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## Basic Study

**Health-related quality of life, anxiety, depression and impulsivity in patients with advanced gastroenteropancreatic neuroendocrine tumours**

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**Abstract****AIM**

To compare health-related quality of life (HRQoL),

anxiety, depression, and impulsivity scores in patients with and without carcinoid syndrome (CS), and correlated them with serum 5-hydroxyindoleacetic acid (5-HIAA) levels.

#### METHODS

Patients with advanced gastroenteropancreatic neuroendocrine tumours (GEPNET), with and without CS completed HRQoL QLQ-C30 and QLQ-GI.NET21, Hospital Anxiety and Depression Scale (HADS) and Barratt Impulsivity Scale (BIS) questionnaires. Two-sample Wilcoxon test was applied to assess differences in serum 5-HIAA levels, two-sample Mann-Whitney *U* test for HRQoL and BIS, and proportion test for HADS, between those with and without CS.

#### RESULTS

Fifty patients were included; 25 each with and without CS. Median 5-HIAA in patients with and without CS was 367nmol/L and 86nmol/L, respectively ( $P = 0.003$ ). Scores related to endocrine symptoms were significantly higher amongst patients with CS ( $P = 0.04$ ) and scores for disease-related worries approached significance in the group without CS, but no other statistically-significant differences were reported between patients with and without CS in responses on QLQ-C30 or QLQ-GI.NET21. Fifteen patients (26%) scored  $\geq 8/21$  on anxiety scale, and 6 (12%) scored  $\geq 8/21$  on depression scale. There was no difference in median 5-HIAA between those scoring  $<$  or  $\geq 8/21$  on anxiety scale ( $P = 0.53$ ). There were no statistically significant differences between groups in first or second-order factors (BIS) or total sum ( $P = 0.23$ ).

#### CONCLUSION

Excepting endocrine symptoms, there were no significant differences in HRQoL, anxiety, depression or impulsivity between patients with advanced GEPNET, with or without CS. Over one quarter of patients had high anxiety scores, unrelated to peripheral serotonin metabolism.

**Key words:** Gastroenteropancreatic neuroendocrine tumours; Carcinoid syndrome; Quality of life; Anxiety; Depression; Impulsivity

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**Core tip:** Patients with functioning gastroenteropancreatic neuroendocrine tumours (GEPNETs) may have higher levels of psychological distress than other patients with cancer due to the symptoms of hormone hypersecretion. This study compares 25 patients with advanced GEPNET and carcinoid syndrome (CS) with 25 patients with advanced, but non-functioning GEPNET. Symptoms of anxiety, depression, impulsivity and health-related quality of life were assessed prospectively using symptom scales. Endocrine symptoms were significantly higher in patients with CS. Disease-related worries were more common in those

with non-functioning tumours. This is a large study in this rare patient group and further prospective studies are required.

Lewis AR, Wang X, Magdalani L, D'Arienzo P, Bashir C, Mansoor W, Hubner R, Valle JW, McNamara MG. Health-related quality of life, anxiety, depression and impulsivity in patients with advanced gastroenteropancreatic neuroendocrine tumours. *World J Gastroenterol* 2018; 24(6): 671-679 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i6/671.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i6.671>

#### INTRODUCTION

Gastroenteropancreatic neuroendocrine tumours (GEPNETs) are a varied group of neoplasms derived from cells of the diffuse endocrine system, normally distributed in the mucosa of organs originating from the embryological intestine<sup>[1]</sup>. GEPNETs are rare, representing only around 2% of all gastrointestinal malignancies<sup>[2]</sup>, with an incidence of 5.25/100000/year and a prevalence of 35/100000 / year<sup>[3]</sup>.

Gastroenteropancreatic neuroendocrine tumours are classified according to site and can be further subdivided into functioning and non-functioning. Functioning tumours can cause symptoms due to hypersecretion of hormones, most commonly serotonin, which causes carcinoid syndrome (CS). Approximately 30%-55% of GEPNETs are functioning<sup>[3]</sup>. CS is associated with flushing, diarrhoea, bronchial constriction and endocardial fibrosis, which can lead to right heart failure<sup>[2]</sup>.

