

World Journal of *Gastroenterology*

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GUIDELINES

- 3517 Chinese expert consensus and practice guideline of totally implantable access port for digestive tract carcinomas

Zhang KC, Chen L, Chinese Research Hospital Association Digestive Tumor Committee; Chinese Association of Upper Gastrointestinal Surgeons; Chinese Gastric Cancer Association and Gastrointestinal Surgical Group of Chinese Surgical Society Affiliated to the Chinese Medical Association

OPINION REVIEW

- 3528 Management of nonalcoholic fatty liver disease in the Middle East

Sanai FM, Abaalkhail F, Hasan F, Farooqi MH, Nahdi NA, Younossi ZM

REVIEW

- 3542 Practical review for diagnosis and clinical management of perihilar cholangiocarcinoma

Dondossola D, Ghidini M, Grossi F, Rossi G, Foschi D

- 3562 Development of innovative tools for investigation of nutrient-gut interaction

Huang WK, Xie C, Young RL, Zhao JB, Ebendorff-Heidepriem H, Jones KL, Rayner CK, Wu TZ

MINIREVIEWS

- 3577 Monoacylglycerol lipase reprograms lipid precursors signaling in liver disease

Tardelli M

ORIGINAL ARTICLE**Basic Study**

- 3586 TBL1XR1 induces cell proliferation and inhibit cell apoptosis by the PI3K/AKT pathway in pancreatic ductal adenocarcinoma

Gu JF, Fu W, Qian HX, Gu WX, Zong Y, Chen Q, Lu L

- 3603 Retrievable puncture anchor traction method for endoscopic ultrasound-guided gastroenterostomy: A porcine study

Wang GX, Zhang K, Sun SY

Case Control Study

- 3611 Risk factors associated with inflammatory bowel disease: A multicenter case-control study in Brazil

Salgado VCL, Luiz RR, Boéchat NLF, Leão IS, Schorr BDC, Parente JML, Lima DC, Silveira Júnior ES, Silva GOS, Almeida NP, Vieira A, de Bueno MLQ, Chebli JM, Bertges ÉR, Brugnara LMDC, Junqueira Neto C, Campbell SBG, Discacciati LL, César JPS, Nunes T, Kaplan GG, Zaltman C

Retrospective Cohort Study

3625 Predictors of irreversible intestinal resection in patients with acute mesenteric venous thrombosis
Sun SL, Wang XY, Chu CN, Liu BC, Li QR, Ding WW

3638 Functionality is not an independent prognostic factor for pancreatic neuroendocrine tumors
Chen HY, Zhou YL, Chen YH, Wang X, Zhang H, Ke NW, Liu XB, Tan CL

Retrospective Study

3650 Chronic atrophic gastritis detection with a convolutional neural network considering stomach regions
Kanai M, Togo R, Ogawa T, Haseyama M

3660 Multiphase convolutional dense network for the classification of focal liver lesions on dynamic contrast-enhanced computed tomography
Cao SE, Zhang LQ, Kuang SC, Shi WQ, Hu B, Xie SD, Chen YN, Liu H, Chen SM, Jiang T, Ye M, Zhang HX, Wang J

Observational Study

3673 Type I and type II *Helicobacter pylori* infection status and their impact on gastrin and pepsinogen level in a gastric cancer prevalent area
Yuan L, Zhao JB, Zhou YL, Qi YB, Guo QY, Zhang HH, Khan MN, Lan L, Jia CH, Zhang YR, Ding SZ

SYSTEMATIC REVIEWS

3686 Quality of life in patients with gastroenteropancreatic tumours: A systematic literature review
Watson C, Tallentire CW, Ramage JK, Srirajaskanthan R, Leeuwenkamp OR, Fountain D

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Prof. Antonio Biondi is an Associate Editor of *Updates in Surgery*, the official journal of the Italian Society of Surgery, and a Full Professor of surgery at the School of Medicine, University of Catania, Italy. Prof. Biondi obtained his MD degree from the University of Catania in 1993, and his PhD degree in 2001. He was promoted to Full Professor in the School of Medicine, University of Catania, in 2018. His ongoing research interests are colorectal surgery and laparoscopic procedures. He is a member of the editorial boards and a reviewer of several scientific journals, and has published more than 150 peer-reviewed articles. Prof. Biondi served as elected member of the Italian National University Council (CUN). Currently, he is the Chief of the Laparoscopic Surgery Division, Department of General Surgery and Medical-Surgical Specialties, University Hospital Policlinico Vittorio Emanuele, Catania and Director of the Multidisciplinary Research Center for Diagnosis and Treatment of Rare Diseases, University of Catania.

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Quality of life in patients with gastroenteropancreatic tumours: A systematic literature review

Catherine Watson, Craig William Tallentire, John K Ramage, Rajaventhana Srirajaskanthan, Oscar R Leeuwenkamp, Donna Fountain

ORCID number: Catherine Watson 0000-0001-8752-0081; Craig William Tallentire 0000-0003-2172-7244; John K Ramage 0000-0003-4824-6600; Rajaventhana Srirajaskanthan 0000-0001-9835-8681; Oscar R Leeuwenkamp 0000-0002-4447-7404; Donna Fountain 0000-0003-4216-1147

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Catherine Watson, Craig William Tallentire, Donna Fountain, PHMR Health Economics, Pricing and Reimbursement, London NW1 8XY, United Kingdom

John K Ramage, Rajaventhana Srirajaskanthan, Kings Health Partners NET centre, Kings College Hospital London, London SE5 9RS, United Kingdom

Oscar R Leeuwenkamp, Advanced Accelerator Applications, Geneva 1204, Switzerland

Corresponding author: Donna Fountain, PhD, Research Scientist, PHMR Health Economics, Pricing and Reimbursement, PHMR Head Office, London NW1 8XY, United Kingdom. donna.fountain@phmr.com

Abstract

BACKGROUND

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) are slow-growing cancers that arise from diffuse endocrine cells in the gastrointestinal tract (GI-NETs) or the pancreas (P-NETs). They are relatively uncommon, accounting for 2% of all gastrointestinal malignancies. The usual treatment options in advanced GEP-NET patients with metastatic disease include chemotherapy, biological therapies, and peptide receptor radionuclide therapy. Understanding the impact of treatment on GEP-NET patients is paramount given the nature of the disease. Health-related quality of life (HRQoL) is increasingly important as a concept reflecting the patients' perspective in conjunction with the disease presentation, severity and treatment.

AIM

To conduct a systematic literature review to identify literature reporting HRQoL data in patients with GEP-NETs between January 1985 and November 2019.

METHODS

The PRISMA guiding principles were applied. MEDLINE, Embase and the Cochrane library were searched. Data extracted from the publications included type of study, patient population data (mid-gut/hind-gut/GI-NET/P-NET), sample size, intervention/comparators, HRQoL instruments, average and data spread of overall and sub-scores, and follow-up time for data collection.

RESULTS

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Forty-three publications met the inclusion criteria. The heterogeneous nature of the different study populations was evident; the percentage of female participants ranged between 30%-60%, whilst average age ranged from 53.8 to 67.0 years. Eight studies investigated GI-NET patients only, six studies focused exclusively on P-NET patients and the remaining studies involved both patient populations or did not report the location of the primary tumour. The most commonly used instrument was the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 ($n = 28$) with consistent results across studies; the GI-NET-specific module Quality of Life Questionnaire-GINET21 was used in six of these studies. A number of randomised trials demonstrated no HRQoL changes between active treatment and placebo arms. The Phase III NETTER-1 study provides the best data available for advanced GEP-NET patients; it shows that peptide receptor radionuclide therapy can significantly improve GEP-NET patients' HRQoL.

CONCLUSION

HRQoL instruments offer a means to monitor patients' general disease condition, disease progression and their physical and mental well-being. Instruments including the commonly used European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 and GINET21 lack, however, validation and a defined minimal clinically important difference specifically for GI-NET and P-NET patients.

Key words: Gastroenteropancreatic neuroendocrine tumours; Health-related quality of life; Systematic literature review; Chemotherapy; Biological therapies; Peptide receptor radionuclide therapy

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Core tip: Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) are slow-growing cancers that arise from diffuse endocrine cells in the gastrointestinal tract and pancreas. An increased emphasis has been placed on health-related quality of life assessment in clinical studies, using reliable and validated patient-reported outcome instruments. Long-term therapeutic options provide symptomatic relief for patients with GEP-NETs, and can slow down or stabilise disease progression, but are not curative. Thus, understanding the impact of the long-term treatment options is particularly important. The aim of this study was to perform a systematic review to assess health-related quality of life focusing on patients with inoperable metastatic GEP-NETs undergoing different treatments in order to uncover areas for future research.

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INTRODUCTION

Gastroenteropancreatic tumours (GEP-NETs) account for 2% of all gastrointestinal malignancies, with a United Kingdom age-standardised incidence rate of 8.6/100000/year^[1]. GEP-NETs tend to be slow-growing cancers arising from diffuse endocrine cells in the gastrointestinal tract (GI-NETs) or pancreas (P-NETs). GEP-NETs are categorised as "functioning" or "non-functioning". Functioning tumours cause symptoms due to the hypersecretion of peptides and hormones^[2,3], whilst non-functioning tumours have no hormone-related clinical features. Specific symptoms vary by primary tumour location^[4,5]. Around 3 in 10 patients with GI-NET develop symptoms of diarrhoea, abdominal pain and flushing due to increased serotonin production^[6], known as carcinoid syndrome (CS). P-NETs can produce a variety of hormones, the most common of which are insulin and gastrin. Other abnormal

hormone production associated with GEP-NETs include glucagon, vasoactive intestinal peptide, adrenocorticotrophic hormone, somatostatin, and parathyroid hormone-related protein^[7].

