

A systematic review and meta-analysis of gastrointestinal events associated with nonoperative therapies for neuroendocrine tumors

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Abstract: The risk of gastrointestinal (GI) events induced by nonoperative therapies in patients with neuroendocrine tumors (NETs) is unclear. Nonoperative therapies include somatostatin analogs, molecular targeted agents, cytotoxic chemotherapy, interferon- α , and peptide receptor radionuclide therapy. We undertook an up-to-date meta-analysis to determine the incidence and relative risks (RRs) of GI events in NET patients treated with these therapies. MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were searched to identify relevant trials. Eligible trials were selected according to the PRISMA statement. Summary incidence, RR, and 95% CIs were calculated using random- and fixed-effects models. We included 2,890 patients from 17 randomized controlled trials in this meta-analysis. The experimental treatments led to increased incidence and risks of GI events compared to the control treatments ($P < 0.05$). Diarrhea was the most common GI event. The experimental treatments were associated with increased risks of high-grade nausea (RR 2.36; 95% CI 1.05–5.25; $P < 0.01$) and vomiting (RR 1.89; 95% CI 1.04–3.44; $P < 0.05$). In regard to specific therapy regimens, everolimus led to increased risks of diarrhea (RR 2.97; 95% CI 1.83–4.83; $P < 0.05$), vomiting (RR 2.19; 95% CI 1.38–3.48; $P < 0.05$), and anorexia (RR 3.20; 95% CI 1.69–6.06; $P < 0.05$), whereas VEGFR inhibitors led to increased risk of diarrhea (RR 2.12; 95% CI 1.39–3.25; $P < 0.05$). Additionally, GI NETs led to higher risk of GI events than pancreatic NETs. Thus, nonoperative therapies are associated with increased risks of GI events in NET patients, and rigorous management is warranted to minimize the adverse impact on treatment outcomes and to improve quality of life.

Keywords: chemotherapy, somatostatin analogs, everolimus, neuroendocrine tumors, meta-analysis, gastrointestinal events

Introduction

Neuroendocrine tumors (NETs) originate from cells across the diffuse endocrine system and include a variety of subtypes, such as pancreatic, gastrointestinal (GI), lung, and thymus NET.¹ The incidence of NETs in the US was 6.98 cases per 100,000 people in 2012.² Treatment guidelines for NETs recommend that therapeutic options for advanced tumors and distant metastasis involve somatostatin analogs (SSAs), molecular targeted agents (eg, everolimus), cytotoxic chemotherapy, interferon- α (IFN- α), and peptide receptor radionuclide therapy (PRRT), as well as surgery in some cases involving limited metastases.¹ This study excluded surgery, and only the abovementioned therapies (designated as “nonoperative therapies”) are included in the meta-analysis.

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Hormonal hypersecretion that is derived from NETs may or may not lead to corresponding symptoms. For example, one of the most common symptoms of carcinoid syndrome (which can occur in NET patients) is diarrhea.³ However, diarrhea is a frequently reported side effect of sunitinib and everolimus.^{4,5} In addition, other GI events, including nausea, vomiting, and anorexia, are also associated with NET treated with cytotoxic chemotherapies, SSAs, and PRRT.^{6–8} In these scenarios, when NET patients are treated with those therapies, the GI events might be exacerbated by the very common effects of the NETs themselves, especially for patients with characteristics of gastroentero-active hormone hypersecretion. Thus, optimizing therapeutic options by reducing GI events is necessary for these patients. Furthermore, early recognition and appropriate management of GI events are helpful to avoid inessential dosage reductions and temporary or permanent treatment discontinuations among NET patients. In this study, we sought to thoroughly investigate the incidence and the relative risks (RRs) of GI events in NET patients receiving nonoperative therapies, including SSAs, molecular targeted agents, cytotoxic chemotherapy, IFN- α , and PRRT, via a meta-analysis of available randomized controlled trials (RCTs).

Acquisition of relevant studies

This study adhered to the PRISMA guidelines.⁹ To select relevant studies, we retrieved trials from MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). In addition, we searched ClinicalTrials.gov to further detect relevant trials. The preliminary retrieval of relevant trials was conducted on July 9, 2018 by a single reviewer (WQ).

The search strategy for MEDLINE was as follows. With regard to the selection of relevant patients, the following MeSH and non-MeSH terms were used: “neuroendocrine tumor” or “tumor neuroendocrine” or “tumors neuroendocrine” or “insulinomas” or “islet cell carcinoma” or “gastroinomas” AND “pancreatic” or “pancreas” or “stomach” or “gastric” or “intestinal” or “intestine” or “digestive track” or “gastrointestinal tract” or “GI tract” or “gastroenteropancreatic”. Regarding selecting relevant interventions, the following MeSH and non-MeSH terms were used: “therapy, drug” or “drug therapies” or “therapies drug” or “chemotherapy” or “chemotherapies” or “pharmacotherapy” or “pharmacotherapies” or “streptozotocin” or “fluorouracil” or “doxorubicin” or “dacarbazine” or “temozolamide” or “interferon” or “everolimus” or “somatostatin analogs” or “octreotide” or “etoposide” or “streptozocin” or “dacarbazine”

or “cisplatin” or “¹⁷⁷Lu-DOTATATE” or “peptide receptor radionuclide therapy” or “PRRT”. With regard to selecting the relevant types of studies, the following terms were used to obtain RCTs: “randomized controlled trial.pt” or “controlled clinical trial.pt” or “randomized.ab” or “placebo.ab” or “clinical trials as topic.sh” or “randomly.ab” or “trial.ti”. Ongoing trials were searched with the terms “neuroendocrine tumor” AND other terms including “chemotherapy” or “somatostatin analogs” or “interferon” or “everolimus” or “sunitinib” or other potential efficient therapies. We only included trials involving humans. When an English version of an article was unavailable, the article would be excluded.

Eligibility criteria

All of the potential publications were independently screened by two reviewers (QW and BC). Duplicates were excluded. Reviews, meta-analyses, conference abstracts, letters, editorials, and protocols were also excluded. Any publications that did not concern nonoperative therapies, NET, and GI events were eliminated. We removed studies involving non-randomized designs, phase I trials, retrospective studies, subgroup reports, and pilot studies. Only studies that met the following criteria were further taken into consideration: 1) RCTs including phase II/III trials of NET patients with double-blind or open-label design; 2) randomized assignment of NET patients into Regimen A arm and placebo arm, or Regimen A+B arm and Regimen B arm; and 3) available data concerning GI events in both arms. The exclusion criteria were as follows: 1) studies involving <20 NET patients and 2) combined data on GI events, with no data on individual types of GI events. When multiple publications concerning the same trial were obtained, we prioritized recently published papers that presented the most data as relevant to our objectives. Full texts of eligible articles were obtained for the final determination of whether to include them, and any disagreements were discussed by the two reviewers until a consensus was reached.

Data extraction and assessment of risk of bias

Two reviewers (QW and JH) independently reviewed the full-text manuscripts of eligible trials and extracted the data using standardized Excel forms. Data on the name of first author, year of publication, study design, randomization method, basic patient characteristics, tumor location, tumor grading, experimental arm, control arm, treatment dosages and durations, and types and numbers of GI events (all grades

and high grades [grades 3 or 4]) in each arm were extracted. We retrieved data on GI events (including diarrhea, nausea, vomiting, and anorexia) in each trial for this meta-analysis. Any discrepancy was resolved by discussion.