Surgery is the only curative treatment available for patients with GEPNETs. Treatment options for advanced disease include somatostatin analogues (SSAs) which may control the disease<sup>[3-5]</sup>, and result in the reduction of hormone levels and the control of symptoms related to hormone hypersecretion. Other treatment options include everolimus for non-functioning GEPNETs<sup>[6]</sup> the use of peptide receptor radionuclide therapy (PRRT)<sup>[7]</sup>, and chemotherapy<sup>[8]</sup>. More recently, among patients with CS not adequately controlled by SSAs, treatment with telotristat ethyl (a tryptophan hydroxylase inhibitor) was reported to be safe and well tolerated and resulted in significant reductions in bowel motion frequency<sup>[9]</sup>.

Despite the availability and use of these treatment options, psychological symptoms may be identified in patients with GEPNETs<sup>[10,11]</sup>. Psychiatric comorbidity in oncological patients is common. Two German studies including 502 and 4020 patients across all disease stages, have reported that about 30% of these patients can be diagnosed with a mental disorder according to the Diagnostic and Statistical Manual of Mental Disorders criteria<sup>[12,13]</sup>. The most prevalent mental disorders associated with cancer in these studies were anxiety disorders, with mood and adjustment disorders also being commonly reported, with rates between

**Table 1** Summary of studies investigating psychological symptoms in patients with neuroendocrine tumours

Ref.	Primary disease site	Correlation with treatment	Treatment	Number of patients with carcinoid syndrome/total patients	Method of investigation	Key results
Major <i>et al</i> <sup>[17]</sup> 1972	Metastatic carcinoid	No	Not reported	22/22	Not reported	50% displaying depressive symptoms
Larsson <i>et al</i> <sup>[11]</sup> 2001	Midgut carcinoid	Yes - prior to and following 12 mo of treatment with somatostatin analogues	Somatostatin analogues	20/24	Questionnaire - EORTC-QLQC30 <sup>1</sup>	Anxiety scores significantly lower at 12 mo than baseline, depression scores significantly higher at 9 mo
Russo <i>et al</i> <sup>[29]</sup> 2003	Metastatic mid-gut carcinoid	No. Experimental tryptophan depletion	12 patients somatostatin analogues, 2 patients no treatment	14/14	Cambridge Neuropsychological tests automated battery (CANTAB): intra-/extra-dimensional shift task, matching to sample visual search, rapid visual information processing and spatial working memory.	Impaired sustained attention. Not mimicking patients with depression
Larsson <i>et al</i> <sup>[27]</sup> 2003	Carcinoid tumour	Yes	Somatostatin analogues or interferon	19/19	Semi-structured interview	Fatigue, diarrhoea, worry about diagnosis and limited physical ability most commonly reported symptoms
Russo <i>et al</i> <sup>[19]</sup> 2004	Mid-gut carcinoid tumour with carcinoid syndrome	No	14 patients on somatostatin analogues, 2 patients on interferon 2 patients no active treatment. 2 patients on somatostatin analogues + interferon	20/20	Semi-structured psychiatric interview	Impulse dysregulation leading to diagnosis of personality change secondary to a medical disorder in 15 patients (75%)

<sup>1</sup>European Organisation for Research and Treatment of Cancer (EORTC) health-related quality of life QLQ-C30 questionnaire.

6.5% and 13.5%. Other studies have reported rates of depression between 18% and 25%<sup>[14,15]</sup>.

Patients with a diagnosis of a neuroendocrine tumour were not considered in these studies, which only addressed the most frequent tumour entities. Patients with advanced GEPNETs experience similar symptoms to those with a diagnosis of gastrointestinal cancers, and there is a perception amongst many treating physicians that patients with functional neuroendocrine tumours, presenting with CS may have higher levels of psychological distress compared to other patients with a cancer diagnosis. However, there is limited data to support this hypothesis<sup>[16,17]</sup>.

It may be, in the case of neuroendocrine tumors, that psychological changes could be related to the effects of biochemical mediators produced by the tumour itself and released into the bloodstream, such as serotonin. For example, in a study by Jacobsen *et al*<sup>[18]</sup>,

which included eleven patients with advanced GEPNET and CS, it was reported that psychological distress decreased, and social functioning increased, following one month of treatment with SSAs.

Several studies and reports in the literature dating back to the 1960s, point out that several types of neuroendocrine tumours, can be associated with depression, sleep disturbances, anxiety, aggressive behaviour, psychosis and altered attention span<sup>[10,17,19-30]</sup>. Studies assessing mood in patients with neuroendocrine tumours are summarised in Table 1.

