BRITISH JOURNAL OF HOSPITAL MEDICINE

REVIEW

Neuroendocrine Tumours in the Gastrointestinal Tract: What You Need to Know

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Abstract

Neuroendocrine neoplasms (NENs) comprise well differentiated neuroendocrine tumours (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). NENs can develop at various anatomical sites, the most common being in the gastrointestinal tract and their incidence is increasing. Although uncommon, they are no longer considered to be rare. Comprehensive biochemical, histopathological and imaging investigations are required to assess an NEN's site, grade and stage and to determine whether it is producing hormones and resulting in a hormonal syndrome. Localised NENs are typically managed with surgery, while metastatic NENs are often treated initially with systemic therapy, such as somatostatin analogue injections. There are multiple options for NEN management, so these patients need to be discussed and managed by a multidisciplinary team of clinicians who have expertise in this tumour type. This article is intended to provide an introduction and summary for clinicians who have little prior experience of NENs.

Key words: neuroendocrine; gastroenteropancreatic; carcinoid; somatostatin receptor; chromogranin

Submitted: 18 October 2024 Revised: 29 November 2024 Accepted: 17 December 2024

Introduction

Neuroendocrine neoplasms (NENs), also sometimes referred to colloquially as neuroendocrine cancers, are a diverse group of neoplasms. They arise from neuroendocrine cells, which produce hormones and other peptides in response to neuronal signals. Such cells occur throughout the body but are particularly abundant in the gastrointestinal tract and pancreas. Approximately 80–90% of NENs are well-differentiated neuroendocrine tumours (NETs) while 10–20% are poorly differentiated neuroendocrine carcinomas (NECs) (Das and Dasari, 2021). Occasionally, NENs can occur in combination with another type of neoplasm such as an adenocarcinoma and these lesions are referred to as Mixed neuroendocrine and non-neuroendocrine neoplasms (MiNENs). NENs can arise at multiple sites in the body, but the commonest sites are in the gastrointestinal (GI) tract and pancreas, hence the term gastroenteropancreatic (GEP)-NEN (Khan and Pritchard, 2022). Clinical presentation, treatment and prognosis vary greatly and are influenced by multiple factors including a NEN's primary site, degree of histological differentiation, grade,

How to cite this article:
Pritchard DM. Neuroendocrine Tumours in the Gastrointestinal Tract: What You Need to Know. Br J Hosp Med. 2025. https://doi.org/10.12968/hmed.2024.0780

stage and secretory status as well as the patient's age and general fitness. Comprehensive investigations and subsequent patient management need to be coordinated by multidisciplinary teams of health care professionals who are aware of the multiple nuances of these tumours and who can provide the full range of diagnostic and therapeutic options that NEN patients often require. The aim of this article is to provide a brief introduction to the field for clinicians who are not familiar with managing patients who have NENs. It has been written primarily as an educational resource and is not intended to represent a comprehensive review of the field for clinicians who are already managing NEN patients.

Epidemiology and Genetics

The incidence of NENs has increased significantly over the last 25 years and this trend has been observed in the USA, England and other European countries (Dasari et al, 2017; White et al, 2022). Much of the increase is thought to be due to increased awareness and detection of NENs using modern endoscopy, imaging and histopathology techniques. As many patients, especially those who have low grade NETs have a very good prognosis and survive for many years, the prevalence of NENs is higher than that of cancers that develop at all other sites in the GI tract, except the colorectum (Dasari et al, 2017).

GEP-NETs also show regional differences in distribution with small intestinal and rectal NETs predominating in North America, rectal and pancreatic NETs in Asia and small intestinal and pancreatic NETs in Europe (Man et al, 2018). This may partly be due to genetic factors associated with particular ethnicities, but unknown environmental factors may also contribute.

