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REVIEW

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Health-related quality of life and treatment effects in patients with well-differentiated gastroenteropancreatic neuroendocrine neoplasms: A systematic review and meta-analysis

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Abstract

Introduction: Gastroenteropancreatic neuroendocrine neoplasms (GEPNENs) are often diagnosed in an advanced stage. As the optimal sequence of therapy remains largely unclear, all treatment-related outcomes, including health-related quality of life (HRQoL) prospects, should be assessed according to patients' preferences.

Methods: A targeted search was performed in PubMed and EMBASE to identify studies on treatment effect and HRQoL, measured using the EORTC QLQ-C30 tool, in patients with advanced, well-differentiated GEPNENs. Study quality was assessed, and meta-analyses were performed for global health status/QOL and tumour response.

Results: The search yielded 1,322 records, and 20 studies were included, examining somatostatin analogues (SSA), peptide receptor radionuclide therapies (PRRT), chemotherapy, SSA-based combination therapies, and targeted therapies. Global HRQoL was stable, and rates for disease stabilisation were moderate to high across all treatments. Meta-analyses for global health status/QOL after SSA treatment were not significant (mean difference: −0.3 [95% CI: −1.3 to 0.7]). The highest pooled overall tumour response rate was 33% (95% CI: 24–45%) for PRRT. The highest pooled clinical benefit rate was 94% (95% CI: 65–99%) for chemotherapy.

Conclusion: All treatments appeared beneficial for disease stabilisation while maintaining stable global health status/QOL. High-quality HRQoL reporting was lacking. HRQoL should be a central outcome next to well-established outcomes.

KEYWORDS

adverse drug events, neoplasms, neuroendocrine tumour, quality of life, treatment, treatment outcome

1 | INTRODUCTION

Gastroenteropancreatic neuroendocrine neoplasms (GEPNENs) are heterogeneous neoplasms, originating from neuroendocrine cells in the gastrointestinal tract (Fraenkel et al., 2012; Öberg et al., 2012). Most GEPNENs are nonfunctioning neoplasms, and half of patients present with advanced disease (Hallet et al., 2015; Pavel, O'Toole, et al., 2016).

Patients with GEPNENs generally have lower HRQoL compared to the general population, due the symptoms associated with functioning tumours as well as treatment-related symptoms and adverse events (AEs) (Beaumont et al., 2012; Haugland et al., 2009; Swinburn et al., 2012). However, the life expectancy of patients with advanced disease may be several years (Dasari et al., 2017), and higher HRQoL has been shown to be associated with longer survival (Coates et al., 1997). Therefore, it is essential to explore treatment options that maintain or improve patients' HRQoL whilst extending progression-free survival (PFS).

Surgical resection with curative intent remains the preferred treatment whenever possible (Delle Fave et al., 2016; Niederle et al., 2016; Pavel, O'Toole, et al., 2016; Ramage et al., 2016). However, advanced and unresectable disease requires other treatment strategies to improve survival and maintain health-related quality of life (HRQoL). Somatostatin analogues (SSA) are currently the first-line treatment of metastatic GEPNENs (Falconi et al., 2016; Pavel, O'Toole, et al., 2016). Second- and third-line therapies include chemotherapy, targeted therapy and peptide receptor radionuclide therapy (PRRT) (Pavel, O'Toole, et al., 2016). However, the optimal sequence of therapy after first-line treatment still needs to be determined (Pavel, O'Toole, et al., 2016).

When several possible treatment options are considered, patients' preferences should play a decisive role during treatment-related shared decision-making (Oshima Lee & Emanuel, 2013). Shared decision-making involves weighing the benefits and harms of treatment options against patients' opinions and preferences (Stiggelbout et al., 2012). Therefore, clinicians need easy access to up-to-date evidence on the advantages and disadvantages of available treatment options. Moreover, the evidence needs to be comprehensive, that is, include all or nearly all important outcomes, as patients may favour HRQoL prospects over prolonged survival (Shrestha et al., 2019).

Previous systematic reviews have described HRQoL and oncological outcomes of treatments separately (Jimenez-Fonseca et al., 2015; Watson et al., 2020). However, to our knowledge, no publication has reported the effects of treatments on survival, tumour regression, adverse events and HRQoL together. This systematic review and meta-analysis is the first to summarise the overall effects of various treatment strategies in patients with GEPNENs, focusing on the validated European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) questionnaire.

2 | METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009). A systematic literature search was conducted in PubMed and EMBASE in July 2019 and was updated in June 2020 and June 2021, to identify publications on treatment effect, including HRQoL, in patients with well-differentiated GEPNENs. The search strategies were constructed with the help of a clinical librarian. A combination of free text and controlled vocabulary were included, using key-words such as neuroendocrine tumour, treatment outcome, and quality of life. The words "tumour" and "neoplasm" were both used in combination with words describing tumour type (e.g., "endocrine" or "neuroendocrine") and location (e.g., "pancreatic" and "duodenal"). The search was limited to full text publications in English. No restriction was placed on publication date. Reference lists of eligible articles were manually screened to identify additional relevant articles. A sample of our search is available in the Supporting Information.

Duplicates were removed prior to study selection. Two reviewers (ER, CH) screened all titles and abstracts against the eligibility criteria. Subsequently, full-texts of selected articles were screened for

TABLE 1 PICO table with inclusion and exclusion criteria

PICO	Inclusion criteria	Exclusion criteria
Patients	≥18 years of age Well-differentiated GEPNENs	<18 years of age Poorly differentiated GEPNENs[a] Neuroendocrine carcinomas[a] Primary tumour located outside of the gastroenteropancreatic tract[a]
Intervention	Any treatment of the primary tumour	Selective treatment of (liver) metastases Treatment focused on adverse effect alleviation (no expected anti-tumour effect)
Comparison	Any comparator (or none)	-
Outcome	HRQoL measured using the EORTC QLQ-C30 (preferably with GINET21 module) Treatment effect outcomes (e.g., tumour response, survival, adverse events)	Other HRQoL questionnaires

[a]Inclusion of less than 1% of poorly differentiated grade 3 NENs or non-GEPNENs was accepted due to the assumption of negligible influence on study results.

inclusion. A third reviewer (END) was consulted in the case of disagreement.

An overview of the in- and exclusion criteria are shown in Table 1. Inclusion criteria were (1) patients ≥18 years of age with histologically well-differentiated GEPNENs (Lloyd et al., 2017), (2) interventions focused on treating the primary tumour, and (3) treatment effect outcomes including HRQOL, measured using the EORTC QLQ-C30 questionnaire with or without the NEN-specific QLQ-GINET21 module (Davies et al., 2006; Yadegarfar et al., 2013). This questionnaire is the most frequently used questionnaire in this patient population (Jimenez-Fonseca et al., 2015; Martini et al., 2016; Watson et al., 2020). As the present review aimed to compare treatments directly, we limited study eligibility to the QLQ-C30 and the NEN-specific module, in order to minimise heterogeneity and maximise comparability. Other outcomes of interest were treatment efficacy outcomes (e.g., tumour response and survival) and adverse events. Cross-sectional studies, reviews, letters and editorials were not eligible for inclusion.

The following data were extracted using a pre-defined form: study characteristics, patient characteristics, tumour type, tumour grade according to the World Health Organization (WHO) classification (Lloyd et al., 2017), presence of metastases and outcome data. Primary outcomes were EORTC QLQ-C30 and GINET21 scores, PFS and overall survival (OS). A change of ≥10 points in HRQoL scores was considered clinically significant, which corresponds to a change reported as "moderate" (10–20 points) or "very much" (>20 points) by patients (Osoba et al., 1998; Osoba et al., 2000). The EORTC QLQ-C30 summary score was calculated if sufficient data was available, according to the EORTC scoring manual (Scoring of the QLQ-C30 Summary Score, 2018).

Secondary outcomes were overall response rate (ORR), clinical benefit (CB) and AEs, reported using a validated scale. ORR was defined as the proportion of patients with minor, partial or complete radiological response, CB was defined as the proportion of patients with radiological response (ORR) or radiological stable disease, according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines and the WHO solid tumour response criteria (Eisenhauer et al., 2009; Miller et al., 1981).

A risk of bias assessment for individual studies was performed by one reviewer (ER) using the Cochrane Risk of Bias tool for randomised-controlled trials (RCT) (Higgins et al., 2011) and the Newcastle Ottawa Scale (NOS) (Wells et al., 2013) for cohort or case–control studies. The other reviewers were consulted in case of any uncertainty. The Cochrane tool evaluates risk of bias as "low," "high" or "unclear" in 6 domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. The NOS awards a maximum of nine stars for study quality in three categories: selection (4 stars), comparability (2 stars) and exposure or outcome (3 stars), for case–control and cohort studies, respectively. The overall score is used to categorise overall study quality as high (>7 stars), moderate (5–7 stars) or low (<5 stars). Risk of bias across studies was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Handbook, rating evidence as high, moderate, low or very low quality (Schünemann et al., 2013).