We assessed the quality of the included trials according to the Cochrane Collaboration checklist,¹⁰ including: 1) method of randomization; 2) method of allocation concealment; 3) blinding of participants, clinicians, and data analysts; 4) presence of incomplete outcome data; and 5) selective outcome reporting.

Statistical analysis

Statistical analyses were conducted using Review Manager version 5.3 (Cochrane Collaboration) and Stata version 15. The principal summary measures were the incidence and RRs of GI events, with corresponding 95% CIs, in each trial. To calculate the incidence of GI events, the number of each event (diarrhea, nausea, vomiting, and anorexia) and the number of patients in each arm were extracted from the safety profiles, while disregarding unrelated tumor types. The RRs and 95% CIs of GI events for each trial were calculated by comparing the incidence of each GI event in the Regimen A and placebo arms or the regimens A+B and B arms. Moreover, we calculated the RRs and corresponding 95% CIs of high-grade (grade 3 or 4) GI events when the data were available.

The heterogeneity of the trials with regard to each variable used in the meta-analyses was tested using Cochran's Q statistic,¹¹ and heterogeneity was established on the basis of a P -value <0.1 . We also used the I^2 statistic [$100\% \times (Q - df)/Q$] to indicate whether there was heterogeneity between the studies by quantifying the percentage of the variability in effect estimates that was due to heterogeneity rather than chance.¹² Heterogeneity was considered substantial when I^2 was $\geq 50\%$. When I^2 was $<50\%$ and $\geq 50\%$, we conducted a meta-analysis using a fixed- and random-effects model, respectively.

We conducted prespecified subgroup analyses for each GI event, stratified by tumor type (pancreatic NETs, GI NETs, and NETs at other sites) and therapy regimens. Therapy regimens were stratified into mTOR inhibitors (everolimus and BEZ235), SSAs (pasireotide, lanreotide, and octreotide), VEGFR inhibitors (bevacizumab and sunitinib), IFN, cytotoxic chemotherapy (cisplatin, 5-fluorouracil, and capecitabine), and PRRT. A sensitivity analysis was conducted to check the robustness of the primary results by excluding low-quality trials (which involved excluding studies one at a time). We evaluated publication bias using funnel plots,

Egger's linear regression approach, and Begg's rank correlation test.^{13,14} A two-tailed P -value <0.05 indicated statistical significance.

Results

Search results

Our search of the literature found 2,791 potentially relevant publications: 1,470 in MEDLINE, 1,239 in EMBASE, and 82 in CENTRAL. Figure 1 presents the processes and reasons for study selection. Among the initial publications, 642 duplicates were excluded. After reading the title, abstract, and full text, 17 RCTs, comprising nine phase III trials and eight phase II trials, were included in the meta-analysis.

Study characteristics

The basic characteristics of the included studies are listed in Table 1. This meta-analysis included a total of 2,890 patients (1,499 in the experimental arms; 1,391 in the control arms) from 17 RCTs. There were 1,303 patients with pancreatic NETs, 608 with GI NETs, 824 with gastroenteropancreatic NETs, 90 with lung NETs, and 65 with NETs at unknown sites.

Two trials evaluated the efficiency and safety of everolimus compared to placebo in pancreatic and GI NETs.^{15,16} One trial compared everolimus plus octreotide long-acting repeatable (LAR) with everolimus in NETs.⁵ One trial evaluated another mTOR inhibitor (BEZ235) in pancreatic NETs.¹⁷ Four trials assessed SSAs (pasireotide, octreotide, and lanreotide) in divergent conditions, either compared to placebo, compared to different SSA doses, or in combination with another regimen (in the experimental arm) as compared to the other regimen (in the control arm).^{18–21} Four trials assessed VEGFR inhibitors (sunitinib and bevacizumab) compared to placebo or in combination with everolimus to everolimus alone.^{4,22–24} Two trials evaluated IFN- α in NETs.^{7,25} Two trials assessed the safety of cytotoxic drugs (5-fluorouracil and cisplatin) in NETs.^{6,26} One trial evaluated the efficiency and safety of PRRT in midgut NETs.⁸

With regard to the trial therapy regimens, the everolimus dose was 10 mg per day; BEZ235 dose was 400 or 300 mg twice daily; pasireotide dose was 60 mg per 28 days; octreotide dose was 30 mg per month; lanreotide dose was 120 mg per 28 days; sunitinib dose was 37.5 mg per day; bevacizumab dose was 10 mg/kg; IFN dose was 5×10^6 IU three times per week; and ¹⁷⁷Lu-Dotatate treatment involved 7.4 GBq.

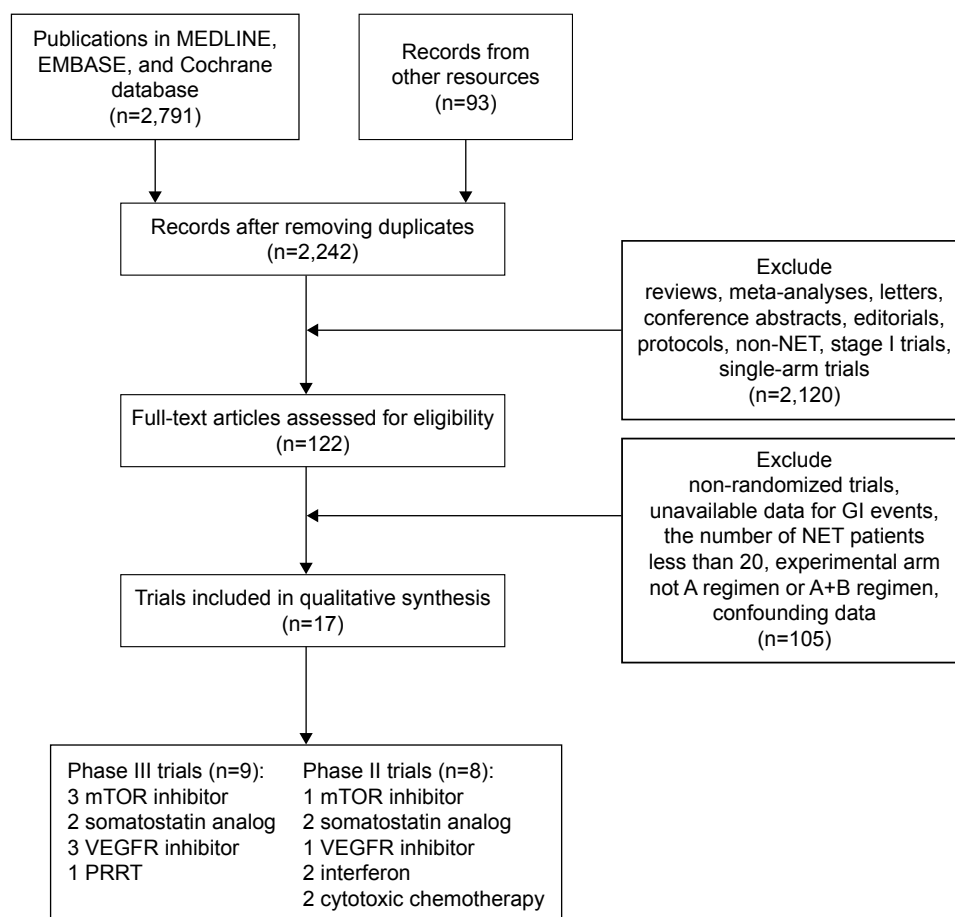


Figure 1 Processes and reasons for study selection.

Abbreviations: GI, gastrointestinal; NET, neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy.