Surgery is the only curative treatment for GEP-NETs and can be performed when tumours are localised and resectable. The majority of GEP-NET patients, however, are diagnosed with metastatic disease requiring systemic treatment^[8,9], including chemotherapy, biological therapies, and peptide receptor radionuclide therapy (PRRT)^[10]. These long-term therapeutic options provide symptomatic relief, and can slow down or stabilise disease progression, but are not curative. The 5-year survival rate for patients with metastatic GI-NETs is approximately 75% and the 5-year survival rate for patient with metastatic P-NETs is > 60%, whilst the prevalence of GEP-NETs has been on the rise in the recent decades^[2,11]. For instance, the median overall time of survival from the date of diagnosis of distant metastatic disease was reported to be 103 mo (8.5 years) in patients with metastatic midgut GI-NETs^[12]. It is therefore vital to assess the patient's health-related quality of life (HRQoL) in general and related to the disease whilst taking treatments which can have a marked impact on well-being.

In oncology, an increased emphasis has been placed on HRQoL assessment as a secondary endpoint in clinical studies, using reliable and thoroughly validated patient-reported outcome (PRO) instruments for which the minimal important difference for improvement/worsening has been defined^[13-17]. High-quality information on HRQoL serves a variety of purposes such as the development of targeted interventions, informed decision making about treatment options and allocation of healthcare resources^[18]. Indeed, the United States Food and Drug Administration and European Medicines Agency have published guidance on the use of PRO measures in oncology studies emphasising the value of patient perspective when evaluating medicinal products^[19,20].

To date, systematic assessments of HRQoL in patients with GEP-NETs have been performed to a limited extent. In the past, where the literature was systematically evaluated, the review focused on the methodological quality of the identified studies^[18]. To our knowledge, there has been no systematic literature review published to provide a comprehensive overview of the different treatment options and associated impact on the patients' HRQoL. The aim of our study was to perform a systematic review to assess HRQoL focusing on patients with inoperable metastatic GEP-NETs undergoing different treatments in order to uncover areas for future research.

MATERIALS AND METHODS

Search strategy and study selection

This systematic review adheres to the established international guidelines for conducting systematic reviews, such as those provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses report (PRISMA Statement^[21]), and the Cochrane Handbook for Systematic Reviews of Interventions^[22]. Methods of analysis and inclusion criteria were defined in advance and outlined in a designated protocol.

An extensive search of MEDLINE, Embase and the Cochrane library was performed by an experienced information specialist to identify relevant studies. We examined articles published in English between January 1985 and November 2019. The protocol outlined the electronic search strategy in full; searches were supplemented by manual searches of relevant review journals.

After de-duplication, article titles and abstracts were independently reviewed by two analysts, with discrepancies resolved *via* discussion with a third reviewer. Full-text articles were then obtained for records that met the inclusion criteria to re-evaluate eligibility.

Eligibility criteria

Eligibility for this systematic review was defined according to the PICOS^[21]. Participants were adult patients (≥ 18 years) with inoperable GEP-NETs. Outcome measures included HRQoL, PROs, utility estimates, validity, and minimally important difference. The study design incorporated studies reporting utility estimates and HRQoL data, including economic evaluations, observational studies, and relevant randomised control trials. Cross-sectional studies were included, as they can provide useful HRQoL data at a specific point in time, although not providing longitudinal changes due to treatment over time. Studies were also required to report at least one relevant outcome for ≥ 15 patients. There were no limits defined in terms of

intervention or comparator PICOS elements.

Articles were excluded if patients were diagnosed with neuroendocrine tumours that did not originate in the gastrointestinal tract or the pancreas, and when the HRQoL data for patients with GEP-NETs were not separated by sub-analysis (*e.g.*, the population included patients with lung and/or thyroid neuroendocrine tumours). Studies indexed as case reports, case series, editorials and letters, conference abstracts, systematic reviews and non-human studies were also excluded. Finally, studies where the treatment applied did not target the malignancies specifically, such as psychotherapeutic interventions, were excluded.

Data extraction

A dedicated data extraction sheet was devised to capture all relevant data, including publication details, study design, country, intervention(s), comparator(s), eligibility, population description (including any specific sub-groups), sample size, age (average and range), sex ratio, tumour location, description of HRQoL measure (including valuation technique, method of elicitation, timepoints, follow-up duration, response rates), utility tool assessment (including disease state, timepoint, average utility) and HRQoL assessment (including scale domain where relevant, timepoint, average score, data spread). Disagreements were resolved by discussion between the two reviewers, with third reviewer involvement as required.

Quality assessment

The quality and relevance of HRQoL studies were assessed based on the key criteria described by Papaioannou *et al*^[23] and Brazier *et al*^[24], where applicable. Papers reporting insufficient information to assess study methods and populate the data extraction sheet were considered lower quality and were excluded on this basis.

RESULTS

Identified literature

A total of 42 studies published between 1985 and 2019 met the inclusion criteria of this study, of which 32 were found electronically and 10 were found by handsearching the reference lists of relevant articles (Figure 1). Of these studies, 6 can be classed as cross-sectional studies. There was a combined total of 3552 participants in the 42 studies, excluding healthy participants used for comparisons and the duplicate patients taken from the same data, with study sample sizes ranging from 17 to 253 patients. The heterogeneous nature of the different study populations was evident; the percentage of female participants ranged between 30%-60%, whilst average age ranged from 53.8 to 67.0 years (Table 1). In terms of disease location, 8 studies focused on GI-NET patients only and 6 studies focused on P-NET patients; the remaining studies were either a combination of both populations or did not report the specific disease location.

Of the total studies, 14 included somatostatin analogues as the intervention, including octreotide ($n = 7$), lanreotide ($n = 3$), pasireotide ($n = 1$), and undefined ($n = 3$). Such treatments slow down the production of hormones, such as serotonin, and thus reduce the symptoms of CS. In two studies, somatostatin analogues were combined with immunotherapy drugs such as interferon^[25,26]. Three studies compared somatostatin analogues with placebos, allocated within the context of a randomised controlled trial^[16,27,28]. Five studies used somatostatin analogues as comparators for an alternative somatostatin therapy, ¹⁷⁷Lu-DOTATATE or octreotide combined with interferon alpha^[17,29-32].

In PRRT, a radioactive substance can be combined with a relevant peptide (or its analogue), such as somatostatin, so that it preferentially binds with a high affinity to the tumour. Nine studies considered PRRT as the intervention: ²²⁵Ac-DOTATATE ($n = 1$), ¹⁷⁷Lu-DOTATATE ($n = 5$), ⁹⁰Y-DOTATOC ($n = 2$) and/or ¹⁷⁷Lu-DOTATOC ($n = 3$) (Table 1). ¹⁷⁷Lu-DOTATATE was compared with octreotide administered at a high dose in one prospective study^[17]. One retrospective study considered PRRT as the comparator^[33], with somatostatin analogues or interferon therapy as the intervention.

Everolimus, sunitinib and erythropoietin were studied as interventions in three, three and one studies, respectively. Two studies compared sunitinib with a placebo within the context of randomised control trials^[34,35]. Sunitinib was investigated as a comparator of everolimus in an additional study^[36]. In some studies, interferon was used within the populations^[25,31,33,37,38], but this was not applied to a specific subgroup.

Six studies used chemotherapy as the intervention: These combined bevacizumab with 5-FU/streptozocin ($n = 2$), capecitabine and streptozocin plus cisplatin ($n = 1$),

Table 1 Extracted literature

Ref.	Intervention	Comparator(s)	Study design, "Open" Label / "Blinded" / "Double blinded"	Total sample size	Patient sub-group	Pt sub-group sample size	Sex (% female)	Average age (yr)	Mean/median	Total GI-NET, %	P-NET, %	Functioning /Non-functioning, "function"	Additional information about disease ¹ : "Stage (TNM)" "progressive" "stable", ("advanced" "metastatic/metastases" "spread") ("grow" "grade" "differentiated")
Zandee <i>et al</i> ^[58] , 2019	¹⁷⁷ Lu-DOTATATE	NA	Retrospective study	34	NA	NA	50	59	Mean	NA	100	Functioning (100%)	Grade 1 or 2 tumours with metastases (stage IV). Metastatic disease sites: Liver (97%), bone (21%), lung (6%)
Ramage <i>et al</i> ^[54] , 2019	Everolimus	NA	Phase IV, open	48	All Patients	46	30	64.3	Median	NR	100	NR	Advanced and/or metastatic, well-differentiated, grade 1 and 2
					Continuing treatment at month 6	30	NR	NR	NR	NR	NR		
Ballal <i>et al</i> ^[8] , 2019	²²⁵ Ac-DOTATATE	NA	Prospective study, open	21	NA	NA	57	54	Median	38	57	NR	Metastatic GEP-NETs with stable disease after completing ¹⁷⁷ Lu-PRRT (57%) or progressive disease on ¹⁷⁷ Lu-PRRT (43%). Grades 1 (<i>n</i> = 9), 2 (<i>n</i> = 11), and 3 (<i>n</i> = 1). Metastatic disease sites: Liver (86%), lymph node (71%), bone (33%)
Marinova <i>et al</i> ^[61] , 2019	¹⁷⁷ Lu-DOTATATE	NA	Retrospective study	70	NA	NA	44.3	64.2	Mean	100	NR	Functioning (83%), non-functioning (17%)	Metastatic. Grade 1 (50%), grade 2 (35.7%), unknown (14.3%). Morphological or clinical progression prior to 1 st cycle PRRT (78.6%)
Rinke <i>et al</i> ^[16] , 2019	Long-acting octreotide	Placebo (sodium chloride)	Clinical trial (RCT), Phase IIIb trial, double blind, placebo controlled	85	Long-acting octreotide	42	49.4	62.4	Mean	NR	NR	Functioning (39%), non-functioning (61%)	Metastatic, liver metastases (86%)
					Placebo	43		60.3	Mean	NR	NR		
					NA	NA		NR	NA	NR	NR		
Martini <i>et al</i> ^[59] , 2018	DOTATATE or ⁹⁰ Y-DOTATOC	General population norms	Retrospective study	61	Small intestine NET patients	37	40.5	62.8	Mean	100	0	NR	No brain metastases; otherwise not defined
					P-NET patients	24	37.5	61.0	Mean	0	100		
Lewis <i>et al</i> ^[3] , 2018	Not defined	Patients with CS vs patients without CS	Prospective study	50	Without CS (CS)	25	48.0	62.0	Median	60.0	40.0	NR	Advanced, well-differentiated, with liver metastases
					With CS (CS)	25	36.0	67.0	Median	96.0	4.0	NR	