Previous studies on this topic have included small numbers of patients, without apparent control groups, with varying psychological tests applied, therefore the aim of this study was to compare health-related quality of life (HRQoL), anxiety, depression, and impulsivity in patients with advanced GEPNETs, with and without CS, and to correlate with biochemical markers of

disease activity such as serum chromogranin A and 5-hydroxyindoleacetic acid (5-HIAA).

## MATERIALS AND METHODS

Patients with advanced well-differentiated GEPNET tumours with liver metastases, with and without CS attending an outpatient NET clinic at a European Neuroendocrine Tumour (ENET) Centre of Excellence; The Christie NHS Foundation Trust, Manchester, United Kingdom, were asked to complete the European Organisation for Research and Treatment of Cancer (EORTC) health-related quality of life QLQ-C30<sup>[31]</sup> and neuroendocrine tumour-specific GINET-21 (GINET21) questionnaires<sup>[32]</sup>, the Hospital Anxiety and Depression scale (HADS)<sup>[33]</sup> and the Barratt Impulsivity Scale (BIS)<sup>[34,35]</sup>. These were completed at a single time point between April and August 2016. The EORTC QLQ-C30 scores patients on scales that assess global health status, social, physical and emotional functioning and common symptoms. Various disease-specific scales have been developed to work in combination with the QLQ-C30 and the GINET-21 is specific to neuroendocrine tumours. In combination with the QLQ-C30, the GINET-21 questionnaire provides information on neuroendocrine symptoms including diarrhoea and flushing, treatment side-effects and disease-related worries<sup>[32]</sup>.

The Barratt Impulsivity scale is a well validated score that examines first-order factors including attention, cognitive instability, motor and perseverance, self-control and cognitive complexity. Second-order factors analysed in this scale are attentional, motor and non-planning<sup>[34]</sup>.

Baseline demographic data collected included age, tumour site, Eastern Cooperative Oncology Group performance status (ECOG PS), time from diagnosis, presence of recurrent disease following initial curative-intent surgery, any previous surgery and current and previous treatments, presence of co-morbidities and use of psychoactive medications. Baseline serum chromogranin A and 5-HIAA at initial presentation with advanced disease, and at the time of questionnaire completion were recorded. Patients identified within this study as having significant symptoms of anxiety and depression were offered referral to the psycho-oncology service.

Inclusion criteria for this study were a diagnosis of advanced GEPNET with liver metastases, with or without CS, understanding the English language and the physical ability to complete questionnaires. Patients with neuroendocrine tumours originating from sites other than the gastroenteropancreatic tract and without liver metastases were excluded, as were those with poorly-differentiated tumours. Patients with functional tumours presenting with other syndromes *e.g.*, gastrinoma were also excluded.

The sample size of 25 patients with CS (with matched controls) was selected on the basis of feasibility and as a representative sample in a large ENETs Centre

of Excellence. A recent analysis of outcomes of patients with GEPNETs and CS presenting to The Christie over a 28 year period identified 139 patients<sup>[36]</sup>. With a median overall survival of 65.4 mo in this study, this would therefore suggest that approximately 40 patients would be alive at any one time. Accounting for patients who only attend the Christie for single appointments or experience ill health or language barriers preventing completion of the questionnaires, 25 patients was identified as an achievable patient group.

The local audit committee approved this study (reference number: CE16/1619).

### Statistical methods

The median time from diagnosis of advanced disease (radiological or histological) was recorded up to date of completion of questionnaires.

The two-sample Wilcoxon (Mann-Whitney test) was applied to assess differences in serum chromogranin A and 5-HIAA in patients with and without CS.

Responses to the EORTC QLQ-C30 and the QLQ-GINET21 were linearly transformed to a 0-100 scale using EORTC guidelines. Two-sample Mann-Whitney *U* test were applied across scales/items to assess the difference between the patient groups with and without CS. A *P* value less than 0.05 indicated a statistically significant difference. For the HADS, 8 out of 21 was used as the cut-off for both the "Anxiety" and "Depression" category as a level representing clinically-significant symptoms warranting further intervention<sup>[33]</sup>. The Proportion test was applied to both the "Anxiety" and "Depression" categories to assess whether there was a statistically significant difference in the proportion of "total score  $\geq 8$ " between patient groups with and without CS. The two-sample Mann-Whitney *U* test was applied to first-order factors, second-order factors and total sum, to compare the patient groups with and without CS.

This study was an exploratory analysis. Detection of a specific effect size (hazard ratio) was not the target, and so power calculations were not used, as detection of an intended hazard ratio was not required.

