This is the peer-reviewed but unedited manuscript version of the following article: Topping, M., Gray, D., Friend, E., Davies, A., & Ramage, J. (2017). A Systematic Review of Symptoms and Quality of Life Issues in Pancreatic Neuroendocrine Tumours, *Neuroendocrinology* (DOI: 10.1159/000475793). The final, published version is available at https://doi.org/10.1159/000475793

Title: A systematic review of symptoms and quality of life issues in pancreatic neuroendocrine tumours.

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Abstract

Purpose Pancreatic neuroendocrine tumours (pNETs) are rare neoplasms, in that they may only present symptoms of the hormone secreted, without any generic cancer issues. It is thus important to measure quality of life (QoL) in these patients by evaluating issues relevant and important to them, as opposed to general cancer issues. This paper systematically reviews papers addressing the symptoms and QoL implications of pNETs, and evaluates each subtype separately, with the aim to create a list of QoL issues relevant to these patient groups.
Methods Medline, EMBASE, CINAHL, PsycInfo, Web of Science, Scopus, OpenGrey and the Cochrane Library were searched for publications (1990-2016) reporting symptoms and QoL issues in pNETs.
Results Following screening of 2797 papers, 69 articles were eligible for data extraction. From these papers, 84 different symptoms or QoL issues were extracted: 21 for gastrinoma, 18 for glucagonoma, 50 for insulinoma, 10 for VIPoma and 15 for non-functioning pNETs. No issues were reported for somatostatinoma, PPoma or ACTHoma. The most frequently reported symptoms vary by subtype.
Conclusions This review emphasises the need to develop a QoL measure for pNETs with specific items relevant to the different subtypes, due to the distinct symptoms reported. Following from this review, patient and healthcare professional interviews will be conducted in large cohorts across many different countries to collect more data on QoL issues specific to pNETs. This data will all be collated with the aim to create a QoL measure for pNETs.

Introduction

Neuroendocrine tumours (NETs) are a heterogeneous group of highly vascular, rare neoplasms that arise from cells of the endocrine and nervous system. NETs account for only 0.5% of all malignancies with an incidence of between 3-5 per 100,000 population per year but with a high prevalence of 35 per 100,000 population because of slow tumour growth [1]. NETs arising in the gastrointestinal tract are the most common, accounting for two thirds of all NETs [2]. Pancreatic NETs (pNET) specifically, have an incidence of ≤1 case per 100,000 population per year and account for 1 to 2 per cent of all pancreatic tumours [3-5].

The clinical presentation of a pNET is dependent on its functionality. pNETs can be classified as functioning (causing hormonal symptoms) or non-functioning [1]. Functioning pNETs secrete a predominant hormone and therefore clinically present with a distinct hormonal syndrome. The main types of functioning pNETs are insulinoma, gastrinoma, glucagonoma and VIPoma, with others such as PPoma, somatostatinoma and ACTH secretion being more rare [6], as demonstrated in Table 1. In contrast, non-functioning pNETs do not present clinically with a hormonal syndrome, but often present with symptoms of local compression or metastatic disease [7-9]. As a result of these symptoms in both functioning and non-functioning tumours, one would expect a pNET to significantly impact a patient's QoL. Further to this, surveillance studies have shown that survival

times are generally better in pNETs than many other malignancies, thus patients live with the disease for longer [10-12], making QoL a crucial measure when considering the care for these patients. Despite this however, little data has been reported on the QoL implications for these patients.

Table 1.
Incidence of subtypes of pNETs [13]

Tumour	**Incidence per million per year**
Insulinoma	1-2
Gastrinoma*	1-2
Glucagonoma	0.1
VIPoma	0.1
Somatostatinoma	<0.1
ACTH secreting	<0.1
Non-syndromic (inc Pancreatic Polypeptide)	1-2

