Gastrointestinal neuroendocrine tumors

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Gastrointestinal neuroendocrine tumors (GI-NETs) are a genetically diverse group of malignancies that sometimes produce peptides causing characteristic hormonal syndromes. NETs can be clinically symptomatic (functioning) or silent (non-functioning); both types frequently synthesize more than one peptide, although often these are not associated with specific syndromes. Based on data from various sources the incidence and prevalence of GI-NETs is increasing. Surgery is the only possible curative approach and so represents the traditional first-line therapy. However, as most patients with NETs are diagnosed once metastases have occurred, curative surgery is generally not possible. Patients therefore require medical management with the aim of relieving symptoms and suppressing tumor growth and spread. Somatostatin analogues can improve the symptoms of carcinoid syndrome and stabilize tumor growth (PROMID study) in many patients. An antiproliferative effect can also be achieved with the m-TOR inhibitor everolimus, alone or in combination with octreotide LAR. The vascular endothelial growth factor inhibitor sunitinib has demonstrated antitumor effects in pancreatic NETs. Pasireotide, the multi-receptor targeted somatostatin analogue, has the potential to be an effective therapy for de novo or octreotide-refractory carcinoid syndrome. Peptide receptor radiotherapy with yttrium 90-DOTATOC or lutetium 177-DOTATE are also new interesting treatment options for NETs.

Key words: chemotherapy, neuroendocrine tumors, PRRT, somatostatin analogues, surgery, VEGF inhibitors

introduction and epidemiology

Gastrointestinal neuroendocrine tumors (GI-NETs) are a genetically diverse spectrum of malignant solid tumors arising from the secretory cells of the neuroendocrine cell system that produce peptides causing characteristic hormonal syndromes. GI-NETs can be clinically symptomatic, i.e. ‘functioning’, or silent, i.e. ‘non-functioning’. Survey data from the Surveillance, Epidemiology, and End Results (SEER) program demonstrated that the incidence of malignant GI-NETs is increasing [1], although this may partly be due to increased physician awareness and improved diagnostic techniques. Nevertheless, in 2004 there were 5.25 new cases of NETs per 100 000 people, compared with 1.09 per 100 000 in 1973 (age-adjusted incidence) [1]. This is in contrast to the overall incidence of malignancies, which has remained relatively constant since 1992. Data from the Norwegian Registry of Cancer showed a similar incidence of NETs; there was a 72% increase between 2000 and 2004 compared with 1993–1997 [2]. Ethnic differences in the risk of developing a NET are also apparent, with a higher incidence in African-American than Caucasian patients [2–4]; the potential genetic factors are currently unknown. The most frequently diagnosed NETs in Europe and the USA are lung, rectum and small intestine tumors, and these three have seen the greatest increase in incidence since 1974. A time-trend analysis demonstrated a statistically significant increase in incidence across all disease stages at diagnosis \( (P < 0.001; \text{Figure 1}) \) [5].

diagnosis

The diagnosis of GI-NETs is multimodal, based on clinical symptoms, hormone levels, radiological and nuclear imaging, and histological confirmation. Most patients with NETs have metastatic disease at diagnosis, with regional or distant metastasis observed in 50% of patients [1]. Initial metastases are usually noted in regional lymph nodes, then in the liver and finally in distant sites such as bone [6]. Large proportions of NETs are non-functioning and are diagnosed incidentally during an unrelated procedure. The clinical symptoms of functioning NETs generally arise after the tumor has metastasized to the liver.

biochemical markers

A variety of generalized and specific biochemical tests are available for symptomatic patients, which can assist with the initial diagnosis and assessment of required treatment, and may offer prognostic information [7]. The most common tests are listed here.

chroomogranin A (CgA). Present in the chromaffin granules of neuroendocrine cells and measurement via a blood test can be used to diagnose both functioning and non-functioning NETs. Recent studies have suggested that CgA should be the primary biomarker used for the diagnosis of NETs as levels correlate...
with tumor burden [8], and provide a more sensitive assessment compared with other biomarkers [9, 10]. In addition, early CgA response (normalization or ≥30% decrease by week 4) may correlate with improved progression-free survival (PFS) [11]. However, CgA levels are non-specific as they are elevated in a number of different NETs [12] and in other unrelated conditions.