## RESULTS

The median age of all patients was 65.5 years. The majority of patients (88%) had an ECOG PS of 0-1. Most patients had tumours originating in the small intestine (58%) or the pancreas (22%). The most frequent current treatment in all patients was SSAs, either alone or in combination. These results are summarised in Table 2. The median time from initial diagnosis for all patients was 40 mo [95% confidence interval (CI): 22-48 mo]; 45 (95%CI: 20-49) and 36 mo (95%CI: 18-56), *P* = 0.66, in the groups with and without CS respectively. Five patients (10%) were taking prescribed psychoactive medications; two patients with CS. The median serum 5-HIAA at

**Table 2 Patient characteristics - advanced gastroenteropancreatic neuroendocrine tumours with and without carcinoid syndrome *n* (%)**

	All patients <i>n</i> = 50	With carcinoid syndrome <i>n</i> = 25	Without carcinoid syndrome <i>n</i> = 25	<i>P</i> value
Age (median)	65.5	67	62	0.19
95%CI	(61.5-68.5)	(61.3-70.9)	(58.0-68.9)	
Gender	F:21 (42) M:29 (58)	F:9 (36) M:16 (64)	F: 12 (48) M: 13 (52)	0.39
Median time since diagnosis (mo)	39	45	36	0.66
(95%CI)	(21.54-48.46)	(20.10-48.90)	(18.21-56)	
Prior Surgery	24 (48)	9 (36)	15 (60)	0.09
Recurrent disease following previous curative intent treatment	8 (16)	3 (12)	5 (20)	0.44
Primary disease site				
Stomach	1 (2)	0 (0)	1 (4)	
Small bowel	29 (58)	18 (72)	11 (44)	
Pancreas	11 (22)	1 (4)	10 (40)	
Large bowel	3 (6)	1 (4)	2 (8)	
Unknown GI tract	6 (12)	5 (20)	1 (4)	
Median Ki-67 % (95%CI)	3 (2-4.8)	2 (2-5)	3 (2-7.7)	0.55
ECOG PS <i>n</i> (%)				
0	14 (27)	7 (28)	7 (28)	
1	30 (60)	16 (64)	14 (56)	
2	4 (8)	1 (4)	3 (12)	
3	2 (4)	1 (4)	1 (4)	
Current treatment				
Nil	5 (10)	2 (8)	4 (16)	
Best supportive care	1 (2)	0 (0)	1 (4)	
Chemotherapy	5 (10)	0 (0)	5 (20)	
Interferon + Somatostatin analogue	2 (4)	2 (8)	0 (0)	
Peptide receptor radionuclide Therapy	2 (4)	1 (4)	1 (4)	
Peptide receptor radionuclide therapy + Somatostatin analogues	2 (4)	1 (4)	1 (4)	
Somatostatin analogues	28 (56)	8 (72)	9 (36)	
Tryptophan hydroxylase inhibitor + Somatostatin analogues	1 (2)	1 (4)	0 (0)	
mTOR inhibitor	4 (8)	0 (0)	4 (16)	
Use of psychoactive medications				
Nil	44 (88)	22 (88)	22 (88)	
Selective serotonin Reuptake inhibitors	3 (6)	1 (4)	2 (8)	
Benzodiazepine	1 (2)	1 (4)	0 (0)	
Selective serotonin reuptake inhibitors + benzodiazepine	1 (2)	0 (0)	1 (4)	
Unknown	1 (2)	1 (4)	0 (0)	

CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status.

diagnosis of advanced disease was 367.0 nmol/L (95%CI: 271.57-1127.89) and 124.0 nmol/L (95%CI: 73.05-200.98) in those patients with and without CS respectively ( $P < 0.001$ ). The median serum 5-HIAA at the time of questionnaire completion was 367.00 nmol/L (95%CI 176.7-855.5) and 86 nmol/L (95%CI: 66.8-123.9) in those patients with and without CS respectively ( $P < 0.001$ ) (normal range 0-140 nmol/L), indicating biochemical differences between groups at baseline and at time of questionnaire completion.

The median baseline chromogranin A at diagnosis of advanced disease was 268 ng/mL (95%CI: 151.6-381.4) and 116 ng/mL (95%CI: 57.77-275.51) in those patients with and without CS respectively ( $P = 0.09$ ). The median chromogranin A measurement at the time of questionnaire completion was 322 ng/mL (95%CI: 215.2-456.5) and 198ng/mL (95%CI: 68.8-392.0) in patients with and without CS respectively ( $P = 0.13$ ) (normal range 0-91 ng/mL).