The sample sizes ranged from 31 to 429 patients, and five trials included >200 patients. In all trials, patients were randomly assigned to either the experimental or control arm. Ten trials reported the follow-up duration. All trials involved both male and female patients, with a mean age of >53 years.

Risk of bias assessment

All the included trials had randomized designs, with 14 trials providing details of the method of random sequence generation. With regard to blinding, eight trials were double-blind (in terms of participants and clinicians or treatment administration) and six trials had open-label designs (with no masking in either arm). Most of the trials reported all of the prespecified outcomes except two ongoing trials that lacked enough data to determine long-term efficiency and safety. Figure 2 illustrates the risk of bias assessments for all of the included trials. According to our assessments, the risk of bias summary suggested a moderate and acceptable bias in most domains, except for allocation concealment (which can lead to selection bias) and blinding of participants and personnel

(which can lead to performance bias). Therefore, the overall quality of the included trials was generally acceptable.

Incidence of GI events

Table 2 presents the incidence of GI events in the included trials. Incidence of any- and high-grade diarrhea in the experimental groups ranged from 1.2% to 62.0% and 0% to 7.3%, respectively. The top three therapy regimens eliciting diarrhea in NET patients were everolimus plus pasireotide LAR, sunitinib, and BEZ235. The incidence of any-grade and high-grade nausea in the experimental groups ranged from 0% to 63.6% and 0% to 18.2%, respectively. An incidence of nausea >50% involved cisplatin plus capecitabine plus streptozocin, octreotide LAR plus ¹⁷⁷Lu-Dotatate, and BEZ235. With regard to any-grade vomiting, the incidence ranged from 6.9% to 64.6% in the experimental groups. Data also suggested that cisplatin plus capecitabine plus streptozocin, octreotide LAR plus ¹⁷⁷Lu-Dotatate, and BEZ235 were the treatments most likely to induce vomiting in NET patients. The incidence of any-grade anorexia ranged from 0% to 22.0% in the experimental groups.

Table 1 Baseline characteristics of the 17 trials included in the meta-analysis

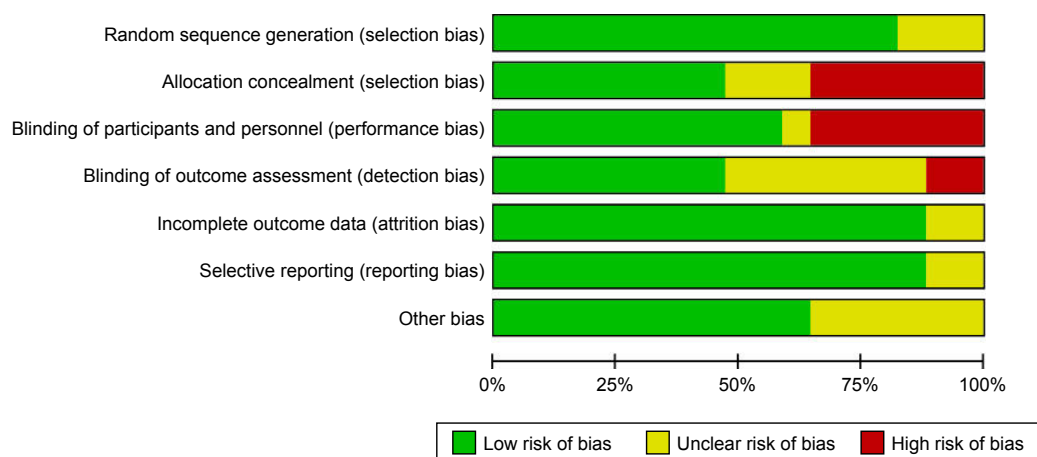
Study	Year	Phase	Masking	Enrolled	Analyzed	Primary sites	Treatment	
							Experimental arm	Control arm
Meyer et al ²⁶	2014	II	Open-label	86	83	Pancreatic 48%; gastroduodenal 20%; unknown site 32%	Capecitabine + streptozocin + cisplatin	Capecitabine + streptozocin
Yao et al ¹⁵	2016	III	Double-blind	410	406	Pancreatic 100%	Everolimus	Placebo
Faiss et al ²⁵	2000	II	Open-label	80	76	Pancreatic 45%; gastrointestinal 41%; unknown site 14%	Lanreotide + interferon- α	Lanreotide or interferon- α
Caplin et al ²¹	2014	III	Double-blind	204	204	Pancreatic 45%; gastrointestinal 43%; unknown site 12%	Lanreotide	Placebo
Arnold et al ⁷	2005	II	Open-label	109	105	Gastroenteropancreatic 100%	Octreotide + interferon- α	Octreotide
Raymond et al ²²	2011	III	Open-label	171	165	Pancreatic 100%	Sunitinib	Placebo
Rinke et al ¹⁸	2009	III	Double-blind	90	85	Gastrointestinal 100%	Octreotide 100%	Placebo
Moertel et al ⁶	1980	II	Unknown	103	84	Pancreatic 100%	Streptozocin + fluorouracil	Streptozocin
Pavel et al ⁵	2011	III	Double-blind	429	426	Pancreatic 6%; gastrointestinal 59%; other sites 35%	Everolimus + octreotide	Octreotide + placebo
Wolin et al ¹⁹	2013	II	Open-label	42	42	Gastroenteropancreatic 100%	Pasireotide 60 mg	Pasireotide 20 mg
Strosberg et al ⁸	2017	III	Open-label	229	221	Gastrointestinal 100%	¹⁷⁷ Lu-Dotatate + octreotide	Octreotide
Yao et al ¹⁶	2016	III	Double-blind	302	302	Gastrointestinal 67%; lung 33%	Everolimus	Placebo
Fazio et al ¹⁷	2016	II	Open-label	31	31	Pancreatic 100%	BEZ235 400 mg	BEZ235 300 mg
Vinik et al ⁴	2016	III	Open-label	171	144	Pancreatic 100%	Sunitinib	Placebo
Kulke et al ²⁰	2017	II	Open-label	160	160	Pancreatic 100%	Everolimus + pasireotide	Everolimus
Kulke et al ³	2015	II	Open-label	150	143	Pancreatic 100%	Everolimus + octreotide + bevacizumab	Everolimus + octreotide
Niccoli et al ²³	2010	III	Open-label	171	165	Pancreatic 100%	Sunitinib	Placebo

When considering the incidence of GI events stratified by therapy regimens, mTOR inhibitors (everolimus and BEZ235) led to any-grade diarrhea ranging from 33.8% to 54.5%; any-grade nausea ranging from 17.1% to 54.5%; any-grade vomiting ranging from 14.8% to 36.4%; and any-grade anorexia ranging from 15.6% to 18.2%. As for SSAs (pasireotide, octreotide, and lanreotide), the incidence of any-grade GI events were as follows: diarrhea ranging from 14.3% to 25.7%; nausea ranging from 6.9% to 12.5%; vomiting ranging from 0% to 6.9%; and anorexia ranging from 0% to 6.3%. Moreover, VEGFR inhibitors (sunitinib and bevacizumab) increased the incidence of any-grade diarrhea, nausea, vomiting, and anorexia, ranging from 1.2% to 60.0%, 2.4% to 45.1%, 2.7% to 34.1%, and 4.1% to 22.0%, respectively. In addition, the incidence of GI events for cytotoxic chemotherapy (cisplatin and 5-fluorouracil) was 43.2% for any-grade diarrhea, 63.6% for any-grade nausea, and 64.6% for any-grade vomiting.

