				
Heterogeneity: Tau <sup>2</sup> = 0.00;	$Chi^2 = 9$	51, df	= 7 (P =	0.22);	$ ^2 = 26\%$		
Test for overall effect: Z = 0.	35 (P = 1)	0.73)					
2.3.2 No PEM							
Aiko et al 2003	16	20	15	19	2.4%	1.01 [0.74, 1.39]	
Brennan et al 1994	44	57	33	60	3.4%	1.40 [1.07, 1.84]	
Fujita et al 2012	64	76	61	88	7.4%	1.21 [1.03, 1.44]	
Hamaoui et al 1990	11	11	8	8	5.8%	1.00 [0.82, 1.22]	
Heylen et al 1987	10	10	10	10	6.6%	1.00 [0.83, 1.20]	+
lovinelli et al 1993	23	24	22	24	9.3%	1.05 [0.90, 1.21]	
Pacelli et al 2001	74	119	74	122	5.6%	1.03 [0.84, 1.25]	+
Sand et al 1997	10	13	13	16	1.8%	0.95 [0.65, 1.38]	
Shirabe et al 1997	13	13	13	13	9.7%	1.00 [0.87, 1.15]	- <del>+</del>
Subtotal (95% CI)		343		360	52.0%	1.06 [0.98, 1.15]	•
Total events	265		249				
Heterogeneity: Tau <sup>2</sup> = 0.00;	$Chi^2 = 1$	0.85,d	f = 8 (P	= 0.21;	); I <sup>z</sup> = 26%	6	
Test for overall effect: $Z = 1$ .	52 (P =	0.13)					
Total (95% CI)		775		808	100.0%	1.03 [0.98, 1.08]	•
Total events	604		606				-
Heterogeneity: $Tau^2 = 0.00$ :	$Chi^2 = 1$	9.13, d	f = 16 (F	9 = 0.2	6); $ ^2 = 16$	5%	
Test for overall effect: Z = 1.	02 (P =	0.31)	v				U.1 U.2 U.5 1 2 5 10
Test for subgroup difference	s: Chi² =	1.68, 0	if = 1 (P	= 0.20	), $ ^2 = 40$ .	.5%	Favours FIN Favours EIN