5-hydroxyindoleacetic acid (5-HIAA). Serotonin metabolite used to identify certain types of functioning NETs; measurement of 5-HIAA has a sensitivity of 73% and a specificity of 100% in predicting the presence of a midgut NET [13]. Certain foods and drugs can affect the urinary excretion of 5-HIAA if taken just before urine collection, which can lead to false positive or negative results.

Pancreatic NETs (pNET) may produce hormones such as gastrin, glucagon, insulin/proinsulin and vasoactive intestinal peptide (VIP) giving specific clinical symptoms [6].

Ki-67. Protein found in the cell nucleus during cell division; its assessment as a marker of tumor proliferation should be considered in patients with GI-NETs [13]. Lower proliferation as indicated by Ki-67 levels correlates with longer survival [14].

Imaging

Imaging techniques can be used to determine the location of the primary tumor and staging of the disease. The optimum imaging technique depends on whether it is detecting disease in a patient with a suspected NET or assessing the extent of disease in a known case. Common imaging techniques include computed tomography (CT) or magnetic resonance imaging (MRI) scans. Positron emission tomography scans are often used to complement information gathered from physical examination, CT and MRI scans. Table 1 summarizes the sensitivities of various imaging techniques for locating specific NETs [7]. Somatostatin receptor scintigraphy (SRS; OctreoScan®)—binding with high affinity to the two most prevalent somatostatin receptors found on GI-NETs (sst2 and sst5)—allows visual evidence of GI-NET localization. SRS is indicated as the first staging procedure and is one of the most sensitive single-screening methods for extrahepatic disease manifestation [15]. Whole-body imaging enables the identification of distant metastases and therefore SRS is the diagnostic test of choice for locating secondaries [16]. PET scanning with gallium 68-DOTATOC is likely to replace SRS in future as it has higher sensitivity and is easier to perform.

Classification

GI-NETs have been variously described in the literature, primarily due to their diversity and complexity. They were first described in 1867 and identified as carcinomas in 1888. Siegfried Oberndorfer termed them ‘carcinoid’ (i.e. cancer-like) in 1907 [17], but later amended this description when he recognized the potential for GI-NETs to become malignant or metastasize. Based on embryological origin, NETs were

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**Table 1.** Sensitivities (%) of various imaging techniques [7]

<table>
<thead>
<tr>
<th></th>
<th>Primary carcinoid</th>
<th>Carcinoid liver metastases</th>
<th>Primary gastrinoma</th>
<th>Gastrinoma liver metastases</th>
<th>Primary insulinoma*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>46</td>
<td>83</td>
<td>23</td>
<td>50</td>
<td>27</td>
</tr>
<tr>
<td>CT</td>
<td>64</td>
<td>88</td>
<td>38–75</td>
<td>54–88</td>
<td>30</td>
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<tr>
<td>MRI</td>
<td>56</td>
<td>85</td>
<td>22–90</td>
<td>63–90</td>
<td>10</td>
</tr>
<tr>
<td>SRS</td>
<td>80</td>
<td>90</td>
<td>72</td>
<td>97</td>
<td>25</td>
</tr>
<tr>
<td>EUS</td>
<td>80 (gastric)</td>
<td>90–100</td>
<td>93</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Angio+Ca Stim</td>
<td></td>
<td></td>
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</table>

EUS, endoscopic ultrasound; Angio+Ca Stim, angiography with calcium stimulation.

*Metastatic insulinoma is rare.
classified in 1963 as foregut (thymus, esophagus, lung, stomach, duodenum, pancreas), midgut (appendix, ileum, cecum, ascending colon) and hindgut (distal large bowel, rectum) tumors [18]. However, this system is now considered outdated as it does not distinguish biologically relevant differences in tumors. Current best practice is to describe NETs according to their location of primary origin (e.g. pancreas, duodenum, small intestine, etc.) and include reference to the resultant hormone secretion or symptoms (e.g. gastrinoma, insulinoma, carcinoid syndrome, etc.).