**About half of cases arise in the duodenum.*

Quality of life (QoL) encompasses a multitude of facets including physical health, psychological state, social relationships and personal beliefs [14]. Thus, many aspects of a disease affect QoL so it is important to assess in patients living with disease, especially for prolonged periods. The EORTC QLQ-GINET21 Module, designed to be used with QLQ-C30 questionnaire, to assess QoL in patients with gastrointestinal NETs was fully validated and published in 2013 on behalf of the EORTC Quality of Life Group [15]. Originally this research aimed to encompass QoL implications for NETs of gut and of pancreatic origin. However, due to the significant prognostic differences between NETs of gut and of pancreatic origin, there is consensus from patients and NET specialists that the QLQ-GINET21 is not comprehensive enough for patients with pNETs, and this module should be re-developed for this specific patient group. Furthermore, as there is a lack of extensive data available on QoL with pNET patients, it is likely that the issues they face have altered due to changes in disease presentation, symptoms and therapeutic advances in ten years following the QLQ-GINET21 module development [16]. Additionally, not enough patients with functioning pNETs were recruited during the phase 3 module development of the QLQ-GINET21 and therefore these patients (with the exception of gastrinoma) were excluded from the phase 4 validation study, meaning the QLQ-GINET21 is not validated for these patients, and further research needs to investigate the QoL issues specific to pNET patients.

The current review aims to identify the QoL issues faced by patients with pNETs by reviewing the published literature.

Method

Search strategy and eligibility criteria

Medline, Embase, CINAHL, PsycInfo, Web of Science, Scopus, OpenGrey and the Cochrane Library were searched for publications reporting QoL issues in pNET patients. The search extended from January 1990 to May 2016. Terms for pancreatic cancer, pNET and QoL were searched, combined using Boolean logic rules. Pancreatic cancer was combined with the free-text term "endocrine" to help limit the results to pancreatic cancer of the endocrine system. The GINET21 and other relevant existing questionnaires were also searched, combined with the pancreatic cancer and pNET terms. To aid the search for literature on QoL in more rare pNETs (i.e. insulinomas, gastrinomas and glucogonomas), known symptoms such as hypoglycaemia, duodenal ulceration and necrolytic migratory erythema were searched combined with QoL terms. See Table 2 for all search terms applied.

Primary or secondary publications documenting symptoms or QoL issues in patients with pNET were included, only excluding conference abstracts, book chapters, literature reviews, case reports (with less than 3 cases reported) and animal/basic science studies. In the initial search phase, no language restrictions were implemented.

Table 2.
Search terms applied

Concept (combined by AND)	Terms (combined by OR)
Pancreatic Cancer	Pancreatic Neoplasms (MeSH term) Pancreatic Ductal Carcinoma (MeSH term) Pancreas Cancer (Emtree term) Pancrea* Cancer Pancrea* Carcinoma Pancrea* Tumo?r Metastatic Pancrea* Cancer Pancreatic Neuroendocrine Tumo?r
Pancreatic Neuroendocrine Tumours	pNET Pancrea* NET Pancreas Islet Cell Tumor (Emtree term) Islet Cell Adenoma (MeSH term) Islet Cell Carcinoma (MeSH term) Endocrine tumo?r pancreas Endocrine pancrea* tumo?r Gastro-enteropancreatic neuroendocrine tumo?r GEPNET Functioning pancrea* endocrine tumo?r Non-Functioning pancrea* endocrine tumo?r Metastatic NET Gastrinoma (MeSH term) Insulinoma (MeSH term) Glucagonoma (MeSH term) VIPoma (MeSH term) Werner-Morrison syndrome Zollinger-Ellison syndrome Hypoglycemia (Emtree term, MeSH term)
Hypoglycaemia	Hypoglyc*emia
Duodenal ulceration	Duodenum ulcer (Emtree term) Duoden* ulcer*
Necrolytic migratory erythema	Necrolytic migratory erythema
Health-related quality of life	Quality of Life (MeSH term) QoL Health related quality of life HRQOL Subjective health status Patient reported outcome Patient based outcome Patient reported outcome measure PROM Self report Side effect Impairment Complaint Symptom
Existing questionnaires*	GINET21 QLQ C30 PAN26 LMC21

	HCC18
	BIL21
	FACT-HEP
	Norfolk QoL-NET

* [17-24]

Results

Literature search

The searches generated 4723 "hits" in total (Fig. 1). This reduced to 2328 after removing duplicates (n=1926) and case reports (n=469). Titles and abstracts were screened against the eligibility criteria by three of the papers authors (MT, JR and AD). Each reference was coded as 'accept' or the reason for exclusion. A first round of screening identified 480 papers for inclusion (agreement= 82.1%). Discussion between the three raters led to the criteria for inclusion being revised. After which a second round of title and abstract screening was conducted. This resulted in 228 papers being identified for inclusion (agreement = 91.1%). Papers selected by any of the three reviewers were included for full paper review (n=228).