Strosberg <i>et al</i> ^[17] , 2018	¹⁷⁷ Lu-DOTATATE	High-dose octreotide	Clinical trial (RCT), phase III, open	231	¹⁷⁷ Lu-DOTATATE	117	NR	NR	NR	100	NR	NR	Advanced, progressive, low- or intermediate-grade
					octreotide LAR	114	NR	NR	NR	100	NR		
Karppinen <i>et al</i> ^[46] , 2018	NA	Control population	Cross-sectional	134	Impaired excretion	87	55	66.8	Mean	100	NR	Flushing (31%), diarrhoea (63%)	Locally advanced or metastatic disease (91%), grade 1 (54.1%), grade 2 (45.9%)
Cella <i>et al</i> ^[44] , 2018	Telotristat ethyl	Placebo	Clinical trial (RCT), phase III trial, double blind	135	NA	135	48.1	63.6	Mean	NR	NR	NR	Well-differentiated, metastatic NETs and CS inadequately controlled by somatostatin analogues (for ≥ 3 mo)
					Durable responders (DR)	48	52.1	63.4	Mean	NR	NR		
					Non-durable responders (DR)	87	46	63.6	Mean	NR	NR		
Meng <i>et al</i> ^[28] , 2017	Somatostatin analogue lanreotide	Placebo	Clinical trial (RCT), phase III trial, double blind	204	Lanreotide	101	48	62.1	Mean	NR	NR	Non-functioning	Advanced, well-differentiated or moderately differentiated, somatostatin receptor-positive NETs of grade 1 or 2
					Placebo	103				NR	NR		
					Overall	204				NR	NR		
Vinik <i>et al</i> ^[35] , 2016	Sunitinib plus best supportive care	Placebo plus best supportive care	Clinical trial (RCT), phase III trial, double blind	171	NA	NA	NR	NR	NR	NA	100	NR	Advanced and/or metastatic, pathologically confirmed, well-differentiated P-NETs with disease progression as assessed by RECIST
Haugland <i>et al</i> ^[9] , 2016	None	None	Cross-sectional	196	None	NA	50.5	65.0	Mean	100.0	0.0	NR	NR
Pavel <i>et al</i> ^[56] , 2016	Everolimus	NA	Clinical trial, Phase IIIb, open, expanded access study	246	P-NET	126	46	61	Median	NR	100	Functioning (<i>n</i> = 38), non-functioning (<i>n</i> = 88)	Metastatic, well differentiated (<i>n</i> = 81), moderately differentiated (<i>n</i> = 26), poorly differentiated (<i>n</i> = 1), unknown (<i>n</i> = 16), missing (<i>n</i> = 2)
					Non P-NET	120	50.8	66	Median	NR	0	Functioning (<i>n</i> = 66), non-functioning (<i>n</i> = 55)	Metastatic, well differentiated (<i>n</i> = 65), moderately differentiated (<i>n</i> = 34), poorly differentiated (<i>n</i> = 2), unknown (<i>n</i> = 19)
Delpassand <i>et al</i> ^[66] , 2014	¹⁷⁷ Lu-DOTATATE	NA	Clinical trial, phase II, open	37	Patients with available data participated in quality of life questionnaire	27	56.8	63.4	Mean	43.2	37.8	NR	Grade 1 and grade 2, disseminated, progressive, somatostatin receptor-positive. Multiple metastases in the liver: grade 2 (<i>n</i> = 4), grade 3 (<i>n</i> = 26), grade 4 (<i>n</i> = 7). Metastatic disease sites: Liver (<i>n</i> = 34), lymph nodes (<i>n</i> = 16), bone (<i>n</i> = 11), pancreas (<i>n</i> = 8), lung (<i>n</i> = 3)
Ducreux <i>et al</i> ^[41] , 2014	Bevacizumab combined with 5-FU/ streptozocin (Mitry <i>et al</i> ^[40])	Capecitabine plus bevacizumab	Clinical trial, phase II, open	34	NA	NA	35	55	Median	NR	100	Functioning (<i>n</i> = 7): CS (<i>n</i> = 3), Zollinger-Ellison syndrome (<i>n</i> = 1), other	Progressive, metastatic disease. Metastatic disease sites: Liver (<i>n</i> = 33), lymph node (<i>n</i> = 14), peritoneum (<i>n</i> = 2), lung (<i>n</i> = 3),

	2014)											(n = 3)	bone (n = 2), other (n = 2)
Mitry <i>et al</i> ^[40] , 2014	Bevacizumab combined with 5-FU/ streptozocin (reported in a companion paper focusing on P-NET patients (Ducreux <i>et al</i> ^[41] , 2014)	Capecitabine plus bevacizumab	Clinical trial, phase II, open	49	NA	NA	47	60	Median	100	NA	NR	Progressive, metastatic well-differentiated. Metastatic disease sites: Liver (n = 46), lymph node (n = 24), peritoneum (n = 23), lung (n = 7), bone (n = 7), other (n = 5)
Meyer <i>et al</i> ^[42] , 2014	Capecitabine and streptozocin plus cisplatin (stratified)	Capecitabine and streptozocin (stratified)	Clinical trial (RCT), Phase II	86	Capecitabine and streptozocin	44	39	57	Median	21	46.0	Functioning (n = 31; 36%)	Advanced and/or metastatic. Metastatic disease sites: Local/regional (n = 2), distant (n = 42), liver (included in distant; n = 41)
					Capecitabine and streptozocin plus cisplatin	42	45	59	Median	19	50.0		
Yadegarfar <i>et al</i> ^[33] , 2013	Somatostatin analogues or interferon therapy (88 patients)	Peptide-receptor radiotherapy (102 patients), chemotherapy (23 patients), surgery (20 patients) or ablative/ other therapies (20 patients)	Phase IV, open	253	P-NET	70	NR	NR	NR	NR	NR	Functioning: Secreting 5-hydroxy-indoloacetic acid (n = 111), gastrin (n = 4), glucagon (n = 3), insulin (n = 5), vasoactive intestinal peptide (n = 1). Non-functioning (secreting only chromogranin-A; n = 124)	Any gut-primary with metastases, lung-primary with liver/abdominal metastases and pancreas with/without metastases
Casciano <i>et al</i> ^[36] , 2012	Everolimus (Afinitor)	Sunitinib (Sutent)	Economic analysis of phase III studies	NA	NA	NA	NA	NA	NA	NA	NA	NR	Advanced, progressive
Kvols <i>et al</i> ^[29] , 2012	Pasireotide	Octreotide	Prospective study, phase II, open	44	Pasireotide responders	12 (Baseline), 12 (Month 1), 10 (Month 2), 11 (Month 3)	44	61	Mean	NR	NR	NR	Advanced, metastatic (symptoms refractory or resistant to octreotide LAR therapy). Metastatic disease sites: Liver (87%), lymph node (n = 16), peritoneum (n = 8), lung (n = 5), bone (n = 3), abdomen (n = 3), pleura (n = 3), retroperitoneal (n = 2), pancreas (n = 2), kidney (n = 1)
					Pasireotide non responders	13 (Baseline), 13 (Month 1), 13 (Month 2), 13 (Month 3)				NR	NR		
					Patients who discontinued treatment before	19 (Baseline), 15 (Month				NR	NR		

