Presenting Symptoms and Delay in Diagnosis of Gastrointestinal and Pancreatic Neuroendocrine Tumours

Ron Basuroy[a]   Cathy Bouvier[b]   John K. Ramage[c]   Maia Sissons[b]
Alexandra Kent[d]   Raj Srirajaskanthan[c, d]

[a]King's College London, London, UK; [b]Neuroendocrine Tumour Patients Foundation, Leamington Spa, UK;
[c]ENETS Centre of Excellence, Neuroendocrine Tumour Unit, King's College Hospital, London, UK; [d]Department of
Gastroenterology, King's College Hospital, London, UK

Abstract

The gastrointestinal tract and pancreas are common primary sites for neuroendocrine tumours (NETs). Patients often report a long duration of non-specific symptoms in the year prior to diagnosis. The aims of this study were, firstly, to establish pre-diagnosis patterns of symptoms, and secondly, to determine the time from onset of symptoms to NET diagnosis and understand the interaction with primary and secondary healthcare providers. A survey was designed on a web-based survey platform with the focus on patient symptoms prior to diagnosis and a screen for functional diarrhoea (Rome III criteria [C4]). A total of 303 responses were received. The median duration from the time of first symptoms to diagnosis was 36 months for small bowel NETs and 24 months for pancreatic NETs. Common first symptoms were pain (36%), flushing (24%), and diarrhoea (24%); 29% of small bowel NET respondents were given an initial diagnosis of irritable bowel syndrome. Dyspepsia was the second most common initial incorrect diagnosis. Respondents saw their GP 5 times over a median 18-month period for their symptoms; 31% of patients were diagnosed following unplanned emergency admission. In conclusion, this survey demonstrates a median time to diagnosis of 36 months for patients with small bowel NETs. Incorrect initial diagnosis appears to be very common, with a high number of attendances in primary and secondary care prior to a correct diagnosis being made. An earlier diagnosis may improve patients' quality of life and possible survival.

© 2018 S. Karger AG, Basel

Introduction

The gastrointestinal tract and pancreas are the most common primary sites for neuroendocrine tumours (NETs) [1, 2]. There is an increasing incidence of these tumours and consequently a rising prevalence. Individuals can present with a multitude of symptoms or these tumours can be found incidentally. The majority of tumours are non-functional in that that they do not cause a clinical syndrome, such as carcinoid syndrome. Symptoms may be related to mass effect of the tumour or metastases or to mesenteric ischaemia or intermittent sub-

Dr. Raj Srirajaskanthan
Consultant in Gastroenterology and Neuroendocrine Tumours
Department of Gastroenterology, King's College Hospital
Denmark Hill, London SE5 9RS (UK)
E-Mail r.srirajaskanthan@nhs.net

acute bowel obstruction. Frequently reported symptoms are abdominal pain or change in bowel habit. Occasionally, patients present with the classical carcinoid syndrome of diarrhoea, flushing, palpitations, and bronchospasm, which develop in the context of serotonin-secreting liver metastases [3, 4]. Patients may experience symptoms of intermittent bowel obstruction from the mechanical effect of the primary small bowel tumour as well as symptoms from mesenteric lymph node involvement, secondary desmoplasia, and bowel ischaemia due to vessel involvement [5, 6].

Patients with NETs complain of symptoms, such as loose bowel motions, that may be mistaken for other conditions like irritable bowel syndrome (IBS). NET patients anecdotally report that they describe florid symptoms to healthcare practitioners but are often reassured and managed with a commonly occurring diagnostic label like functional bowel disorders or dyspepsia. There is no clear data on whether the symptoms described by NET patients overlap with those of benign conditions like IBS or whether differentiating symptoms co-exist. Delays in diagnosis are frequently reported, with studies suggesting a delay of years in diagnosis following the onset of symptoms [7].