The majority of NENs arise sporadically and the risk factors responsible for their development remain largely unknown in most cases. A minority of cases (mostly NETs located in the pancreas) develop in patients who have inherited cancer syndromes such as multiple endocrine neoplasia (MEN)-1, Von Hippel Lindau syndrome and type 1 neurofibromatosis. MEN-1 associated pancreatic NENs develop as a consequence of mutations that affect the expression of the tumour suppressor protein menin. These NENs are more frequently multiple and are more likely to be functional than sporadic pancreatic NETs; they also require nuanced management (Niederle et al, 2021). The pathogenesis of some other specific types of NEN is also well understood, such as the development of type 1 gastric NETs in patients who have autoimmune atrophic gastritis, consequent hypochlorhydria and hypergastrinaemia (Lamberti et al, 2024; Panzuto et al, 2023). An altered gastric microbiota may also contribute to type 1 gastric NET development (Parsons et al, 2017) and there is emerging evidence to suggest that the gut microbiome may also be involved in the pathogenesis of NENs at other sites in the GI tract (Cao et al, 2024).

Clinical Presentation

Patients who have NENs can present in multiple and diverse ways. They may present with symptoms that result from the anatomical site of their tumour (e.g., a

Table 1. Types of pancreatic NET and the hormonal syndromes that they can produce.

Pancreatic NET type	Resulting syndrome and symptoms
Non-functional	Pancreatic mass
Insulinoma	Hypoglycaemia
Gastrinoma	Zollinger Ellison syndrome (increased gastric acidity and peptic ulceration)
VIPoma	Verner Morrison syndrome (profuse secretory diarrhoea, hypokalaemia)
Glucagonoma	Necrolytic migratory erythema (skin rash), diabetes mellitus, weight loss
Somatostatinoma	Diabetes mellitus, steatorrhoea, gallstones

NET, neuroendocrine tumour; VIP, vasoactive intestinal peptide.

patient with an ileal NET may develop subacute small bowel obstruction), they may present with non-specific symptoms such as weight loss and fatigue that can be associated with any metastatic cancer or they may have symptoms from a syndrome that results from a NET secreting hormones. Many patients are also diagnosed incidentally when having endoscopic or imaging investigations for some other reason and sometimes the diagnosis of a NEN is made post-operatively after histopathological examination of a surgically resected specimen.

Only a minority of NETs secrete enough hormones to cause functional or secretory syndromes. Most NETs are therefore non-functional, as are the vast majority of NECs. The commonest functional syndrome that is encountered is carcinoid syndrome. This most frequently results from the secretion of serotonin and other peptides by an ileal NET with liver metastases and leads to symptoms of flushing, diarrhoea and rarely wheezing (Lamarca et al, 2024). A small proportion (approximately 20%) of patients who have carcinoid syndrome also develop carcinoid heart disease, which is characterised by fibrosis of the right-sided heart valves (Grozinsky-Glasberg et al, 2022). Carcinoid syndrome can also rarely result from NETs that originate at other sites such as the lung. Most of the other functional/secretory NETs arise in the pancreas. These tumours can secrete various hormones and lead to diverse clinical syndromes as summarised in Table 1 (Hofland et al, 2023). In some cases (especially some gastrinomas and insulinomas), the primary NET can be very small and difficult to detect using conventional imaging techniques.

Some patients who have NETs, especially those which arise in the small bowel, can present with non-specific abdominal symptoms which overlap considerably with the clinical features of other more common conditions such as irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD). This means that there are frequently considerable delays in diagnosis for such symptomatic patients. A UK study found that patients experienced a median 3 year delay in diagnosis with five visits to their General Practitioner (GP) prior to their diagnosis of a small bowel NET (Basuroy et al, 2018). Older age and the presence of unusual IBS symptoms such as flushing or weight loss should prompt investigations such as computed tomography (CT) scan to evaluate for the possible diagnosis of small bowel NET.

Investigations

Comprehensive investigations are required to fully characterise a NEN in order to decide on the most appropriate management approach (Fig. 1).