Raymond <i>et al</i> ^[34] , 2011	Sunitinib plus Best Supportive Care	Placebo plus Best Supportive Care	Clinical trial (RCT), phase III, double blind	171	3 mo	1), 8 (Month 2)								
					sunitinib	86	51	56	Median	NR	100	Sunitinib Arm: Functioning: Gastrinoma (<i>n</i> = 9), glucagonoma (<i>n</i> = 3), insulinoma (<i>n</i> = 2), somatostatinoma (<i>n</i> = 1), other, multisecretory, or unknown (<i>n</i> = 10). Non-functioning (<i>n</i> = 42)	Advanced and/or metastatic, progressive, well-differentiated	
					Placebo	85	53	57	Median	NR	100	Placebo Arm: Functioning: Gastrinoma (<i>n</i> = 10), glucagonoma (<i>n</i> = 2), insulinoma (<i>n</i> = 2), vasoactive intestinal peptide-secreting tumour (<i>n</i> = 2), other, multisecretory, or unknown (<i>n</i> = 5). Non-functioning (<i>n</i> = 44)		
Pezzilli <i>et al</i> ^[49] , 2009	NA	NA	Prospective study	51	NA	NA	58.8	61	Mean	NR	100	NR	Advanced disease (lymph node involvement/liver metastases) (<i>n</i> = 22)	
Rinke <i>et al</i> ^[27] , 2009	Octreotide LAR	Placebo	Clinical trial (RCT), phase IIIb, double blind	85	Octreotide LAR	42	52.4	63.5	Median	100	NR	Octreotide LAR arm: Functioning: CS (<i>n</i> = 17) 40.5%	Well-differentiated, metastatic. Metastatic disease sites: Liver (<i>n</i> = 73), regional lymph node involvement (<i>n</i> = 6)	
					Placebo	43	46.5	61	Median	100	NR	Placebo arm: Functioning: CS (<i>n</i> = 16) 37.2%		
Korse <i>et al</i> ^[30] , 2009	Long-acting sandostatin LAR	Short-acting Sandostatin	Clinical trial, phase II	39	NA	NA	51.3	61	Mean	51.3	NR	Functioning: CS (<i>n</i> = 39)	Metastatic: Liver metastases (<i>n</i> = 35)	
van der Horst-Schrivers <i>et al</i> ^[67] , 2009	NA	NA	Prospective study	43	NA	NA	37.2	60.6	Mean	NR	NR	NR	Metastatic midgut carcinoid tumours: Liver metastases (<i>n</i> = 37)	
Haugland <i>et al</i> ^[47] , 2009	NA	NA	Cross-sectional	5341	NET patients	189	50	65	Mean	100	NR	NR	GI-NET patients (excluded radical surgery that may have been curative), otherwise undefined	
					General population	5152	48.8	NR	NR	NA	NA			
Larsson and Janson ^[50] ,	Erythropoietin	None	Pilot study	18	None	NA	50.0	63.0	Mean	100	NR	NR	NR	

2008													
Kulke <i>et al</i> ^[55] , 2008	Sunitinib	NA	Clinical trial, phase II, open	107	NA	NA	40.2	Carcinoid tumour = 58, P-NET= 56	Median	37.3	61.7	P-NET: Functioning: Gastrinoma <i>n</i> = 5 (7.6%), insulinoma <i>n</i> = 3 (4.5%), VIPoma <i>n</i> = 2 (3.0%), glucagonoma <i>n</i> = 4 (6.1%), other <i>n</i> = 5 (7.6%). Non-functioning <i>n</i> = 46 (69.7%)	Advanced carcinoid or P-NET
Fröjd <i>et al</i> ^[37] , 2007	Various included	None	Longitudinal, prospective, comparative study	59	T1-T4 successful	36	47.0	60.0	Mean	NR	NR	NR	Metastatic (70% metastatic at start; 78% metastatic at end)
Davies <i>et al</i> ^[68] , 2006	NA	NA	Cross-sectional, open	50	Patients	35	42.9	60	Mean	NR	NR	NR	Metastatic
					Healthcare workers	15	NR	NR	NR	NA	NA		
Frilling <i>et al</i> ^[48] , 2006	⁹⁰ Y-DOTATOC then ¹⁷⁷ Lu-DOTATOC	NA	Prospective study	20	Excluding pt (no 3) with Paraganglioma-neck	19	30	53.8	Median	NR	NR	NR	Advanced, progressive, and metastatic
Arnold <i>et al</i> ^[31] , 2005	Octreotide plus interferon alpha	Octreotide monotherapy	Clinical trial (RCT), open	114	Octreotide monotherapy	51	47.1	58	Median	NR	NR	Octreotide: Functioning (<i>n</i> = 23), non-functioning (<i>n</i> = 28). Octreotide plus Interferon-alpha: functioning (<i>n</i> = 24), non-functioning (<i>n</i> = 30)	Metastatic or locally advanced disease without curative therapeutic option
					Octreotide plus interferon alpha	54	44.4	57	Median	NR	NR		
					Nonrandomised	9	33.3	60	Median	NR	NR		
Teunissen <i>et al</i> ^[62] , 2004	¹⁷⁷ Lu-DOTATOC	None	Clinical trial	50	None	NA	56.0	58.3	Mean	NR	26.0	NR	Metastatic
Pasieka <i>et al</i> ^[43] , 2004	I-MIBG	NA	Clinical trial, open	19	I-MIBG	10	40	59	Mean	90	10	NR	Progressive
					Octreotide	9	55.6	55.6	Mean	66.6	33.3		
Kwekkeboom <i>et al</i> ^[60] , 2003	Somatostatin analogue ¹⁷⁷ Lu-DOTATOC	NA	Clinical trial, open	35	None	NA	60	54	Mean	NR	NR	NR	Metastatic
Larsson <i>et al</i> ^[25] , 2001	Interferon, somatostatin analogue, interferon, and a somatostatin	None	Prospective study	24	None	NA	42.0	62.0	Median	100	NR	NR	NR
O'Toole	Octreotide	Lanreotide	Clinical trial	33	Patients received	16	50	63	NR	62.5	0		

<i>et al</i> ^[32] , 2000	followed by lanreotide	followed by octreotide	(RTC), double blind		octreotide followed by Lanreotide									
					Patients received lanreotide followed by octreotide	17	53	64	NR	76	5.9	NR		NR
Wymenga <i>et al</i> ^[37] , 1999	Lanreotide prolonged release	NA	Clinical trial, phase II, open	55	NA	NA	49.1	59.7	Mean	NR	5.5	NR		Advanced (Stage IV), metastatic. Metastatic disease sites: Lymph nodes (<i>n</i> = 39), distant organs (<i>n</i> = 44)
Larsson <i>et al</i> ^[26] , 1999	Ongoing treatment: interferon and octreotide, other	NA	Cross-sectional	119	Patients with carcinoid tumours	64	43.7	64	Median	53.8	NA	NR		NR
					Patients with EPT	55	37.5	54	Median	NR	46.20			
					Overall	119	43.7	61	Median	53.8	46.20			
Larsson <i>et al</i> ^[38] , 1999	Interferon and/or a somatostatin analogue	NA	Clinical trial	99	NA	NA	39.4	59	Mean	NR	NR	NR		Stage = not terminal, no other status provided.
					HADS Anxiety (cases)	19	NR	NR	NR	NR	NR			
					HADS Depression (cases)	13	NR	NR	NR	NR	NR			
Larsson <i>et al</i> ^[69] , 1998	Interferon and/or a somatostatin analogue	NA	Cross-sectional	17	NA	NA	47	58	Mean	NR	NR	NR		NR

¹Disease description provided in each reference. NA: Not available; P-NET: Pancreas-neuroendocrine tumours; CS: Carcinoid syndrome; NR: Not relevant; HADS: Hospital Anxiety and Depression Scale; PRRT: Peptide receptor radionuclide therapy.

and bevacizumab plus capecitabine (*n* = 1). Two studies followed patients with various ongoing treatments^[37,39]. Three studies used chemotherapy treatments as the comparators to chemotherapeutic interventions; two studies combined capecitabine with the anti-angiogenic drug bevacizumab and used the same population data^[40,41], whilst one study combined capecitabine and streptozocin as the comparator^[42].

Two additional studies identified within the scope of this review focused on meta-iodobenzylguanidine (MIBG) therapy and telotristat ethyl^[43,44], respectively. MIBG is a radiometabolic therapy with limited antitumor effect on GEP-NETs. Telotristat ethyl is used to inhibit L-tryptophan hydroxylases TPH-1 and TPH-2 and reduce the production of serotonin, thereby alleviating CS symptoms^[44]; this was assessed in the context of a randomised controlled trial, randomised 1:1:1 to receive 250 mg TID, 500 mg TID, and placebo.

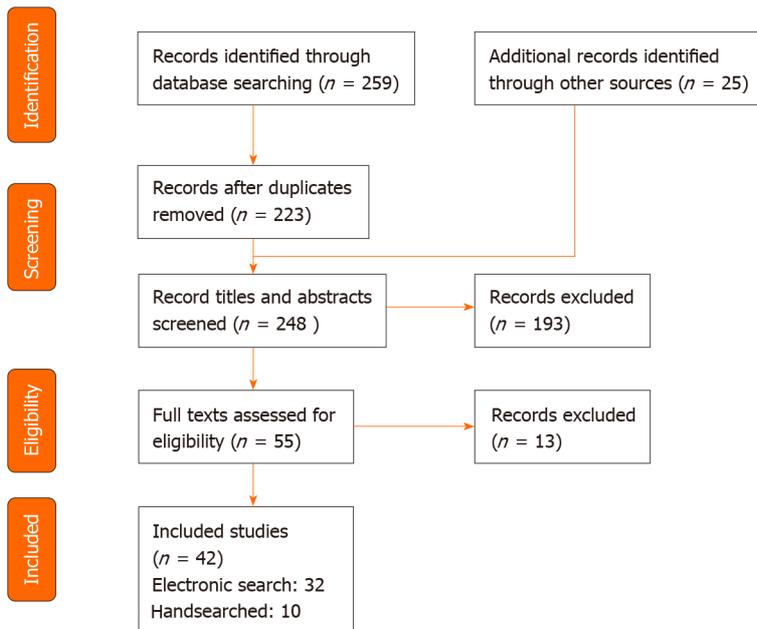


Figure 1 PRISMA diagram of included and excluded studies; the number of studies propagating to each stage of the process are included.