The Rome III criteria for adult functional gastrointestinal disorders describe IBS (functional bowel disorder C1) as recurrent abdominal pain at least 3 days/month in the last 3 months associated with at least two of the following symptoms: an improvement with defecation, onset associated with a change in frequency of stool, and onset associated with a change in form (appearance) of stool. Functional diarrhoea (functional bowel disorder C4) is separately described as loose (mushy) or watery stools without pain occurring at least 75% of the time without pain or discomfort for at least 3 months [8]. The presence of pain differentiates IBS (C1) from functional diarrhoea (C4) in the Rome criteria. Furthermore, a diagnosis of a functional gastrointestinal disorder is dependent on the exclusion of alarm symptoms like weight loss of >4.5 kg, age >50 years with a change in bowel habit, blood loss or anaemia, and significant family history.

There are no published data on the frequency and severity of bowel symptoms in patients with gastrointestinal and pancreatic NETS (pNETs) prior to diagnosis. Assessment of frequency of misdiagnosis and time to diagnosis has not been reported in this group of patients. Furthermore, no accurate comparison of the overlap in symptoms between IBS and diarrhoea has been reported. The aim of this study was to establish pre-diagnosis patterns of symptoms, including overlap with functional diarrhoea criteria through an online survey of NET patients.

Methods

The survey was designed on SurveyMonkey, a web-based survey solution, in collaboration with the NET Patient Foundation (NPF), a UK-based neuroendocrine patient organization. The survey was designed to cover patient symptoms prior to diagnosis. It incorporated a screen for functional diarrhoea (Rome III criteria [C4] – loose stool for at least 75% of stools occurring 75% of the time without pain for at least 3 months) across subset questions. An introduction section with agreement to proceed was incorporated on the survey-landing page. No personal data questions, including contact details, were incorporated into the survey. Using the Health Research Authority (HRA) decision aids tool an online form was completed; it was confirmed that NHS Research Ethics Committee approval was not required. The survey was entirely voluntary, and respondents were fully informed on the website about why the survey was being done.

Free-text open questions were used at the start of the survey to avoid influencing respondents with closed symptom questions. Mandatory questions acted as filters to proceed through a related subset or to skip to the next filter question (skip logic). Where possible previous answers (free-text or categorical) were piped into later questions to help with continuity and framing for respondents. Questions were developed based on multiple choice, 5-point scale, or free-text responses. Question and block randomization was not incorporated due to the designed flow of questions and the use of skip logic and piping. Duration and timeline questions were anchored on the baseline of the patient's current age and survey completion date.

The question set was tested and adapted from patient and clinician input from the King's College Hospital Neuroendocrine Tumour Service and from subject matter experts at the NPF. The finalized survey contained 130 questions and was estimated to take 30 min to complete online. Subsets of questions included first and worst symptoms, weight and appetite change, pain and discomfort, nausea and vomiting, change in bowel habit, alarm signs, GP and hospital interactions, and diagnosis. The survey was promoted and distributed via clinical nurse specialists from NET centres using business cards containing the URL and via the NPF using their regular email newsletter and Twitter update. The survey was closed after a predetermined number of responses ($n = 300$) to ensure that the data would be sufficiently robust to describe patterns in symptoms and healthcare interactions. Data coding and analysis was performed with Microsoft® Excel® for Mac (2011). Free-text response data was searched and categorized with key word searches. Descriptive statistics were used given the lack of counterfactual data.

Results

There were a total of 303 responses of which 229 completed the whole survey (75.6%). The mean time to complete the survey was 34 min. The survey was predominantly accessed by click-through soon after promotions in the NPF newsletter and Twitter feed. The participants responded between September 25, 2014 and May 2, 2015.