Full paper screening resulted in a further 159 papers being excluded, including 31 conference abstracts, 1 editorial, 21 review articles, 9 case reports, 15 with no mention of QoL or symptoms, 29 on the wrong patient group, 14 did not specify the type of pNET the patients had and 10 only referred to post-treatment issues. The 29 foreign language articles found were rejected since facilities were not available for full translation of all these papers. Thus, 69 papers [25-93] were eligible for data extraction, of which most were retrospective in nature but there were also some prospective observational studies and quasi-experimental trials.

Fig. 1.
Flow chart of the paper selection process

Issues Generation

A total of 69 papers were coded for QoL issues/symptoms. All coding for issues was carried out by the lead author (MT) using NVivo™ Software [94]. Coding included: the type of pNET the patients had, the symptom or quality of life issue reported, and the percentage of patients reporting that symptom in each paper (<20%; 20-50%; 50-80%; >80%). All symptoms or quality of life issues reported in the papers were coded.

A total of 141 potential pNET QoL issues were extracted from the literature. Duplicates, test results and medical terms (as opposed to symptoms) were removed from the list following review by MT and JR, and the list was reduced to 84 issues. There were 21 issues reported for gastrinoma, 18 for glucagonoma, 50 for insulinoma, 10 for VIPoma and 15 for non-functioning pNETs. No issues were reported for somatostatinoma, PPoma or ACTHoma. All reported issues are displayed in Table 3, listed by frequency with most frequently reported at the top of the list. Only two issues were common for all subtypes: weight loss and abdominal pain. Weight loss was reported in 21 papers, and abdominal pain was reported in 29 papers.

The five most frequently reported QoL issues for each of the subtypes are shown in Table 4. This data demonstrates the variation in symptoms between subtypes. The numbers reported in table 4 are the number of papers in which the symptoms are reported for each subtype of pNET and (right hand column) the number of papers in which the symptoms were reported by more than 50% of patients. The symptoms were all reported by patients in some way, but since most papers are retrospective analyses, the mode of patient reporting is not standardised.

Of interest is that in gastrinoma the most prominent symptom is of diarrhea, whereas standard teaching would suggest that dyspepsia and symptoms from ulcers are most common [95]. Similarly diarrhea as a symptom of glucagonoma is not commonly mentioned, but is reported in the most number of papers in this study. However, it is not mentioned by more than 50% of the patients in any one study with weight loss, abdominal pain and rash being reported more commonly. The symptoms of insulinoma as above are similar to what would be expected from standard teaching [95]. The top 3 symptoms of VIPoma are well known but flushing is not usually thought to be a prominent symptom [95]. The abdominal pain of non-functioning pNET may be expected [96] and although jaundice, vomiting anorexia and back pain were reported in some papers, only abdominal pain was reported by more than 50% of patients.

There were no specific symptoms reported for PPoma, confirming the belief that there are often no symptoms caused by these tumours [95]. For somatostatinomas, a number of symptoms are quoted by clinicians in the literature [95], but there are no papers giving reports of these directly from patients. ACTH secreting tumours are very rare and there are again no directly reported symptoms but these are well described since they are essentially the same as for (pituitary) Cushings syndrome.