HRQoL assessment

In total, 30 studies employed a version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ), in which linear transformation is used to standardise the raw score, so that scores range from 0 to 100. The majority of these studies utilised the EORTC QLQ-C30 HRQoL measure ($n = 28$). One study developed a disease-specific quality of life score questionnaire for patients with GI-NETs to supplement EORTC QLQ-C30. Six studies employed the GI-NET specific module QLQ-GI.NET21, of which one study apparently did not use the HRQoL measure in conjunction with EORTC QLQ-C30^[6], thus will not show valid data. Others administered the EQ-5D or EQ-VAS to assess patient utilities and/or the Hospital Anxiety and Depression Scale (HADS) (Although HADS is not strictly a HRQoL measure, it provides insight into the anxiety and depressive symptoms of GEP-NET patients' underlying HRQoL) in addition to the EORTC measures ($n = 5$)^[45]. Larsson *et al*^[25] reported mean baseline HADS anxiety and depression scores of 4.6 (SD: 4.0) and 3.2 (SD: 2.7), respectively. Four studies applied the Short Form-36 (SF-36) questionnaire^[9,46-48], three of which were cross-sectional studies. Other measures used include the SF-12^[49], the Functional Assessment of Cancer Therapy-Anaemia^[50] and the Functional Assessment of Chronic Illness Therapy-Diarrhoea (FACIT-D). Pezzilli *et al*^[49] reported no significant difference between P-NET patients and a sample of age- and sex-matched subjects in terms of physical domain (44.7 ± 11.0 vs 46.1 ± 9.9 , $P = 0.610$), but a significantly lower mental score in the same patients compared to the normative population (42.4 ± 13.0 vs 48.2 ± 9.8 , $P = 0.036$).

The average HRQoL global health score at baseline and at different timepoints during each trial, obtained by asking patients to rate their overall health, have been reported for the EORTC QLQ-C30 (Table 2). A higher score represents a higher ("better") level of functioning, including the global health score. This particular tool became the primary focus of this manuscript, as EORTC QLQ-C30 was the single most commonly cited HRQoL dimension ($n = 24$), with global health score providing a single HRQoL dimension for comparison between studies. The average value for the baseline global health score had a range of 56–70. A higher score for symptoms represents a "worse" level of symptoms. Lowest average score ranges were observed for baseline EORTC QLQ-C30 scores in the following symptoms: nausea and vomiting (4.1–20), insomnia (11.0–38.6), appetite loss (9.2–27.8), constipation (0–24.4) and financial difficulties (6–23.6). Diarrhoea demonstrated a wide range of mean values (16.7–78.3), which can be attributed to the heterogeneity of disease symptoms in GI-NET and P-NET patients, indicating that diarrhoea in GEP-NET patients is multifactorial and very variable. Considering disease location, the average baseline global health scores were comparable, ranging from 56–68 for GI-NETs (4 studies) and

Table 2 Literature reporting scores for health-related quality of life average global health score for gastroenteropancreatic neuroendocrine tumours patients using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30

Ref.	Intervention/comparator	Time point	Global health score	Statistical analysis and <i>P</i> values, as presented in the literature
Arnold <i>et al</i> ^[31] , 2005	Octreotide plus interferon alpha	Baseline	57.9	0.04 (between treatment arms at 3 mo)
		3 mo	51.2	
	Octreotide monotherapy	Baseline	63	
		3 mo	74.4	
Cella <i>et al</i> ^[44] , 2018	Telotristat ethyl	-	Overall: 55.4; Durable responders: 40; Non-durable responders: 66	NR (NS)
Fröjd <i>et al</i> ^[37] , 2007	Various (<i>i.e.</i> interferon, octreotide, chemotherapy and other)	Timepoint 1	58	NR
		Timepoint 2	61	NR
		Timepoint 3	58	NR
		Timepoint 4	58	NR
van der Horst-Schrivers <i>et al</i> ^[67] , 2009	NA	-	61.8	NR
Korse <i>et al</i> ^[30] , 2009	Long-acting sandostatin LAR	Baseline	70	0.275 (repeated measurement analysis using mixed linear models)
		3 mo	71	
		6 mo	67	
		9 mo	68	
		12 mo	64	
Larsson <i>et al</i> ^[50] , 2008	Erythropoietin	Baseline	56	NR (NS)
		4 mo	55	
		8 mo	66	
		2 yr	70	
Larsson <i>et al</i> ^[25] , 2001	Interferon, somatostatin analogue, interferon, and a somatostatin.	Baseline	68	NR (NS)
		3 mo	59	
		6 mo	58	
		9 mo	50	

		12 mo	63	
Larsson <i>et al</i> ^[26] , 1999	Interferon and/or a somatostatin analogue for at least 4 weeks - Five patients were treated with interferon, three with a somatostatin analogue, and nine with a combination	-	64.71	NR
Larsson <i>et al</i> ^[38] , 1999	Interferon and/or a somatostatin analogue	-	Overall: 66.7; HADS Anxiety (cases): 46; HADS Anxiety (non-cases): 71.6; HADS Depression (cases): 43; HADS Depression (non-cases): 70.2	< 0.001 between HADS anxiety "cases" (<i>n</i> = 19) and "non-cases" (<i>n</i> = 80) and 0.001 between HADS depression "cases" (<i>n</i> = 13) and "non-cases" (<i>n</i> = 86)
Larsson <i>et al</i> ^[69] , 1998	Interferon and/or a somatostatin analogue and/or a combination	-	64.71	NR
Lewis <i>et al</i> ^[3] , 2018	NA	-	Without CS: 63.0; With CS: 61.7	0.04 (between subpopulations)
Marinova <i>et al</i> ^[61] , 2019	¹⁷⁷ Lu-DOTATATE	Baseline	62.6	
		3 mo	66.7	< 0.05 (compared to baseline using mixed longitudinal model)
		6 mo	69.6	< 0.01 (compared to baseline using mixed longitudinal model)
		9 mo	69.4	< 0.01 (compared to baseline using mixed longitudinal model)
Meyer <i>et al</i> ^[42] , 2014	Capecitabine and streptozocin plus cisplatin.	Baseline	69.3	
		≤ 9 wk - after 3 × 3 weekly cycles	52.2	0.052 (compared to baseline)
		6 mo	56	0.68 (compared to baseline)
	Capecitabine and streptozocin	Baseline	67	
		≤ 9 wk - after 3 × 3 weekly cycles	62.2	0.5 (compared to baseline)
		6 mo	68.9	0.75 (compared to baseline)
Mitry <i>et al</i> ^[40] , 2014	Bevacizumab plus capecitabine	Baseline	67	
		6 mo	63	NR (NS)
		12 mo	71	NR (NS)
Pavel <i>et al</i> ^[56] , 2016	Everolimus	End of treatment (compared to baseline)	P-NET: -3.9; non P-NET: -13	NR
Ramage <i>et al</i> ^[54] , 2019	Everolimus	1 mo	FAS Population (paired scores baseline and 1 m): 58	NR (NS)
			Continuing tx at 6m (paired scores baseline and 1 m): 56.9	NR (NS)

		2 mo	FAS Population (paired scores baseline and 2 m): 57.6	NR (NS)
			Continuing tx at 6m (paired scores baseline and 2 m): 56.9	NR (NS)
		3 mo	FAS Population (paired scores baseline and 3 m): 56.7	NR (NS)
			Continuing tx at 6m (paired scores baseline and 3 m): 56.3	NR (NS)
		4 mo	FAS Population (paired scores baseline and 4 m): 56	NR (NS)
			Continuing tx at 6 m (paired scores baseline and 4 m): 56.8	NR (NS)
		5 mo	FAS Population (paired scores baseline and 5 m): 56.6	NR (NS)
			Continuing tx at 6 m (paired scores baseline and 5 m): 58.6	NR (NS)
		6 mo	FAS Population (paired scores baseline and 6 m): 56.9	NR (NS)
			Continuing tx at 6 m (paired scores baseline and 6 m): 56.9	NR (NS)
Raymond <i>et al</i> ^[34] , 2011	Sunitinib	Baseline	67	
		"post-baseline"	62.4	NR
	Placebo	Baseline	64	
		"post-baseline"	61.3	NR
Rinke <i>et al</i> ^[16] , 2019	Long-acting octreotide	Baseline	64	
	Placebo	Baseline	65.7	
		12 wk	+4.13 (difference in global health score compared to placebo)	NR
		24 wk	+5.05 (difference in global health score compared to placebo)	NR
		36 wk	+1.85 (difference in global health score compared to placebo)	NR
Strosberg <i>et al</i> ^[17] , 2018	¹⁷⁷ Lu-DOTATATE	Baseline	67	NR
	High-dose octreotide	Baseline	64	NR
Teunissen <i>et al</i> ^[62] , 2004	¹⁷⁷ Lu-DOTATOC	Baseline	69	
		6 wk	78.2	< 0.01 (Analysis of variance (two-sided) compared to baseline)

Vinik <i>et al</i> ^[35] , 2016	Sunitinib	Baseline	67	NR (NS difference between arms)
		Up to cycle 10 (about 9 mo)	60.4	
	Placebo	Baseline	64	NR (NS difference between arms)
		Up to cycle 10 (about 9 mo)	61.3	
Wymenga <i>et al</i> ^[57] , 1999	Lanreotide prolonged release	Baseline	60.4	0.001 (compared to baseline using t tests or Wilcoxon signed rank)
		1 mo	69.7	
		End of treatment	65.5	
Yadegarfar <i>et al</i> ^[33] , 2013	Somatostatin analogues or interferon therapy	Baseline	61	NR
		3 mo	67	
		6 mo	67	
Zandee <i>et al</i> ^[58] , 2019	¹⁷⁷ Lu-DOTATATE	Baseline	61.7	0.002 (compared to baseline using paired t test)
		3 mo (after final PRRT cycle)	79.5	

NA: Not available; NET: Neuroendocrine tumours; CS: Carcinoid syndrome; NR: Not relevant; PRRT: Peptide receptor radionuclide therapy; NS: Not significant.