Overall RR of GI events

Sixteen RCTs were available to calculate the RRs of diarrhea; 446 diarrhea events were reported in 1,415 patients enrolled in the experimental groups, compared to 265 diarrhea events in 1,307 patients in the control groups. The pooled RR of any-grade diarrhea for nonoperative therapies vs controls was 1.55 (95% CI 1.21–1.98, $P=0.0005$), suggesting a significant increase in the risk of diarrhea for nonoperative treatments compared with controls. Similarly, the pooled RRs (encompassing eight trials) of any-grade nausea for nonoperative therapies vs controls was 1.55 (95% CI 1.14–2.10, $P=0.005$), suggesting a significant increase in the risk of nausea for nonoperative treatments compared with controls. The pooled RR (encompassing eight trials) of any-grade vomiting was 1.79 (95% CI 1.08–2.97, $P=0.02$) and the pooled RR (encompassing eight trials) of any-grade anorexia was 1.87 (95% CI 1.22–2.87, $P=0.004$), suggesting that nonoperative therapies elicit significantly increased risks of vomiting and anorexia compared with controls. These results are presented in Figure 3.

The risks of high-grade GI events, including diarrhea and anorexia, associated with nonoperative therapies were not significantly increased when compared with the controls ($P>0.05$). In contrast, the risks of high-grade nausea and vomiting were significantly increased ($P<0.05$). The pooled RRs of high-grade GI events for nonoperative therapies vs controls were 1.69 (95% CI 0.80–3.55) for diarrhea, 2.35 (95% CI 1.05–5.27) for nausea, 1.89 (95% CI 1.04–3.44) for vomiting, and 1.79 (95% CI 0.26–12.05) for anorexia (Figure 4). Although the data indicated nonsignificant



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Vinik et al, ⁴ 2016	+	+	+	?	?	+	?
Rinke et al, ¹⁸ 2009	+	+	+	+	+	+	+
Moertel et al, ⁶ 1980	?	?	+	?	+	+	?
Wolin et al, ¹⁹ 2013	+	+	+	+	+	+	+
Raymond et al, ²² 2011	+	+	+	?	+	+	+
Yao et al, ¹⁵ 2016	+	+	+	+	+	+	?
Yao et al, ¹⁶ 2016	+	+	+	+	+	+	+
Kulke et al, ²⁰ 2017	+	-	-	+	+	+	+
Pavel et al, ⁵ 2011	+	+	+	?	+	+	+
Caplin et al, ²¹ 2014	+	+	+	+	+	+	+
Kulke et al, ³ 2015	?	-	-	-	+	+	+
Niccoli et al, ²³ 2010	?	?	+	+	+	?	?
Fazio et al, ¹⁷ 2016	+	-	-	?	?	?	?
Arnold et al, ⁷ 2005	+	-	-	?	+	+	+
Faiss et al, ²⁵ 2003	+	-	-	-	+	+	+
Strosberg et al, ⁸ 2017	+	-	-	+	+	+	+
Meyer et al, ²⁶ 2014	+	?	?	?	+	+	?

Figure 2 Risk of bias assessments for all included trials.

Table 2 Incidences of GI events associated with nonoperative therapies

Study	T. arm	C. arm	N		Diarrhea incidence			Nausea incidence		
			T. arm	C. arm	T. arm	Grade 3/4	All grade	T. arm	Grade 3/4	All grade
Meyer et al ²⁶	Capecitabine + streptozocin	Capecitabine + streptozocin	44	42	All grade	4 (0.091)	22 (0.523)	28 (0.636)	7 (0.159)	27 (0.643)
Yao et al ¹⁵	Everolimus	Placebo	204	203	Grade 3/4	7 (0.034)	21 (0.103)	42 (0.206)	2 (0.01)	37 (0.182)
Faiss et al ²⁵	Lanreotide + interferon- α	Lanreotide or interferon- α	21	23	All grade	NA	1 (0.043)	NA	NA	NA
Caplin et al ²¹	Lanreotide	Placebo	101	103	Grade 3/4	NA	9 (0.087)	7 (0.069)	NA	2 (0.019)
Arnold et al ¹⁷	Octreotide + interferon- α	Octreotide	54	51	All grade	NA	19 (0.373)	11 (0.204)	NA	NA
Raymond et al ²²	Sunitinib	Placebo	82	83	Grade 3/4	4 (0.049)	32 (0.390)	37 (0.451)	1 (0.012)	24 (0.289)
Rinke et al ¹⁸	Octreotide 100%	Placebo	42	43	All grade	NA	6 (0.140)	NA	NA	NA
Moertel et al ¹⁶	Streptozocin + fluorouracil	Streptozocin	42	42	Grade 3/4	NA	NA	35 (0.833)	15 (0.357)	35 (0.833)
Pavel et al ⁵	Everolimus + octreotide	Octreotide + placebo	216	213	All grade	13 (0.06)	33 (0.155)	42 (0.194)	1 (0)	34 (0.160)
Wolin et al ¹⁹	Pasireotide 60 mg	Pasireotide 20 mg	16	12	Grade 3/4	NA	4 (0.330)	2 (0.125)	NA	2 (0.166)
Strosberg et al ⁸	¹⁷⁷ Lu-Dotatate + octreotide	Octreotide	111	110	All grade	3 (0.027)	21 (0.189)	65 (0.585)	4 (0.036)	13 (0.117)
Yao et al ¹⁶	Everolimus	Placebo	204	203	Grade 3/4	15 (0.073)	16 (0.165)	35 (0.171)	3 (0.015)	10 (0.103)
Fazio et al ¹⁷	BEZ235 400 mg	BEZ235 300 mg	11	20	All grade	2 (0.100)	16 (0.800)	6 (0.545)	2 (0.182)	9 (0.450)
Vinik et al ⁴	Sunitinib	Placebo	73	71	Grade 3/4	NA	15 (0.211)	14 (0.192)	NA	12 (0.169)
Kulke et al ²⁰	Everolimus + pasireotide	Everolimus	79	81	All grade	4 (0.051)	43 (0.531)	NA	NA	NA
Kulke et al ³	Everolimus + octreotide + bevacizumab	Everolimus + octreotide	73	74	Grade 3/4	NA	5 (0.068)	18 (0.246)	NA	6 (0.080)
Niccoli et al	Sunitinib	Placebo	83	82	All grade	NA	0 (0)	2 (0.024)	NA	1 (0.012)
Anorexia incidence										
T. arm			N		Vomiting incidence			T. arm		
C. arm			C. arm		C. arm			C. arm		
T. arm			T. arm		T. arm			T. arm		
C. arm			C. arm		C. arm			C. arm		
Meyer et al ²⁶	Capecitabine + streptozocin	Capecitabine + streptozocin	44	42	All grade	7 (0.159)	27 (0.643)	NA	NA	NA
Yao et al ¹⁵	Everolimus	Placebo	204	203	Grade 3/4	0 (0)	13 (0.064)	34 (0.167)	0 (0)	8 (0.039)
Faiss et al ²⁵	Lanreotide	Placebo	101	103	All grade	0 (0)	0 (0)	NA	NA	NA
Caplin et al ²¹	Octreotide + interferon- α	Octreotide	54	51	Grade 3/4	NA	3 (0.058)	NA	NA	NA
Arnold et al ¹⁷	Sunitinib	Placebo	82	83	All grade	0 (0)	23 (0.277)	18 (0.220)	2 (0.024)	17 (0.204)
Raymond et al ²²	Streptozocin + fluorouracil	Streptozocin	42	42	Grade 3/4	16 (0.381)	35 (0.833)	NA	NA	NA
Rinke et al ¹⁸	Everolimus + octreotide	Octreotide + placebo	216	213	All grade	1 (0)	11 (0.052)	29 (0.136)	NA	13 (0.061)
Moertel et al ¹⁶	Pasireotide 60 mg	Pasireotide 20 mg	16	12	Grade 3/4	NA	NA	1 (0.063)	NA	1 (0.083)
Pavel et al ⁵	¹⁷⁷ Lu-Dotatate + octreotide	Octreotide	111	110	All grade	8 (0.072)	11 (0.100)	NA	NA	NA
Wolin et al ¹⁹	Everolimus	Placebo	204	203	Grade 3/4	NA	NA	32 (0.156)	1 (0.005)	6 (0.062)
Strosberg et al ⁸	BEZ235 400 mg	BEZ235 300 mg	11	20	All grade	1 (0.091)	6 (0.300)	2 (0.182)	0 (0)	6 (0.300)
Yao et al ¹⁶	Sunitinib	Placebo	73	71	Grade 3/4	NA	12 (0.169)	27 (0.370)	NA	21 (0.300)
Fazio et al ¹⁷	Everolimus + octreotide + bevacizumab	Everolimus + octreotide	73	74	All grade	NA	1 (0.014)	3 (0.041)	NA	2 (0.027)
Vinik et al ⁴	Sunitinib	Placebo	83	82	Grade 3/4	NA	3 (0.037)	NA	NA	NA

