SPOTLIGHT ON
NEUROENDOCRINE
CANCER

Neuroendocrine Cancer UK
Incorporating The Ann Edgar Trust

NEUROENDOCRINE CANCER

An overview for Endocrinologists

KEY FACTS

- **Neuroendocrine cancers, often referred to as neuroendocrine neoplasms (NENs), are now the second most prevalent GI cancers and the 10th most prevalent cancers in England.** (1)
- **There are challenges to diagnosing NENs** because individual symptoms may mimic or be masked by more common conditions such as IBS. This can also be exacerbated by a perceived pressure to discharge patients with these symptoms who have had a normal gastroscopy and / or colonoscopy. (2)
- **Many gastrointestinal NEN patients are initially misdiagnosed and treated for the wrong disease.**
- **CT and/or MR imaging can assist in detecting NENs in symptomatic patients where a diagnosis has not been established by endoscopic or other means.** Clinical features that may suggest a need for further investigations such as contrast-enhanced abdominal CT scan may include persistent symptoms (e.g., diarrhoea or abdominal pain), new onset of symptoms in older patients in whom a new diagnosis of IBS is less likely, the presence of one or more carcinoid syndrome symptoms (facial flushing, diarrhoea, bronchospasm), weight loss or bowel obstructive symptoms. (2)
- **Multiple Endocrine Neoplasia syndromes.** These are rare but we should be aware of them particularly in patients presenting with a family history, of young age presenting with hypercalcaemia.
- **The diagnosis of a neuroendocrine cancer can result in a significant and negative impact on quality of life for patients** (and their families). This is due to multiple factors including the impact of a new cancer diagnosis, potential tumour-associated hormonal symptoms, information and diagnostic barriers and delays, alongside an often incurable and uncertain prognosis. (3)
- **Diagnosing patients earlier is life-changing because there are treatments that can improve the prognosis as well as symptoms even in the presence of metastatic disease.**

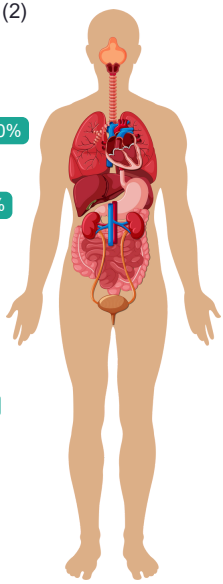
Lung / Bronchus: 20-30%

Digestive System: 60%

Stomach: 5%
Pancreas: 10%
Small Intestine: 5-25%
Colon: 13%
Rectum: 10-25%

Other Locations: 15%

Skin
Thymus
Ovary



The diagram above shows the likely locations of Neuroendocrine neoplasms (5)

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Syndromic features may present to endocrinology. This can be related to functional NENs commonly which may have metastasised or located in the pancreas. But can arise from any site (see table 12).

Tumour (syndrome)	Hormone	Clinical symptoms	Biochemical diagnosis
Insulinoma (Whipple's triad)	Insulin	Hypoglycemia	At hypoglycemia: • Insulin > 6 µU/L • Glucose 40mg/dL • C-peptide 0.6 ng/mL • Proinsulin ≥ 20 pmol/L
Gastrinoma (Zollinger-Ellison)	Gastrin	Abdominal pain, Gastroesophageal reflux, Diarrhoea, Duodenal ulcers	Serum fasting gastrin level ≥ 10 times normal range
VIPoma (Verner Morrison)	Vasoactive intestinal peptide (VIP)	Severe watery diarrhoea, Hypokalemia	Fasting serum VIP > 60 pmol/L
Glucagonoma	Glucagon	Rash, Glucose intolerance (diabetes), Necrolytic migratory erythema, Weight loss	Fasting glucagon > 500 pg/mL

“ NENs are not as rare as you may think

“Most gastroenterologists will intermittently diagnose new cases of NET and, in addition, they are likely to regularly encounter patients who have established NET diagnoses.” (2)

Between 1995-2018 the incidence of NENs has risen 371%: age-adjusted incidence increases from 2.35 to 8.61 per 100,000. (1)