Meta-analyses were performed using R for Mac version 4.0.2 via the R-studio interface, to investigate the unstandardized mean difference of HRQoL scales and to investigate the overall ORR and CB results for each treatment category (RCoreTeam, 2020). A random effects model with inverse variance weighting was used to pool these results due to expected heterogeneity. The I^2 statistic was used to measure the proportion of variance due to differences in studies, where 0% implied homogeneity and 100% heterogeneity. If the I^2 statistic was >75%, heterogeneity was considerable, and the results were unsuitable for meta-analysis. Pooled global HRQoL results are presented as mean difference with a 95% confidence interval (CI). Pooled ORR and CB results were presented as proportions with their 95% CI. Finally, results were summarised into a table that can be used as guide for treatment planning and informing patients about treatment options.

3 | RESULTS

The systematic search and cross-referencing identified 1,322 records after removal of duplicates. A review of titles and abstracts excluded 917 records. Subsequently, 407 full-text articles were assessed for eligibility, and 20 were included (Arnold et al., 2005; Caplin et al., 2014; Cwikla et al., 2010; Delpassand et al., 2014; Ducreux et al., 2014; Faivre et al., 2017; Fazio et al., 2021; Mitry et al., 2014; Pavel, Unger, et al., 2016; Phan et al., 2016; Ramage et al., 2019; Raymond et al., 2011, 2018; Rinke et al., 2009, 2017, 2019; Strosberg et al., 2017, 2018, 2020; Vinik et al., 2016). The study selection process is shown in Figure 1. Five publications reported further results of previously published studies: two published long-term survival results (Faivre et al., 2017; Rinke et al., 2017); one reported tumour response outcomes of the CLARINET trial (Phan et al., 2016); one published HRQoL results from the NETTER-1 trial (Strosberg et al., 2018); and one published updated efficacy and safety results (Fazio et al., 2021). Furthermore, two publications reported post-hoc HRQoL analyses (Rinke et al., 2019; Vinik et al., 2016) and one reported on the impact of liver tumour burden in the NETTER-1 trial (Strosberg et al., 2020). These studies were analysed in combination with the original publication. In summary, 20 publications reporting on 12 study populations and 1,256 patients with well-differentiated GEPNENs were included. Out of these 12 study populations, five were randomised-controlled trials (RCT) (Arnold et al., 2005; Caplin et al., 2014; Raymond et al., 2011; Rinke et al., 2009; Strosberg et al., 2017), and seven were cohort populations (Cwikla et al., 2010; Delpassand et al., 2014; Ducreux et al., 2014; Mitry et al., 2014; Pavel, Unger, et al., 2016; Ramage et al., 2019; Raymond et al., 2018). The included studies reported on the SSAs

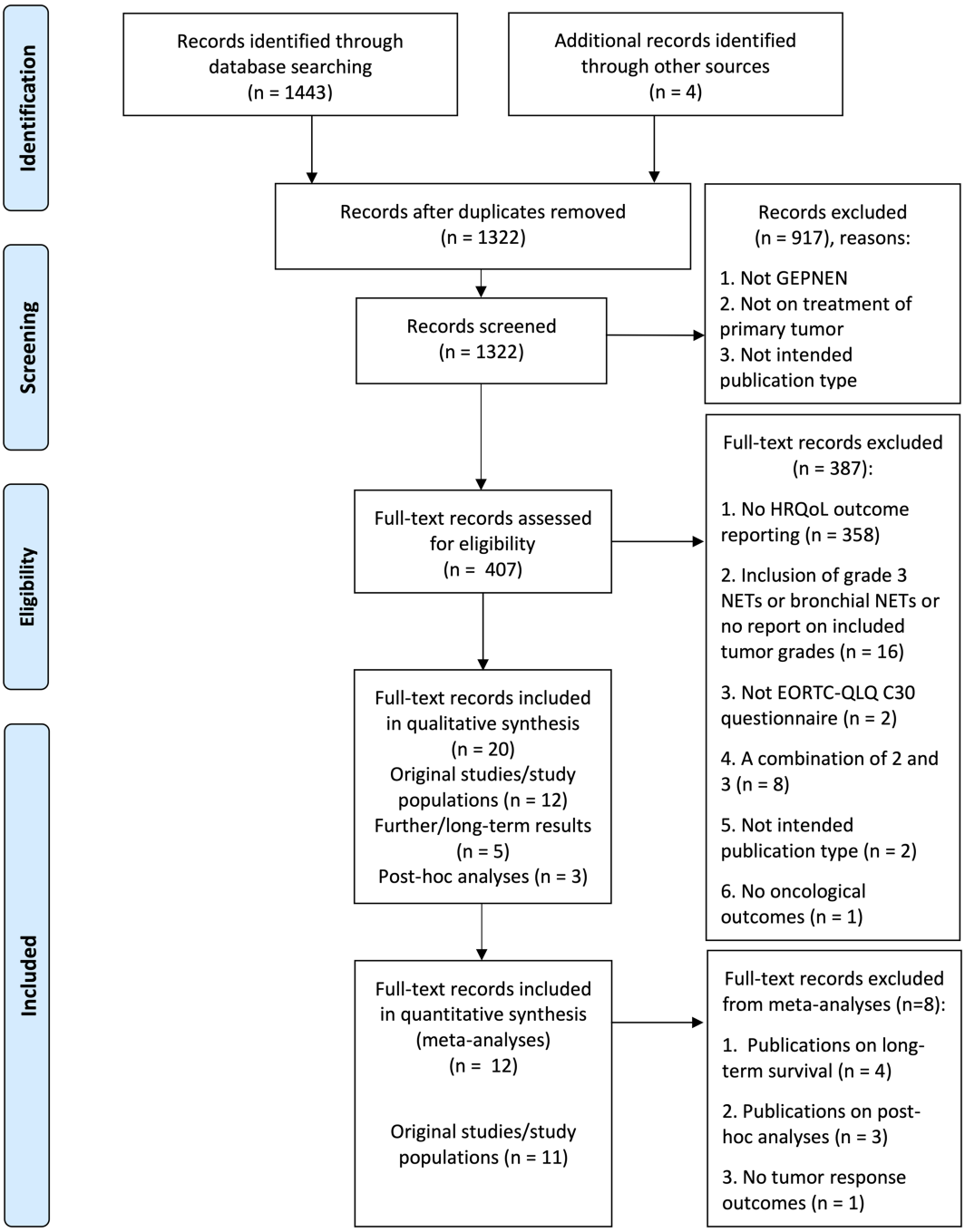

FIGURE 1 Prisma flow diagram of study identification and selection process

octreotide or lanreotide (Caplin et al., 2014; Rinke et al., 2009), the PRRTs ^{90}Y-DOTATATE or ^{177}Lu-DOTATATE (Cwikla et al., 2010; Delpassand et al., 2014), the chemotherapy modalities bevacizumab and capecitabine (Mitry et al., 2014) or bevacizumab combined with 5-fluorouracil and streptozocin (Ducreux et al., 2014), the targeted therapies sunitinib or everolimus (Pavel, Unger, et al., 2016; Ramage et al., 2019; Raymond et al., 2011, 2018) or a combination of two of these treatment modalities (Arnold et al., 2005; Strosberg et al., 2017). Detailed study characteristics are presented in Table 2.

3.1 | Risk of bias assessment outcomes

Only one RCT was considered having a "low" risk of bias (Caplin et al., 2014). All other RCT's had "unclear" or "high" risk of bias associated with one or more domains in the Cochrane Risk of Bias tool, shown in Figure 2 (Arnold et al., 2005; Raymond et al., 2011; Rinke et al., 2009; Strosberg et al., 2017). Five cohort studies were awarded a "moderate" quality rating (5 stars) (Ducreux et al., 2014; Mitry et al., 2014; Pavel, Unger, et al., 2016; Ramage et al., 2019;