The first World Health Organization (WHO) classification of NETs was published in 1980 and applied the term ‘carcinoid’ to most tumors. In order to standardize terminology this was updated in 2000–2004 based on tumor histopathology, eliminating the term ‘carcinoid tumor’ (Table 2) [19, 20]; patient prognosis is dependent upon the biological behavior of the tumor and its histological differentiation. Complementary tumor–node–metastasis (TNM) classification guidelines for the staging and grading of NETs were published by the European NET Society (ENETS) in 2006 and 2007 (Table 3) [21, 22]. The ENETS TNM system is based on the WHO system and assists with the further stratification, treatment and follow-up of patients. ENETS also proposed three tumor grades based on mitotic count and proliferative index (Ki-67). Most recently (November 2009), the International Union Against Cancer/American Joint Committee on Cancer published a new TNM classification system, which is somewhat different from the ENETS system [20].

**functioning GI-NETs**

NETs can arise in various organs and from various cell types. Functioning NETs are characterized by the hormones they produce and/or the symptoms they cause; clinical symptoms are typically observed following metastasis to the liver.

carcinoid syndrome

Many NETs of non-pancreatic origin release vasoactive peptides and amines, such as serotonin and tachykinins, into the systemic circulation and cause a characteristic set of symptoms called ‘carcinoid syndrome’, which occurs in ~10% of patients with metastatic NETs. It is characterized by flushing (63%–94% of patients), diarrhea (68%–84%), abdominal pain (10%–55%), telangiectasia (25%) and bronchoconstriction (3%–19%) [12, 24, 25]. A recent study found that patients with NETs report worse health-related quality of life (HRQoL) than the general population, primarily due to the presence of carcinoid syndrome [26].

Carcinoid crisis is the most immediate life-threatening complication of carcinoid syndrome and is thought to result from a massive release of bioactive products from the tumor [12]. Crises can occur spontaneously, but often arise in response to stress, anesthesia, chemotherapy or surgery. Symptoms are an exacerbation of the usual clinical symptoms of carcinoid syndrome, including severe flushing with or without bronchospasm, tachycardia and hypo/hypertension [27]. Failure to effectively manage carcinoid syndrome can lead to exposure of the heart to high levels of vasoactive substances released from hepatic metastases, which causes carcinoid heart disease; between 10% and 20% of patients with carcinoid syndrome have heart disease at diagnosis [5, 28]. Carcinoid heart disease is characterized by plaque-like, fibrous thickening of the endocardium (classically on the right side of the heart) [24], tricuspid and pulmonary valves [28]; right-sided carcinoid heart disease is associated with substantial morbidity and mortality.

**other syndromes**

PNETs are the most common functioning NETs and they cause various well-established syndromes. For example, gastrinomas cause Zollinger–Ellison syndrome, which is characterized by peptic ulcers, diarrhea and abdominal pain. A gastrinoma is also more commonly found in the duodenum. Glucagonomas produce excess glucagon, which leads to hyperglycemia and is associated with diabetes mellitus, thrombosis, anemia and atypical skin rash. Insulinomas cause hypoglycemia due to excess insulin, whilst VIPomas produce excess VIP leading to Verner–Morrison syndrome with profuse secretory diarrhea, hypokalemia and metabolic acidosis.

**non-functioning NETs**

Non-functioning GI-NETs are not associated with a distinct hormonal syndrome so are more difficult to detect than functioning GI-NETs; due to this, patients generally present late with large primary tumors and advanced disease. However,

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**Table 2. WHO classification of NETs [19, 20]**

<table>
<thead>
<tr>
<th>Biological behavior</th>
<th>Well-differentiated neuroendocrine carcinoma</th>
<th>Poorly differentiated neuroendocrine carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastases</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Ki-67 index, %a</td>
<td>&gt;30</td>
<td>Poor</td>
</tr>
<tr>
<td>Histological differentiation</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Infiltration/angioinvasion</td>
<td>Any size</td>
<td>Any size</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>≥3; ≥2</td>
<td>Any size</td>
</tr>
</tbody>
</table>

*aIdentical to MIB1.

*aGI-NET.

*aPNET.

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non-functioning GI-NETs may secrete bioactive amines at subclinical levels, or secrete compounds that lead to other, still under-recognized hormonal syndromes. They can also cause non-specific symptoms related to increased tumor mass and/or metastasis such as weight loss, bleeding or abdominal pain [6]. The most common localizations of the primary tumors are in the pancreas, duodenum, colon and rectum.