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

	EN		DN			Pick Patio	Pick Patio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H Random 95% Cl	M-H Random 95% CI			
1.4.1 Tube Feeding	Events	Total	Events	Total	weight	M-1, Randoni, 55% CI	M-1, Kandoli, 55% Cl			
Aika at al 2002	20	20	10	10	2.0%	1 00 10 91 1 101	1			
Roolens et al 2003	20 61	61	67	67	19.7%					
Drovtrijov ot al 2014	60	60	52	52	15.4%	1.00 [0.97, 1.03]	I			
Entite of al 2017	74	76	22	00	7 0%	1.00 [0.97, 1.04]	I			
Hamaqui et al 1990	10	11	00	00	0.2%					
Hultondor et al 2005	26	76	72	72	2.5%	1 00 [0 92 1 07]	1			
lovinalli at al 1992	20	20	27	27	2.0%	1.00 [0.93, 1.07]	$\perp$			
liona at al 2002	24	24	24	24	5.0%	1.00 [0.92, 1.00]	1			
Jiang et al 2005 Klok et al 2014	20	20	20	20	11 19/	0.00[0.91, 1.10]				
List of 2012	202		202	20	11.1/0 D 49/	1 00 10 07 1 001	1			
Lietal 2012	23	23	20	20	2.4%	1.00 [0.92, 1.09]				
Limetal 1981	10	12	11	12	0.2%	0.91[0.67, 1.23]				
Liu et al 2011 Deservisionel 2004	28	28	30	30	4.3%	1.00 [0.94, 1.07]	I			
Pacelli et al 2001	112	119	119	122	6.6%	0.96 [0.92, 1.02]	1			
Park et al 2012	18	18	20	20	1.9%	1.00 [0.91, 1.10]	Ť			
Reynolds et al 1997	31	55	33	34	1.7%	0.97 [0.87, 1.07]	-			
Rickard et al 1983	6	- 6	10	10	0.3%	1.00 [0.78, 1.27]				
Sako et al 1981	33	33	33	36	1.5%	1.09 [0.97, 1.22]	<u> </u>			
Sand et al 1997	13	13	15	16	0.6%	1.06 [0.88, 1.26]	+-			
Shirabe et al 1997	13	13	13	13	0.9%	1.00 [0.87, 1.15]	+			
Von Meyenfeldt et al 1992	46	50	49	51	1.9%	0.96 [0.87, 1.06]	-†			
Subtotal (95% CI)		730		747	86.1%	1.00 [0.98, 1.01]				
Total events	710		733							
Heterogeneity: Tau <sup>2</sup> = 0.00;	$Chi^2 = 6$	37, df	= 19 (P	= 1.00	); $ ^2 = 0\%$					
Test for overall effect: Z = 0	.65 (P = 1	0.52)								
1.4.2 Standard Care										
Bronnon at al 1994	56	57	56	60	> > <b>%</b>	1 05 10 08 1 141	_			
Donaldson et al 1997	12	12	11	12	0.2%	1 01 [0 80, 1 27]				
Charles of al 1902	10	14	11	11	0.3%	0.08 [0.60, 1.27]				
How of al 1992	10	14	5	11	0.1%	1 00 10 71 1 411				
Hays et al 1905	ر 4 م	76	ر مر	20	0.2%	1.00 [0.71, 1.41]				
Kompi et al 2005	24	20	20	50	0.9%	1.00 (0.03, 1.13)	1			
Namer et al 2005	27	27	21	21	2.0%	1.00 [0.92, 1.08]	T			
Muller et al 1982	48	150	120	150	1.1%	0.85 [0.75, 0.97]				
Saudstrom et al 1993	140	150	138	150	4.6%	1.01 [0.95, 1.08]	Т			
Smith et al 1992	2	6	10	10	0.1%	0.85 [0.55, 1.31]				
I nompson et al 1981	9	9	12	12	0.6%	1.00 [0.84, 1.20]				
Van Eyes et al 1980	9	11	18	25	0.1%	1.14 [0.78, 1.65]				
Subtotal (95% CI)		5//		290	15.9%	1.00 [0.97, 1.04]				
lotal events	345		366							
Heterogeneity: Tau <sup>e</sup> = 0.00;	$Chi^{2} = 9$	11, df	= 10 (P	= 0.52	); l* = 0%					
Test for overall effect: $Z = 0$	.21 (P = 1	0.83)								
Total (95% CI)		1107		1145	100.0%	1.00 [0.98, 1.01]				
Total events	1055		1099							
Heterogeneity: Tau <sup>2</sup> = 0.00;	$Chi^2 = 1$	5.47, d	f = 30 (F	9 = 0.9	9); $ ^2 = 0$ ;	%				
Test for overall effect: Z = 0	.52 (P = 1	0.60)					0.1 0.2 0.5 1 2 5 10 Eavours PN Eavours EN			
Test for subgroup differences: Chi <sup>2</sup> = 0.19, df = 1 (P = 0.66), $l^2 = 0\%$										

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.