TABLE 2 Study characteristics

SSA therapies							
First author	**Year**	**Type of study**	**Study treatment**	**Number of patients**	**Included tumour types**	**Included tumour grades**	**Outcomes reported**
Rinke	2009	Phase IIIb RCT PROMID trial	Octreotide LAR vs. placebo	42 vs. 43	All midgut NETs	Ki-67 ≤ 2%: 97.6% vs. 93.0% Ki-67 > 2%: 2.4% vs. 7.0%[a]	PFS, OS, tumour response, adverse events, global health status/QOL[b]
Caplin	2014	Phase IIIb RCT CLARINET trial	Lanreotide autogel vs. placebo	101 vs. 103	Pancreas (91), midgut (73), hindgut (14), unknown (26)	Ki-67 ≤ 2%: 68% vs. 70% Ki 67 3%–10%: 32% vs. 28% Missing data: 0% and 2%	PFS, OS, adverse events, all EORTC QLQ-C30 and GINET21 scales[c]
Phan	2016	Phase IIIb RCT CLARINET trial	Lanreotide autogel vs. placebo	101 vs. 103	Reported by Caplin et al., 2014		Tumour response
Rinke	2017	Phase IIIb RCT PROMID trial	Octreotide LAR vs. placebo	42 vs. 43	Reported by Rinke et al., 2009		Long-term PFS, long-term OS
Rinke	2019	Phase IIIb RCT PROMID trial (post-hoc analysis)	Octreotide LAR vs. placebo	42 vs. 43	Reported by Rinke et al., 2009		Time to definitive deterioration (all EORTC QLQ-C30 scales)
PRRT therapies							
First author	Year	Type of study	Study treatment	Number of patients	Included tumour types	Included tumour grades	Outcomes reported
Cwikla	2010	Phase II	^{90}Y-DOTATATE	60	Foregut (25), midgut (29), unknown (6)	Grades 1 and 2 (proportions unknown)	PFS, OS, tumour response, adverse events, EORTC QLQ-C30 and GINET items: Diarrhoea, flushing[d]
Delpassand	2014	Phase II	^{177}Lu-DOTATATE	37	Pancreas (14), small bowel (12), rectum (3), large bowel (1), unknown (7)	Grades 1 and 2 (proportions unknown)	PFS, tumour response, adverse events, EORTC QLQ-C30 items: Overall QOL, stamina for daily activities, diarrhoea[d]
SSA combination therapies							
Author	Year	Type of study	Study treatment	Number of patients	Included tumour types	Included tumour grades	Outcomes reported
Arnold	2005	RCT	Octreotide vs. octreotide and INFa	51 vs. 54	Foregut (pancreas) (40), midgut (45), unknown (20)	Ki-67 ≤ 2%: 55.2% Ki-67 > 2%: 44.8% (67 evaluable patients at baseline)	PFS, OS, tumour response, adverse events, global health status/QOL[b]

(Continues)

TABLE 2 (Continued)

SSA therapies							
First author	**Year**	**Type of study**	**Study treatment**	**Number of patients**	**Included tumour types**	**Included tumour grades**	**Outcomes reported**
Strosberg	2017	Phase III RCT NETTER-1 trial	^{177}Lu-DOTATATE and octreotide LAR vs. high dose octreotide LAR	116 vs. 113	Ileum (168), small intestine, not otherwise specified (23), midgut not otherwise specified (16), jejunum (15), right colon (4), appendix (3)	Grade 1: 66% vs. 72% Grade 2: 35% vs. 28%	PFS, OS, tumour response[e], adverse events
Strosberg	2018	Phase III RCT NETTER-1 trial	^{177}Lu-DOTATATE and octreotide LAR vs. high dose octreotide LAR	117 vs. 114[f]	Ileum (168), small intestine, not otherwise specified (23), midgut not otherwise specified (16), jejunum (15), right colon (4), appendix (3)	Unknown for larger cohort[a]	Time to deterioration (all EORTC QLQ-C30 scales)
Strosberg	2020	Phase III RCT NETTER-1 trial	^{177}Lu-DOTATATE and octreotide LAR vs. high dose octreotide LAR	117 vs. 114[f]	Ileum (168), small intestine, not otherwise specified (23), midgut not otherwise specified (16), jejunum (15), right colon (4), appendix (3)	Unknown for larger cohort[a]	PFS, HRQoL, hepatic toxicity and live lesion shrinkage by extent of liver tumour burden
Chemotherapies							
First author	Year	Type of study	Study treatment	Number of patients	Included tumour types	Included tumour grades	Outcomes reported
Mitry	2014	Phase II BETTER trial	Bevacizumab and capecitabine	49	Small intestine (40), caecum (3), stomach (2)	Ki-67 ≤ 2%: 35% Ki-67 < 15%: 64% Missing: 1%	PFS, OS, tumour response, adverse events, global health status/QOL
Ducreux	2014	Phase II BETTER trial	Bevacizumab and 5-FU/ streptozocin	34	Pancreas (33), duodenopancreatic tumour (1)	Grade 1: 25% Grade 2: 75%	PFS, OS, tumour response, adverse events, global health status/QOL[d]
Targeted therapies							
First author	Year	Type of study	Study treatment	Number of patients	Included tumour types	Included tumour grades	Outcomes reported
Raymond	2011	Phase III RCT	Sunitinib vs. placebo	86 vs. 85	All pancreas	Ki-67 ≤ 2%: 19% vs. 17% Ki-67 > 2%–10%: 58% vs. 67% Ki-67 > 10%: 22% vs. 17%[a]	PFS, OS, tumour response, adverse events, all EORTC QLQ-C30 scales[d]
Vinik	2016	Phase III RCT (post-hoc analysis)	Sunitinib vs. placebo	73 vs. 71 (from Raymond 2011)	All pancreas	Proportions unknown for smaller cohort[a]	Time to deterioration (all EORTC QLQ-C30 scales)

TABLE 2 (Continued)

SSA therapies							
First author	**Year**	**Type of study**	**Study treatment**	**Number of patients**	**Included tumour types**	**Included tumour grades**	**Outcomes reported**
Pavel	2016	Phase III b	Everolimus	126	All pancreas	Well differentiated: 64.3% Moderately differentiated: 20.6% Poorly differentiated: 0.8%[g] Unknown/missing: 14.3%	PFS, tumour response, adverse events, all EORTC QLQ-C30 and GINET21 scales[d]
Faivre	2017	Phase III RCT	Sunitinib vs. placebo	86 vs. 85	Published by Raymond et al. (2011)		Long-term PFS, long-term OS
Raymond	2018	Phase IV	Sunitinib	106	All pancreas	All well-differentiated	PFS, OS, tumour response, adverse events, all EORTC QLQ-C30 and GINET21 scales
Raymond	2018	Phase IV	Sunitinib	106	All pancreas	All well-differentiated	OS, tumour response, adverse events
Ramage	2019	Phase IV OBLIQUE study	Everolimus	48 (safety)/46 (full analysis)	All pancreas	Grade 1: 33% Grade 2: 52% Grade 3: 0.02%[g] Unknown: 13%[a]	PFS, OS, tumour response, adverse events, all EORTC QLQ-C30 and GINET21 scales

Abbreviations: SSA, somatostatin analogues; PRRT, peptide receptor radionuclide therapy; RCT, randomised-controlled trial; PFS, progression-free survival; OS, overall survival; HRQoL, health-related quality of life; QOL, quality of life.

[a]All included tumours are described as well-differentiated.

[b]Reported as "global QOL" and scored on 0 (worst) to 100 (best) scale and therefore assumed to represent global health status/QOL scale.

[c]Baseline scores for quality of life scales/items not reported.

[d]Scores for scales/items not reported.

[e]Proportion of patients with stable disease not reported.

[f]No description of additional two patients included in cohort compared to Strosberg et al. (2017) ($n = 229$).

[g]Inclusion of ≤1% of poorly differentiated NETs was accepted due to the assumption of negligible interference.

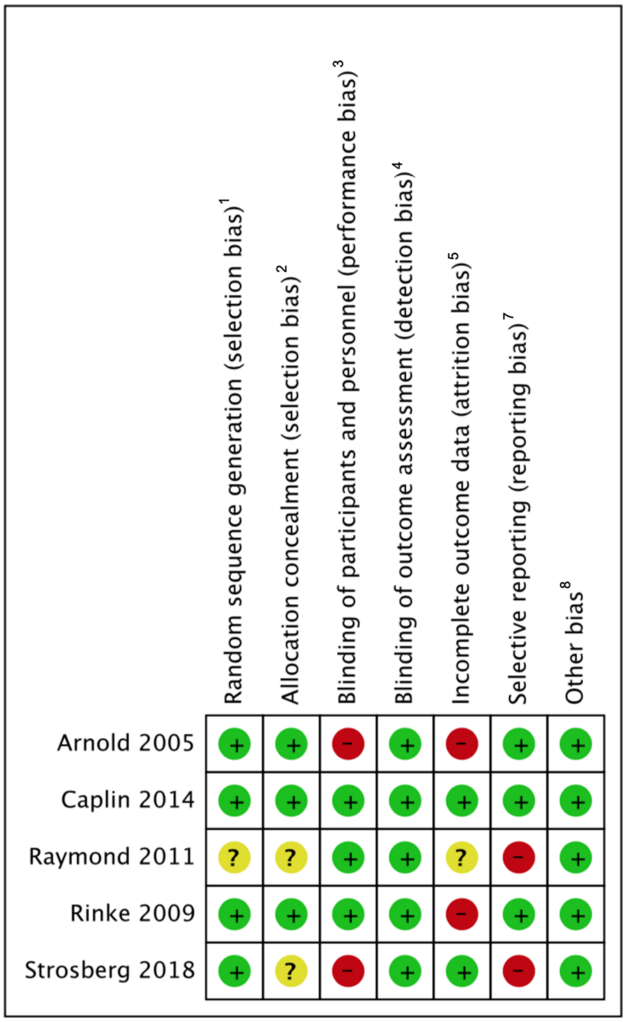

FIGURE 2 Risk of bias summary for each RCT. (1) *Random sequence of generation:* "unclear" risk of bias allocated to one study for lacking description of sequence generation; (2) *Allocation of concealment:* "unclear" risk of bias allocated to two studies for lacking description of concealment allocation; (3) *Blinding of participants and personnel:* "high" risk of bias allocated to two studies for incomplete blinding of participants due to subsequent high risk of bias associated with any patient-reported outcomes (HRQoL). Strosberg et al. did not explicitly describe blinding of participants, but treatment administration protocols differed greatly between treatment groups, and therefore any blinding was deemed inadequate; (4) *Blinding of outcome assessment:* a "low" risk of bias was awarded to all studies for adequate blinding; (5) *Incomplete outcome data:* "high" risk of bias was allocated to two studies for low HRQoL follow up numbers. An "unclear" risk of bias was allocated to one study for lacking "lost to follow up" reasons; (6) *Selective reporting:* "high" risk of bias awarded to one study for not reporting CB outcomes and for insufficient HRQoL result reporting. Caplin et al. did not report baseline QoL scores, but reported HRQoL change scores for all categories of both QoL scales and was therefore awarded a "low" risk of bias; (7) No other sources of bias were identified

Raymond et al., 2018) and two studies a "low" quality rating (4 stars) (Cwikla et al., 2010; Delpassand et al., 2014) using the NOS (Table 3).

