SYMPTOMS AND QUALITY OF LIFE IN GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOURS

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ABSTRACT

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) have the ability to induce symptoms either by their direct mass effect on local tissues (symptoms such as pain, bowel obstruction, obstructive jaundice, and bleeding), or by the ectopic secretion of bioactive compounds. GEP-NETs are frequently associated with significant diagnostic delays, and metastatic disease is often a feature at initial presentation. Quality of life (QoL) research in GEP-NETs is a comparatively new field, with a disease-specific QoL questionnaire, the QLQ-GINET21, having been fully validated only as recently as 2013. It has been reliably demonstrated to date that diarrhoea, fatigue, and flushing are the symptoms provoking the greatest decline in patient QoL. Furthermore, depression is highly prevalent in the GEP-NET population. This paper reviews current understanding and potential future developments in this field.

Keywords: Quality of life, patient-reported outcome measures (PROMs), gastroenteropancreatic neuroendocrine tumours (GEP-NETs), symptoms, GINET21, QLQ-C30, syndromes, neuroendocrine tumours (NETs).

INTRODUCTION: SYMPTOM SCORES, PATIENT-REPORTED OUTCOMES, AND QUALITY OF LIFE

Patient-reported outcomes are fundamentally important measures of clinical intervention, both in clinical practice and as trial endpoints. The term PROM (patient-reported outcome measure) refers to any symptom or feeling that the patient can describe. Quality of life (QoL) is (usually) a patient-reported measure which is designed to include symptoms as well as emotional domains such as anxiety and depression. Measuring symptoms and emotional domains is not easy, but there is extensive research on these measures in other cancers (http://groups.eortc.be/qol). With the advent of new therapies for gastroenteropancreatic neuroendocrine tumours (GEP-NETs), it is essential that these measures are used to test PROMs before and after any novel intervention in order to inform future practice of their impact.

Gastroenteropancreatic Neuroendocrine Tumours

GEP-NETs are a rare, heterogeneous group of neoplasms that arise from neuroendocrine tissue in the digestive tract. Whilst the overall majority of GEP-NETs are non-functional (NF), in a significant proportion the neoplasm secretes bioactive peptides congruent with the cell type of tumour origin, giving rise to a diverse array of distinct clinical syndromes. The most common of these is the carcinoid syndrome.[1] Despite their heterogeneous origins, most GEP-NETs share a number of biochemical markers, chromogranin A being the most diagnostically significant.[2] The majority occur as sporadic tumours, and some are found as part of defined familial cancer

syndromes.[3] Incidence in industrialised nations ranges from 2 to 4.4 per 100,000 per year, with marginally higher prevalence in women and persons of African-American descent.[4-6] The surveillance, epidemiology, and end results program (SEER) data suggest that GEP-NETs are generally slow-growing neoplasms with overall 5-year survival rates of 60-65%. Prognostic factors include tumour site, type, degree of differentiation, and degree of spread. Thus, well-differentiated locally invasive tumours may yield a 5-year survival of up to 82%, whilst poorly differentiated metastatic neoplasms a 5-year survival as low as 4%. The best outcomes are seen in benign insulinomas and rectal NETs with 95% and 88% 5-year survival, respectively.[4,6,7]

Disease-Specific Symptoms

i) Universal symptoms

All GEP-NETs may present with features unrelated to their source of origin, functionality, or location within the gastrointestinal (GI) tract. These include pain, nausea, diarrhoea, vomiting, iron deficiency anaemia arising from occult blood loss, bowel obstruction, obstructive jaundice, ascites, and rarely frank rectal bleeding. NF GEP-NETs may only manifest with these signs and symptoms once distant metastatic spread generates mass effects in other tissues. The commonest presenting symptoms of non-functional pancreatic NETs (NF-pNETs), which are over twice as common as functional pNETs,[8] are abdominal pain (40-60%), jaundice (30-40%), and weight loss (25-50%). Due to the absence of a distinct hormonal syndrome, NF-pNETs are often detected as an incidental finding,[9] and at diagnosis 60% of NF-pNETs will have metastasised, the liver being the commonest site.[10]