In the HRQoL QLQ-GI.NET21 questionnaire, scores related to endocrine symptoms (flushing and night sweats) were significantly higher in those with CS ( $P = 0.04$ ). Disease-related worries (related to tumour progression, health in the future and test results) appeared more prominent in the group without CS and the difference approached statistical significance ( $P = 0.05$ ). There were no significant differences in responses between those patients with and without CS for all other symptoms in both health-related quality of life questionnaires (QLQ-C30 and QLQ-GI.NET21). These results are summarised in Tables 3 and 4.

Out of the total of 50 patients, fifteen patients (30%) scored  $\geq 8/21$  on the HADS anxiety scale; 8 had CS, and 6 (12%) scored  $\geq 8/21$  on the HADS depression scale; 3 with CS. There was no difference in the median serum 5-HIAA between those scoring  $<$  or  $\geq 8/21$  on the anxiety scale ( $P = 0.53$ ). The Proportion test was not statistically significant between

**Table 3** Comparison of responses in patients with and without carcinoid syndrome in the HRQoL QLQ-C30 questionnaire

	Without carcinoid syndrome		With Carcinoid syndrome		Difference between groups	P value
	Mean score	(95%CI)	Mean score	(95%CI)		
Global health status	63	52.3-73.7	61.7	49.6-73.7	1.3	0.92
Physical functioning	79.9	73.0-86.8	77.9	67.9-87.9	2.0	0.79
Role functioning	74	61.3-86.7	70.7	56.3-85.0	3.3	0.77
Emotional functioning	73	63.0 – 83.0	74.7	63.7-85.6	-1.7	0.73
Cognitive functioning	76.7	66.3-87.0	74.0	61.0-87.0	2.7	0.93
Social functioning	70	58.6– 81.4	79.3	67.2-91.5	-9.3	0.15
Fatigue	34.7	23.6-45.8	37.8	23.9-51.7	-3.1	0.84
Nausea and vomiting	11.3	4.0-18.7	8.00	1.4-14.6	3.3	0.31
Pain	25.3	11.8-38.8	26.7	13.5-39.8	-1.3	0.81
Dyspnoea	12.5	1.7-23.3	24.0	10.5-37.5	-11.5	0.15
Insomnia	36	22.9-39.1	22.7	10.9-34.3	13.3	0.12
Appetite loss	18.7	8.1-29.2	22.7	9.7-35.7	-4	0.81
Constipation	9.3	1.9-16.8	9.30	1.9-16.8	0	1.00
Diarrhoea	24	9.4-38.6	32.0	17.4-46.6	-8.0	0.27
Financial difficulties	13.3	3.6-23.1	8.00	-18.2	5.3	0.30

HRQoL: Health-related quality of life.

**Table 4** Comparison of responses in patients with and without carcinoid syndrome in the HRQoL QLQ-GI.NET21 questionnaire

	Without carcinoid syndrome		With Carcinoid syndrome		Difference between groups	P value
	Mean score	(95%CI)	Mean score	(95%CI)		
Endocrine symptoms	16.7	8.4-24.9	28.4	18.1-38.8	-11.8	0.04
Gastrointestinal symptoms	18.9	12.7-25.3	24.0	16.5-31.5	-5.1	0.37
Treatment-related symptoms	17.5	8.6-26.4	10.1	4.1-16.2	7.4	0.20
Social functioning	60.0	50.0-70.0	68.4	58.7-78.1	-8.4	0.19
Disease-related worries	56.9	43.0-70.8	38.7	26.2-51.2	18.2	0.05
Body image	15.3	4.3-26.2	13.3	2.1-24.6	1.9	0.57
Weight gain	18.7	7.4-30.0	13.3	2.1-24.6	5.3	0.30
Muscle/ bone pain	41.3	28.6-54.1	46.7	31.3-62.1	-5.3	0.62
Information	10.7	2.0-19.3	16.0	4.7-27.3	-5.3	0.51
Sexual functioning	60.8	35.6-85.9	68.4	47.4-89.5	-7.6	0.82

groups with and without CS for anxiety ( $P = 0.76$ ) or depression ( $P = 1.0$ ). There were no statistically-significant differences between groups with and without CS in first or second-order factors (BIS) or total sum ( $P = 0.23$ ).