Table 3:

Symptoms/Quality of Life Issues (listed from most frequently reported to least)

GASTRINOMA	GLUCAGONOMA	INSULINOMA	VIPOMA	NF PNET
Diarrhea	Diarrhea	Hypoglycaemia	Weight loss	Abdominal pain
Abdominal pain	Weight loss	Confusion	Diarrhea	Jaundice
Heartburn	Abdominal pain	Sweating	Dehydration	Anorexia
Nausea	NME*	Weight gain	Flushing	Vomiting
Vomiting	Nausea	Syncope	Abdominal pain	Back pain
Duodenal ulceration	Cheilitis	Hunger	Backache	Diarrhea
GI bleeding	IOM*	Palpitations	Coma	Dyspepsia
Peptic ulceration	Jaundice	Seizures	Skin rash	Fatigue
Weight loss	Peptic ulceration	Abnormal behaviour	Vomiting	Weakness
Dyspepsia	Rash	Dizziness	Weakness	Weight loss
Hematemesis	Vomiting	Tremors		Acute pancreatitis
Painful swallowing	Anorexia	Coma		Bowel habit change
Tarry stools	Conjunctivitis	Weakness		Lethargy
Appetite change	GERD*	Convulsions		Nausea
Constipation	Glossitis	Headaches		Pruritus
Dysphagia	Malaise	Drowsiness		
Epigastralgia	Pruritus	Amnesia		
Jaundice	Reduction in taste	Paresthesias		
Limb edema		Personality change		
Regurgitation		Visual disturbance		
Weakness		Abdominal pain		
		Anxiety		
		Blurred vision		
		Fainting		
		Weight loss		
		Diplopia		
		Irritability		
		Light-headedness		
		Nausea		
		Pallor		
		Speech disturbances		
		Vertigo		
		Aggressiveness		
		Altered mental states		
		Awake to eat at night		
		Cognitive dysfunction		
		CD*		
		Fatigue		
		Giddiness		
		Hallucinations		
		Hysteria		
		Lack of coordination		
		Lethargy		
		Memory disorder		
		Nocturia		
		NAB*		
		Peptic ulceration		
		Shortness of breath		
		Slow reactions		
		UAM*		

* NME = necrolytic migratory erythema, IOM = inflammation of oral mucosa, CD = concentration disturbances, NAB = nocturnal abnormal behaviour, UAM = unable to awaken in morning, GERD = gastroesophageal reflux disease