3.2 | Outcome reporting

Six studies measured HRQoL using the EORTC QLQ-C30 in combination with the NEN symptom-specific QLQ-GINET21 module (Caplin et al., 2014; Cwikla et al., 2010; Pavel, Unger, et al., 2016; Ramage et al., 2019; Raymond et al., 2018; Strosberg et al., 2018), and six studies used only the EORTC QLQ-C30 questionnaire (Arnold et al., 2005; Delpassand et al., 2014; Ducreux et al., 2014; Mitry et al., 2014; Raymond et al., 2011; Rinke et al., 2009). Four studies reported complete data on the global health status/QOL, functional and symptom scales (Ramage et al., 2019; Raymond et al., 2018; Rinke et al., 2019; Vinik et al., 2016), one study reported change scores for all scales without providing baseline data (Caplin et al., 2014), and one study published results of a time to deterioration (TTD) analysis for all scales without providing change from baseline or final visit scores (Strosberg et al., 2018). Two studies reported results of all scales without providing supporting data (Pavel, Unger, et al., 2016; Raymond et al., 2011). Furthermore, two studies reported quantitative results of the global health status/QOL scale alone (Arnold et al., 2005; Mitry et al., 2014), one study described results of this scale alone without providing data (Ducreux et al., 2014) and two reported qualitative results of individual items (Cwikla et al., 2010; Delpassand et al., 2014). All included studies reported results on median PFS, and 10 studies on OS (Arnold et al., 2005; Caplin et al., 2014; Cwikla et al., 2010; Ducreux et al., 2014; Mitry et al., 2014; Ramage et al., 2019; Raymond et al., 2011, 2018; Rinke et al., 2009; Strosberg et al., 2017). Overall response rate was reported in all but one study (Ramage et al., 2019), and clinical benefit was reported in 10 studies (Arnold et al., 2005; Caplin et al., 2014; Cwikla et al., 2010; Delpassand et al., 2014; Ducreux et al., 2014; Mitry et al., 2014; Pavel, Unger, et al., 2016; Raymond et al., 2011, 2018; Rinke et al., 2009). All studies reported on AEs: two using the WHO scale (Arnold et al., 2005; Cwikla et al., 2010), two using the Medical Dictionary for Regulatory Activities (Caplin et al., 2014; Ramage et al., 2019), one using the WHO criteria or the National Cancer Institute Common Toxicity Criteria (version 2.0) (Rinke et al., 2009), four using the Common Terminology Criteria for Adverse events version 3.0 (Ducreux et al., 2014; Mitry et al., 2014; Raymond et al., 2011, 2018), two using version 4.03 (Delpassand et al., 2014; Strosberg et al., 2017) and one using version 4.0 (Pavel, Unger, et al., 2016). Detailed results on PFS, OS, tumour response rates and AEs are presented in Table 4.

3.3 | SSA therapy outcomes

Five publications on two randomised and placebo-controlled trials reported solely on SSA therapies: the CLARINET trial on lanreotide (Caplin et al., 2014; Phan et al., 2016) and the PROMID trial on octreotide LAR (Rinke et al., 2009, 2017, 2019).

A meta-analysis revealed no statistically significant mean difference in global health status/QOL between intervention and

TABLE 3 Newcastle Ottawa scale—Quality assessment for cohort studies

Author	Selection (max. 4)[a]	Comparability (max. 2)[b]	Exposure/outcome (max. 3)[c]	Overall quality[d]
Cwikla et al. (2010)	★★	-	★★	**Low**
Delpassand et al. (2014)	★★	-	★★	**Low**
Mitry et al. (2014)	★★★	-	★★	**Moderate**
Ducreux et al. (2014)	★★★	-	★★	**Moderate**
Pavel (2014)	★★	-	★★★	**Moderate**
Raymond et al. (2018)	★★★	-	★★★	**Moderate**
Ramage et al. (2019)	★★★	-	★★★	**Moderate**

[a]All studies received a star for "representativeness of the exposed cohort" and "ascertainment of exposure" each. None of the studies received a star for "selection of the non-exposed cohort", since control groups were not included. Three studies failed to receive a third star for "demonstration that the outcome of interest was not present at the start of the study" due missing HRQoL baseline scores.
[b]No stars awarded (none of the studies included a control group).
[c]All studies received a star for "assessment of outcome" and length of follow up each. Four studies failed to receive a star for "adequacy of follow up of cohorts" due to low follow-up numbers for HRQoL.
[d]Overall study quality: high (>7 stars), moderate (5–7 stars), low (<5 stars).

placebo arms (−0.3 [95% CI: −1.3–0.7], test for subgroup differences: $I^2 = 0\%$, $p = 0.63$, Figure 3). Furthermore, changes in functional and symptom scales were not clinically or statistically significant between treatment arms in the CLARINET trial. In the PROMID trial, scores for the fatigue, insomnia and pain scales statistically favoured the octreotide LAR arm, though individually, scores were not clinically significant (Table 5). Furthermore, time to definitive deterioration (TDD), defined as the time to a deterioration of ≥10 points with no further improvement, was significantly longer for fatigue, pain and insomnia, favouring the octreotide LAR arm (Rinke et al., 2019). Summary scores could only be calculated for the PROMID trial, and did not show a clinically significant change (Table 6).

The proportion of grade 3–4 AEs were similar in intervention and placebo arms. Both trials reported positive effects on disease progression as median PFS was significantly longer in both lanreotide and octreotide arms when compared to placebo. However, neither treatment resulted in a longer median OS when compared to placebo (Table 4).

Tumour response outcomes, including the octreotide and octreotide LAR control groups from the combination studies by Arnold et al. (2005) and Strosberg et al. (2017), respectively, were pooled ($I^2 = 0\%$) (Phan et al., 2016; Rinke et al., 2009). Pooled ORR was 2% (95% CI: 1–5%), Figure 4a. Due to statistical heterogeneity, a meta-analysis on clinical benefit rates could not be performed ($I^2 = 93\%$). Individual CB rates after SSA therapy are shown in Figure S2a. Strosberg et al. (2017) did not publish data on CB.

3.4 | PRRT outcomes

Two cohort studies reported on the PRRT therapies ^{90}Y-DOTATATE (Cwikla et al., 2010) and ^{177}Lu-DOTATATE (Delpassand et al., 2014), respectively. Delpassand et al. (2014) described a significant improvement in overall quality of life from baseline ($p < 0.05$), as well as a significant improvement in stamina for daily activities and diarrhoea after ^{177}Lu-DOTATATE therapy. (Cwikla et al., 2010) found ^{90}Y-DOTATATE therapy to reduce diarrhoea in 53%, abdominal pain in 63% and flushing in 75% of patients (Table 5).

Neither study reported overall rates of grade 3–4 AEs. However, hematologic AEs were the most common grade 3–4 AEs in both studies and occurred in 33% and 12.5% of patients under ^{90}Y-DOTATATE and ^{177}Lu-DOTATATE therapies, respectively. Both studies reported similar median PFS results: 17 months under ^{90}Y-DOTATATE therapy and 16.1 months under ^{177}Lu-DOTATATE. Median OS was 22 months after ^{90}Y-DOTATATE therapy (Table 4).

The pooled ORR was 33% (95% CI: 24–45%) (Figure 4b). Due to heterogeneity, a meta-analysis on clinical benefit could not be performed ($I^2 = 76\%$). Individually, CB rates are presented in Figure S2b.