Note: Numbers in brackets indicate the percentage of each event among corresponding subjects.

Abbreviations: N, subject; number of subjects; NA, not available; C, arm, control arm; GI, gastrointestinal; T, arm, treatment arm.

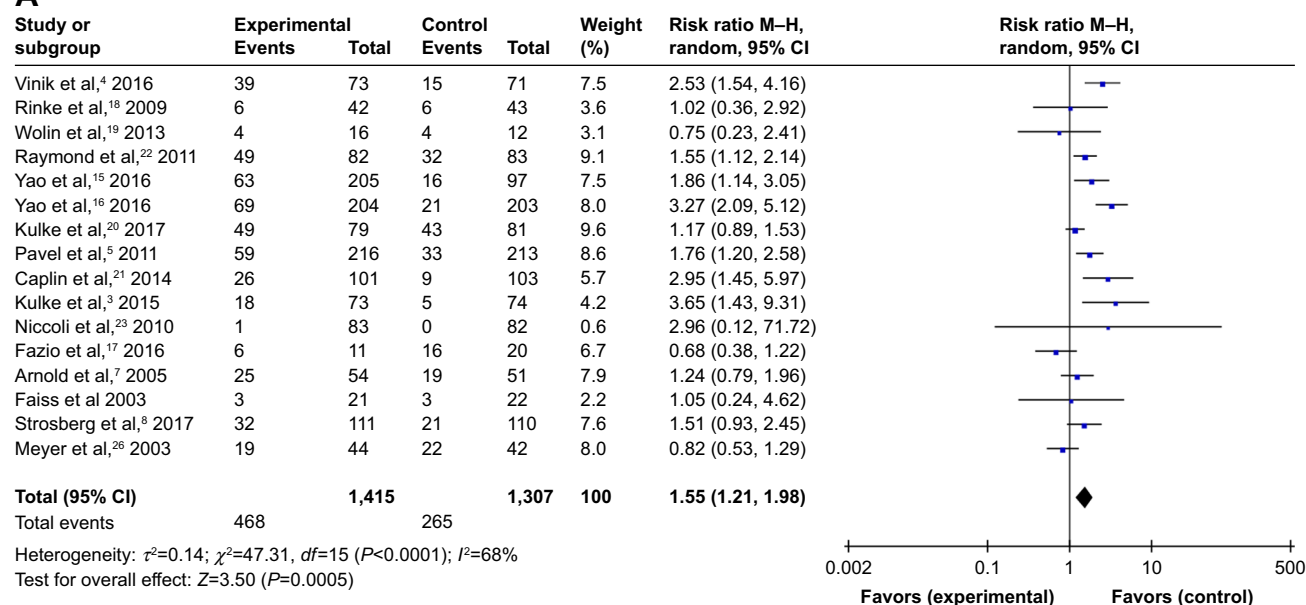
RRs >1 for diarrhea and anorexia, there were wide 95% CIs (crossing 1).

RRs of GI events stratified by therapy regimen

We conducted a subgroup risk analysis stratified by therapy regimen (Table 3). A total of 435 GI events occurred in 625 patients in the everolimus groups, compared to 239 GI events in 513 patients in the control groups. The RR of any-grade GI events associated with everolimus was 1.47 (95% CI 1.22–1.78, $P<0.0001$). Although there was high

heterogeneity in this meta-analysis ($I^2=69\%$), we omitted one study at a time to test the influence of each trial on the overall heterogeneity. When we omitted the trial by Yao et al,¹⁵ the heterogeneity of the included trials decreased to 0. Thus, the risk of GI events due to everolimus compared with controls in NET patients significantly increased. SSA treatment in NETs did not lead to an increased risk of any-grade GI events ($P=0.28$). Additionally, no significant difference in GI event risk was noted between the IFN- α and control groups ($P=0.24$). The RR of any-grade GI events associated with combined chemotherapies vs single-drug

A



B

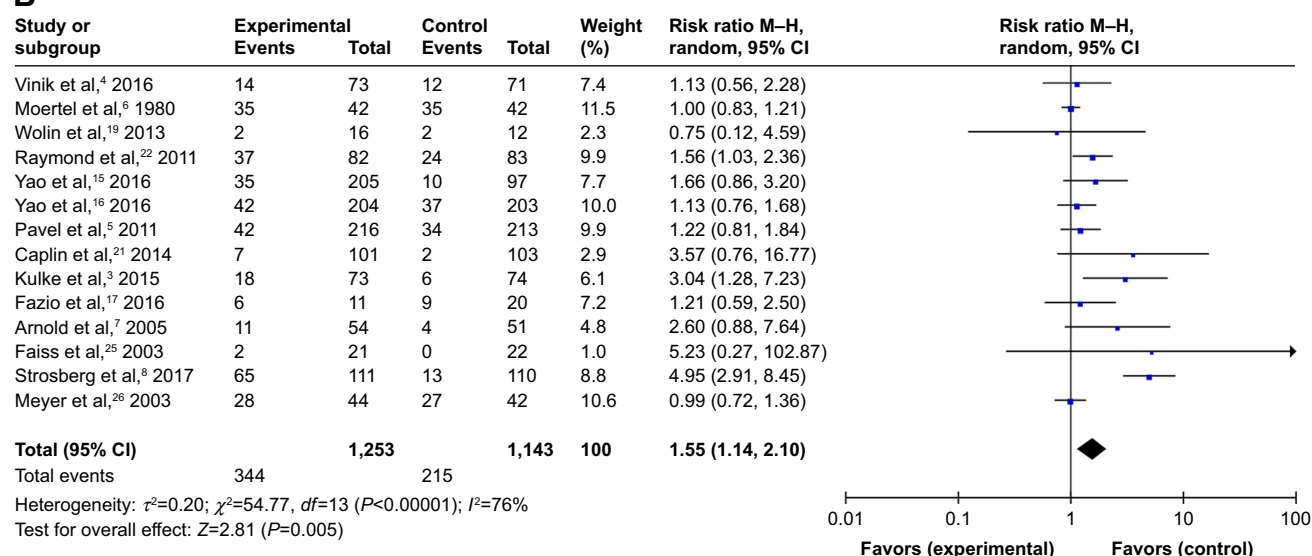
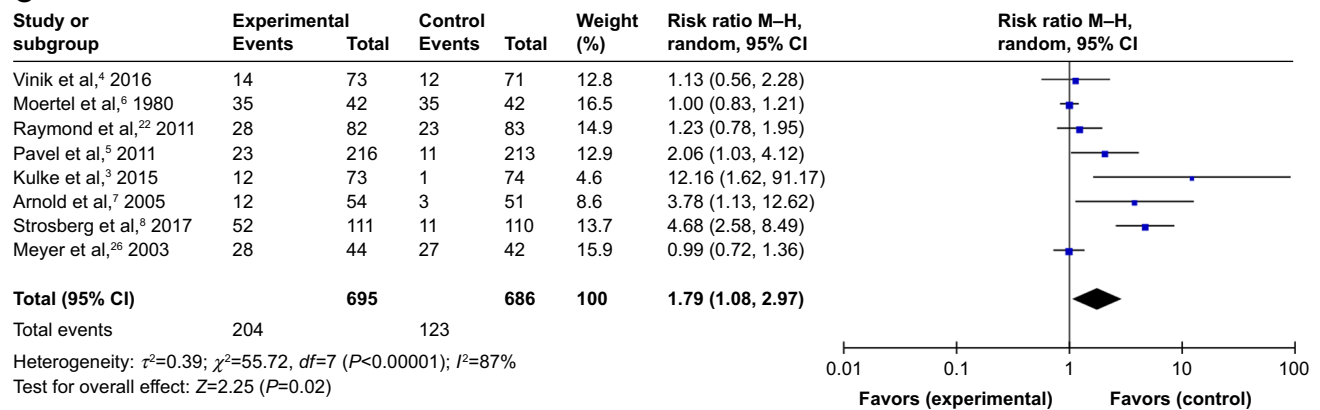