Table 4.
Five most frequently reported symptoms by pNET subtype

SYMPTOM	No. OF PAPERS REPORTING ISSUE		No. OF PAPERS WHERE ISSUE REPORTED BY > 50% PATIENTS	
GASTRINOMA				
Diarrhea	**16**	Crona, J. et al. 2016 [40]; Morocutti, A. et al. 2006 [71]; Matthews, B. D. et al. 2002 [68]; Waxman, I. et al. 1991 [89]; Wilcox, C. M. et al. 2011 [93]; Hirschowitz, B. I. et al. 1996 [58]; Larkin, C. J. et al. 1998 [66]; Wermers, R. A., Fatourechi, V. & Kvols, L. K. 1996 [90]; Roy, P. K. et al. 2000 [79]; Roy, P. K. . et al. 2001 [78]; Collen, M. J. et al. 1994 [37]; Grozinsky-Glasberg, S. et al. 2011 [54]; Hoffmann, K. M. et al. 2006 [60]; Smallfield, B. et al. 2010 [80]; Benya, R. V. et al. 1994 [27]; Eriksson, B. et al. 1990 [47]	**8**	Wermers, R. A., Fatourechi, V. & Kvols, L. K. 1996 [90]; Roy, P. K. et al. 2000 [79]; Roy, P. K. . et al. 2001 [78]; Collen, M. J. et al. 1994 [38]; Grozinsky-Glasberg, S. et al. 2011 [54]; Hoffmann, K. M. et al. 2006 [60]; Smallfield, B. et al. 2010 [80]; Benya, R. V. et al. 1994 [27]
Abdominal pain	**9**	Morocutti, A. et al. 2006 [71]; Larkin, C. J. et al. 1998 [66]; Wilcox, C. M. et al. 2011 [93]; Wermers, R. A., Fatourechi, V. & Kvols, L. K. 1996 [90]; Smallfield, B. et al. 2010 [80]; Roy, P. K. et al. 2000 [79]; Roy, P. K. et al. 2001 [78]; Hoffmann, K. M. et al. 2006 [60]; Collen, M. J. et al. 1994 [37]	**5**	Smallfield, B. et al. 2010 [80]; Roy, P. K. et al. 2000 [79]; Roy, P. K. . et al. 2001 [78]; Hoffmann, K. M. et al. 2006 [60]; Collen, M. J. et al. 1994 [37]
Heartburn	**9**	Morocutti, A. et al. 2006 [71]; Wilcox, C. M. et al. 2011 [93]; Roy, P. K. . et al. 2001 [78]; Roy, P. K. et al. 2000 [79]; Waxman, I. et al. 1991 [89]; Collen, M. J. et al. 1994 [37]; Benya, R. V. et al. 1994 [27]; Hoffmann, K. M. et al. 2006 [60]; Smallfield, B. et al. 2010 [80]	**4**	Collen, M. J. et al. 1994 [37]; Benya, R. V. et al. 1994 [27]; Hoffmann, K. M. et al. 2006 [60]; Smallfield, B. et al. 2010 [80]
Nausea	**9**	Collen, M. J. et al. 1994 [37]; Waxman, I. et al. 1991 [89]; Morocutti, A. et al. 2006 [71]; Wermers, R. A., Fatourechi, V. & Kvols, L. K. 1996 [90]; Benya, R. V. et al. 1994 [27]; Roy, P. K. . et al. 2001 [78]; Roy, P. K. et al. 2000 [79]; Wilcox, C. M. et al. 2011 [93]; Hoffmann, K. M. et al. 2006 [60]	**1**	Hoffmann, K. M. et al. 2006 [60]
Vomiting	**9**	Waxman, I. et al. 1991 [89]; Collen, M. J. et al. 1994 [37]; Crona, J. et al. 2016 [40]; Wilcox, C. M. et al. 2011 [93]; Roy, P. K. et al. 2001 [78]; Benya, R. V. et al. 1994 [27]; Roy, P. K. et al. 2000 [79]; Smallfield, B. et al. 2010 [80]; Wermers, R. A., Fatourechi, V. & Kvols, L. K. 1996 [90]	**0**	
GLUCAGONOMA				
Weight loss	**6**	Matthews, B. D. et al. 2002 [68]; Crona, J. et al. 2016 [40]; Chu, Q. D. et al. 2001 [35]; Wermers, R. A. et al. 1996 [91]; Wermers, R. A., Fatourechi, V. & Kvols, L. K. 1996 [90]; Eldor, R. et al. 2011 [45]	**4**	Chu, Q. D. et al. 2001 [35]; Wermers, R. A. et al. 1996 [91]; Wermers, R. A., Fatourechi, V. & Kvols, L. K. 1996 [90]; Eldor, R. et al. 2011 [45]
Diarrhea	**6**	Tomassetti, P. et al. 2000 [86]; Wermers, R. A., Fatourechi, V. & Kvols, L. K. 1996 [90]; Wermers, R. A. et al. 1996 [91]; Chu, Q. D. et al. 2001 [35]; Eldor, R. et al. 2011 [45]; Tomassetti, P. et al. 1998 [87]	**0**	
Abdominal pain	**5**	Eldor, R. et al. 2011 [45]; Wermers, R. A. et al. 1996 [91]; Wermers, R. A., Fatourechi, V. & Kvols, L. K. 1996 [90]; Matthews, B. D. et al. 2002 [68]; Chu, Q. D. et al. 2001 [35]	**2**	Matthews, B. D. et al. 2002 [68]; Chu, Q. D. et al. 2001 [35]
Necrolytic migratory erythema	**4**	Tomassetti, P. et al. 2000 [86]; Chu, Q. D. et al. 2001 [35]; Echenique-Elizondo, M. et al. 2004 [44]; Eldor, R. et al. 2011 [45]	**2**	Echenique-Elizondo, M. et al. 2004 [44]; Eldor, R. et al. 2011 [45]
Nausea	**3**	Wermers, R. A., Fatourechi, V. & Kvols, L. K. 1996 [90]; Wermers, R. A. et al. 1996 [91]; Chu, Q. D. et al. 2001 [35]	**0**	