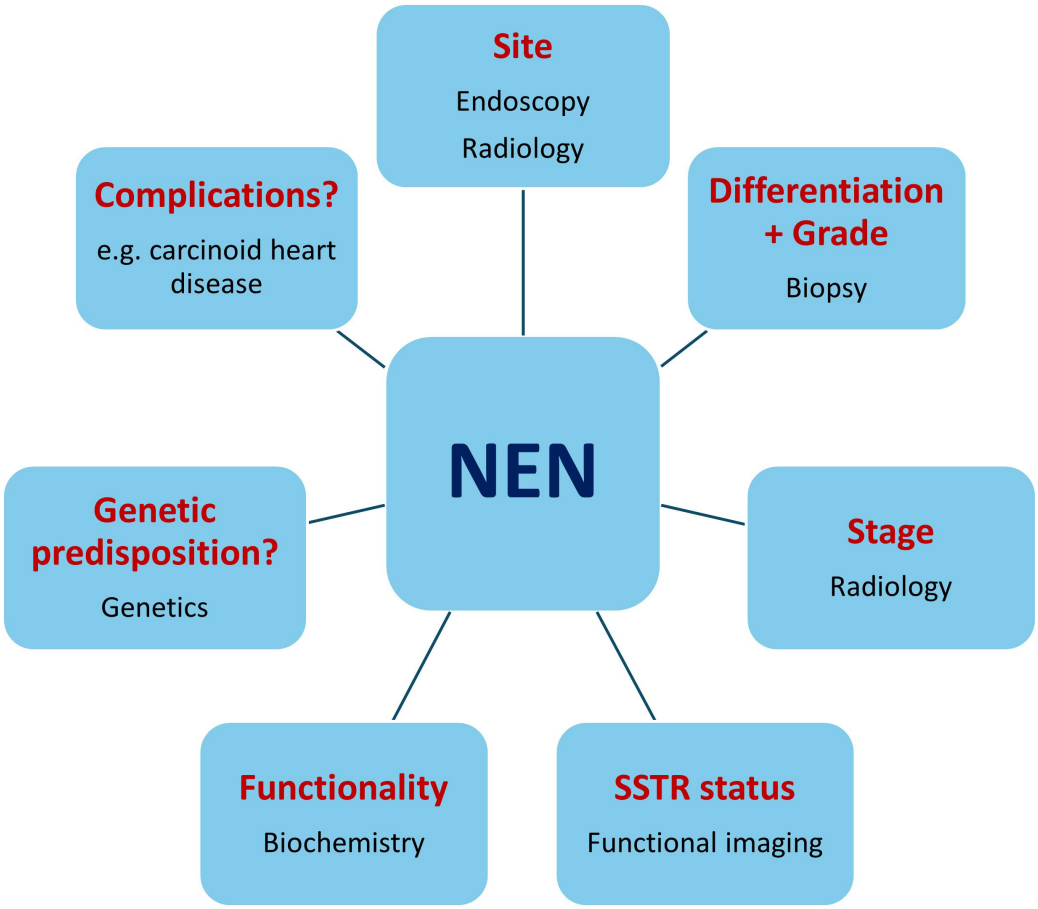

Fig. 1. Comprehensive characterisation of a neuroendocrine neoplasm (NEN) requires extensive multimodal investigations (involving biochemistry, histology and imaging) to establish the tumour's characteristics and thus allow treatment planning. The figure was created with Microsoft Powerpoint (Office 16, Microsoft Corporation, Redmond, WA, USA). SSTR, somatostatin receptor.

Histopathology

Histopathological examination of a biopsy or surgical resection specimen is the only definitive way of diagnosing a NEN. An attempt should therefore be made to obtain a histopathological diagnosis in most patients. However, occasionally this may not be possible due to the inaccessible location of a tumour (e.g., a mesenteric mass), or if the patient is not fit enough to undergo a required diagnostic procedure. Comprehensive assessment of the histology specimen involves performing immunohistochemistry for various specific neuroendocrine markers such as chromogranin A and synaptophysin as well as for the proliferative marker Ki67 (Rindi et al, 2022). The pattern of immunohistochemical staining allows a pathologist to de-

Table 2. Histological grading system for GEP-NENs.