Table 1. Primary site of neuroendocrine tumour (NET) according to study respondents

Type of NET	n	Age at diagnosis, years	Duration of 1st symptom prior to diagnosis, months	Age >50 years at time of 1st symptom, %
Appendix	14	44.2 (15–60.2)	12.0 (10.0–60.0)	29
Lung	51	50.7 (25.2–71.3)	48.0 (14.8–117.0)	54
Not sure	20	47.5 (14.4–71.2)	36.0 (18.0–84.0)	55
Ovary	2	44.3 (41.6–46.9)	5.0 (4.5–5.5)	0
Pancreas	64	49.2 (6.9–86.8)	24.0 (10.5–53.3)	42
Rectal	5	45.4 (11.0–59.2)	7.0 (6.0–72.0)	60
Renal/kidney	1	48.0 (–)	–	0
Small bowel	99	55.2 (28.9–77.7)	36.0 (17.0–96.0)	69
Stomach/gastric	14	55.1 (42.7–76.3)	15.0 (6.0–60.0)	71
Unknown primary	33	52.9 (35.5–77.9)	24.0 (4.5–66.0)	55
Total	303	51.6 (6.9–86.8)	30.0 (12.0–84.0)	56

Data for age are presented as mean (range); data for duration of 1st symptom are presented as median (IQR).

The majority of respondents were female patients (205/303, 67.65%), including those who completed the whole survey (154/229, 67.2%); 76% of respondents (231/303) completed the ethnicity question (grouped as per UK Office for National Statistics) with the overwhelming majority describing themselves as of white ethnicity (94%). The mean age of respondents completing the survey was 55.7 years (53.3 and 60.8 years for female and male respondents, respectively). Respondents completed the survey a median of 48.1 months after their initial NET diagnosis (IQR 41–57.6 months) with results for small bowel NETs (sbNETs; 36.7 months, IQR 42.9–58.6 months) and pNETs (29.2 months, IQR 11–50.7 months). The majority of responses (214/303) were from patients with small bowel (n = 99), pancreatic (n = 64), and lung (n = 51) primary sites. Table 1 illustrates the full breakdown of primary site responses. The mean age at diagnosis was 51.6 years for all respondents and 55.2 and 49.2 years for sbNETs and pNETs respondents, respectively (Table 1). The responses for pNETs and sbNETs have been highlighted, with a focus on the responses obtained from these two groups.

Symptoms Prior to Diagnosis
The median duration of the first symptom prior to diagnosis for all respondents was 30 months overall (IQR 12–84 months): 36 months for sbNETs (IQR 17–96 months) and 24 months for pNETs (IQR 10.5–53.3 months) (Table 1). Respondents aged >50 years before developing symptoms (168/303) reported that the medi-an duration of their first symptom was 29 months overall: 33 months for sbNETs and 24 months for pNETs. This is despite the majority of sbNET and pNET respondents reporting severe symptoms: 70% of sbNET and 64% of pNET respondents reported severe or very severe symptoms.

NET respondents often reported that they suffered from a range of symptoms prior to diagnosis. However, respondents were able to describe the single symptom that they first experienced prior to diagnosis. Common first symptoms reported by sbNET respondents were pain (36%) followed by flushing (26%) and diarrhoea (24%). pNET respondents reported pain (39%) followed by diarrhoea (26%) and fatigue or tiredness (26%) as the common first symptoms.

While over a third of sbNET respondents experienced pain as the first symptom, the majority of sbNET respondents (81%, 80/99) reported that they experienced pain as part of their range of symptoms prior to diagnosis. They described the pain as starting in the periumbilical (26%) or pelvic area (24%) before becoming more generalized to the abdominal midline and lower abdomen (62%) prior to diagnosis. In contrast, a smaller proportion of pNET respondents (55%, 35/64) experienced pain as part of their range of symptoms, closer to the proportion experiencing pain as the first symptom. pNET respondents described the pain as starting in the epigastric (39%) or upper right abdominal area (10%) before becoming more diffuse in its location prior to diagnosis. The frequency of the pain was similar for both sbNETs and pNETs, occur-

ring a few times a month or more than once a week. sbNET respondents described a more severe pain profile than pNET respondents.