INSULINOMA				
Hypoglycaemia	**25**	Wermers, R. A., Fatourechi, V. & Kvols, L. K. 1996 [90]; Gillams, A. et al. 2005 [52]; Van Den Akker, M. et al. 2012 [88]; Toaiari, M. et al. 2013 [85]; Placzkowski, A. et al. 2009 [77]; Mitrakou, A. et al. 1993 [70]; Gopal, R. A. et al. 2010 [53]; Matthews, B. D. et al. 2002 [68]; Komatsu, Y. et al. 2016 [64]; Jyotsna, V. P. et al. 2006 [62]; Hoem, D. et al. 2008 [59]; Mazzaglia, P. J. et al. 2007 [69]; Ayav, A. et al. 2005 [25]; Fu, W. et al. 2015 [50]; Fouda, M. A. . & Malabu, U. H. 2008 [49]; Ferrer-García, J. C. et al. 2013 [48]; Hellman, P. et al. 2000 [57]; Grygiel, K. et al. 2012 [55]; Crippa, S. et al. 2012 [39]; Bonato, F. T. et al. 2012 [32]; Bernard, V. et al. 2013 [28]; Bartsch, D. K. et al. 2000 [26]; Boukhman, M. P. et al. 1998 [33]; Creutzfeldt, W. et al. 1991 [38]; Eriksson, B. et al. 1990 [47]	**23**	Gillams, A. et al. 2005 [52]; Van Den Akker, M. et al. 2012 [88]; Toaiari, M. et al. 2013 [85]; Placzkowski, A. et al. 2009 [77]; Mitrakou, A. et al. 1993 [70]; Gopal, R. A. et al. 2010 [53]; Matthews, B. D. et al. 2002 [68]; Komatsu, Y. et al. 2016 [64]; Jyotsna, V. P. et al. 2006 [62]; Hoem, D. et al. 2008 [59]; Mazzaglia, P. J. et al. 2007 [69]; Ayav, A. et al. 2005 [25]; Fu, W. et al. 2015 [50]; Fouda, M. A. . & Malabu, U. H. 2008 [49]; Ferrer-García, J. C. et al. 2013 [48]; Hellman, P. et al. 2000 [57]; Grygiel, K. et al. 2012 [55]; Crippa, S. et al. 2012 [39]; Bonato, F. T. et al. 2012 [32]; Bernard, V. et al. 2013 [28]; Bartsch, D. K. et al. 2000 [26]; Boukhman, M. P. et al. 1998 [33]; Creutzfeldt, W. et al. 1991 [38]
Confusion	**13**	Besim, H. et al. 2002 [29]; Bonato, F. T. et al. 2012 [32]; Ferrer-García, J. C. et al. 2013 [48]; Tavčar, I. et al. 2014 [84]; Boukhman, M. P. et al. 1998 [33]; Ding, Y. et al. 2010 [41]; Komatsu, Y. et al. 2016 [64]; Larijani, B. et al. 2005 [65]; Nikfarjam, M. et al. 2008 [72]; Chung, J. C. et al. 2006 [36]; Dizon, A. M. et al. 1999 [42]; Doherty, G. et al. 1991 [43]; Eriksson, B. et al. 1990 [47]	**8**	Tavčar, I. et al. 2014 [84]; Boukhman, M. P. et al. 1998 [33]; Ding, Y. et al. 2010 [41]; Komatsu, Y. et al. 2016 [64]; Larijani, B. et al. 2005 [65]; Nikfarjam, M. et al. 2008 [72]; Chung, J. C. et al. 2006 [36]; Dizon, A. M. et al. 1999 [42]
Sweating	**12**	Grygiel, K. et al. 2012 [55]; Besim, H. et al. 2002 [29]; Boukhman, M. P. et al. 1998 [33]; Bonato, F. T. et al. 2012 [32]; Jyotsna, V. P. et al. 2006 [62]; Nikfarjam, M. et al. 2008 [72]; Tavčar, I. et al. 2014 [84]; Karakoc, D. et al. 2008 [63]; Dizon, A. M. et al. 1999 [42]; Chung, J. C. et al. 2006 [36]; Larijani, B. et al. 2005 [65]; Eriksson, B. et al. 1990 [47]	**5**	Tavčar, I. et al. 2014 [84]; Karakoc, D. et al. 2008 [63]; Dizon, A. M. et al. 1999 [42]; Chung, J. C. et al. 2006 [36]; Larijani, B. et al. 2005 [65]
Weight gain	**12**	Grygiel, K. et al. 2012 [55]; Fouda, M. A. . & Malabu, U. H. 2008 [49]; Karakoc, D. et al. 2008 [63]; Komatsu, Y. et al. 2016 [64]; Crippa, S. et al. 2012 [39]; Nikfarjam, M. et al. 2008 [72]; Dizon, A. M. et al. 1999 [42]; Bonato, F. T. et al. 2012 [32]; Boukhman, M. P. et al. 1998 [33]; Crona, J. et al. 2016 [40]; Jyotsna, V. P. et al. 2006 [62]; Doherty, G. et al. 1991 [43]	**5**	Bonato, F. T. et al. 2012 [32]; Boukhman, M. P. et al. 1998 [33]; Crona, J. et al. 2016 [40]; Jyotsna, V. P. et al. 2006 [62]; Doherty, G. et al. 1991 [43]
Syncope - temporary loss of consciousness	**10**	Nikfarjam, M. et al. 2008 [72]; Bonato, F. T. et al. 2012 [32]; Grygiel, K. et al. 2012 [55]; Chung, J. C. et al. 2006 [36]; Crona, J. et al. 2016 [40]; Dizon, A. M. et al. 1999 [42]; Jyotsna, V. P. et al. 2006 [62]; Karakoc, D. et al. 2008 [63]; Tavčar, I. et al. 2014 [84]; Besim, H. et al. 2002 [29]	**8**	Grygiel, K. et al. 2012 [55]; Chung, J. C.. et al. 2006 [36]; Crona, J. et al. 2016 [40]; Dizon, A. M. et al. 1999 [42]; Jyotsna, V. P. et al. 2006 [62]; Karakoc, D. et al. 2008 [63]; Tavčar, I. et al. 2014 [84]; Besim, H. et al. 2002 [29]
VIPOMA				
Diarrhea	**7**	Song, S. et al. 2009 [82]; Smith, S. L. et al. 1998 [81]; Peng, S. Y. et al. 2004 [75]; Nikou, C. et al. 2005 [73]; Matthews, B. D. et al. 2002 [68]; Ghaferi, A. A. et al. 2008 [51]; Bartsch, D. K. et al. 2000 [26]	**7**	Song, S. et al. 2009 [82]; Smith, S. L. et al. 1998 [81]; Peng, S. Y. et al. 2004 [75]; Nikou, C. et al. 2005 [73]; Matthews, B. D. et al. 2002 [68]; Ghaferi, A. A. et al. 2008 [51]; Bartsch, D. K. et al. 2000 [26]
Weight loss	**5**	Nikou, C. et al. 2005 [73]; Ghaferi, A. A. et al. 2008 [51]; Smith, S. L. et al. 1998 [81]; Peng, S. Y. et al. 2004 [75]; Matthews, B. D. et al. 2002 [68]	**3**	Peng, S. Y. et al. 2004 [75]; Matthews, B. D. et al. 2002 [68]; Smith, S. L. et al. 1998 [81]
Dehydration	**3**	Smith, S. L. et al. 1998 [81]; Nikou, C. et al. 2005 [73]; Peng, S. Y. et al. 2004 [75]	**2**	Nikou, C. et al. 2005 [73]; Peng, S. Y. et al. 2004 [75]
Flushing	**3**	Ghaferi, A. A. et al. 2008 [51]; Smith, S. L. et al. 1998 [81]; Peng, S. Y. et al. 2004 [75]	**0**	
Abdominal pain	**1**	Smith, S. L. et al. 1998 [81]	**0**	
NON-FUNCTIONING				