Figure 3 (Continued)

C



D

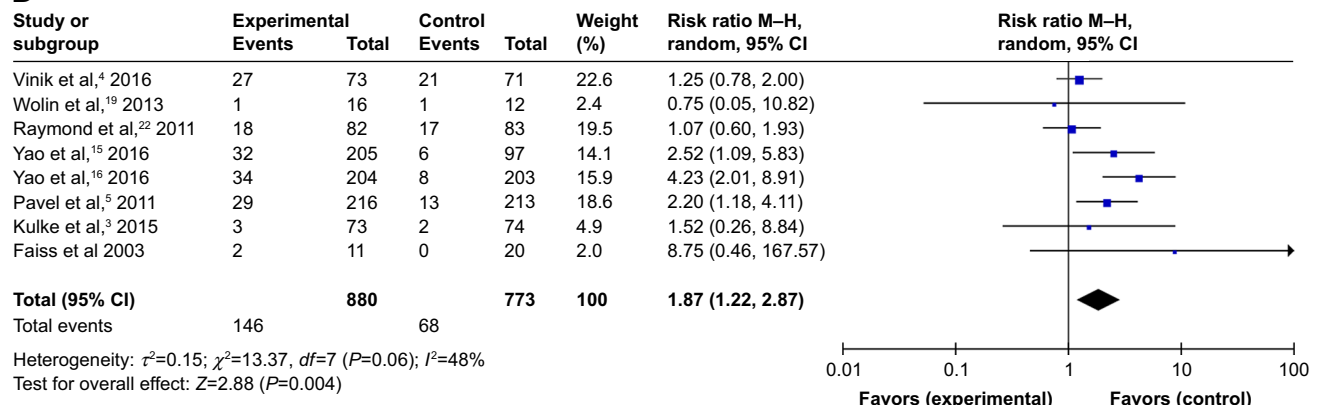


Figure 3 Relative risks of any-grade GI events associated with nonoperative therapies.

Note: Relative risk associated with nonoperative therapies of any-grade (A) diarrhea, (B) nausea, (C) vomiting, and (D) anorexia.

Abbreviation: GI, gastrointestinal.

chemotherapy was not significant ($P=0.97$), whereas the risk of high-grade GI events significantly increased (RR 1.97, 95% CI 1.24–3.11, $P=0.004$).

RRs of GI events stratified by tumor site

We further conducted a meta-analysis of RRs of GI events stratified by tumor site (Table 4). In pancreatic NET patients, the RR was 1.77 (95% CI 1.13–2.79, $P=0.01$) for any-grade diarrhea, 1.39 (95% CI 0.92–2.10, $P=0.12$) for any-grade nausea, 1.37 (95% CI 0.88–2.13, $P=0.17$) for any-grade vomiting, and 1.48 (95% CI 0.81–2.73, $P=0.21$) for any-grade anorexia. These pooled results indicated that nonoperative therapies significantly increased the risk of diarrhea in patients with pancreatic NET.

In GI NET patients, the RR was 1.66 (95% CI 1.05–2.63, $P=0.03$) for any-grade diarrhea, 1.57 (95% CI 0.84–2.94, $P=0.15$) for any-grade nausea, 4.68 (95% CI 2.58–8.49, $P<0.001$) for any-grade vomiting, and 2.52 (95% CI 1.09–5.83, $P=0.03$) for any-grade anorexia. Thus, the risks of GI events, except for nausea, significantly increased with nonoperative therapies in GI NET patients.

Several trials concurrently included pancreatic and GI NET patients, and the safety profiles were not reported by tumor site. The pooled RRs of these trials for diarrhea, nausea, vomiting, and anorexia were 1.56 (95% CI 0.89–2.75, $P=1.12$), 1.28 (95% CI 0.88–1.87, $P=0.20$), 2.16 (95% CI 0.84–5.60, $P=0.11$), and 2.08 (95% CI 1.13–3.83, $P=0.02$), respectively. Thus, the data from these trials only suggested an increased risk of anorexia due to nonoperative therapies in patients with gastroenteropancreatic NET.

Publication bias

The funnel plots did not show significant publication bias for any GI events. The P -values of Begg's test for the association between nonoperative therapies and risks of diarrhea, nausea, vomiting, and anorexia were 0.507, 0.876, 0.745, and 0.445, respectively (Figure S1).

Discussion

Studies on NETs mostly concern the efficacy and safety of certain therapies (eg, octreotide LAR) and surgical management, as well as the verification of the use of Ki-67