A greater proportion of sbNET respondents (64%, 63/99) experienced bowel symptoms as part of their range of symptomatology than the proportion reporting it as their first symptom. The proportion of pNET respondents experiencing bowel symptoms was lower (36%, 23/64) as well as being closer to the proportion reporting it as their first symptom. Three quarters of sbNET respondents (75%, 62/83) experienced problems with loose, mushy, or watery stools prior to diagnosis; 46% of sbNET respondents (21/46) described the problem with loose bowels as severe or very severe, 60% of sbNET patients reported that 75% of their stools were loose prior to diagnosis and 40% had this problem 75% of the time or more; 66% of sbNET respondents (57/87) reported some degree of urgency to open their bowels and 78% (68/87) reported some degree of bloating. Only a small fraction of sbNET patients (6%, 5/87) reported the red flag symptom of blood in their stool.

Although a quarter of sbNET respondents experience flushing as their first symptom, a far greater proportion (83%, 72/87) experienced flushing as part of their range of symptoms prior to diagnosis. Alcohol and large meals were reported by sbNET respondents to make the flushing worse. sbNET respondents (66%, 57/87) reported anxiety more than pNET respondents (50%, 27/54) prior to diagnosis. Only a small proportion of sbNET respondents described the anxiety as severe or very severe (16%, 9/57).

There were similar proportions of sbNET (37/99, 37%) and pNET (19/64, 30%) respondents reporting weight loss. The median weight change for sbNET and pNET respondents was a loss of –6.4 kg (IQR –12.7 to 5.6) and –2.0 kg (IQ –6.4 to 10), respectively. However, 60% of sbNET and 45% of pNET respondents reported the red flag symptom of weight loss >4.5 kg; 48% of sbNET and 26% of pNET respondents reporting weight loss >4.5 kg were aged >50 years prior to developing symptoms. Weight change was reported over a median duration of 12 months for all respondents, with a similar duration for pNETs (12 months) but a longer duration for sbNETs (18 months). There were similar proportions of sbNET (31/99, 31%) and pNET (14/64, 22%) respondents reporting appetite loss. However, the majority of sbNET, pNET, and lung NET respondents reported no change to their appetite prior to diagnosis: 61% (60/99), 53% (34/64), and 65% (33/51), respectively.

Initial Diagnosis Given to NET Respondents

A total of 29% of sbNET respondents were given an initial diagnosis of IBS in primary care, while 12% were initially diagnosed with IBS in secondary care. Dyspepsia was the next most common initial diagnosis in primary care for both pNETs (9%) and sbNETs (16%) but was an uncommon initial diagnosis in secondary care. Only 1% of respondents reported that they were given an initial NET diagnosis in primary care compared to 21% in secondary care. Cancer was considered more often in secondary care (15%) than in primary care (4%). Table 2 lists the initial diagnoses given to patients following consultation in either primary or secondary care.

Overall, 30% of sbNET or pNET respondents (47/155) reported that they were already diagnosed with IBS or were considered to have IBS from their NET symptoms. The proportion was slightly greater for sbNET respondents: just over a third (36%, 34/95) reported that IBS was considered or previously diagnosed. However, the proportion of respondents meeting all the criteria for functional diarrhoea was less than the proportion considered or previously diagnosed by healthcare practitioners. Only 5% of respondents (7/155) reported symptomatology that met the full criteria for functional diarrhoea, in contrast to the 30% (47/155) who reported that IBS was considered or previously diagnosed by healthcare practitioners. A fifth of sbNET or pNET respondents (21%, 32/155) met the criteria for IBS with diarrhoea. In IBS with diarrhoea, pain can be a feature of symptoms, hence the higher rate of patients meeting the majority of the criteria. Importantly, respondents with red flag factors aged >50 years or with weight loss >4.5 kg reported that IBS was still considered. Over two thirds of sbNET patients (68%, 23/34) who were considered or diagnosed with IBS by healthcare practitioners were >50 years of age at the start of their symptoms. Similarly, almost half of those considered to have or who were diagnosed with IBS had weight loss > 4.5 kg (44%, 15/34) during the period of their symptoms. Table 3 illustrates that only a low percentage of patients with pNETs or sbNETs had symptoms that met the functional diarrhoea criteria compared to the actual numbers who were given this as a provisional diagnosis.