Abdominal pain	**10**	Bilchik, A. J. et al. 1997 [31]; Fu, W. et al. 2015 [50]; Butturini, G. et al. 2006 [34]; Eriguchi, N. et al. 1999 [46]; Gullo, L. et al. 2003 [56]; Liang, H. et al. 2004 [67]; Phan, G. Q. et al. 1998 [76]; White, T. J. et al. 1994 [92]; Tomassetti, P. et al. 2000 [86]; Hung, J. S. et al. 2007 [61]	**6**	Eriguchi, N. et al. 1999 [46]; Gullo, L. et al. 2003 [56]; Liang, H. et al. 2004 [67]; Phan, G. Q. et al. 1998 [76]; White, T. J. et al. 1994 [92]; Tomassetti, P. et al. 2000 [86]
Jaundice	**7**	Nikou, G. C. et al. 2008 [74]; Liang, H. et al. 2004 [67]; Gullo, L. et al. 2003 [56]; Butturini, G. et al. 2006 [34]; Phan, G. Q. et al. 1998 [76]; White, T. J. et al. 1994 [92]; Hung, J. S. et al. 2007 [61]	**0**	
Anorexia	**3**	Gullo, L. et al. 2003 [56]; Phan, G. Q. et al. 1998 [76]; Butturini, G. et al. 2006 [34]	**0**	
Vomiting	**3**	Butturini, G. et al. 2006 [34]; Liang, H. et al. 2004 [67]; Phan, G. Q. et al. 1998 [76]	**0**	
Back pain	**3**	Eriguchi, N. et al. 1999 [46]; Liang, H. et al. 2004 [67]; Hung, J. S. et al. 2007 [61]	**0**	