**management of GI-NETs: surgery**

The primary treatment goal for patients with GI-NETs should be curative surgery. Surgery to remove the primary malignancy and/or local lymph nodes (if affected) is currently the only possible cure and represents traditional first-line therapy; the minimum practical requirements include resectable, well-differentiated liver disease with <5% mortality, and absence of right heart insufficiency, extra-abdominal metastases and diffuse peritoneal carcinomatosis. However, curative surgery is often not feasible since most patients present with metastases at diagnosis. It is commonly accepted that resection of at least 90% of the tumor is required to achieve symptom control [29–31]. Approximately 60% of patients will experience symptom recurrence after surgery and the 5-year survival rate for localized and regional metastases is 35%–80% [29, 32]. During palliative surgery the primary tumor should also be removed, if possible. Tumor debulking may also render medical therapy more effective by decreasing the secretion of bioactive substances.

**management of NETs: medical therapy**

**somatostatin analogues**

As curative surgery is generally not possible, many patients require chronic postoperative medical management to relieve symptoms and, in recent years, to suppress tumor growth and spread. Somatostatin is an endogenous inhibitor of various hormones secreted from the endocrine system, including serotonin, insulin, glucagon and gastrin. It binds with high affinity to the five somatostatin receptor subtypes (sst1–5) on secretory endocrine cells [33], which have different inhibitory effects in the body. Subtypes sst2 and sst3 are the most important in inhibiting hormonal secretions in functioning NETs due to their wide-ranging effects; it is thought the dual inhibition of both subtypes may have an increased inhibitory effect [34]. The two subtypes may also mediate antiproliferative effects.

Somatostatin has limited clinical use due to its short half-life (≤3 min). Therefore, specific somatostatin analogues have been developed that work as receptor agonists and block hormone release. These analogues form the first-line medical therapy for well-differentiated NETs [12]. Octreotide, the first somatostatin analogue available commercially, is an sst2-preferring agonist that also has moderate affinity for sst3 and sst5. It has a different chemical structure from somatostatin and a much longer half-life of 2 h. Lanreotide was the second analogue available and has a similar binding profile to octreotide. Pasireotide is a novel multi-receptor ligand analogue that has high affinity for four of the five somatostatin receptor subtypes (sst2, sst3 and sst5) [35, 36]; it has 40-fold higher affinity and 158-fold higher functional activity for sst5 than octreotide.

Octreotide. Initial evidence demonstrating that octreotide can reduce symptoms of carcinoid syndrome and decrease U-5-HIAA levels was shown with the subcutaneous (sc) formulation [37, 38]. Currently, the long-acting (LAR) formulation, which is administered monthly, thus eliminating the need for daily injections, is the mainstay of treatment of carcinoid syndrome. The first controlled study of octreotide LAR for treating carcinoid syndrome was conducted in 93 patients with NETs over at least 20 weeks [24]. There was a significant decrease in the number of daily stools (42%) and an 84% reduction in the incidence of flushing. In addition, complete or partial symptom control was achieved in 66% of patients receiving octreotide LAR 10–30 mg/month. Octreotide LAR also decreased 5-HIAA levels by 50% [25]. The efficacy of octreotide LAR for symptomatic and biochemical control in NETs has subsequently been demonstrated in a number of studies [39, 40]. The mechanism by which somatostatin analogues normalize bowel function is not yet clear; however, it is thought to involve inhibition of gut hormone secretion [41, 42], shortening of intestinal transit time [43], increased water and
electrolyte absorption [25, 44] and reduced splanchnic blood flow [43]. Treatment with octreotide can also improve survival in patients with carcinoid crisis [45]; prophylactic use is mandatory to prevent the development of a crisis. Octreotide is generally well tolerated during the treatment of carcinoid syndrome [25]; these findings have been confirmed during long-term (3-year) treatment [39]. Octreotide may have direct antiproliferative effects on tumors via stimulation of sst2, which mediates cell-cycle arrest and apoptosis. It also has various indirect antiproliferative effects such as inhibition of the anti-apoptotic hormone insulin-like growth factor 1 (IGF-1), inhibition of the release of growth factors and trophic hormones, inhibition of angiogenesis and immune system modulation [46]. A number of studies have highlighted the antiproliferative effects of octreotide in patients with NETs and shown that approximately two-thirds experience stable disease for up to 5 years, although objective tumor responses are uncommon (5% of patients) [47, 48]. The recent double-blind, placebo-controlled randomized phase IIIb study (PROMID) of octreotide LAR or placebo in patients with well-differentiated metastatic midgut NETs demonstrated that octreotide LAR 30 mg/month (n = 42) more than doubled the time to tumor progression compared with placebo (n = 43; 14.3 versus 6.0 months, respectively, P = 0.000072; Figure 2), in both functioning and non-functioning NETs [49]. The PROMID study demonstrated that the benefits of octreotide treatment in NETs are independent of functionality, CaA level, Karnofsky performance status or age [49]. The National Comprehensive Cancer Network has updated its guidelines based on the PROMID data, to include octreotide LAR as a management option for asymptomatic patients with recurrent, unresectable metastatic NETs.