Grade	Differentiation	Mitotic count/10 HPF	Ki67 index
1	Well differentiated	<2	<3%
2	Well differentiated	2–20	3–20%
3 (NET)	Well differentiated	>20	>20%
3 (NEC)	Poorly differentiated	>20	>20%

HPF, high power field; NET, neuroendocrine tumour; NEC, neuroendocrine carcinoma; GEP, gastroenteropancreatic.

termine whether the neoplasm is a NEN, whether it is well or poorly differentiated (i.e., a NET vs NEC) and the tumour grade. Other histological features associated with NECs are high nuclear-to-cytoplasmic ratios, numerous mitotic and apoptotic cells and necrosis (Rindi et al, 2022). NENs are classified into grades 1, 2, or 3 neoplasms, with grade 3 NENs being subclassified into NETs or NECs according to their differentiation status. Tumour grade is determined by counting the number of mitotic cells per high power field (HPF) and/or the percentage of tumour cells which are positive for Ki67 by immunohistochemistry (see Table 2). In addition to this characterisation of tumour type and grade, surgical resection specimens should be assessed as to whether the tumour resection is complete (R0/R1) and its TNM (tumour, node, metastasis) status according to World Health Organisation (WHO) criteria (Rindi et al, 2022).

Imaging

Endoscopy

Diagnostic gastroscopy and colonoscopy are useful for detecting, sampling and characterising the NENs that arise at the sites which these procedures inspect (Khan et al, 2025). The commonest sites for endoscopic NET detection are the stomach, duodenum and rectum. Endoscopic evaluation should as a minimum include assessment of the site, size and number of lesions, because treatment (especially suitability for endoscopic resection) is influenced in particular by lesion size (Khan et al, 2025). Some smaller gastric, duodenal and rectal NETs (especially those <1 cm in diameter) can be safely and appropriately resected using endoscopic techniques, but this should occur as a planned procedure following comprehensive evaluation of the lesion. Endoscopic ultrasound is sometimes required prior to endoscopic resection to assess the depth of tumour invasion and for the presence of lymph node metastases (Panzuto et al, 2023). Endoscopic ultrasound is also used to characterise and biopsy (usually via fine needle aspiration) potential pancreatic NENs.

Endoscopic evaluation is also required to determine the aetiology of a gastric NET and thus its type (Lamberti et al, 2024; Panzuto et al, 2023). There are three main types of gastric NET. The commonest type 1 lesions develop in patients who have autoimmune atrophic gastritis, hypochlorhydria and hypergastrinaemia. Type 2 gastric NETs are rare and also caused by hypergastrinaemia, but on this occasion gastrin is secreted by a gastrinoma, usually in the setting of MEN-1. Type 3 gastric NETs carry the worst prognosis and are sporadic lesions whose development

is not promoted by gastrin. Histopathological evaluation of biopsies taken from the background gastric corpus mucosa, as well as measurement of fasting serum gastrin concentrations usually allows determination of gastric NET type and this information is crucial for management.

Radiology

Various imaging techniques are useful to determine the primary site of a NEN, the extent to which it has metastasised and whether or not the neoplasm expresses somatostatin receptors, which aids in treatment decision-making. The main radiological modalities employed are contrast enhanced CT scans of the thorax, abdomen and pelvis and Magnetic resonance (MR) scans (especially of the liver which is the most frequent site of GEP-NEN metastasis). In addition, specialised nuclear medicine scans are often helpful. The classical nuclear medicine scan which is still frequently used in many hospitals is the ^{111}In octreotide Single-photon emission computed tomography (SPECT)/CT scan. However, nowadays, many specialist NEN centres use Gallium-68 dodecanetetraacetic acid (^{68}Ga DOTA)-peptide positron emission tomography (PET)/CT scans instead, as these are more sensitive (Fig. 2). These functional imaging modalities sometimes detect sites of primary or metastatic NEN which are not visible on conventional cross sectional imaging, but they also provide information about the somatostatin receptor status of a patient's tumour. F-18 fluorodeoxyglucose (^{18}F-FDG) PET/CT scans are also useful for staging higher grade 2 and grade 3 NENs, as these high grade neoplasms (especially NECs) are often not tracer avid on the somatostatin receptor based scans. Another imaging modality which is useful to evaluate for the presence of carcinoid heart disease in at risk patients (in particular those who have metastatic small bowel NETs and carcinoid syndrome) is transthoracic echocardiography (Grozinsky-Glasberg et al, 2022).