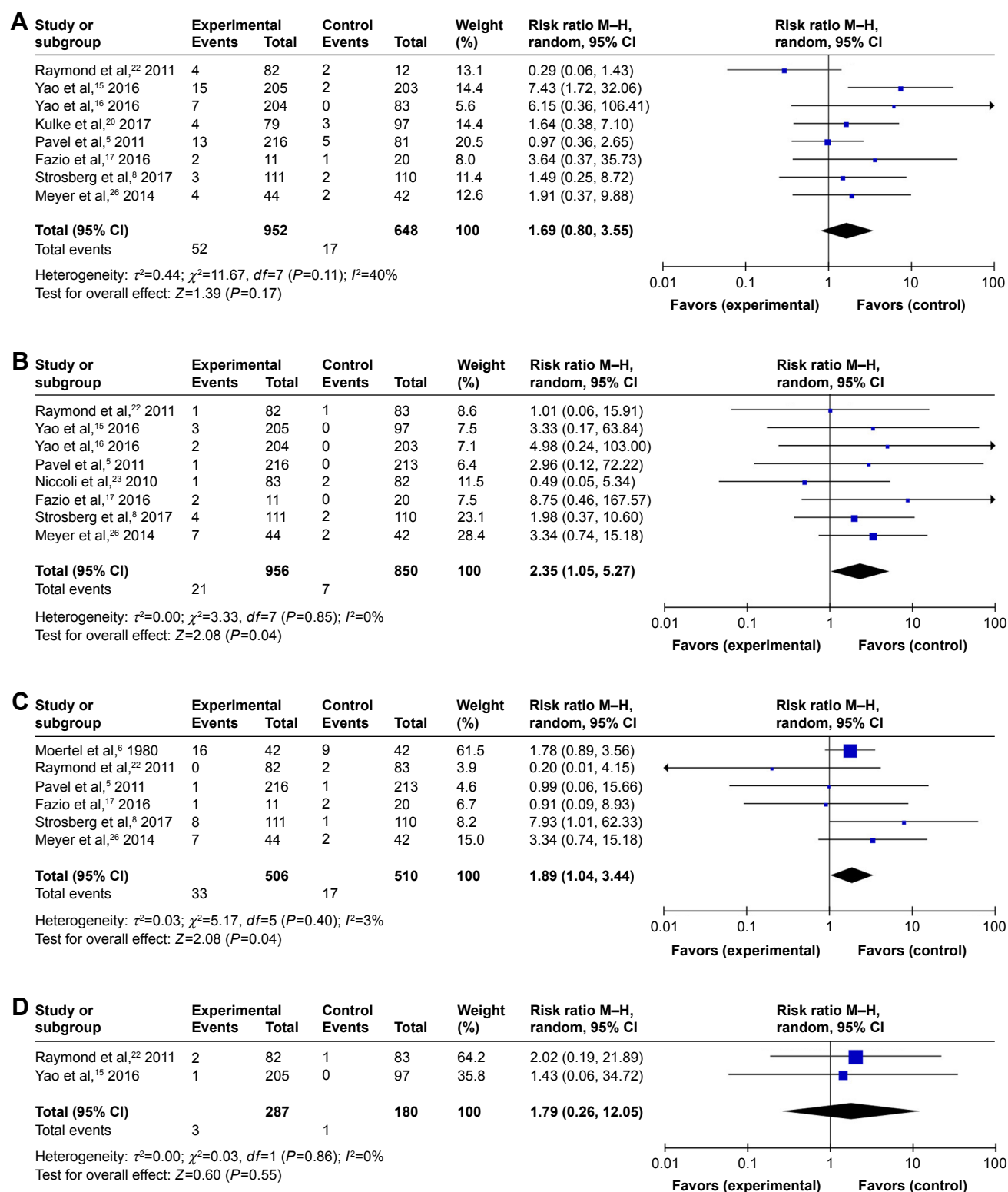


Figure 4 Relative risks of high-grade GI events associated with nonoperative therapies.

Note: (A) Relative risk associated with nonoperative therapies of high-grade (A) diarrhea, (B) nausea, (C) vomiting, and (D) anorexia.

Abbreviation: GI, gastrointestinal.

in prognostic and therapeutic decisions for patients with pancreatic NET.^{27–29} To the best of our knowledge, this is the first meta-analysis focusing specifically on GI events associated with nonoperative therapies in NET patients,

which widely include chemotherapy, molecular targeted therapy, IFN, SSAs, and PRRT. Except for patients with limited metastases who can undergo complete resection of the primary and metastatic tumors, nonoperative therapies

Table 3 Relative risks of GI events stratified by therapy regimens

Subgroup	Whole GI events						Diarrhea			
	Number of subjects		Number of events		RR (95% CI)	P-value	Number of events		RR (95% CI)	P-value
	T. arm	C. arm	T. arm	C. arm			T. arm	C. arm		
Everolimus	625	513	435	239	1.47 (1.22–1.78)	<0.0001	191	50	2.97 (1.83–4.83)	<0.0001
SSAs	259	261	106	66	1.57 (0.76–3.23)	0.22	88	63	1.43 (0.84–2.42)	0.19
Interferon- α	75	73	53	29	1.73 (1.32–2.30)	<0.0001	28	20	1.29 (0.83–2.03)	0.26
Cytotoxic drugs	86	84	NA	NA	NA	NA	19	22	0.82 (0.53)	0.39
VEGFR inhibitors	311	310	NA	NA	NA	NA	107	52	2.12 (1.39–3.25)	0.0005
Subgroup	Vomiting						Anorexia			
	Number of events		Number of events		RR (95% CI)	P-value	Number of events		RR (95% CI)	P-value
	T. arm	C. arm	T. arm	C. arm			T. arm	C. arm		
Everolimus	119	81	53	24	2.19 (1.38–3.48)	0.0009	95	27	3.20 (1.69–6.06)	0.0004
SSAs	9	4	7	0	15.29 (0.88–264.31)	0.06	1	1	0.75 (0.05–10.82)	0.83
Interferon- α	13	7	12	3	3.78 (1.13–12.62)	0.03	NA	NA	NA	NA
Cytotoxic drugs	63	62	63	62	1.00 (0.85–1.17)	0.97	NA	NA	NA	NA
VEGFR inhibitors	56	36	56	39	1.38 (0.71–2.68)	0.35	48	40	1.19 (0.83–1.70)	0.34

Abbreviations: C. arm, control arm; GI, gastrointestinal; NA, not available; SSAs, somatostatin analogs; T. arm, treatment arm.

are the main recommendation for patients with locoregional advanced NETs or distant metastases.¹

As most NETs upregulate the receptors of somatostatin (a peptide hormone), treatment with synthetic SSAs leads to obvious improvements in hormone-related symptoms and inhibits tumor growth.^{30,31} However, the expression of somatostatin receptors in the GI tract and pancreas can lead to significant disturbances in homeostasis induced by SSA treatment, as exemplified by the frequent occurrence of diarrhea in NET patients treated with the SSA lanreotide.²¹ In addition, targeted therapies (eg, everolimus and VEGFR inhibitors) lead to increased GI events, such as diarrhea, nausea, and vomiting.^{5,22} Cytotoxic chemotherapeutic agents (eg, doxorubicin and capecitabine), which are Category 3 recommendations for the treatment of NETs, can also markedly increase the frequency of diarrhea.^{32,33} Thus, GI events caused by these therapies can attenuate their pro-survival benefits and even lead to treatment discontinuation.⁵ Furthermore, diarrhea is one of the most common syndromes in NET patients with carcinoid syndrome. Before providing nonoperative therapies for NETs, pre-management of potential GI events with the conditions of nonoperative therapies should be ensured to promote patients' quality of life. However, the contribution of nonoperative therapies to the development of GI events is difficult to define when only individual RCTs are available, because they are not powered to clarify significant relationships.

This study pooled data from 17 RCTs to address the limited power of individual RCTs, and we found that nonoperative therapies generally increase the incidences and risks of GI events in NET patients. The RRs of diarrhea, nausea, vomiting, and anorexia associated with nonoperative therapies were 1.55 (95% CI 1.21–1.98), 1.55 (95% CI 1.14–2.10), 1.79 (95% CI 1.14–2.10), and 1.87 (95% CI 1.22–2.87), respectively. Among them, diarrhea was the most common GI event (33.1%), and anorexia was the least common GI event (16.6%) in the experimental groups. These results were largely consistent with the reported rates of GI events in several double-blind RCTs that tested sunitinib, everolimus, and SSAs in NET patients.^{5,21,22} Because high-grade adverse events often lead to therapy termination, we also evaluated the risks of high-grade GI events associated with nonoperative therapies. The data showed that the differences in the risks of high-grade diarrhea and anorexia between the experimental and control arms were not significant, whereas there were slight increases in the risks of high-grade nausea and vomiting.