ii) Carcinoid tumours

Carcinoid tumours are neoplasms that arise from enterochromaffin cells, a class of secretory neuroendocrine cells widely distributed in the enteral epithelium. Functional carcinoid tumours are most commonly found in the jejunum and ileum,[11] secreting 5-hydroxytryptamine (serotonin, 5-HT) as well as histamine, bradykinin, and kallikrein. It is secretion of these vasoactive peptides into the systemic circulation that generates the carcinoid syndrome, classically a triad of dry flushing (flushing without sweating, occurs in 70% of patients), diarrhoea (occurs in 50% of patients), and dyspnoea (triggered by histamine-mediated bronchospasm, seen in 50% of patients).[12,13] Approximately 10% of patients with a secretory carcinoid will exhibit all three symptoms concurrently. Abdominal pain, related to mesenteric desmoplasia, necrosis of hepatic metastases, or capsular stretch is found in up to 50% of patients.

The commonest carcinoid syndrome symptom is fatigue (69% of patients), appearing more commonly than in many other cancers, and may be a specific effect of hormone secretion. Other common features are nausea (seen in 39%), loss of appetite (39%), myalgia (up to 42%), insomnia (36%), and dry skin (39%).[14] Bowel obstruction arises in up to 20% of cases at presentation.[15] Lacrimation, rhinorrhoea, and a pellagra-like syndrome resulting from depletion of niacin due to a high 5-HT turnover may also be seen in rare cases.[16] Therefore all patients experiencing psychological effects in carcinoid disease should be considered for intravenous or oral vitamin B replacement.[1,17]

Up to 20% of patients exhibit features of carcinoid heart disease (CHD) at presentation,[18] a secondary restrictive cardiomyopathy resulting from fibrosis of the tricuspid and pulmonary valves. Left-sided heart disease may be seen in up to 15% of patients with CHD. The presence of CHD has been shown to dramatically worsen outcomes, with 3-year survival as low as 31% (versus 68% in patients without CHD).[19] Initially presenting with murmurs, CHD will eventually progress to peripheral oedema, pulsatile hepatomegaly, and ascites if left untreated. A rare complication of carcinoid syndrome is the carcinoid crisis, most commonly precipitated by induction of anaesthesia or direct handling of the tumour. Caused by the sudden release of large amounts of vasoactive mediators into the systemic circulation, it is characterised by tachycardia, labile blood pressure, profound flushing, and bronchospasm.[1]

Timely diagnosis in carcinoid tumours is an ongoing problem.[20] The commonest misdiagnoses are irritable bowel syndrome (leading to a mean diagnostic delay of 68 months), food allergies or intolerance (leading to a mean diagnostic delay of 168 months), depression (mean diagnostic delay of 205 months), other psychiatric disorders (mean diagnostic delay of 86 months), and lactose intolerance (mean diagnostic delay of 180 months). A survey of 154 patients undertaken by the United Kingdom's NET Patient Foundation found that 19% had waited for more than 5 years for a diagnosis.

iii) Insulinomas

Insulinomas are rare neoplasms derived from pancreatic β-cells. Overall incidence was up to 4 per million per year in one case series,[21] making insulinomas the commonest functional pNET. Approximately 5% of cases can be attributed to multiple endocrine neoplasia Type 1 (MEN1).[22] Up to 10% of cases metastasise.[23] Insulinomas become symptomatic due to ectopic hypersecretion of insulin into the systemic circulation triggering episodes of hypoglycaemia, with symptoms classically worsening during periods of exercise, fasting, or intercurrent illness, and improving on eating. Symptoms[24-29] can be grouped into three categories:

a) Neuroglycopaenic symptoms (overall seen in 90% of patients) such as slurred speech, confusion (80%), blurred vision (59%), drowsiness or coma (38% and 47%, respectively), inattention, overeating (15-50%), and eventually a hypoglycaemic neuropathy in rare cases.
b) Adrenergic symptoms (seen in 60-70% of cases) such as anxiety, palpitations (seen in around 12%), sweating (up to 69%), xerostomia, and tremor (up to 24%).
c) Cholinergic symptoms such as hunger and paraesthesia.
The mean delay in diagnosis for insulinomas is around 4 years.[25]

iv) Gastrinomas

Gastrinomas are rare tumours of the pancreas and duodenum characterised by the hypersecretion of gastrin. Overall incidence is around 1-2 per million per year. Gastrinomas show approximately equal preponderance for the duodenum or pancreas. It is thought that up to 70% occur within a triangle defined inferiorly by the 2nd and 3rd portion of the duodenum, medially by the pancreatic neck and body, and superiorly by the confluence of the common bile and cystic ducts.[30] Up to 10% will occur elsewhere in the abdomen (stomach, spleen, omentum, liver, ovary). Up to 60% will metastasise, and up to 25% are associated with MEN1.[22,23]

Hypersecretion of gastrin triggers both parietal cell hypersecretion of hydrochloric acid into the stomach and parietal cell hyperplasia.[31] The resulting combination of severe peptic ulceration and diarrhoea is termed Zollinger-Ellison Syndrome. In 35% of cases diarrhoea is the sole feature. Commonest presenting symptoms are epigastric and abdominal pain (up to 100% of patients),[32] diarrhoea (up to 73% of patients, often with steatorrhoea due to inactivation of lipase), gastro-oesophageal reflux disease (up to 64% of cases), upper GI bleeding (up to 17% of patients), perforation (up to 5% of presenting cases), and obstruction (up to 5% of cases). On endoscopy, up to 91% of patients with a gastrinoma will show duodenal or pyloric ulcers.[33] The mean delay in diagnosis is 6.1 years.

v) Glucagonomas

Glucagonomas arise from pancreatic α-cells with an incidence of around 0.1 per million per year. 50-80% of cases metastasise, and 10% of cases are associated with MEN1.[22,23] Symptoms are triggered by ectopic hypersecretion of glucagon, leading to persistent gluconeogenesis and lipolysis. The pathogenomic feature of hyperglucagonaemia is migratory necrolytic erythaema (MNE), a cutaneous eruption seen in 70-90% of cases. MNE presents as a maculopapular rash that becomes vesicular and necrotic, eventually healing with pigmented scarring. MNE is most commonly seen on the limbs and perioral skin, and appears to be triggered at sites of skin pressure, friction, or trauma.[34,35] Other common symptoms are weight loss (seen in up to 80%), insulin resistance or frank Type 2 diabetes mellitus (40-90%), anaemia (up to 90%), hypoaminoacidaemia (up to 80%), and diarrhoea (around 25% of cases). The mean delay in diagnosis is 7 years.

vi) VIPomas

VIPomas secrete vasoactive intestinal peptide (VIP) and are amongst the rarest GEP-NETs with an incidence of 0.1 per million per year. Up to 70% will metastasise and up to 5% occur in conjunction with MEN1.[22,23] Ectopic hypersecretion of VIP leads to VIPoma, characterised by profuse watery diarrhoea and electrolyte disturbances. Diarrhoea output above 700 ml per day is seen in all patients, with up to 70% exceeding 3,000 ml per day. Hypokalaemia, often severe, and dehydration are universal. Hypercalcaemia and hyperglycaemia occur in up to 50% of cases and hypochlorhydria in up to 76%. One-third of patients may also experience intermittent flushing.[36-39]

vii) Somatostatinomas

Somatostatinomas are neoplasms of δ-cells that secrete somatostatin. Overall incidence is thought to be <1 per 10 million per year. Up to 45% are associated with MEN1, and up to 70% of tumours

will metastasise.[22,23] They are most commonly found in the pancreatic head and duodenum (ampulla and periampullar), although only 20% of duodenal tumours secrete clinically significant quantities of somatostatin (versus over 90% of pancreatic neoplasms). Duodenal somatostatinomas are sometimes associated with neurofibromatosis Type 1. Classically, hypersecretion of somatostatin results in the triad of diabetes mellitus (due to inhibition of insulin secretion), cholelithiasis (due to inhibition of cholecystokinin-mediated gall bladder emptying), and diarrhoea with steatorrhoea. Gastric hypochlorhydria, weight loss, and hypoglycaemia have also been reported.[40-42]