## DISCUSSION

In this study, there were no significant differences identified in the majority of health-related quality of life responses, anxiety, depression or impulsivity in patients with advanced GEPNET, despite observed significant differences in median serum 5-HIAA between those patients with and without CS. There were more endocrine-related symptoms, specifically flushing and sweating, in patients with CS and those without CS had more disease-related worries (progression, test results and the future). The reasons for increased disease-related worries in those without CS may be due to masking of these symptoms in patients with CS, where the worry may be shifted due to endocrine symptoms.

In patients with GEPNETs, serotonin produced peripherally by the tumour, cannot cross the blood-brain barrier and, as a result, is unable to exert direct effects on the central nervous system (CNS)<sup>[29]</sup>. However, it has been hypothesised that diversion of

dietary tryptophan to peripheral serotonin production, thereby causing a relative CNS depletion may be a cause of emotional disturbances in these patients<sup>[29]</sup>. Various studies have demonstrated cognitive changes when healthy control subjects have induced tryptophan depletion<sup>[37-43]</sup>. In a study testing the blockade of the enzyme tryptophan hydroxylase as a method of reducing CS symptoms<sup>[43]</sup>, depression was a severe side-effect. The study investigating the effects of telotristat ethyl for symptom control in patients with CS specifically focused on depression as an “adverse event of special interest”, and did report increased rates of depression in the group taking 500 mg three times daily compared to those taking 250 mg three times daily. However, this did not delay treatments or require the introduction of anti-depressant therapy<sup>[9]</sup>.

The lack of difference in scores on the majority of the symptom scales of the questionnaires completed in this study may be related to a long median time from diagnosis, and so many symptoms may be controlled on treatment, and thus there would be a reduced impact on the patient’s psychological distress. A meta-analysis of studies which included patients with early-stage and advanced disease reported a mean prevalence of depression amongst patients with cancer of 18%, and reported that rates tended to be lower for those greater

than 1 year from diagnosis<sup>[14]</sup>. Similarly in a study by Larsson *et al.*<sup>[11]</sup>, patients with advanced GEPNETs completed the EORTC QLQ30 at baseline, 3, 6, 9 and 12 mo from commencement of treatment with interferon or SSAs. The authors reported that the scores for physical functioning decreased, whereas those for emotional role and cognitive function improved during the study.

In addition, it has previously been reported that global health scores may not be particularly sensitive in this patient population<sup>[32,44,45]</sup>. Similarly, with regards to physical symptoms, despite there being increased flushing reported, diarrhoea was not reported as a significant symptom in patients with CS in our study, and again could be a reflection of the impact of disease control on psychological state.

In the study by Russo *et al.*<sup>[19]</sup>, formal psychiatric interviews were used to assess patients with CS. The authors identified a significant proportion of patients with impulse dysregulation leading to reduced social functioning. The authors were able to make a diagnosis of "Personality change secondary to a medical condition" in some of these patients. In the study by Larsson *et al.*<sup>[27]</sup> which examined distress and strategies for maintaining good mood in patients with carcinoid tumours, some factors contributing to distress in their study are not covered by either the EORTC-QLQ30 or the HADS questionnaire used in the current study. Therefore, it is possible that the questionnaires used in the current study were not sufficiently sensitive to detect personality changes or some more subtle features of psychological distress.

In the current study, a high number of patients with and without CS had high scores on the anxiety and depression scale. The rate of depression in the current study was 12%, and since the median time from diagnosis was 40 mo in this study, the rate for depression seems proportional to the general cancer population<sup>[14]</sup>.

However, the rates of anxiety reported in the current study (approximately 25% of the patients assessed) were significantly higher than those of 8%-11%<sup>[12,13]</sup> reported elsewhere in patients with cancer. It is of note that our study included only patients with advanced GEPNET, whereas the studies by Mehnert *et al.*<sup>[12]</sup> and Singer *et al.*<sup>[13]</sup> included patients with early stage and advanced disease.

A limitation of this study was that it included only fifty patients and it may be that it was not large enough to detect small differences in psychological state between the patients with and without CS. Another limitation is that patient questionnaires were completed at a single time point only, and this may not have been a representative view of the patient's psychological symptoms over the course of their disease. There was also variation in time from diagnosis to completion of surveys which could have an impact on psychological

effects. Furthermore, there may have been impact from treatments on results. Patients in the group without CS had undergone more prior lines of treatment (mean 2.12 vs 1.87 in the group with CS) and had received more systemic treatments including mTOR inhibitors and chemotherapy that are associated with toxicities, which may have an impact on psychological state. However, GEPNETs are a rare tumour group and most studies reported to date included an average of twenty patients without control groups, and so the current study is comparably more robust and informs on a poorly studied topic.