When stratified by therapeutic regimen, it was more likely to be referred by physicians concerning the optimal

Table 4 Relative risks of GI events stratified by tumor sites

Subgroup	Diarrhea					Nausea				
	Number of subjects		Number of events		RR (95% CI)	P-value	Number of events		RR (95% CI)	P-value
	T. arm	C. arm	T. arm	C. arm			T. arm	C. arm		
Pancreatic NET	647	656	231	132	1.77 (1.13–2.79)	0.01	112	86	1.39 (0.92–2.10)	0.12
Gastrointestinal NET	358	250	69	22	1.66 (1.05–2.63)	0.03	37	12	1.57 (0.84–2.94)	0.15
Gastroenteropancreatic NET	415	409	95	60	1.56 (0.89–2.75)	0.12	92	69	1.28 (0.88–1.87)	0.20

Subgroup	Vomiting				Anorexia			
	Number of events		RR (95% CI)	P-value	Number of events		RR (95% CI)	P-value
	T. arm	C. arm			T. arm	C. arm		
Pancreatic NET	125	93	1.37 (0.88–2.13)	0.17	84	54	1.48 (0.81–2.73)	0.21
Gastrointestinal NET	52	11	4.68 (2.58–8.49)	<0.0001	32	6	2.52 (1.09–5.83)	0.03
Gastroenteropancreatic NET	70	41	2.16 (0.84–5.60)	0.11	30	14	2.08 (1.13–3.83)	0.02

Note: P-value<0.05 indicated statistical significance.

Abbreviations: C. arm, control arm; GI, gastrointestinal; NET, neuroendocrine tumor; T. arm, treatment arm.

therapy option for an individual NET patient on the basis of the precaution for GI events (especially high-grade events) during therapeutic process. Everolimus led to high risks of diarrhea, vomiting, and anorexia; IFN- α increased the risk of vomiting; VEGFR inhibitors resulted in an increased risk of diarrhea; combination chemotherapy showed no difference in GI events compared with single-drug chemotherapy. Intriguingly, SSAs led to no significant difference in the risk of diarrhea; however, a recent double-blind, placebo-controlled RCT of the SSA lanreotide suggested that the most common adverse event was diarrhea (26% in the lanreotide group and 9% in the placebo group).²¹ This discrepancy could be explained by the high heterogeneity ($I^2=78\%$) in this subgroup meta-analysis.

Furthermore, we evaluated the risks of GI events stratified by tumor site. Patients with pancreatic NET exhibited a high risk of diarrhea, without evidence of increased risk of other GI events. In addition, GI NET patients had a higher risk of diarrhea. Further, therapies significantly increased the risks of vomiting and anorexia in GI NET patients. It is reasonable to speculate that targeting therapy toward tumors in GI sites could further disturb the functions of the GI tract, resulting in enhanced risks of therapy-related GI events.

PRRT with ¹⁷⁷Lu-Dotatate was newly approved in January 2018 for the treatment of advanced and metastatic gastroenteropancreatic NETs. Studies showed that this therapy was helpful to improve symptoms and remarkably increase the progression-free survival (PFS) and overall survival (OS) in NET patients.^{8,34,35} ¹⁷⁷Lu-Dotatate showed very limited long-term toxicity, with no incidences of therapy-related renal and hepatic failure during follow-up.³⁵ However, it led to significant GI events, including nausea (59% of patients) and

vomiting (52% of patients).⁸ This finding was derived from a trial in which patients were randomly allocated to a ¹⁷⁷Lu-Dotatate plus octreotide group or an octreotide group. Future placebo-controlled RCTs are needed to research the risks of GI events posed by ¹⁷⁷Lu-Dotatate in NET patients.

Despite the number of trials included in this meta-analysis, our study has several limitations. First, it was based on data from trial reports, not on individual patient data; therefore, we were unable to clarify the confounding variables, such as comorbidities, previous therapeutic interventions, and concomitant therapies. The inherent confounders may underestimate, overestimate, or bias the direction of the risk estimates. Second, the standards for attributing various GI events were not the same across the trials; GI events were the secondary endpoints (rather than the primary endpoints) of the included trials, resulting in a great bias with regard to the reported incidence rates. Third, all of the included trials required participants to have generally adequate organ functions, which suggests that the rates of real-world GI events would be higher. Finally, the number of enrolled patients was still inadequate for a meta-analysis of SSAs- and ¹⁷⁷Lu-Dotatate-induced GI events, especially due to lack of data from placebo-controlled RCTs.

In conclusion, our findings indicate that nonoperative therapies in NET patients lead to significantly increased risks of any- and high-grade nausea and vomiting. Strikingly, everolimus led to high risks of diarrhea, vomiting, and anorexia; VEGFR inhibitors led to an increased risk of diarrhea; and GI NETs led to more GI events than pancreatic NETs. Thus, rigorous management of these adverse events is warranted to minimize adverse impacts on treatment outcomes and quality of life. Once NET patients are assigned

to systematic treatments, those who are prone to or suffering from severe GI events are eligible for treatments with lesser GI disturbance.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

A

Egger's test for diarrhea

• Metabias loger selogor, egger

Note: Data input format theta se_theta assumed.

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies=16 Root MSE= 1.76

Std_Eff	Coef.	Std. Err.	t	P> t	(95% CI)
Slope	0.2590915	0.2484044	1.04	0.315	-0.2736829 0.7918658
Bias	0.6718425	0.9858039	0.68	0.507	-1.442497 2.786182

Test of H0: no small-study effects P=0.507

B

Egger's test for nausea

• Metabias loger selogor, egger

Note: Data input format theta se_theta assumed.

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies= 14 Root MSE= 1.823

Std_Eff	Coef.	Std. Err.	t	P> t	(95% CI)
Slope	0.4915572	0.5095023	0.96	0.354	-0.618553 1.601667
Bias	0.1950709	1.220379	0.16	0.876	-2.463906 2.854048

Test of H0: no small-study effects P=0.876

C

Egger's test for vomiting

(Five missing values generated)

• Metabias logor selogor, egger

Note: Data input format theta se_theta assumed.

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies= 12 Root MSE= 1.715

Std_Eff	Coef.	Std. Err.	t	P> t	(95% CI)
Slope	0.5604197	0.6391969	0.88	0.401	-0.8637997 1.984639
Bias	0.4384769	1.31318	0.33	0.745	-2.48747 3.364424

Test of H0: no small-study effects P=0.745

D

Egger's test for anorexia

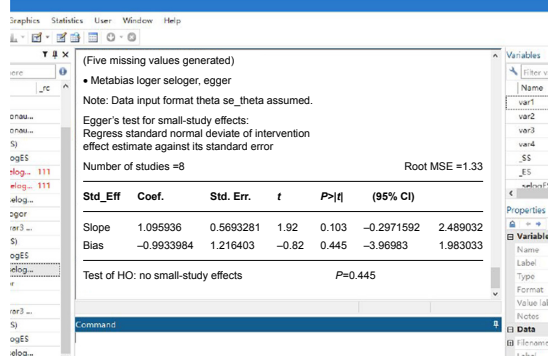


Figure S1 Begg's test for the association between nonoperative therapies and risks of GI events.

Abbreviation: GI, gastrointestinal.

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