3.5 | SSA combination therapy outcomes

Four studies on two populations published results on SSA combinations (Arnold et al., 2005; Strosberg et al., 2017, 2018; Strosberg et al., 2020). Results of the NETTER-1 trial, a RCT on ^{177}Lu-DOTATATE and octreotide LAR combination treatment versus high dose octreotide LAR alone, were published in three separate studies (Strosberg et al., 2017, 2018, 2020). TTD, defined as the time to a deterioration of ≥10 points, and TDD were significantly improved in the ^{177}Lu-DOTATATE/octreotide arm in the global health status/QOL, physical functioning, role functioning, diarrhoea, pain, body image and disease-related worries scales (Table 5). TDD was further delayed in the emotional functioning, social functioning, insomnia, appetite loss, constipation, gastrointestinal symptoms and treatment-related symptoms scales. However, grade 3–4 AEs occurred more frequently in the ^{177}Lu-DOTATATE/octreotide arm, compared to the octreotide LAR arm (41% vs. 33%; $p < 0.05$).

TABLE 4 Survival, response, and adverse events results

SSA therapies						
Study	**Study treatment**	**PFS (months)**	**OS (months)**	**ORR (%)**	**CB (%)**	**G3/4 AEs (%)**
Rinke 2009 2017 2019	Octreotide LAR vs. placebo	14.3 vs. 6.0***	84.3 vs. 83.7 NS	2.4 vs. 2.3	69.0 vs. 39.5	26 vs. 23 NS
Caplin 2014 Phan 2016	Lanreotide autogel vs. placebo	Not reached vs. 18***	Not reached	2.0 vs. 0.0	66.3 vs. 42.7	25 vs. 32 NS
PRRT						
Study	Study treatment	PFS (months)	OS (months)	ORR (%)	CB (%)	G3/4 AEs (%)
Cwikla 2010	^{90}Y-DOTATATE	17	22	24.9	90.7	-
Delpassand 2014	^{177}Lu-DOTATATE	16.1	-	31.3	71.9	-
SSA combination therapies						
Study	Study treatment	PFS (months)	OS (months)	ORR (%)	CB (%)	G3/4 AEs (%)
Arnold 2005	Octreotide vs. octreotide and INFa	6 vs. 6	32 vs. 54 NS	2.0 vs. 9.3	17.7 vs. 24.1	-
Strosberg 2017 2018	^{177}Lu-DOTATATE and octreotide LAR vs. high dose octreotide LAR	Not reached vs. 8.4***	Not reached	18 vs. 3*	-	41 vs. 33*
Chemotherapies						
Study	Study treatment	PFS (months)	OS (months)	ORR (%)	CB (%)	G3/4 AEs (%)
Mitry 2014	Bevacizumab and capecitabine	23.4	Not reached	18.4	87.8	84
Ducreux 2014	Bevacizumab and 5-FU/streptozocin	23.7	Not reached	55.9	100	65
Targeted therapies						
Study	Study treatment	PFS (months)	OS (months)	ORR (%)	CB (%)	G3/4 AEs (%)
Raymond 2011 Vinik 2016 Faivre 2016	Sunitinib malate vs. placebo	11.4 vs. 5.5***	38.6 vs. 29.1 NS	9.3 vs. 0.0	72.1 vs. 60.0	-
Pavel 2016	Everolimus	7.6	-	1.6	60.3	41.2
Raymond 2018 Raymond 2020	Sunitinib	13.2	54.1	24.5/21.7¶¶	89.6§§	50
Ramage 2019	Everolimus	25.1‡‡	Not reached	-	-	7.5

Abbreviations: SSA, somatostatin analogues; PRRT, peptide receptor radionuclide therapy; PFS, progression-free survival; OS: overall survival; ORR, overall response rate; CB, clinical benefit; G3–4 AE, grade 3–4 adverse events; TD, treatment discontinuations due to adverse events; NS, not significant; NR, significance not reported; S, reported as "significant", but statistical significance unclear.

[a]All baseline global health values are stated as mean ± standard error, unless otherwise stated.

[b]Change in global health values are stated as mean change, mean change ± standard error or mean change (95% CI).

[c]"Quit voluntarily" (unclear whether AE related).

[d]16% of patients discontinued bevacizumab and 24% of patients discontinued capecitabine due to AEs.

[e]HRQoL results were not presented for the whole population.

[f]Disease progression assessed by investigator based on clinical and/or radiological findings.

[g]ORR updated by independent assessment. Updated data not given for clinical benefit.

[h]ORR was 21.7% in the independent third-party assessment; data only given in percentage.

*$p < 0.05$.

**$p < 0.01$.

***$p < 0.001$.

****$p < 0.0001$.

TABLE 4 Continued

SSA therapies				
Study	**Most common G3/4 AEs intervention arm (%)**	**Most common G3/4 AEs control arm (%)**	**TD (%)**	**AE-related deaths (%)**
Rinke 2009 2017 2019	Fatigue and fever 19; GI tract symptoms 14	Fatigue and fever 5; GI tract symptoms 19	11.9 vs. 0.0	0 vs. 0
Caplin 2014 Phan 2016	GI disorders 16; infections 11	GI disorders 19 infections 8	3 vs. 3	-
PRRT				
Study	Most common G3/4 AEs intervention arm (%)	Most common G3/4 AEs control arm (%)	TD (%)	AE-related deaths (%)
Cwikla 2010	Hematologic 33; renal 3	-	13	-
Delpassand 2014	Hematologic 12.5; hepatic 9.4	-	13.5 §	0
SSA combination therapies				
Study	Most common G3/4 AEs intervention arm (%)	Most common G3/4 AEs control arm (%)	TD (%)	AE-related deaths (%)
Arnold 2005	-	-	3.9 vs. 20.4	0 vs. 0
Strosberg 2017 2018	Lymphopenia 9; vomiting 7;	Abdominal pain 5; decreased appetite 3	5 vs. 0	0
Chemotherapies				
Study	Most common G3/4 AEs intervention arm (%)	Most common G3/4 AEs control arm (%)	TD (%)	AE-related deaths (%)
Mitry 2014	Hypertension 31, diarrhoea 14	-	16/24	4
Ducreux 2014	Hypertension 21; abdominal pain 12	-	47	3
Targeted therapies				
Study	Most common G3/4 AEs intervention arm (%)	Most common G3/4 AEs control arm (%)	TD (%)	AE-related deaths (%)
Raymond 2011 Vinik 2016 Faivre 2016	Neutropenia 12; hypertension 10	Abdominal pain 10; back pain 8	17 vs. 8	1 vs. 1
Pavel 2016	Hyperglycemia 6.5; infections 5.7	-	17.1	0
Raymond 2018 Raymond 2020	Neutropenia 20.8; thrombocytopenia 7.5	-	9.4	0
Ramage 2019	Mucosal inflammation 10.4; diarrhoea 4.2	-	48	0

Abbreviations: SSA, somatostatin analogues; PRRT, peptide receptor radionuclide therapy; PFS, progression-free survival; OS: overall survival; ORR, overall response rate; CB, clinical benefit; G3–4 AE, grade 3–4 adverse events; TD, treatment discontinuations due to adverse events; NS, not significant; NR, significance not reported; S, reported as "significant", but statistical significance unclear.

[a]All baseline global health values are stated as mean ± standard error, unless otherwise stated.

[b]Change in global health values are stated as mean change, mean change ± standard error or mean change (95% CI).

[c]"Quit voluntarily" (unclear whether AE related).

[d]16% of patients discontinued bevacizumab and 24% of patients discontinued capecitabine due to AEs.

[e]HRQoL results were not presented for the whole population.

[f]Disease progression assessed by investigator based on clinical and/or radiological findings.

[g]ORR updated by independent assessment. Updated data not given for clinical benefit.

[h]ORR was 21.7% in the independent third-party assessment; data only given in percentage.

$^{*}p < 0.05$. $^{**}p < 0.01$. $^{***}p < 0.001$.

$^{****}p < 0.0001$.

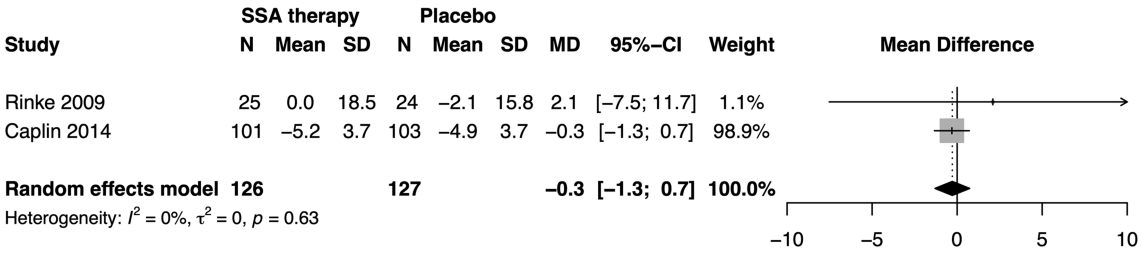

FIGURE 3 Forest plot of mean difference in global health for SSA therapies

Grade 3–4 haematological AEs occurred in 13% of patients in the combination arm. Furthermore, the median PFS was significantly longer in the combination arm (not reached in 30 months vs. 8.4 months, $p < 0.001$). Furthermore, in a post-hoc analysis, PFS benefit was not dependent on liver tumour burden (Strosberg et al., 2020). The combination of ^{177}Lu-DOTATATE and octreotide LAR resulted in an ORR of 18% (95% CI: 11–27%), significantly higher than in the octreotide LAR arm ($p < 0.001$) and the pooled ORR of SSA therapies, but lower than the pooled ORR of PRRT monotherapies. Results on clinical benefit were not reported (Table 4).