Biochemistry

Laboratory tests are used to characterise NENs and in particular to determine whether a specific tumour is functional/secretory. The fasting gut hormone test measures the serum concentrations of several hormones (gastrin, glucagon, somatostatin, vasoactive intestinal peptide (VIP) and pancreatic polypeptide) that can potentially be secreted by functional pancreatic NETs (Hofland et al, 2023). Of note though, elevated serum gastrin concentrations can result from a number of factors such as the use of acid suppressing medications, chronic atrophic gastritis and *Helicobacter pylori* infection, so a finding of hypergastrinaemia is not diagnostic of gastrin secreting tumours (Murugesan et al, 2009; Veysey-Smith et al, 2021). Measurement of the 24-hour urine (or in some hospitals serum) concentration of 5-hydroxyindole acetic acid (5-HIAA) is also useful for the investigation of possible carcinoid syndrome, but it should be noted that 5-HIAA is not a biomarker of NETs in general. The more general biomarker of NETs is the serum concentration of chromogranin A. However chromogranin A is non-specific and its serum concentration can be increased in the settings of renal impairment, liver failure, IBD and (depending on the specific assay used) by proton pump inhibitor use. Due to

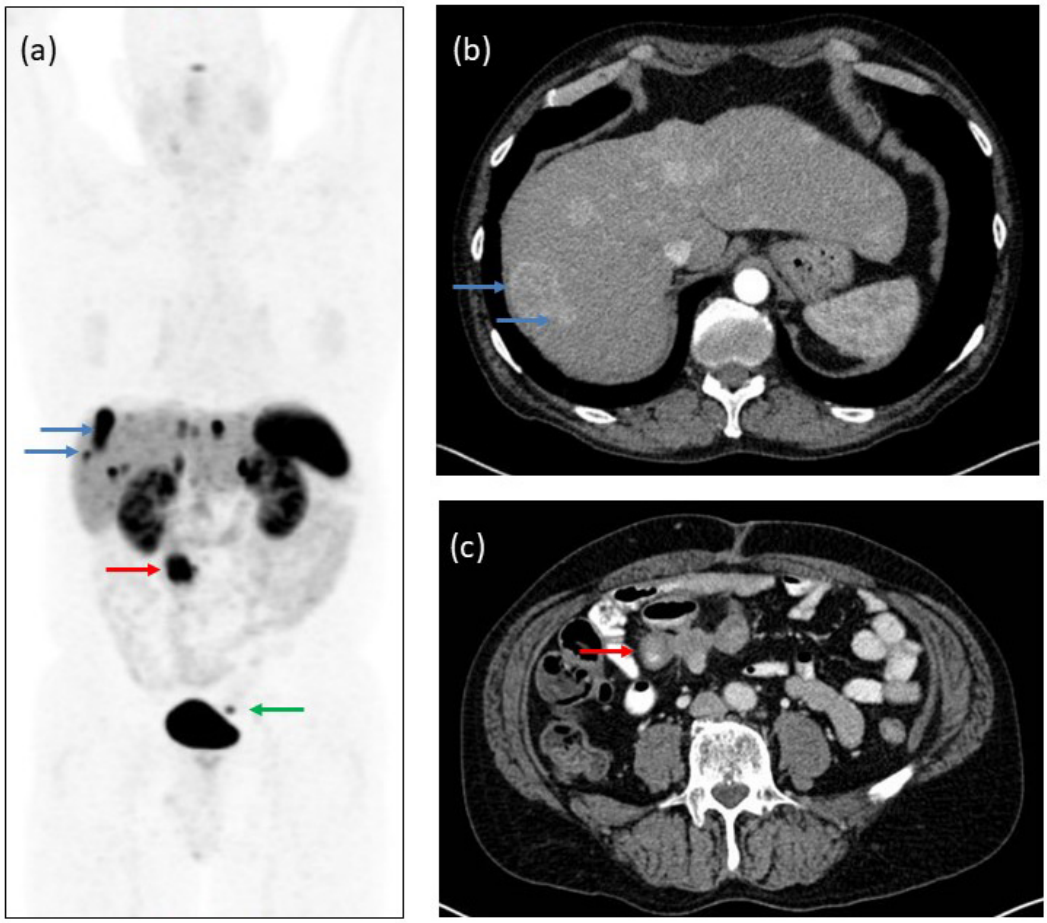

Fig. 2. Imaging in a patient with a metastatic small bowel NET. (a) ^{68}Ga DOTATATE PET/CT maximum intensity projection (MIP) image and corresponding (b,c) contrast enhanced CT scan images demonstrating a tracer avid calcified mesenteric mass (red arrows) with multiple bilobar liver metastases (corresponding metastases shown by blue arrows on both imaging modalities) and an unexpected pelvic peritoneal metastasis (the green arrow). The tracer avidity in the pituitary gland, spleen, kidneys and bladder is physiological. CT, computed tomography; PET, positron emission tomography; ^{68}Ga DOTATATE, Gallium- 68 dodecanetetraacetic acid-tyrosine-3-octreotate.

the relatively low specificities and sensitivities of all these biomarkers, they should therefore not be used as screening tests for NENs, rather for the characterisation of patients who have already received this diagnosis (Butler et al, 2020). The results of biochemical tests should always be interpreted alongside complementary investigation results, in particular radiology and histology, as well as in the context of the symptoms that the patient is experiencing.

Other blood tests are also useful in specific patients. These include measurement of parathyroid and pituitary hormones in patients in whom MEN-1 is suspected and assessment of haemoglobin, vitamin B12 and iron levels in patients who have type 1 gastric NETs. Measurement of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) is also helpful for screening and monitoring of carcinoid heart disease (Dobson et al, 2013; Grozinsky-Glasberg et al, 2022).