Quality of Life

GEP-NETs are frequently diagnosed at a late stage, when metastatic disease is already present, and maximising QoL is therefore increasingly supplanting a curative approach. Prior to 2013, the European Organisation for Research and Treatment of Cancer (EORTC) generic cancer QLQ-C30 questionnaire was the only widely used tool to assess QoL.

i) QLQ-GINET21

The GINET21 module was first conceived in 2006[43] and underwent final Phase IV psychometric validation in 2013.[44] It focuses on flushing, GI symptoms, weight, anxiety, communication with patients, and treatment side-effects. Whilst the GINET21 has been validated for all types of GEP-NET, data on the rarer functional pNETs have been difficult to generate in statistically significant quantities. Only a limited number of insulinoma patients were included in the original development of the GINET21 and there is to date no separate QoL measure available for use for these patients. As the majority of patients will be curatively treated by surgery and the number of metastatic insulinoma patients is so small, developing a questionnaire would be very challenging. A small number of patients with secretory gastrinomas were included in the early stages of the development of the GINET21, but it was felt that there were not enough to make GINET21 a valid measure for this particular patient subgroup. As they have very specific symptoms, developing a QoL measurement tool for these patients may be feasible. The functional pNETs in iv-vii above are so rare that very little is known about patients' QoL. Despite the GINET21 having been validated for their use, the specificity of the syndromes generated by pNETs as a group gives rise to the question as to whether a separate QoL questionnaire, or an amended GINET21 is required in future to fully capture the issues experienced by patients in these circumstances. To date there are no published data to support this, a reflection on the difficulty of acquiring statistically significant data quantities.

ii) Norfolk QoL NET

The Norfolk QoL NET was developed in 2009 with a focus on symptom frequency, duration, and severity, impact on activities of daily living (ADLs), and effects of treatment with somatostatin analogues.[45] A comparative study published in 2011 suggests that there is strong correlation between the final scores for both the QLQ-GINET21 and the Norfolk QoL NET. Furthermore, serum 5-HT levels and, significantly, overall tumour burden appear to correlate strongly with final QoL scores in both QLQ-GINET21 and Norfolk QoL NET.[46]

There is some evidence that overall QoL is perceived as good by patients, as suggested by a 1999 study of 119 patients (carcinoid: n=64 and pNETs: n=55) using the QLQ-C30.[47] However, a 2009 study in Norway using the SF-36 short form health survey comparing 196 NET patients with a healthy sample of 5,258 found significantly lower scores across all domains, in particular, the ability to complete ADLs and mental health.[48] Poor mental health in particular appears to be prevalent in patients with pNETs, as demonstrated by a 2009 study of 55 pNET patients using the SF-12, BDIII, GHQ-12, and state-trait anxiety inventory (STAI) questionnaires found an overall prevalence of mild to-moderate depression of 40%.[49]

Symptoms appearing to have the greatest impact on patient QoL have been identified as fatigue and diarrhoea (flushing to a lesser extent) in a study of 36 consecutive patients with carcinoid tumours in Sweden using the QLQ-C30.[14] Fatigue and diarrhoea were the reason for patients scoring poorly in their ability to complete ADLs, work, and social activities. The same study identified that the worst aspect of emotional distress was anxiety related to disease progression. Diarrhoea and flushing were identified as the most significant factors in determining QoL in an American study of 663 patients using online SF-36 and PROMIS-29 questionnaires.[50]