A randomised trial, comparing octreotide combined with IFNa to octreotide monotherapy, found a significant difference in global health status/QOL, favouring octreotide monotherapy ($p < 0.01$) (Arnold et al., 2005). Additionally, severe AEs occurred more frequently in the octreotide/IFNa combination arm compared to the octreotide arm (statistical significance not reported). Furthermore, neither PFS nor OS differed significantly between octreotide and octreotide/IFNa arms. Arnold et al. reported an ORR of 9% (95% CI: 3–20%) in the octreotide/IFNa combination arm, not significantly differing from the pooled ORR of SSA therapies.

3.6 | Chemotherapy outcomes

Two included cohort studies reported on chemotherapy modalities: one on the combination of bevacizumab with 5-fluorouracil and streptozocin (Ducreux et al., 2014), and the other on the combination treatment of bevacizumab and capecitabine (Mitry et al., 2014).

Both studies reported non-significant changes in the global health status/QOL scale (Table 5). Grade 3–4 AEs were reported in 84% of -patients during bevacizumab and capecitabine treatment and 65% of patients during bevacizumab combined with 5-FU and streptozocin treatment. AE-related deaths occurred in 3% and 4% of patients receiving bevacizumab/5-FU/streptozocin and bevacizumab/capecitabine, respectively. Furthermore, PFS was similar (both 23 months), while OS was not reached in either study (Table 4).

Due to heterogeneity, results on overall response rates could not be pooled ($I^2 = 91\%$). Individual ORR results are shown in Figure S1a. The pooled CB rate was 94% (95% CI: 65–99%) for the chemotherapy studies (Figure 5).

3.7 | Targeted therapies outcomes

Seven studies on four populations with pancreatic NENs reported on targeted therapies: three studies published results of a randomised, placebo-controlled trial on sunitinib treatment (Faivre et al., 2017; Raymond et al., 2011; Vinik et al., 2016), one phase three trial reported on everolimus treatment (Pavel, Unger, et al., 2016) and two phase four trials evaluated the efficacy and safety of sunitinib (Fazio et al., 2021; Raymond et al., 2018) and everolimus (Ramage et al., 2019), respectively.

In the RCT, global health status/QOL did not differ significantly between sunitinib and placebo arms (Raymond et al., 2011). However, sunitinib treatment resulted in clinically worsened diarrhoea ($p < 0.001$) and statistically worsened insomnia (<10 points), when compared to placebo. Significantly delayed TTD in global health status/QOL, emotional functioning, physical functioning and constipation were found in the sunitinib arm when compared to placebo arm (Vinik et al., 2016). Similarly, stable global health status/QOL and clinically worsened diarrhoea was reported by the phase four trial on sunitinib (Raymond et al., 2018) (Table 5). Summary scores did not show clinically significant changes in any of the studies (Table 6).

Grade 3–4 AEs were more common in the sunitinib arm than in the placebo arm, and median PFS was significantly longer in the sunitinib arm (11.4 months vs. 5.5 months, $p < 0.001$) (Raymond et al., 2011). OS was similar in both groups (38.6 months vs. 29.1 months) (Faivre et al., 2017). PFS was comparable in the phase four trial, median OS was 54.1 months and grade 3–4 AEs occurred in 50% of patients (Fazio et al., 2021; Raymond et al., 2018). Neutropenia was the most common grade 3–4 AE in both the RCT and the phase four trial on sunitinib (Raymond et al., 2011, 2018).

Both studies on everolimus reported stable global health status/QOL scores (Pavel, Unger, et al., 2016; Ramage et al., 2019). Ramage et al. further reported some clinically significant changes in the physical functioning, dyspnea, constipation, disease-related worries and social functioning scales during follow-up, but none were statistically significant 6 months after treatment (Table 5). Similarly, summary scores remained stable (Table 6). Grade 3–4 AEs occurred in 41.2% and 7.5% of patients in the studies of Pavel et al. and Ramage et al., respectively. The latter reported more treatment discontinuations due to AEs than the former. Furthermore, Pavel, Unger, et al. (2016) reported the shortest PFS of 7.6 months, while Ramage et al. (2019)

TABLE 5 Health-related quality of life results

SSA therapy							
Study	**Study treatment**	**Timepoints of HRQoL measurements**	**Δ global health status/QOL**	**Δ functional scales**	**Δ symptom scales**	**Δ GINET 21 scales**	**Time to deterioration (months)**
Rinke et al. (2009, 2019)	Octreotide LAR vs. placebo	Baseline and at 12-week intervals until progression (up to 22 months)	6 months: 0.0 ± 18.5 vs. −2.1 ± 15 NS Last observation: 0.71 vs. −1.79 NS	All NCS/NS	Fatigue −1.1 vs. +9.7* Pain −8.4 vs. +4.1* Insomnia −7.6 vs. +7.3* Others NCS/NS	-	Definitive deterioration: Fatigue 18.5 vs. 6.8*** Pain NR vs. 18.2* Insomnia NR vs. 16.4** Others NS
Caplin et al. (2014)	Lanreotide autogel vs. placebo	Weeks 1, 12, 24, 36, 48, 72, and 96	−5.2 ± 3.7 vs. −4.9 ± 3.7 NS	All NCS/NS	All NCS/NS	Weight gain +14.6 vs. +12.8 NS All others NCS/NS	-
PRRT							
Study	Study treatment	Timepoints of HRQoL measurements	Δ global health status/QOL	Δ functional scales	Δ symptom scales	Δ GINET 21 scales	Time to deterioration (months)
Cwikla et al. (2010)	^{90}Y-DOTATATE	Baseline and 4–6 weeks after each cycle.	-	-	Decrease in pain (12/24 patients) and diarrhoea (10/19 patients) SNR[a]	Decrease in flushing (9/11 patients) SNR[a]	-
Delpassand et al. (2014)	^{177}Lu-DOTATATE	Baseline, after treatment and at 3-month follow-up.	Significant improvement of "overall QOL"* [a]	Significantly improved stamina for daily activities SNR[a]	Significantly decreased diarrhoea SNR[a]	-	-
SSA combination therapies							
Study	Study treatment	Timepoints of HRQoL measurements	Δ global health status/QOL	Δ functional scales	Δ symptom scales	Δ GINET 21 scales	Time to deterioration (months)
Arnold et al. (2005)	Octreotide vs. octreotide and INFa	Baseline and 3 months after start of treatment.	"Global QOL": +11.4 ± 18.6 vs. −6.4 ± 18.6**	-	-	-	-
Strosberg (2018)	^{177}Lu-DOTATATE and octreotide LAR vs. high dose octreotide LAR	Baseline and every 12 weeks until 72 weeks or progression.	-	-	-	-	Global health status: 28.8 vs. 6.1 (HR0.41, 95% CI 0.24–0.69***); Physical functioning: 25.2 vs. 11.5 (HR 0.52, 95% CI 0.30–0.89*) Diarrhoea: HR 0.47 (95% CI 0.26–0.85)* Pain: HR 0.57 (95% CI 0.34–0.94)*

(Continues)

TABLE 5 (Continued)

SSA therapy							
Study	**Study treatment**	**Timepoints of HRQoL measurements**	**Δ global health status/QOL**	**Δ functional scales**	**Δ symptom scales**	**Δ GINET 21 scales**	**Time to deterioration (months)**
							Body image: HR 0.43 (95% CI 0.23–0.80)** Disease-related worries: HR 0.57 (95% CI 0.35–0.91)*; Fatigue HR 0.6 (95% CI 0.40–0.96)* Others NS
Chemotherapies							
Study	Study treatment	Timepoints of HRQoL measurements	Δ global health status/QOL	Δ functional scales	Δ symptom scales	Δ GINET 21 scales	Time to deterioration (months)
Mitry et al. (2014)	Bevacizumab and capecitabine	At 0, 3, 6 and 12 months	6 months: −4 NS 12 months: +4 NS	-	-	-	-
Ducreux et al. (2014)	Bevacizumab and 5-FU/ streptozocin	At 0, 3, 6 and 12 months	NS[a]	-	-	-	-
Targeted therapies							
Study	Study treatment	Timepoints of HRQoL measurements	Δ global health status/QOL	Δ functional scales	Δ symptom scales	Δ GINET 21 scales	Time to deterioration (months)
Raymond et al. (2011); Vinik et al. (2016)	Sunitinib malate vs. placebo	Baseline and every 4 weeks (1 cycle). Total of 10 cycles.	5 cycles: −5.1 vs. −1.7 NS 10 cycles: −4.6 vs. −2.7 NS	5 cycles: Role −13.2 vs. −5.3 NS 10 cycles: Role −13.4 vs. −8.1 NS Others NCS/NS	5 cycles: Diarrhoea +18.6 vs. −4.1***; fatigue +10.3 vs. 2.7 NS 10 cycles: Diarrhoea: +16.8 vs. −3.4***; fatigue +11.1 vs. +4.7 NS; insomnia: +7.2 vs. −1.4* Others NCS/NS	-	Global health status: 5.5 vs. 3.5*; Emotional functioning 7.5vs. 4.7**; Physical functioning 5.5 vs. 3.5*; Constipation: 8.3 vs. 3.9*** Sensitivity analyses (PFS and death controlled): Sunitinib accelerated TTD in diarrhoea*** and dyspnea*
Pavel (2016)	Everolimus	Baseline and cycles 1, 2, and 3 (28-day intervals) and then once every three cycles (84-day intervals) until the end of treatment	−3.9 ± 21.0 SNR	All NCS[a]	All NCS[a]	All NCS[a]	-