Principles of Management

The management of NENs is complex; therefore, treatment should always be discussed by a multidisciplinary team (MDT) of health care professionals who have expertise in this tumour type and who can access the various treatments that can be helpful. This MDT discussion can only take place after the tumour's grade, stage and secretory status has been fully characterised using the investigations described above (Fig. 1). Moreover, the patient's comorbidities, overall performance status and individual treatment wishes/goals should be taken into consideration. The clinical specialists needed to attend NEN MDT meetings include gastroenterologists, endocrinologists, oncologists, surgeons, nuclear medicine physicians, radiologists, pathologists and clinical nurse specialists. Other specialists such as respiratory physicians, cardiologists and clinical geneticists may also be required for individual cases. There are several specialist NEN MDTs throughout the UK, many of which have been accredited by the European Neuroendocrine Tumour Society (ENETS).

Some patients who are asymptomatic and who have low volume, low grade NETs may need no treatment initially and such patients are sometimes enrolled onto 'watch and wait' surveillance programmes. If NENs are localised and are amenable to endoscopic or surgical resection with curative intent, that strategy is usually advocated (Fig. 3). However, many patients present when they have surgically incurable disease, due to the extent and location of metastases. These patients usually receive systemic therapy as outlined below. Such patients may however also be suitable for palliative surgery (e.g., to treat small bowel obstruction). As many patients survive for several years, especially those who have low grade NETs, they require regular clinical and radiological follow-up and if their tumour progresses during treatment with one particular agent, additional or alternative therapy may be required. Some patients therefore receive multiple types and lines of therapy during the course of their illness.

Treatments With Potential for Cure

Some patients who have small NETs within the lumen of some organs in the GI tract (e.g., stomach, duodenum, rectum) and who do not have lymph node or distant metastases on imaging may be suitable for endoscopic resection techniques. Other patients who have localised tumours with or without regional lymph node metastases (e.g., small intestine, pancreas) should be considered for surgical resection with the intent of cure. Some of these procedures can be performed using minimally invasive surgical techniques (e.g., robotic pancreatic resections). Some patients may also be suitable for resection or locoregional therapy (e.g., radiofrequency ablation) with curative intent if they have liver metastases that are small, few in number, or confined to a single lobe of the liver.