56–67 for P-NETs (5 studies).

Whilst the most popular HRQoL measure was EORTC QLQ-C30, studies that employed the QLQ-GI.NET21 module provided domain scores specific to the disease that is the focus of this report, including: endocrine systems, gastrointestinal systems, disease-related worries, bone/muscle pain *etc.* Table 3 presents the scores given for these domains. The average HRQoL score ranges for body image (13.3–29.1), weight gain (9–27.8) information/communication (1.1–16.0) and treatment-related symptoms (6.5–26.24) showed that these were only minor problems experienced by patients with GI-NETS. Other domains displayed a wide range of scores, *e.g.* sexual function (28.2–68.4), social function (30.0–72.9) and disease-related worries (37.6–84.2), making these some of the most important problems experienced by many patients. The QLQ-GI.NET21 module has been validated as a responsive tool for assessing HRQoL of patients with GEP-NETs^[33], although it is accepted that numbers were too small for a proper validation in patients with P-NETs alone. This is of relevance, as P-NET patients often present with a more aggressive disease and concomitant treatments may be used.

In addition, a 10-point change in an EORTC domain score is frequently considered a minimal clinically important difference and, using Kaplan-Meier methodology, time to

Table 3 The specific domain scores reported in the literature for gastroenteropancreatic neuroendocrine tumours patients using QLQ-GI.NET21

Ref.	Intervention/comparator	Time point	Endocrine Symptoms	Gastrointestinal Symptoms	Social function	Disease related worries	Muscle/bone pain symptom	Weight gain	Information/Communication function	Body Image	Sexual function	Treatment related symptoms scale
Ramage <i>et al</i> ^[54] , 2019	Everolimus	Baseline (paired scores with 3 mo)	14.8	24.4	44.1	51.1	35.2	NR	1.9	25.9	37	NA
		3 mo	12.3	20.2	42.6	44.8	35.2	NR	4.6	24.1	42.6	22
		Baseline (paired scores with 6 mo)	14.4	25.8	44.8	50.9	33.3	NR	1.1	20	35.6	NA
		6 mo	12.6	21.8	34.4	43.7	30	NR	1.1	21.1	37.8	14.1
Lewis <i>et al</i> ^[6] , 2018	NA	Single timepoint (patients without CS)	16.7	18.9	60.0	56.9	41.3	18.7	10.7	15.3	60.8	17.5
		Single timepoint (patients with CS)	28.4	24.0	68.4	38.7	46.7	13.3	16.0	13.3	68.4	10.1
Yadegarfar <i>et al</i> ^[33] , 2013	Various	Baseline (P-NETs)	22	26	39	56	25	11	10	25	32	18
		3 mo (P-NETs)	16	18	33	44	31	9	4	21	31	22
		6 mo (P-NETs)	18	22	30	50	32	13	10	19	31	23
Ballal <i>et al</i> ^[8] , 2019	²²⁵ Ac-DOTATATE TAT	Baseline	21.4	40.2	64.3	61.2	38.8	25	NR	28.8	40	6.53
		End of assessment	3.57	22.8	72.9	84.2	26.8	27.8	NR	15.6	45	26.24
Strosberg <i>et al</i> ^[17] , 2018	¹⁷⁷ Lu-DOTATATE	Baseline	NR	22.8	33.4	43.7	29	NR	5.4	20	30.6	11.6
	High-dose octreotide	Baseline	NR	23.8	37.1	43.8	34.6	NR	12.3	20.3	28.2	11.9
Cella <i>et al</i> ^[44] , 2018	Telotristat ethyl	Baseline (Durable responders)	37.8	33.8	46.7	41.1	35	NR	5	29.1	47.2	18.1
		Baseline (Nondurable responders)	29.5	28.5	38.5	37.6	30.3	NR	7	26.9	32.6	12.8
		Difference in change from baseline between subpopulations	-1.9	-9.6	-2.8	1.9	-4.5	NR	3.9	1	-1.6	-3.4

NA: Not available; P-NET: Pancreas-neuroendocrine tumours; CS: Carcinoid syndrome; NR: Not relevant.

deterioration (TTD) can be measured using a 10-point decline in analogy with time to event curves^[51,52]. Two studies identified in the literature search applied the use of minimal important difference in the change in HRQoL domains as a means of assessing the impact of interventions using TTD, and time until definitive deterioration (TUDD), *i.e.* ≥ 10 point worsening of a HRQoL domain score from baseline without further improvement^[16,17].

The SF-36 measures eight dimensions of HRQoL, where item scores are linearly transformed into scales ranging from 0 to 100, with higher scores indicating better HRQoL. In cross-sectional studies, HRQoL has been shown to be significantly reduced in patients with GEP-NETs compared to the general population in every SF-36 dimension^[46,47]: 77.9 *vs* 70.0 for physical functioning, 65.0 *vs* 40.2 for role physical, 69.1 *vs* 64.3 for bodily pain, 74.3 *vs* 54.8 for general health, 60.9 *vs* 49.5 for vitality, 83.9 *vs* 75.5 for social functioning, 77.4 *vs* 64.4 for role emotional and 80.6 *vs* 74.9 for mental health. Mean scores for each scale were consistently worse in a sub-population of patients with impaired bowel/bladder function, which was strongly correlated with high scores for diarrhoea^[46], a symptom of CS which reduces patient HRQoL. Elsewhere, Haugland *et al*^[9] reported only the physical component (39.6) and the mental component (45.9) scores; these were similar to baseline scores previously reported^[53]. Frilling *et al*^[48] reported improved HRQoL (assessed using SF-36) in 50% of patients in their prospective study of ⁹⁰Y-DOTATOC therapy followed by ¹⁷⁷Lu-DOTATOC, but sample size was low ($n = 20$).

Various studies used other HRQoL tools to evaluate HRQoL in GEP-NET patients; direct comparisons between these studies were limited by the small number of studies using each tool ($n \leq 2$) and the heterogenous population and treatment interventions. Pezzilli *et al*^[49] was the only identified publication to use SF-12 in a population of P-NET patients, reporting a good physical HRQoL that was not significantly different to the normative population (44.7 ± 11.0 *vs* 46.1 ± 9.9 , $P = 0.610$), but a significantly impaired mental component (42.4 ± 13.0 *vs* 48.2 ± 9.8 , $P = 0.036$). Pezzilli *et al*^[49] was also the only study to employ the Beck Depression Inventory and State Anxiety Inventory Y-1; 8 patients (18.2%) identified with moderate depression, 9 patients (20.5%) with mild moderate depression, and 27 patients (61.4%) with no depression. Anxiety results were similar in the patients and in the normative population. Ramage *et al*^[54] used the EQ-5D-5L (in addition to EORTC QLQ-C30 and GINET21), with no significant difference for the composite health index or self-rated (global) health score noted between baseline and 6-mo treatment with everolimus. The EQ-5D VAS was employed in two studies: Kulke *et al*^[55] examined patients receiving repeated 6-weekly cycles of oral sunitinib, noting no significant difference in VAS scores over the study period, whilst Pavel *et al*^[56] reported a reduced mean VAS from baseline to end of treatment with oral everolimus (10 mg daily, in 28-d cycles) in non-P-NET patients (63.9 ± 19.0 *vs* 55.3 ± 23.0 , respectively) compared to P-NET patients (68.8 ± 19.9 *vs* 66.5

± 20.6 , respectively). The FACIT-D measure is a symptom-specific measure used by Kvols *et al.*^[29] in a Phase II, open-label, multicentre prospective study of self-administered pasireotide. Clinical responders were noted to have improved mean scores at the end of treatment compared to baseline. Kulke *et al.*^[55] reported that the mean FACIT-fatigue score remained stable for each treatment cycle of sunitinib with a “modest” score increase during the dosing period. Elsewhere, Larsson *et al.*^[50] used the Functional Assessment of Cancer Therapy-Anaemia measure to assess the HRQoL of GEP-NET patients with anaemia being treated with erythropoietin; no significant changes were observed over the study period. Finally, O’Toole *et al.*^[32] showed no significant difference in HRQoL scores between lanreotide and octreotide using the Index de Santé Perceptuel de Nottingham measure. These studies provide a basis for future randomised control trials to test whether interventions improve HRQoL for patients with GEP-NETs.

All studies included in this review reported the HRQoL of patients with inoperable tumours; the majority of which described the disease as metastatic and/or advanced (Table 1), and thus the disease could be categorised as stage IV. Out of these studies, only two provided explicit information regarding disease stage for the entire study population^[57,58]. Notably, no studies investigated how disease stage and tumour functionality affect HRQoL in GEP-NET patients, with HRQoL data most often presented according to treatment comparator.