The most common side-effects, such as abdominal discomfort and bloating, are generally mild and resolve spontaneously within the first week. Gallstones can develop, although only a small proportion of patients develop clinical symptoms. Local pain at the injection site has also been reported.

Lanreotide. Lanreotide is less widely studied than octreotide for symptomatic and biochemical control and no directly comparative trials have been conducted. The sustained release (SR) formulation, which is administered every 7–14 days, has shown little overall improvement in symptom control compared with octreotide sc, as reviewed by Modlin et al. [31]. The effects of lanreotide SR on symptom relief are comparable to those of octreotide [31]. A newer formulation of lanreotide that allows for monthly administration, Lanreotide Autogel®, is also available. One study of 71 patients who received lanreotide autogel for 6 months found that 65% achieved a ≥50% reduction in flushing episodes, and 18% had a ≥50% reduction in diarrhea episodes [50]. The biochemical response rate observed with lanreotide is also comparable to that of octreotide [31, 51], with response being greater in patients naive to somatostatin analogue therapy [50]. There are few studies evaluating the antiproliferative effects of lanreotide in patients with NETs, and there are no phase III data with tumor control as the primary endpoint. One study evaluated the antiproliferative efficacy of lanreotide in 25 patients: partial tumor remission was seen in one patient and stable disease was observed in seven patients, whereas tumor progression occurred in 14/25 patients [52]. There is an ongoing phase III study in patients with non-functioning NETs comparing lanreotide autogel with placebo.

Patients with NETs receiving sst2-preferring analogues such as octreotide and lanreotide may experience a loss of response (the ‘escape from response’ phenomenon or tachyphylaxis) ~6–18 months after the initiation of treatment; this is usually related to increased morbidity and mortality [53–55]. The precise mechanism behind this phenomenon is still unknown. It has led to interest in new, multi-receptor ligand somatostatin analogues that could be as effective and well tolerated in patients who experience an escape from response. Pasireotide may fulfill this role in the future due to its high affinity for sst1–3 and sst5 receptors. Preliminary data are promising, with effective control of diarrhea and flushing observed in NET patients refractory or resistant to octreotide LAR [56]. A phase III study of pasireotide LAR versus octreotide LAR is ongoing in patients with metastatic carcinoid tumors (GI-NETs) whose disease-related symptoms are inadequately controlled by somatostatin analogues. Carcinoid tumors express dopamine D2 as well as sst2 receptors. A new compound has been developed that binds to both D2 and sst2 receptors. The first clinical trials will start later this year.

Chemotherapy

Patients with pNETs have a less favorable prognosis than those with non-pNETs. The typical treatment approach for pNETs is chemotherapy with streptozotocin (as it is currently the only FDA-approved drug for this indication) [57], either alone or in combination with other chemotherapeutic agents.

GI-NETs with high proliferation need to be healed with cytotoxic agents. Poorly differentiated GI-NETs receive standard treatment with platinum-based therapies combined with etoposide [57]. Temozolomide alone or in combination with capcitabine or bevacizumab is a new therapeutic concept for PNETs [58].