TABLE 5 (Continued)

SSA therapy							
Study	**Study treatment**	**Timepoints of HRQoL measurements**	**Δ global health status/QOL**	**Δ functional scales**	**Δ symptom scales**	**Δ GINET 21 scales**	**Time to deterioration (months)**
Raymond et al. (2018)	Sunitinib	Baseline, first day of each cycle, until end of treatment or withdrawal (max 10 cycles)	Treatment naïve (TN): −6.0 ± 19.0 SNR Previously treated (PT): −2.2 ± 17.6 SNR	Social: −11.6 ± 26.3 (PT) SNR Others NCS	Diarrhoea: +13.3 ± 27.1 (TN) SNR, +17.4 ± 31.6 (PT) SNR Others NCS	Disease-related worries: −11.1 ± 29.2 (PT) SNR; sexual function −12.1 ± 34.2 (PT) SNR Others NCS	-
Ramage et al. (2019)	Everolimus	Baseline, 1, 2, 3, 4, 5 and 6 months following everolimus initiation.	−1.9 (95% CI: −10.9 to 7.0) NS	Month 3: Physical −8.8 (95% CI: −15.1 to −2.5)** Others NCS/NS	Month 3: Dyspnea +12 (95% CI 1.9–22.2) NS Month 6: Constipation −10 (95% CI −2.7 to 2.7) NS Others NCS/NS	Month 1: Disease-related worries −11.5 (95%CI −19.1 to −3.9)*** Month 2: Disease-related worries −8.8 (95% CI −16.4 to −1.2)* Month 6: Social −10.4 (95% CI −18.4 to −2.4) NS	-

Note: Global health status/QOL scores presented regardless of significance, for other scales clinical and statistically significant changes presented.

Abbreviations: SSA, somatostatin analogues; PRRT, peptide receptor radionuclide therapy; HRQoL, health-related quality of life; QOL, quality of life; Δ, change in score from baseline to last post-baseline visit or end of treatment, unless otherwise stated; TDD, time to definitive deterioration; TTD, time to deterioration; NR, not reached; HR, hazard ratio; CI, confidence interval; NS, not statistically significant ($p > 0.05$); SNR, statistical significance not reported; NCS, not clinically significant (<10 points).

[a]Data not given.

*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

****$p < 0.0001$.

TABLE 6 EORTC QLQ-C30 summary scores

SSA therapy			
Study	Study treatment	Baseline	Last measurement
Rinke et al. (2019)	Octreotide LAR	75.2	75.5
	Placebo	73.1	70.8
Targeted therapies			
Study	Study treatment	Baseline	Last measurement
Vinik et al. (2016)	Sunitinib malate	75.5	69.3
	Placebo	73.6	71.4
Raymond et al. (2018)	Sunitinib (treatment naïve)	80.5	77.0
	Sunitinib (previously treated)	78.2	77.5
Ramage et al. (2019)	Everolimus	69.0	68.6

[a]Missing baseline score for treatment-related symptoms.

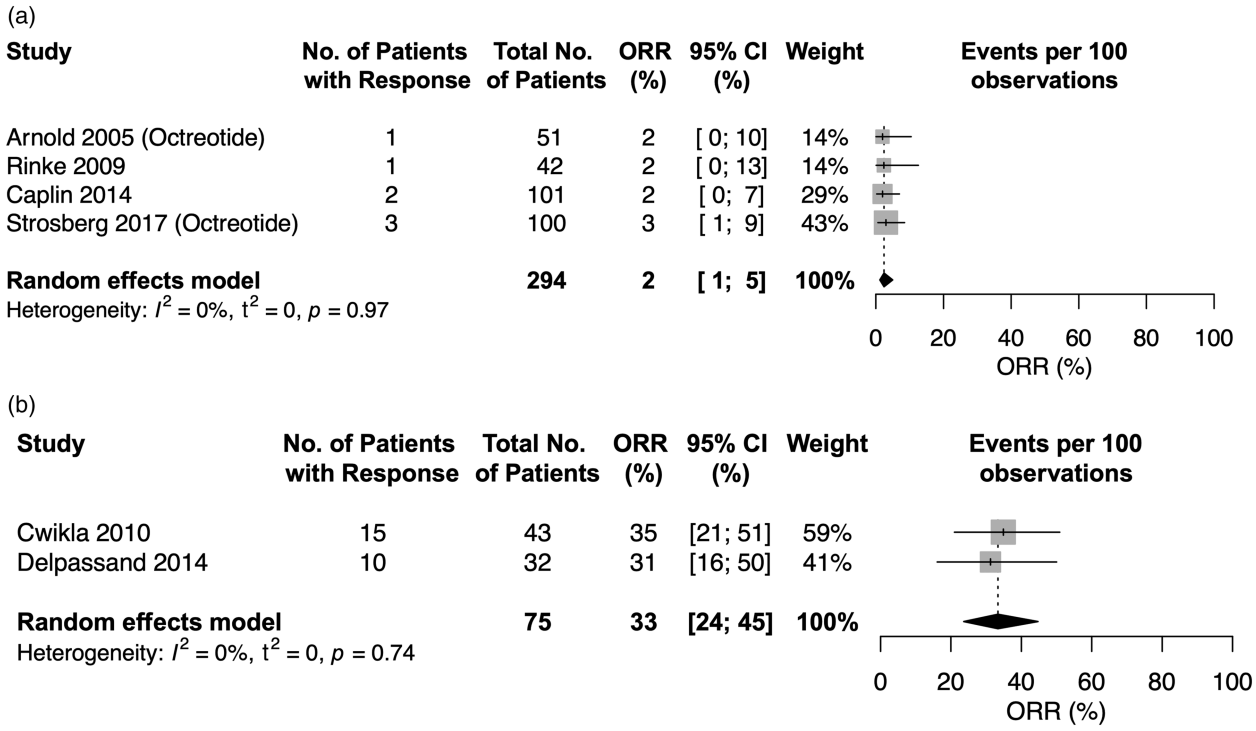

FIGURE 4 Forest plots of pooled ORR results for SSA therapies (a) and PRRT (b)

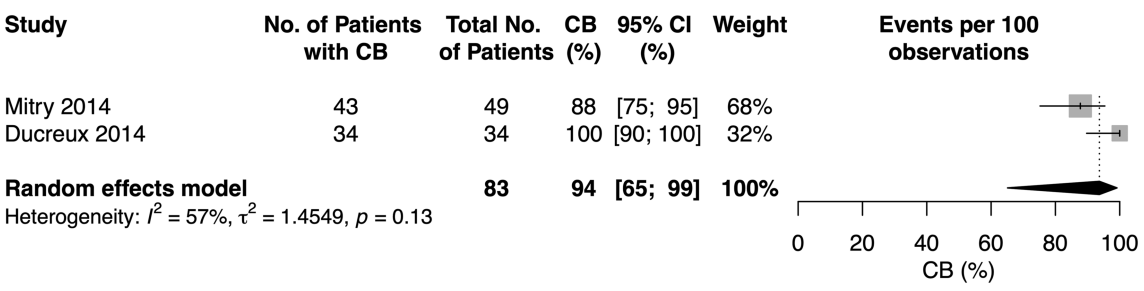

FIGURE 5 Forest plot of pooled CB results for chemotherapy modalities

reported the longest mean PFS of 25.1 months. OS was not reported by Pavel et al. and not reached in Ramage et al. (2019) (Table 4).

Three studies reported on ORR and CB (Pavel, Unger, et al., 2016; Raymond et al., 2011, 2018). Due to heterogeneity, meta-analyses could not be performed ($I^2 = 90\%$ for ORR and $I^2 = 91\%$ for CB). Individual ORR and CB results are presented in Figures S1b and S2c, respectively.

3.8 | Overall evidence quality

The overall quality of evidence was graded low to very low for all outcomes using the GRADE approach (Table S1). Evidence levels were mainly downgraded due to poor HRQoL outcome reporting, a lack of RCTs and small study populations.

3.9 | Practical guide

Table 7 summarises the clinical outcomes for all treatments in this current review. Shared decision-making is supported with these data; treatment decisions can, for example, be focused on improving HRQoL (PRRT, SSA and PRRT, SSA and IFNa or sunitinib) or more on disease control (SSA, PRRT, chemotherapy and targeted therapies). The proportion of patients with serious adverse events may also support patients in deciding between treatment options.