QoL changes during treatment are poorly understood at present, and research focus has

been overwhelmingly on medical therapies. A 2014 randomised, double-blind controlled trial (CLARINET)[51] in patients with metastatic GEP-NETs comparing lanreotide (n=101) to placebo (n=103) found no significant difference in overall QoL or overall survival (OS), although the primary endpoint of the study, progression-free survival (PFS), was significantly improved, with an estimated 24-month PFS of 65.1% in the lanreotide arm versus 33% in the placebo arm. Due to the high rate of crossover from placebo to lanreotide of over 50%, differences in OS and QoL may not be expected. Diarrhoea was the most frequently reported adverse effect, found in 26% of patients in the lanreotide arm of the trial (versus 9% in the placebo group). Similarly, a 2011 randomised, double-blind, placebo-controlled trial in patients with advanced pNETs compared sunitinib (n=86) to placebo (n=85) and demonstrated no appreciable difference in QoL as measured by the QLQ-C30 between study groups, with the exception of diarrhoea, which worsened in the sunitinib group.[52]

An earlier study[53] following 50 patients with metastatic GEP-NETs being treated with ^{177}Lu-octreotate showed significant improvements in global QoL as measured by the QLQ-C30, with particular improvements in fatigue, insomnia, and pain. Improvements in QoL were seen irrespective of tumour progression or regression. A similar trial in the palliative setting[54] with ^{131}I-metaiodobenzylguanidine (n=13) showed symptomatic improvement in 92% and 55% with ^{111}In-octreotide (n=11). A larger 2011 trial[55] of ^{177}Lu-octreotate in 256 patients with metastasised neuroendocrine tumours measuring QLQ-C30 and Karnofsky Performance Status found significant global improvements in appetite, diarrhoea (67% showed improvement), social functioning, and fatigue (improved in 49%) regardless of treatment outcome. Pain improved in 53% of patients.

DISCUSSION

QoL research in the field of GEP-NETs has been impeded by a lack of consistent measurement tools and a paucity of data relating to the individual GEP-NET subtypes. The availability of the GINET21 is anticipated to generate better quality and more relevant data.[56] Most trials and studies that have examined QoL in GEP-NETs to date have made use of general cancer QoL questionnaires such as the QLQ-C30. However, one must take into account that in those patients with disseminated or high-grade GEP-NETs, the majority of symptoms may relate to disseminated malignant disease in general rather than to a specific hormonal syndrome. In these instances a general cancer QoL questionnaire may be more applicable. There is also a strong argument to suggest a separate QoL assessment tool for NF GEP-NETs, as most development has focused on functional syndromes. The question persists as to whether separate QoL questionnaires are required for the functional pNETs in order to accurately quantify the issues faced by these patients. At present, there are no available data to settle this issue.

A novel, rapid, and comparatively resource-sparing method of data collection could be found in internet-based online questionnaires, using them to validate, update, and generate QoL questionnaires. This method is of particular interest in the study of the vanishingly rare secretory pNETs, as generating statistically significant amounts of data is exceedingly challenging. This is an issue that could be overcome by allowing patients from around the globe to contribute data, thus dramatically increasing yield. Research into the feasibility of this strategy for data collection is currently in its infancy, with the first studies due for publication in the coming months.

The availability of the GINET21 is anticipated to greatly facilitate the acquisition of QoL data as a routine aspect of clinical trials, if not as their primary outcome. Collection of patient-reported outcome data is already being integrated into routine clinical care in at least one UK centre, with patients completing a GINET21 as part of clinic visits. Adapting QoL measurement tools to routine clinical practice still faces a number of challenges. The length of the combined QLQ-C30 and GINET21 (51 questions) makes it comparatively cumbersome to administer in a clinical setting, and a shortened version, or computer-adaptive questionnaire may be a desirable tool. IT provisions will undoubtedly be key in facilitating adoption in clinical practice, with the ability to present changes in QoL to the clinician in graph form, potentially proving decisive.

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