Accessing Healthcare Services and Diagnosis

The majority of respondents (80%) reported that they saw their GP with symptoms prior to their NET diagnosis. Respondents reported they saw their GP over a median period of 18 months and had a median of 5 interactions. There was no marked difference in the median period and number of interactions in primary care for

Basuroy/Bouvier/Ramage/Sissons/Kent/
Srirajaskanthan

Table 2. Initial diagnosis given to respondents following assessment in primary and secondary care

Potential cause	Primary care, %			Secondary care, %		
	pNETs	sbNETs	all NETs	pNETs	sbNETs	all NETs
IBS	16	29	24	5	12	9
Dyspepsia	9	16	13	3	3	3
Depression	5	3	4	2	1	1
UTI	5	3	4	0	0	0
Constipation	3	5	4	2	1	1
Gall stones	8	12	10	3	5	4
Menopause	2	11	7	0	3	2
Chest infection	2	2	2	0	0	0
Kidney stones	5	3	4	3	1	2
Anaemia	5	5	5	2	0	1
Crohn disease	0	2	1	2	1	1
NET	0	2	1	20	22	21
Ulcerative colitis	5	4	4	0	1	1
Cancer	3	4	4	17	14	15
Doctor not sure	9	19	15	6	15	12
Respondent not sure	8	8	8	6	5	6
Other	22	25	24	23	23	23
Total	n = 64	n = 99	n = 163	n = 64	n = 99	n = 163

NET, neuroendocrine tumour; pNETs, pancreatic NETs; sbNETs, small bowel NETs; IBS, irritable bowel syndrome; UTI, urinary tract infection.

Table 3. The percentage of patients meeting the requirements for functional diarrhoea based on the Rome III criteria

Type	Total, n	Functional diarrhoea criteria, %			IBS considered or diagnosed by healthcare practitioner	
		no	yes	total	n	%
pNET	60	85	15	100	13	22
No pain	25	37	5	42	4	7
Pain	35	48	10	58	9	15
sbNET	95	76	24	100	34	36
No pain	15	12	4	16	3	3
Pain	80	64	20	84	31	33
Total	155	79	21	100	47	30
No pain	40	21	5	26	7	4
Pain	115	58	16	74	40	26

pNET, pancreatic neuroendocrine tumour; sbNET, small bowel NET; IBS, irritable bowel syndrome.

sbNET and pNET respondents. Over half of the respondents (58%, 122/210) reported that they first interacted with secondary care from a GP referral to a local hospital clinic. Almost a third of respondents (31%, 66/210) reported that their first secondary care interaction was via an unplanned emergency admission from A&E. Again, there was no marked difference in the routes that sbNET and pNET respondents first interacted with secondary care; 43% of pNET and sbNET respondents reported that they were investigated in gastroenterology clinics prior to diagnosis, with the remainder mainly investigated in surgical or oncology clinics. Respondents reported that they

Table 4. The median number of attendances and time investigated in primary and secondary care prior to diagnosis being made

Site of NET	Primary care				Secondary care			
	n	seen by GP, %	times seen, n	time investigated, months	n	seen in clinic, %	times seen in clinic, n	time investigated, months
Pancreas	52	73	5 (2–9.8)	18 (3.0–48.0)	50	50	3 (1–5)	3.0 (1.0–8.8)
Small bowel	86	86	5 (3–10)	24 (3.8–60)	85	62	2 (1–4)	3.0 (1.0–12)
All sites	257	80	5 (2.3–12)	18 (3–48)	246	58	2.0 (0–4.0)	2.4 (1.0–12)

Data for times seen and time investigated are presented as median (IQR). NET, neuroendocrine tumour.

were investigated in a clinic for a median period of 2.4 months over a median of 2 occasions. There was no information collated on the referral pathways from primary care to secondary care. It is not clear whether there is an overlap in primary and secondary care management (median 18 and 2.4 months, respectively) given that respondents reported being symptomatic for a longer period of time (median 30 months) than investigated. However, it is likely that symptomatic respondents delayed accessing healthcare for the first time for many months. However, it was not possible to quantify the overlap in primary and secondary care or the period of symptoms without investigation given the questionnaire design. Table 4 shows the interaction of patients with both their primary and secondary care providers prior to diagnosis.