4 | DISCUSSION

This systematic review and meta-analysis assessed HRQoL, treatment efficacy and AEs in patients with well-differentiated, advanced GEPNENs. All included treatment modalities were associated with stable global health status/QOL scores and disease stabilisation. Serious AEs were most frequently reported during chemotherapy and PRRT. To our knowledge, this systematic review is the first to compare treatments in GEPNEN patients in terms of HRQoL and treatment efficacy in one publication.

Global health status/QOL scores remained stable across all modalities, irrespective of the frequency of serious AEs. Interestingly, the meta-analysis for SSA therapy revealed no significant difference in global health status/QOL between intervention and placebo arms, although SSA treatment was associated with improved symptom scores in the PROMID trial and in previous publications (Appetecchia & Baldelli, 2010; Rinke et al., 2009). Acquired drug tolerance negating an initial improvement in HRQoL scores could explain the stable HRQoL found in our analysis (Appetecchia & Baldelli, 2010). Further HRQoL results corresponded to previous

TABLE 7 Summarised treatment outcomes for shared decision-making

	Time to disease progression	Proportion of patients with tumour response or tumour stabilisation	Proportion of patients with serious adverse events	Most common serious adverse events	Effect on HRQoL
SSA therapy	Significantly longer compared to placebo.	66–63%	25–26% no difference between treatment and placebo.	• Fatigue and fever • GI tract symptoms	Stable HRQoL. No difference between treatment and placebo
PRRT	Uncleara	72–91%	13–33%	• Hematologic effects	Decrease in symptom-burden.
SSA and IFNa combination	No difference compared to SSA alone.	24%	-	-	Significantly improved compared to SSA alone.
SSA and PRRT combination	Significantly longer compared to SSA therapy alone.	-	41% significantly more in combination arm.	• Hematologic effects • Vomiting	Delayed deterioration in HRQoL in combination arm.
Chemotherapy	Uncleara	88–100%	65–84%	• Hypertension • GI tract symptoms	Stable HRQoL.
Targeted therapy: Sunitinib	Significantly longer compared to placebo.	72–90%	50%	• Hematologic effects	Decrease in GI symptoms, delayed deterioration in HRQoL.
Targeted therapy: Everolimus	Uncleara	60%	7.5–41%	• Infections	Stable HRQoL.

Note: Serious adverse events are events requiring hospitalisation or invasive intervention, and events with life-threatening consequences.
Abbreviations: SSA, somatostatin analogue; IFNa, interferon alpha; PRRT, peptide radionuclide therapy; HRQoL, health-related quality of life.
[a]Studies did not compare treatment to placebo.

reporting: PRRT was associated with improved scores in symptom scales in non-placebo-controlled studies (Hirmas et al., 2018), and sunitinib treatment was associated with worsening diarrhoea (Valle et al., 2014). However, HRQoL results did not reflect the frequency of serious AEs reported, as chemotherapy studies reported the highest proportion of serious AEs out of all studies, and PRRT was associated with a high occurrence of grade 3–4 hematologic AEs. It is possible that final HRQoL scores were recorded after successful treatment of these AEs, i.e. after a decrease in AE-related symptom burden. This potential "response shift" was recently highlighted by Watson et al., who suggested TTD and TDD analyses as a potential solution due to the significant results of the NETTER-1 trial in terms of HRQoL (Watson et al., 2020). In contrast, time-to-event analyses do not depend on the number of patients at (the last) follow-up. However, as suggested by Watson et al., more research is needed to establish whether the existing thresholds for clinical significance and definite deterioration are meaningful in GEPNEN patients.

All modalities reported good CB rates, with chemotherapy and PRRT showing promising effects on tumour regression. A previous review and meta-analysis, investigating systemic treatment of advanced well-differentiated pancreatic NENs, found chemotherapy alone or in combination with anti-VEGF to be the best cytoreductive treatment. However, studies on PRRT alone were not included in this review (Pozzari et al., 2018). Even though past reviews have concluded that PRRT shows promising tumour response, SSA remains the first-line treatment option for metastatic GEPNENs as not all patients are eligible to receive PRRT (Carmona-Bayonas et al., 2017; Gulenchyn et al., 2012; Michael et al., 2017; Pasricha et al., 2017). In the present study, SSA was associated with a low ORR in the meta-analysis and moderate CB rates in both RCTs. This is in accordance with a systematic review by Chan et al. who reported a significant rate of disease control, but no disease regression during escalated-dose SSA (Chan et al., 2017). Of note, a systematic review suggested bevacizumab combinations (with mTOR inhibitors and chemotherapy) to be a more effective and tolerable treatment for advanced GEPNENs. In turn, ORR results showed large variation (0–64%) similar to our review (Abdel-Rahman & Fouad, 2015). In the current study, the combination of ^{177}Lu-DOTATATE with octreotide resulted in a lower ORR than reported in the other included PRRT studies, and more adverse events than generally reported by SSA studies. Still, a study assessing CB of currently used systemic treatments using scales published by the European and American societies for Oncology (ESMO-MCBS and NHB-ASCO-F) was unable to demonstrate a meaningful CB in any included study on SSA therapy, PRRT, chemotherapy or targeted therapies. Yet, only eight and six trials of 32 included studies were eligible for grading using the NHB-ASCO-F and ESMO-MCBS scores, respectively (de Hosson et al., 2017).

Notably, past systematic reviews have reported either on the effect of treatment on oncological outcomes (Abdel-Rahman & Fouad, 2015; Chan et al., 2017; Pozzari et al., 2018) or on HRQoL (Jimenez-Fonseca et al., 2015; Watson et al., 2020) alone. This illustrates a persistent divide between traditional treatment outcomes and HRQoL reporting. A recent systematic review found that not even half (47%) of phase III oncology trials conducted between 2012 and 2016 included HRQoL as an end point, suggesting that HRQoL is frequently not an outcome of interest (Marandino et al., 2018). Moreover, another systematic review found that just 40% of Food and Drug Administration (FDA) approved, and 58% of European Medicines Agency (EMA) approved oncology therapies published HRQoL outcomes, and that the majority of drugs were approved based on survival outcomes, illustrating that research on therapies that improve HRQoL is lacking (Arciero et al., 2021). These findings are further exemplified in the current review, where 358 articles were excluded at full text review due to a lack of HRQoL outcomes. Survival and HRQoL outcomes may be variably important in treatment related shared decision-making, depending on patient age, health status and future expectations of life (Shrestha et al., 2019). Therefore, both HRQoL and traditional oncological outcomes are necessary for treatment-related shared decision-making. A summary table was designed which may be used to facilitate treatment-related shared decision-making.

It is important to highlight that overall evidence quality of studies included in this review was poor. We found significant heterogeneity, a lack of randomised-controlled trials as well as poor HRQoL reporting, hindering definite conclusions. An earlier systematic review, conducted on the quality of HRQoL reporting in patients with GEPNENs, reported a detailed analysis of the shortcomings in both processing and reporting of HRQoL data (Martini et al., 2016). In our review, notable limitations included inconsistent use of terminology when describing HRQoL outcomes, limited completeness in reporting HRQoL and the lack of randomised-controlled trials focusing on HRQoL. Due to these limitations, only two of the 12 studies could be included in the meta-analysis, which could only be conducted for the global health status/QOL scale due to missing data. Furthermore, HRQoL results were reduced to just the global health status/Qol scale or preselected individual items in five publications on HRQoL. The QLQ-C30 summary score may be more appropriate when summarising HRQoL data (Giesinger et al., 2016). In fact, the summary score was shown to have a strong prognostic value for overall survival in cancer patients (Husson et al., 2020). Neuroendocrine tumour guidelines should advocate the use of these specific questionnaires as well as complete reporting of QoL in every therapeutic study, to enable future comparisons and further meta-analyses (Falconi et al., 2016; Kulke et al., 2010, 2015).

No publications on cytoreductive surgery of the primary tumour were included despite evidence of longer survival after resection of advanced tumours (Capurso et al., 2012; Partelli et al., 2014). Therefore, no conclusions could be drawn on the effectiveness and safety of surgical debulking in advanced disease.

5 | CONCLUSIONS

In summary, SSA therapy, PRRT, chemotherapy and targeted therapies showed stable global HRQoL and benefits for disease stabilisation in patients with well-differentiated GEPNENs.

Unfortunately, high-quality HRQoL reporting was lacking and the best order of treatment after progression on SSA therapy remains unknown. Subjective experience of health and quality of life prospects may be decisive in treatment-related decision making. With research focusing on combination therapies and reducing tumour-burden, HRQoL should be investigated along with survival outcomes. Standard use of the EORTC QLQ-C30 questionnaire with the QLQ-GINET21 module should be advocated for all studies with GEPNEN patients.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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Ethical approval was not required for this study.

AUTHOR CONTRIBUTIONS

All listed authors contributed to this project according the ICMJE criteria for authorship.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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