Discussion

This is the first systematic review of the literature relating to symptoms and QoL issues in all types of pNET for 20 years [97]. There are reviews investigating specific types of pNETs, such as insulinoma [98], glucagonoma [99], VIPoma [51];[81] and carcinoid pNETs [100], but not systematically reviewing the symptoms for all types. Much of the literature reviewed in this paper is a combination of clinical observation, and repetition of anecdotal historical observation. There are few papers systematically asking patients to record and score their symptoms, or asking health care workers to score patient symptoms.

It is clear that many pNETs are now being picked up incidentally on routine scans, in patients without any symptoms. Those that can be removed surgically and cured will not have tumour-related symptoms, but many will have widespread disease and will develop symptoms later. The aim of this review has been to formally document what is known from the literature, with a view to developing more specific PROM/QoL outcome measures relating to the specific syndromes. We have used a systematic process to try to understand the most common PROMs in each of the pNET subtypes.

pNETs are unique tumours setting them apart from most cancers, in that the symptoms of the hormone secreted may be the only symptoms present, without any generic cancer issues. It is evident from our findings that each pNET subtype presents differently, with different critical symptoms, thus it is likely that using generalised cancer questions in these patients may miss specific issues that are important. The main problem with assessing issues is that these tumours are rare and the subtypes of functioning tumours even more rare. It is therefore difficult to get a consensus of symptoms in so few patients. With the onset of global reach of patient networks and online reporting worldwide, it is now easier to collect symptom data and a reasonable attempt can be made to get PROM data from the rarer syndromes.

As described, the mode of patient reporting is not often reported in the papers, so it is often not clear if patient views are being reported verbatim. There may well be a bias towards the clinician's views of what is most important [101]. In addition the rarity of some of these syndromes prevents large datasets and by necessity involves recall of symptoms from small numbers of patients. The observed symptoms of the functional syndromes are slightly different to standard teaching hence this study provides evidence as to which symptoms should be measured in trials of novel therapies.

The next stage from this data will be to do patient and healthcare professional interviews in large cohorts in many different languages across multiple countries to get their views on symptoms in pNET. The aim is to use the findings from this literature review, alongside the patient and healthcare workers interview data to create a list of QoL issues relevant and important to these patient groups, and from this create a QoL measure specific to pNET patients.

Acknowledgements

This review was partly funded by the European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QOL) and the NET Patient Foundation (www.netpatientfoundation.org) as

part of a project to develop a module to supplement the core instrument for assessment of QOL in patients with pNETs.

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