Limitations could potentially be overcome by conducting a prospective study with repeated questionnaire sampling from the time of diagnosis of advanced GEPNET and matching of controls by treatment.

In conclusion, this study contributes to the limited evidence base regarding psychological symptoms for this rare disease group, and includes a relatively large cohort of patients with a diagnosis of GEPNET, with and without CS, reviewed at a tertiary referral centre. This study also highlights the importance of recognition by treating physicians of psychological distress in patients with advanced GEPNET, and the need for input from the psycho-oncology services. Prospective multi-centre studies are required to further enhance the understanding of psychological distress in this disease group and the relation, if any, with biochemical abnormalities and indeed their therapeutic management.

## ARTICLE HIGHLIGHTS

### Research background

Psychological issues in patients with gastroenteropancreatic neuroendocrine tumours (GEPNETs), with or without carcinoid syndrome (CS), are rarely studied. There is a physician perception of higher levels of psychological distress amongst patients with CS. There is some data to support this in the form of case reports, but not large comparative studies and it is unclear whether this takes the form of anxiety, depression or even impulsivity. The aim of this study was therefore to compare health-related quality of life, anxiety, depression, and impulsivity in patients with advanced GEPNET, with and without CS, and to correlate with biochemical markers of disease activity.

### Research motivation

An improved understanding of the psychological issues for these patients will help better inform management of their symptoms.

### Research objectives

To assess whether patients with advanced GEPNET and CS have increased levels of anxiety, depression, impulsivity or worse quality of life than patients with advanced GEPNET, but non-functioning tumours.

### Research methods

Patients with advanced GEPNET with and without CS were invited to fill out questionnaires at outpatient clinics at The Christie NHS Foundation Trust, which is a European centre of excellence for neuroendocrine tumours. Patients completed the hospital anxiety and depression scale (HADS), the EORTC QLQ-C30 and GINET-21 quality of life scales and the Barrett Impulsivity scale (BIS) at a single time point. Demographic information with regards to gender, time from diagnosis and treatment history was collected from casenotes, as

were serum markers of disease [5-hydroxyindoleacetic acid (5-HIAA)].

### Research results

Fifty patients were included; 25 each with and without CS (CS). Median serum 5-HIAA in patients with and without CS was 367nmol/L and 86nmol/L, respectively ( $P = 0.003$ ). Scores related to endocrine symptoms were significantly higher amongst patients with CS ( $P = 0.04$ ) and scores for disease-related worries approached significance in the group without CS, but no other statistically-significant differences were reported between patients with and without CS in responses on QLQ-C30 or QLQ-GI.NET21. Fifteen patients (26%) scored  $\geq 8/21$  on anxiety scale, and 6 (12%) scored  $\geq 8/21$  on depression scale. There was no difference in median 5-HIAA between those scoring  $<$  or  $\geq 8/21$  on anxiety scale ( $P = 0.53$ ). There were no statistically significant differences between groups in first or second-order factors (BIS) or total sum ( $P = 0.23$ ).

### Research conclusions

There were no significant differences between groups with regards to anxiety, depression or impulsivity. Serum 5-HIAA and endocrine symptoms were more prevalent in the group with CS as would be expected. Disease-related worries were higher in the group without CS. Results may have been impacted by a long time from diagnosis in the CS group or limited sensitivity of screening tools to detect subtle differences in mental state. Results may also have been impacted by small sample size however in this rare disease group the sample size is robust in a comparative study. Levels of anxiety and depression were high in both groups and may be higher in patients with GEPNET than with other solid tumours. This is one of few comparative prospective studies in this patient group and established methods of assessment were used and correlated with serum biochemistry. More sensitive tools need to be developed to assess psychological symptoms in these patients.

### Research perspectives

This prospective comparative study included single time point assessment of symptoms. Studies with questionnaires distributed at varying times would be helpful to assess the impact of changes throughout the patient journey.

Futures prospective studies are needed, ideally involving multiple centres with considered methodology such as psychiatric interviews including the use and development of more selective psychological assessment tools.

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