Treatment impact on HRQoL

Few studies reported a significant difference ($P < 0.05$) in the patients’ global health score between baseline and after a period of treatment (Table 2).

HRQoL was maintained with few deteriorations in patients receiving long-acting octreotide compared to the deterioration observed in patients who received a placebo^[16,27]. Octreotide improved HRQoL scores for the clinically important GEP-NET symptoms such as fatigue, insomnia, diarrhoea and pain; whereas significantly earlier TUDD was observed in the placebo arm for fatigue, pain and insomnia in patients with GI-NETs than those treated with long-acting octreotide ($P < 0.05$)^[66]. An improvement in the EORTC global health score was shown after 3 mo on octreotide but not when octreotide was combined with interferon alpha^[51]. Flushing was shown to be reduced significantly following 12 mo of treatment with long-acting octreotide^[30]. Further studies are deemed necessary to assess the HRQoL of GEP-NET patients treated with pasireotide, who are refractory or resistant to octreotide; symptom-specific scores and total FACIT-D assessments showed some variability and no clear trends but sample size was small ($n = 30$)^[29].

Another somatostatin analogue shown to bring about significant improvement in the global health score of GEP-NET patients was prolonged-release lanreotide^[57], possibly driven by improvements in symptom scales or single-term measures such as fatigue, pain, nausea/vomiting, sleeping problems, appetite, constipation, diarrhoea and financial problems; although dyspnoea became more severe during the 6-mo treatment period. O’Toole *et al.*^[32] found no significant HRQoL differences between lanreotide and octreotide, although most patients prefer lanreotide due to its simplified mode of administration. However, examining evidence from the CLARINET study, and mapping EORTC QLQ-C30 to EQ-5D-based utility values, no significant differences in HRQoL were noted between the lanreotide and placebo arms^[28].

PRRT treatment for GEP-NETs has been shown to result in stable HRQoL scores during and after a 3-mo treatment period, compared to baseline levels using the EORTC QLQ-C30 measure^[59,60]. In more recent studies, treatment with ¹⁷⁷Lu-DOTATATE was shown to be a safe and effective therapy in the treatment of functioning P-NETs^[58] leading to a significant increase in the global health score observed at follow-up compared to baseline (79.5 vs 61.7, $P = 0.002$). Furthermore, significant improvements in the physical functioning, role functioning, emotional functioning, and social functioning were reported. Of all symptom scales, only “fatigue” was found to have significantly decreased (27.3 vs 17.2, $P = 0.02$). These results are consistent with a recent retrospective analysis study conducted by Marinaova^[61]; HRQoL was significantly improved in GI-NET patients receiving ¹⁷⁷Lu-DOTATATE compared to baseline, revealing an increased global health score (3 mo after 1st, 2nd, and 3rd treatment cycle $P = 0.049$, $P = 0.004$, and $P = 0.041$, respectively).

In the Phase III NETTER-1 study, 231 patients were recruited with 117 randomised to the ¹⁷⁷Lu-DOTATATE arm (200 mCi every 8 wk for four treatments) and 114 to the high-dose octreotide long-acting repeatable arm (60 mg every 4 wk)^[17]. HRQoL analysis, conducted on an intention-to-treat basis, demonstrated that ¹⁷⁷Lu-DOTATATE provides a significant and clinically robust HRQoL benefit for patients

with progressive GI-NETs (compared to high-dose octreotide). TTD, defined as the time from randomisation to first HRQoL deterioration of ≥ 10 points from baseline score, was significantly longer in the ^{177}Lu -DOTATATE arm ($P < 0.001$); the hazard ratio was 0.406 for global health status, 0.518 for physical functioning, 0.580 for role functioning, 0.621 for fatigue, 0.566 for pain, 0.473 for diarrhoea, 0.425 for body image and 0.572 for disease-related worries. Differences in median TTD were clinically significant in several domains: 28.8 mo *vs* 6.1 mo for global health status, and 25.2 mo *vs* 11.5 mo for physical functioning. Significant improvements in TUDD were also observed for the global health score ($P < 0.001$), as well as for physical functioning ($P = 0.002$), role functioning ($P < 0.001$), emotional functioning ($P = 0.020$), social functioning ($P = 0.001$), pain ($P = 0.002$), insomnia ($P = 0.026$), appetite loss ($P = 0.009$), constipation ($P = 0.042$), diarrhoea ($P = 0.001$), GI scale ($P = 0.005$), treatment scale ($P = 0.002$), social function scale ($P = 0.011$), disease-related worries scale ($P = 0.001$), and body image ($P = 0.002$).

Other PRRT interventions included the use of ^{177}Lu -DOTATOC^[62], ^{90}Y -DOTATOC^[59] and ^{225}Ac -DOTATATE^[8]. ^{177}Lu -DOTATOC treatment improved functional scales and most single item scores in GEP-NET patients, whilst symptom scale scores for fatigue and pain decreased significantly from 31.9 to 22.8 ($P < 0.01$) and 23.3 to 15.0 ($P < 0.05$), respectively^[62]. Martini *et al*^[59] examined HRQoL following 4–6 cycles of ^{177}Lu -DOTATATE or ^{90}Y -DOTATOC. The most significant domain change for GI-NETs was noted for diarrhoea (-16.3 points, $P = 0.008$). Compared to ^{90}Y -DOTATOC, ^{177}Lu -DOTATATE demonstrated a reduced score for fatigue (-27.7 points, $P = 0.020$) and better physical functioning (+22.4 points, $P = 0.050$), cognitive functioning (+23.1 points, $P = 0.003$) and global health score (+17.3 points, $P = 0.029$) in P-NET patients. ^{225}Ac -DOTATATE therapy has the potential to overcome the resistance of GEP-NET to ^{177}Lu -DOTATATE beta therapy and promote remission with minimal or transient toxicity, whilst reducing endocrine ($P = 0.001$) and gastrointestinal symptoms ($P < 0.001$), although treatment-related symptoms were worsened by the end of the assessment ($P = 0.001$)^[8].

A significant difference in the EORTC QLQ-C30 physical functioning scale was noted by Ramage *et al*^[54] following 6-mo treatment with everolimus, but no other significant differences were noted during this treatment period; in line with what was also shown by analysis conducted in conjunction with the RADIANT trial^[56]. Likewise, sunitinib has no significant impact on global health score of EORTC QLQ-C30, but it has been shown to improve the HRQoL symptom scores of insomnia and diarrhoea compared to placebo in P-NETs^[34,35]. In another study^[55], there was no significant difference in EQ-VAS scores over 6 treatment cycles of sunitinib. There was no significant impact on the HRQoL of patients with GI-NETs when treated with erythropoietin for the anaemia associated with interferon therapy^[50].

Chemotherapy in the BETTER trial was chosen based on NET location; GI-NETs were treated with capecitabine and bevacizumab, whilst P-NETs patients received 5-fluorouracil/streptozocin with bevacizumab. Differences in the EORTC QLQ-C30 global health score between baseline, 3-mo, 6-mo and 12-mo follow-up assessments were not significant^[40,41]. The NET01 trial suggested that the addition of cisplatin to the combined capecitabine and streptozocin regimen worsened HRQoL^[42]. After three cycles, the mean global health score was 67.0 *vs* 62.2 ($P = 0.5$) in the capecitabine and streptozocin arm and 69.3 *vs* 52.2 ($P = 0.052$) in the capecitabine and streptozocin plus cisplatin arm. After 6 cycles, mean global health score remained virtually unchanged in the capecitabine and streptozocin arm from 66.7 *vs* 68.9 ($P = 0.75$) and 59.8 *vs* 56.0 ($P = 0.68$) in the capecitabine and streptozocin plus cisplatin arm. All three studies were based on small HRQoL sample sizes (less than 100).

Of the remaining treatments identified within the scope of this study, the HRQoL was improved or remained the same in all GEP-NET patients treated with MIBG therapy. Three studies used more than one treatment in the populations studied without breaking down HRQoL results into treatment categories^[26,37,38]. Using HADS, Larsson *et al*^[25] noted a lower anxiety rating at 12 mo ($P < 0.05$) following treatment with interferon, somatostatin analogue or a combination of both, whilst the depression score was significantly higher at 9 mo ($P < 0.01$) when compared to baseline. The study by Fröjd *et al*^[37] suggested a slight increase in HADS anxiety over time (timepoints unspecified) in a longitudinal study of octreotide and/or interferon or chemotherapy or no treatment, but sample size was small and significance was not reported. Finally, telotristat ethyl therapy was not shown to be associated with any measurable short-term HRQoL benefits when assessed using the EORTC QLQ-30 measure, beyond diarrhoea^[44].

DISCUSSION

Given the indolent nature and slow progression of disease in most GEP-NET patients, assessment of HRQoL is vital for monitoring impact of treatment. The lack of conclusive data on outcomes in GEP-NETs can be attributed, in part, to the small sample size of clinical trials involving GEP-NETs that makes it difficult to capture clinically meaningful changes or a significant benefit in terms of HRQoL^[6]. Moreover, the work by Martini *et al*^[18] showed that a transfer of HRQoL results into clinical practice is hindered by the scarcity of robust studies and the quality of HRQoL assessment^[18]. To our knowledge, our study is the first to report a systematic review investigating the impact of treatments on the HRQoL of GEP-NET patients and the development status of instruments used in terms of validation and minimal important difference.