	EN		DN			Dick Patio	Pick Patio
Study or Subaroup	EN	Total	Events	Total	Weight	M-H Random 95% CL	M-H Random 95% CI
2 4 1 PFM	Lvents	Total	Lvents	Total	weight	M-1, Random, 55% CI	M-II, Kandolii, 55% Cl
Dependence of al 1987	10	17	11	17	0.29	1 01 (0 90 1 27)	
Dollaiusoli et al 1962	12	15	11	12	0.5%	1.01[0.80, 1.27]	
Hultender et al 2005	24	20	20	50	2.5%	1 00 [0.03, 1.13]	1
Kiek et al 2014	20	20	27	27	11 19/	1.00 [0.95, 1.07]	I
Line et al 1081	10	17	02	10	0.7%	0.99[0.95, 1.03]	
Muller et al 1991	10	12	67	12	1 19/	0.91[0.07, 1.23]	
Muller et al 1982	48	29	03	20	1.1%	0.85 [0.75, 0.97]	
Park et al 2012	18	18	20	20	1.9%	1.00 [0.91, 1.10]	I
Reynolds et al 1997	51	55	22	34	1.7%	0.97 [0.87, 1.07]	T
Rickard et al 1983		5	10	10	0.3%	1.00 [0.78, 1.27]	
Sako et al 1981	55	33	33	36	1.5%	1.09 [0.97, 1.22]	
Sandstrom et al 1993	140	150	138	150	4.6%	1.01 [0.95, 1.08]	Ť
Smith et al 1992	5	6	6	6	0.1%	0.85 [0.55, 1.31]	
Thompson et al 1981	9	9	12	12	0.6%	1.00 [0.84, 1.20]	+
Van Eyes et al 1980	9	11	18	25	0.1%	1.14 [0.78, 1.65]	
Von Meyenfeldt et al 1992	46	50	49	51	1.9%	0.96 [0.87, 1.06]	+
Subtotal (95% CI)		536		574	29.8%	0.99 [0.97, 1.02]	
Total events	499		541				
Heterogeneity: Tau <sup>2</sup> = 0.00;	$Chi^2 = 1$	0.64, d	f = 14 (F)	P = 0.7	1); $ ^2 = 09$	6	
Test for overall effect: $Z = 0$ .	72 (P =	0.47)					
2.4.2 No PEM							
Aiko et al 2003	20	20	19	19	2.0%	1.00 [0.91, 1.10]	+
Boelens et al 2014	61	61	62	62	18.7%	1.00 [0.97, 1.03]	•
Brennan et al 1994	56	57	56	60	3.2%	1.05 [0.98, 1.14]	-
Dmvtrijev et al 2014	60	60	52	52	15.4%	1.00 (0.97, 1.04)	•
Fujita et al 2012	74	76	86	88	7.8%	1.00 [0.95, 1.05]	+
Ghavimi et al 1982	10	14	8	11	0.1%	0.98 [0.60, 1.60]	
Hamanui et al 1990	10	11	8		0.3%	0.93 [0.71, 1.21]	
Havs et al 1983	5		5	5	0.2%	1 00 [0 71 1 41]	
Invinelli et al 1993	24	24	24	24	3.0%	1 00 [0 92 1 08]	+
liang et al 2003	20	20	20	20	2 1%	1 00 [0.92, 1.00]	<u> </u>
Kamei et al 2005	27	27	21	21	2.2%	1 00 [0 97 1 08]	1
Liet al 2017	22	22	20	20	7 4%	1 00 [0.92, 1.08]	1
Liu et al 2011	22	78	20	20	4 2%	1 00 [0.92, 1.03]	+
Pacelli et al 2001	112	110	110	122	6.6%	0.96 (0.97, 1.07)	1
Sand at al 1997	12	12	15	16	0.6%	1.06 (0.92, 1.02)	
Shiraha at al 1997	12	12	12	12	0.0%	1.00 [0.00, 1.20]	
Subtotal (95% CI)	15	571	15	571	70.2%	1.00 [0.98, 1.02]	
Total events	556		558				
Heterogeneity: $Tau^2 = 0.00$ :	$Chi^2 = 4$	.23. df	= 15 (P	= 1.00	$  ^2 = 0\%$		
Test for overall effect: $Z = 0$ .	15 (P =	0.88)	v				
Total (95% CI)		1107		1145	100.0%	1.00 [0.98, 1.01]	
Total events	1055		1099		/ •	,,,	
Heterogeneity Tau <sup>2</sup> = 0.00:	$Chi^2 = 1$	5 47 4	1099		a): 12 - 09	v	
Test for overall effect: 7 = 0	57 /P	ວ. <del>ຈ</del> 7, u ລ.ຣດນ	(r	- 0.9	5,1 = 07	v	0.1 0.2 0.5 1 2 5 10
Test for subgroup difference	$\nabla Z (r = r$ $c: Chi^2 = r$	0.00	f = 1 /₽	- 0.60	0 J <sup>2</sup> − 0%		Favours PN Favours EN
Test for suburoup unreferice	S. CHI =	V.27.U	41 = I (F	= 0.00	9. F = 0.⁄∞		

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

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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 metaanalysis 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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