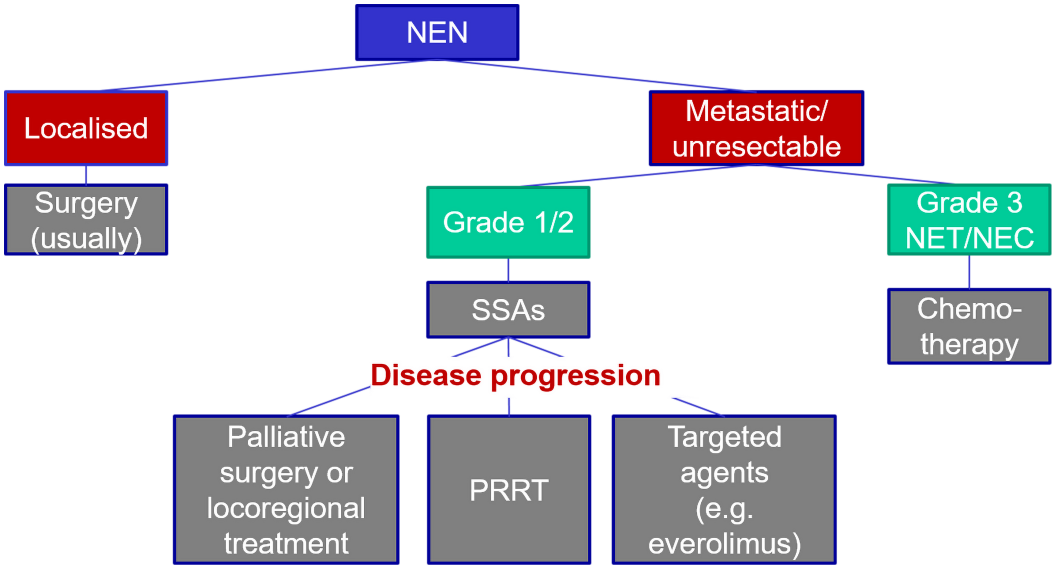

Fig. 3. Simplified management algorithm for patients with NENs. SSAs, somatostatin analogues; PRRT, peptide receptor radionuclide therapy; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; NEC, neuroendocrine carcinoma. The figure was created with Microsoft Powerpoint (Office 16, Microsoft Corporation, Redmond, WA, USA).

Systemic Treatment of Unresectable/Metastatic Disease

Over the last 20 years, several international phase 3 trials have provided high quality evidence to support the use of the systemic treatments that are now effectively employed in many patients who have metastatic low grade NETs. The first line of systemic therapy in most patients who have metastatic or unresectable grade 1 and 2 NETs usually involves monthly long acting somatostatin analogue injections. This treatment, which is usually very well tolerated, reduces the severity of any functional symptoms, but has also been shown to reduce the rate of tumour growth (PROMID (Rinke et al, 2009) and CLARINET (Caplin et al, 2014) trials). The median progression free survival (PFS) for patients receiving lanreotide in the CLARINET open label extension study was 38.5 months (Caplin et al, 2021). The most common side effect of somatostatin analogue treatment is steatorrhea, which can usually be effectively managed using oral pancreatic enzyme supplements.

In patients whose tumours progress on somatostatin analogue therapy, second line systemic treatments are usually considered. The main two options are oral targeted agents (in particular the mammalian target of rapamycin (mTOR) inhibitor Everolimus (supported by the RADIANT-3 and -4 trials (Yao et al, 2016a; Yao et al, 2016b)) and the tyrosine kinase inhibitor (TKI) Sunitinib (supported by SUTENT trial (Raymond et al, 2011))) and peptide receptor radionuclide therapy (PRRT, supported by the NETTER-1 trial (Strosberg et al, 2017)). PRRT involves intravenously administering a radioactive substance (in this case ^{177}Lu) which is bound to a somatostatin analogue, so that this agent binds to the tumour cells wherever they are located, releasing radioactivity at that site to treat the tumour (Kuiper et al, 2024).