Martini *et al*^[18] performed a systematic review examining methodological robustness of HRQoL studies of patients with GEP-NETs. They concluded that heterogeneity and limited methodological quality of considered studies did not permit them to draw conclusions regarding the impact of HRQoL in clinical practice. In agreement, our review confirmed heterogeneity of studies and patient characteristics, including variety in intervention or comparator treatment, disease severity and location of primary tumour, age, gender and other symptoms or comorbidities. Sample size for studies considered eligible for inclusion ranged from 17 to 253 patients, with a median of 57, highlighting the usual small number of study participants. A similar median value of 51 (range 9–663 patients) was reported by Martini *et al*^[18]. Further, where comparator groups were used, HRQoL scores were sometimes reported for the entire study population and not for the respective treatment groups in the study^[29,33,40,41,44]. Due to the wide range of comparators identified and the significant heterogeneity across the studies included in this review, which would violate the assumptions of meta-analysis, HRQoL related to various GEP-NET treatments was assessed in a qualitative manner rather than quantitative (*e.g.* meta-analysis).

In line with Martini *et al*^[18], we identified the well-validated EORTC QLQ-C30 as the most commonly used HRQoL instrument in GEP-NET patients. The EORTC instrument has been used in 30 out of 43 published studies; however, validation and definition of minimal important difference have not been reported to date specifically for GEP-NET patients. The EORTC QLQ-GINET21 module ($n = 6$) and the SF-12/36 tools ($n = 5$) have occasionally been used, with other instruments used in two or less publications.

Where change in the EORTC QLQ-C30 global health score could be calculated from baseline scores (Table 2), six studies demonstrated a trend towards an improved score, three showed a decline, with the remaining studies presenting mixed or inconsistent responses depending on intervention and/or follow-up time point. However, results should be interpreted with caution for the reasons given above. The mixed HRQoL trends are comparable to those reported by Jimenez-Fonseca *et al*^[63], who highlighted the existing evidence for improved treatment efficacy, safety or toxicity for a range of therapies, including somatostatin analogues, sunitinib and everolimus, but with mixed HRQoL response. Jimenez-Fonseca *et al*^[63] suggested the generic EORTC QLQ-C30 has not been developed specifically for GEP-NET patients and, therefore, may lack the sensitivity to detect subtle HRQoL changes in association with disease items that are relevant to GEP-NET patients.

Given the potentially long treatment duration in GEP-NET patients, one challenge of HRQoL analysis is taking the potential occurrence of a response shift into consideration. This can occur as self-assessment of HRQoL is inherently subjective; patients can adapt to their disease and the treatment toxicities resulting in changing standards of HRQoL over time^[51]. Thus, the choice of the reference score to qualify a change such as deterioration is a major concern. With this in mind, it is difficult to determine the change in HRQoL over time in most studies identified in this systematic review. One approach that deals with response shift effect as a concept is evaluation of TTD, making use of minimal important difference as a criterion for signalling deterioration. In the Phase III trial NETTER-1, it was shown that adjusting for significant covariates (HRQoL baseline values, OctreoScan maximum tumour uptake score, and/or age), the impact of treatment remained statistically significant for global health score, physical functioning, diarrhoea, and body image domains^[17]. Osoba *et al*^[52] rated patients' perceived change in EORTC QLQ-C30 in breast cancer or small-cell lung cancer patients, concluding a "moderate" change equated to a 10–20 change in mean scores. Use of a minimal important difference of at least 10 points as a criterion for deterioration yielded TTD curves with a time course similar to that of the curves for centrally reviewed radiological progression^[17]. It should be noted, however,

that the “minimal important difference” was not defined specifically for patients with midgut NETs participating in the NETTER-1 study. Moreover, the TTD and TUDD criterion of a drop in ≥ 10 points in a domain score was used to show more than half of the EORTC QLQ-30 domains improved for patients treated with ^{177}Lu -DOTATATE compared to a control arm; the same TUDD criterion was also applied by Rinke *et al*^[16], who showed long-acting octreotide significantly extended TUDD for fatigue, pain and insomnia HRQoL domains compared to a placebo.

Treatment of GEP-NETs with ^{177}Lu -DOTATATE consistently improved global health score compared to baseline^[58,61,62] and increased TTD. The Phase III NETTER-1 study provides the best information available regarding HRQoL in patients with advanced progressive GEP-NETs not only in terms of benefit but also in terms of TTD^[17]. However, the minimal important difference (and clinically meaningful thresholds) for improvement/worsening has not been defined yet for the EORTC QLQ-C30 specifically in GEP-NET patients, although it has for a number of other common cancers^[64,65]. It is conceivable that the abbreviated version of the EORTC QLQ-C30 (possibly combined with GINET21 and computer adaptive testing) can be developed especially for use in clinical practice. Thus, there is scope for further research in this area and exploration of HRQoL as a potential tool for monitoring disease progression. Longitudinal studies with a long-term follow-up and involving clinical practice patients may provide further insight into the potential role of HRQoL in patient monitoring and management.

In conclusion, study and patient heterogeneity, small sample sizes and limited methodological quality in terms of assessing HRQoL has impaired definitive statements being made regarding the impact of the various treatment options for GEP-NETs in terms of HRQoL^[66-69]. A number of randomised trials demonstrated only small or no HRQoL changes between active treatment and placebo arms. The Phase III NETTER-1 is the only study to have shown more significant and robust differences between active and placebo groups. It demonstrated that PRRT can delay the time to worsening of HRQoL in GEP-NET patients. However, validation of QLQ-C30 and GINET21 specifically for GI-NET and P-NET patients, and definition of minimal important difference and clinical thresholds, are still lacking for these patients. As such, further research is necessary in order to offer a benchmark for interpreting the clinical importance of differences in HRQoL domain scores between groups or changes in these scores over time in conjunction with different treatment modalities.

ARTICLE HIGHLIGHTS

Research background

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) are slow-growing cancers that arise from diffuse endocrine cells in the gastrointestinal tract (GI-NETs) and pancreas (P-NETs). The majority of patients who are diagnosed with GEP-NETs have metastatic disease. Despite this, systemic therapies provide a 5-year survival rate of about 75% for patients with GI-NETs and $> 60\%$ for patients with P-NETs.

Research motivation

Health related quality of life (HRQoL) is an increasingly important concept, reflecting the patients’ perspective in conjunction with the disease presentation, severity, and treatment. Although not curative, long-term therapeutic options are available for patients with GEP-NETs to provide symptomatic relief, and these can even slow down and stabilise disease for multiple years. Since patients can live many years by managing their disease in this way, understanding the impact of treatment on GEP-NETs patients’ HRQoL is paramount especially given the indolent course the disease may take in patients.

Research objectives

The aim of this study was to perform a systematic review to assess the HRQoL of patients with inoperable metastatic GEP-NETs undergoing various treatments in order to uncover areas for future research. This systematic literature review is a response to the increased importance of assessing HRQoL with validated patient-reported outcome instruments for which the minimal important difference has been defined.

Research methods

The systematic review performed here adhered to the established international

guidelines for conducting systematic reviews. A search strategy was developed and refined to recover relevant publications reporting HRQoL data for adult patients with GEP-NETs. Data were extracted from every record returned by the literature search that met the inclusion criteria of the study.

Research results

A total of 42 studies met the inclusion criteria of the study. The EORTC QLQ-C30 and gastrointestinal GI-NET module (QLQ-GI.NET21) were the most used HRQoL instruments, exhibiting a range of outcomes compared to baseline for the specific interventions.

The worst HRQoL observed at baseline were related to the following symptoms: Nausea and vomiting (4.1–20.0), insomnia (11.0–38.6), appetite loss (9.2–27.8), constipation (0–24.4) and financial difficulties (6.0–23.6). Diarrhoea demonstrated a wide range of mean values (16.7–78.3), which can be attributed to the heterogeneity of involved GEP-NET patients.

The average value for the baseline global health score had a range of 56–70. Where change in the EORTC QLQ-C30 global health score could be calculated from baseline scores, five studies demonstrated a significant trend towards an improved score. Treatment of GEP-NETs with ¹⁷⁷Lu-DOTATATE consistently improved global health score compared to baseline and increased time-to-deterioration, *i.e.* time until HRQoL worsens by at least 10 points for each domain (*e.g.* global health, physical functioning). The Phase III NETTER-1 study resulted in time-to-deterioration curves consistent with the curves for progression free survival for ¹⁷⁷Lu-DOTATATE. However, the EORTC QLQ-C30 and QLQ-GINET21 have not been validated, and the minimal important differences have not yet been defined, specifically for GI-NET and P-NET patients.

Research conclusions

Study and patient heterogeneity, small sample sizes and limited methodological quality in terms of assessing HRQoL has impaired definitive statements being made regarding the impact of the various treatment options for GEP-NETs in terms of HRQoL. A notable finding was that PRRT can delay the time to worsening of HRQoL in GEP-NET patients. However, validation of EORTC QLQ-C30 and GINET21 specifically for GI-NET and P-NET patients and the definitions of minimal important difference and clinical thresholds are still lacking for these patients. As such, further research is necessary in order to offer a benchmark for interpreting the clinical importance of differences in HRQoL domain scores between treatment groups or changes in these scores over time in conjunction with different treatment modalities.

Research perspectives

Further research is necessary in order to offer a benchmark for interpreting the clinical importance of differences in HRQoL domain scores over time and between treatment groups.

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