Other medical therapy

Mammalian target of rapamycin (mTOR) is a central regulator of protein synthesis important in cancer, including cell growth
and proliferation, angiogenesis and cell metabolism. Several genetic syndromes associated with NETs involve signaling through the mTOR pathway. Everolimus (RAD001) is a new oral, once-daily mTOR inhibitor that blocks the mTOR pathway by binding to its intracellular receptor FKBP-12. A synergistic antiproliferative effect may be achieved by combining everolimus with octreotide; this was demonstrated in a study of 60 patients with metastatic low-to-intermediate-grade NETs (30 with pNETs and 30 with non-pNETs), where promising antitumor activity and PFS was observed [59]. Those who received a higher dose of everolimus (10 versus 5 mg/day) had slightly better partial response and PFS rates, the latter of which compared favorably with those reported in phase II/III studies with chemotherapy, bortezomib, imatinib, sorafenib, sunitinib and bevacizumab [60]. A phase II trial of everolimus with or without octreotide LAR in patients with advanced pNETs following chemotherapy failure (RADIANT-1) found that in those receiving everolimus monotherapy median PFS was 9.7 months and 59.3% experienced a stabilization or decrease in tumor size [11]. In contrast, patients receiving everolimus 10 mg/day plus octreotide ≤30 mg/month achieved a median PFS of 16.7 months and 84.2% had tumor

**Figure 3.** Suggested treatment algorithm for patients with metastatic NETs.

**Figure 4.** Survival duration in patients with NETs during the last four decades: a clinician’s view.
stabilization or shrinkage. Phase III trials of combination octreotide LAR and everolimus are ongoing. RADIANT-2, a randomized phase III, double-blind, multicenter trial of combination octreotide LAR plus everolimus versus octreotide LAR plus placebo, is ongoing in patients with advanced carcinoid tumors. RADIANT-3 is a randomized phase III, double-blind, multicenter trial in pNET patients comparing everolimus 10 mg plus best supportive care with placebo plus best supportive care.

interferon therapy

Interferon therapy is generally recommended as a second-line approach in patients with functioning GI-NETs and low proliferation [13]. The effect of interferons on symptom control is similar to that of somatostatin analogues and they may have greater antiproliferative activity [61]; however, they do not act as rapidly and have a less favorable safety profile (fever, fatigue, anorexia and weight loss are commonly reported). Interferon-α is the most widely studied and a pooled analysis of trials investigating this agent in patients with NETs demonstrated that ~40% had biochemical responses (which is comparable to that observed with octreotide and luteotide) whilst ~10% had objective tumor responses. Although the number of trials is small and studies may be underpowered, combination of interferon-α with somatostatin analogues might not appear to have a demonstrated synergistic effect [62, 63].

angiogenesis inhibitors

Sunitinib and sorafenib as well as bevacizumab have been applied as single therapy in small series of GI-NETs with response rates of 5%–15%. In a recent study sunitinib 37.5 mg was compared with placebo in patients with pancreatic endocrine tumors demonstrating a significantly larger PFS, 11.4 months versus 5.5 months for placebo (P = 0.0001) [64].

radionuclide therapy

The response rate of NETs to external beam radiation is limited. However, the introduction of systemic receptor-targeted therapy (peptide receptor radiotherapy—PRRT) has provided beneficial effects in patients with unresectable somatostatin receptor-positive NETs [65, 66]. Current data suggest objective response rates of 30%–40% with disease stabilization in 40% of patients.

management of NETs: summary

A suggested algorithm for the treatment of patients with metastatic NETs is included in Figure 3.

survival data

Data from the SEER database demonstrated a dramatic improvement in survival in patients with GI-NETs diagnosed between 1988 and 2004 compared with those diagnosed earlier; the authors suggested that this may be related to the introduction of octreotide in 1987. The literature appears to support this, as shown in a study reporting 5-year survival rates of 67% in patients receiving somatostatin analogues compared with 18% for historical controls. The survival duration of patients with metastatic midgut tumors, as recorded in the SEER database (representing standard care in the USA) and as observed in a specialty center in Uppsalan managing patients with a multidisciplinary team, is shown in Figure 4.

conclusions

The incidence and prevalence of GI-NET has been increasing over the past decades, possibly related to an increase in awareness among physicians, but also improved diagnosis and treatment. In the future new more sensitive biomarkers will be developed and with molecular imaging will become cornerstones in the management of NETs. Treatment will be personalized based on tumor biology and molecular genetics and also include completely new therapeutics, based on the unique features of NETs.

disclosures

Dr Öberg has indicated that he belongs to the Speakers’ Bureau of Novartis, and to the Advisory Boards of Novartis and Ipsen.

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