Most low grade NETs do not respond very well to conventional cytotoxic chemotherapy drugs, due to their relatively slow growth rates. However, this treatment modality is still occasionally used, especially if other therapeutic options have been exhausted. However, cytotoxic chemotherapy is used more commonly in metastatic grade 3 NETs and it is the only treatment option for metastatic NECs. The first line chemotherapy regime for NECs usually involves cisplatin/carboplatin alongside etoposide. Although many neoplasms initially respond quite well to this treatment (response rate 30–50%), the duration of this response is unfortunately often short (PFS 4–6 months) and second line treatment options are often ineffective (Sorbye et al, 2023).

Prognosis

The prognosis in people who have NENs is highly variable and is dependent on the site, grade and stage of tumour as well as other patient factors such as age and overall performance status (Man et al, 2018; White et al, 2022). Median overall survival has been estimated at 41 months (Man et al, 2018). Some patients, such as those who have <1 cm type 1 gastric NETs or <1 cm non-functional grade 1 pancreatic NETs have an excellent prognosis and may never even require any treatment. Similarly, patients who have been able to have a complete surgical resection of a localised low grade NET are often cured of their disease by this treatment. However, patients who have surgically incurable or metastatic disease in general have a poorer prognosis. This is again highly variable though and one of the main prognostic indicators is tumour grade. Whereas some patients who have metastatic grade 1 small bowel NETs survive for many years with a good quality of life, those who have grade 2 or 3 NETs, especially if these originated in the pancreas, often have shorter survival times. NECs, especially if they are metastatic at the time of diagnosis, have an extremely poor prognosis, with median overall survival being only 11–12 months, despite treatment (Sorbye et al, 2023).

Professional and Patient Support Organisations

UKINETS, the UK and Ireland Neuroendocrine Tumour Society (https://www.ukinets.org) and ENETS (https://www.enets.org) provide comprehensive guidelines for the management of patients who have NENs and both societies also organise annual educational events (e.g., the UKINETS NETs for Newcomers course) and scientific conferences. Patients should receive local support from their local NET clinical nurse specialist, but those who live in the UK can also access professional and peer support as well as information about their disease from the national charity Neuroendocrine Cancer UK (https://www.neuroendocrinecancer.org.uk). Similar organisations exist in other countries.

Conclusion

NENs are becoming increasingly prevalent, so many physicians are likely to encounter such patients during their routine clinical practice. Most patients require

extensive and comprehensive investigations and should be managed by a multidisciplinary team of health care professionals who are familiar with and have access to the various treatment options that can be offered. Recent publications have documented detection of NENs at earlier tumour stages and as a consequence improved patient survival over recent years. In the near future, advances in diagnosis including the development of novel biomarkers and molecular imaging techniques as well as new therapeutic approaches (including different types of radioligand therapy and novel tyrosine kinase inhibitors) promise significant improvements in NEN diagnosis and treatment.

Key Points

- The incidence of NENs is increasing (probably largely as a result of increased awareness and detection by health care professionals) and they are now the second most prevalent type of GI neoplasm.
- Patients who have NENs can present in various ways, including incidentally. Symptomatic patients often experience delays in diagnosis.
- Comprehensive biochemical tests, biopsies and radiological scans are required in most patients to determine a NEN's site, grade, stage and functional status.
- Multiple localised and systemic treatments can be used to treat NENs - these should be advised by a fully complemented NEN MDT.
- Prognosis varies considerably and is influenced by NEN site, differentiation status, grade and stage.

Availability of Data and Materials

Not applicable.

Author Contributions

DMP made substantial contributions to conception. DMP has been involved in drafting the manuscript and revising it critically for important intellectual content. DMP gave the final approval for the version to be published. DMP agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

This study adhered to the Declaration of Helsinki.

Acknowledgement

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

DMP has received consultancy funding/speaker fees from Ipsen, Novartis and OranoMed and research funding to investigate gastric NETs from Trio Medicines Ltd.

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