Discussion

The survey is one of the largest of NET patients exploring symptoms and healthcare access. The majority of respondents were sbNET and pNET patients who reported free-text symptoms that helped inform pre-diagnosis patterns. sbNET respondents frequently reported pain, flushing, and diarrhoea while pNET respondents reported pain, fatigue, and diarrhoea. There were 51 respondents whose primary site was the lung; their data has not been analysed in this paper since we focused primarily on the gastrointestinal symptoms prior to diagnosis in gastroenteropancreatic NET patients.

Over half of all respondents were aged >50 years at the start of their symptoms with many reporting associated red flags of appetite and weight loss. The triad of age >50 years, weight loss >4.5 kg, and pain reported by NET respondents is inconsistent with functional diarrhoea and other benign conditions. Only a fraction (5%) of sbNET and pNET respondents met the symptom criteria for functional diarrhoea (C4) compared to a greater proportion (30%) being labelled or continuing to be managed as IBS. A proportion of NET patients may have had overlap in their IBS and NET symptoms that masked an obvious change and reason for earlier reinvestigation or clinical assessment. However, many patients presented on multiple occasions to primary and secondary care due to persistent symptomatology that should trigger the index of suspicion of alternative diagnoses to IBS. It is important that patients presenting with new symptoms, even if insidious in onset, who are >50 years of age are appropriately investigated rather than giving a functional bowel disorder diagnosis given the increased risk of malignancy in this cohort.

This is the first survey to establish a median time to diagnosis of 36 months for sbNETs and 24 months for pNETs. A multi-year delay in diagnosis from onset of symptoms may be leading to a worse prognosis for patients. However, there are no data available to support this fact, though the delay in diagnosis and consequent high utilization of primary and secondary care resources due to undiagnosed persistent symptoms is likely to be costly for healthcare providers. Furthermore, a high proportion of patients appear to have been diagnosed in an emergency setting. In other cancers it is known that presentation with malignancy via an acute admission is a negative prognostic indicator [9]. Awareness of this condition and consideration of earlier use of cross-sectional imaging needs to occur to help with shorter time to diagnosis and possibly diagnosis at an earlier stage of disease.

The survey did not ask for the duration of previous IBS diagnoses or if the reported NET symptoms differed from any pre-existing IBS symptoms. However, there still ap-

pears to be a clear disparity between a healthcare practitioner's labelling of IBS and the presence of clear exclusion criteria for IBS with red flags like onset age and weight loss.

Since this study was performed the Rome criteria have recently been revised to the 4th iteration. Earlier versions of the Rome criteria were less clear in the subtyping of patients and just required the exclusion of organic disease with non-specific abdominal symptoms that were present for 3 months in the 6 months prior to diagnosis. The Rome II criteria had an unhelpful C5 unspecified functional bowel disorder, the criteria for which were vague, and hence patients could have been given the diagnosis of IBS incorrectly. The C5 unspecified functional bowel disorder was based on the diagnostic criteria of bowel symptoms not attributable to an organic aetiology that do not meet the criteria for the previously defined categories and duration of these symptoms for at least 3 months with onset of symptoms for at least 6 months prior to diagnosis. Whilst this criterion is no longer part of the new Rome criteria it is possible that many primary and secondary care providers feel that once an endoscopy or colonoscopy has been performed and is normal then the bowel symptoms can be attributed to this type of functional bowel disorder.

An additional limitation of the survey was through its distribution channels and open inclusion criteria, irrespective of the length of time since diagnosis. The survey was open to all historical patients but was predominantly accessed via the NPF digital promotional channels. This could result in survey respondents being a self-selecting informed and proactive cohort of NET patients. This may have led to respondents being more informed and opinionated about their pre-diagnosis journey than a typical newly diagnosed NET patient. A degree of selection bias is suggested by the high percentage (26%) of respondents with sbNETs reporting flushing as a predominant symptom.

The survey also explored access to healthcare services and diagnostic work up without validation from actual healthcare records, particularly around the duration of primary and secondary management prior to diagnosis. The effect of information asymmetry between patients and clinicians may limit the pre-diagnosis healthcare insights, including those around IBS. Future studies may wish to consider limiting respondents to those newly diagnosed with linkage to data from healthcare records to reduce selection, recall, and reporting biases. Alternatively, a prospective study reviewing newly diagnosed patient pathways would help reduce selection and recall bias.

Patients with symptoms like diarrhoea and pain may be investigated with simple and accessible diagnostics, such as abdominal ultrasound, endoscopy, and blood testing, that may be falsely reassuring given the low sensitivity for early NET disease. Cross-sectional modalities like CT may reveal earlier stage disease, particularly when used in patients who are 50 years old with new abdominal symptoms. Survey respondents often reported more than one symptom and a proportion had red flags like weight loss and loss of appetite. This indicates that NET patients may have an evolving range of symptoms and persistence or worsening in existing symptoms despite medical therapy prescribed for alternative conditions.

Interestingly, 43% of respondents with sbNETs or pNETs were referred to secondary care under gastroenterology and, even within the secondary care system and access to the full range of diagnostics, the duration under investigation prior to diagnosis was reported to be 3 months (median). This may be due to the fact that endoscopy, abdominal ultrasound, and standard blood tests would not normally identify the underlying tumour but are believed by healthcare practitioners to exclude the majority of concerning pathologies. The earlier use of CT in symptomatic patients aged >50 years may lead to an earlier diagnosis in secondary care through the identification of mesenteric disease or enhancing lesions in the pancreas or liver that suggest sbNETs, pNETs, or metastatic disease, respectively.

In conclusion, this is the first survey to establish a median time to diagnosis of 36 months for sbNETs and 24 months for pNETs. The most frequent incorrect initial diagnosis was IBS in patients with gastroenteropancreatic NETs, with respondents accessing healthcare services repeatedly with a broad range of persistent or evolving symptomatology. A significant number of these patients are >50 years of age and, therefore, investigation of other pathology should be considered prior to making a diagnosis of IBS. Better awareness in primary care of alarm symptoms and the new Rome criteria for functional bowel disorders may lead to earlier referral to secondary care for investigation to exclude malignancy. Only 5% of respondents met the Rome criteria for functional diarrhoea (C4). An increased level of suspicion in primary care for malignancy in patients with persistent symptoms or red flags may lead to an earlier referral to secondary care cancer services, which may lead to an earlier diagnosis and improved quality of life and clinical outcomes.

References

1 Yao JC, et al: One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063–3072.

2 Cheema A, Weber J, Strosberg JR: Incidental detection of pancreatic neuroendocrine tumors: an analysis of incidence and outcomes. Ann Surg Oncol 2012;19:2932–2936.

3 Srirajaskanthan R, Shanmugabavan D, Ramage JK: Carcinoid syndrome. BMJ 2010;341: c3941.

4 Ramage JK, et al: Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 2012;61:6–32.

5 Eckhauser FE, et al: Mesenteric angiopathy, intestinal gangrene, and midgut carcinoids. Surgery 1981;90:720–728.

6 Kulke MH, Mayer RJ: Carcinoid tumors. N Engl J Med 1999;340:858–868.

7 Singh S, Granberg D, Wolin E, Warner R, Sissons M, Kolarova T, Goldstein G, Pavel M, Öberg K, Leyden J: Patient-reported burden of a neuroendocrine tumor (NET) diagnosis: results from the first global survey of patients with NETs. J Glob Oncol 2016;3:43–53.

8 Rome Foundation: Guidelines – Rome III diagnostic criteria for functional gastrointestinal disorders. J Gastrointestin Liver Dis 2006; 15:307–312.

9 Markar SR, Mackenzie H, Jemal S, Faiz O, Cunningham D, Hanna GB: Emergency presentation of esophagogastric cancer: predictors and long-term prognosis. Ann Surg 2018; 267:711–715.