Neuroendocrine neoplasms have a higher prevalence than incidence: incidence ~ 9 per 100,000(1), prevalence ~ 35 per 100,000. (8)

DEFINITION OF NEUROENDOCRINE CANCER

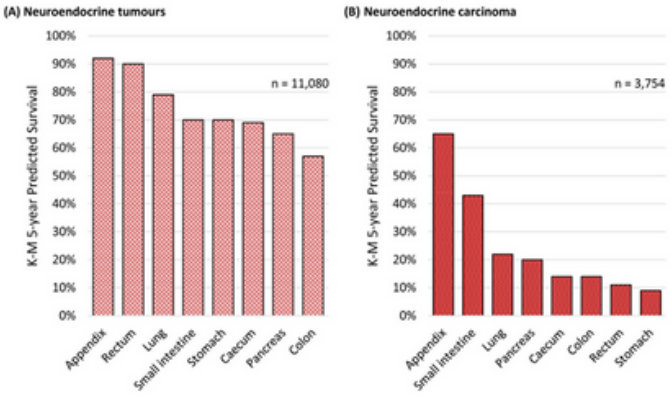
Neuroendocrine neoplasms (NENs) are a heterogeneous group of cancers, which arise in the neuroendocrine cells. The WHO has defined two principal subtypes – neuroendocrine tumours (NETs) and neuroendocrine carcinomas (NECs):

Neuroendocrine Tumours (NETs) and Neuroendocrine Carcinomas (NECs).
Both subtypes are considered as malignant tumours.

Neuroendocrine tumours (NETs)	Neuroendocrine carcinomas (NECs)
• Two-thirds of NENs are NETs ~70% • Well-differentiated • Slow to rapid growth - Graded 1-3 • Relatively good prognosis • May present/develop site- associated hormone syndrome	• One-third of NENs are NECs ~30% • Poorly differentiated • Rapid growth - Grade 3 • Poor prognosis • May present/develop paraneoplastic syndrome

- NENs are complex with aspects of both a cancer and a chronic disease and may develop almost anywhere in the body, most commonly within the respiratory or digestive tracts (GI tract /pancreas).
- Neuroendocrine neoplasms arising from the digestive tract are referred to as gastro-entero-pancreatic NENs (GEP-NENs), and these account for over 60% of NENs (4). The respiratory system represents the site of disease in 20-30% of patients, and less commonly affected sites include skin, thymus, and reproductive system structures, such as the ovaries.

Determining whether patients have NETs or NECs is of vital importance, as this can have a significant impact on prognosis as well as treatment planning. (6) There are significant differences in 5-year survival of NETs and NECs. (7)



CLINICAL PRESENTATION

- **Diagnosing NENs is challenging with data and patient experience reports indicating an average time to diagnosis of 3 years. (2)**
  - Symptoms may mimic or be masked by more common conditions such as IBS, Asthma or Menopause. (9)
  - **Routine tests may not raise suspicion or diagnosis of NENs, e.g., small bowel NENs may have negative endoscopy and normal FBC and CEA, despite bowel symptoms.**
  - Symptoms may be tumour and/or hormone excess related. However, many may be asymptomatic at early stages, found incidentally through screening or other tests.
- Those with functioning tumours can have specific symptoms for example, those with carcinoid syndrome may present with the classical triad of diarrhoea, flushing and/or wheeze.
- More than 50% of all cases, will have Stage III-IV disease at time of diagnosis. (10)
- In contrast to most other GI cancers, some patients who have widespread stage 4 NETs have a relatively good prognosis, especially when the tumour is grade 1.

THINGS TO LOOK OUT FOR THAT COULD BE INDICATIVE OF NEUROENDOCRINE NEOPLASMS:

- Peptic Ulcers (especially if unusual in size or number) in patients with no obvious cause such as H. pylori infection or aspirin/NSAID use and/or with an incomplete response to standard doses of PPIs.
- Continuing abdominal pain
- Small amounts of weight loss
- Minimal response to routine medications such as loperamide or antispasmodics
- Symptoms similar to those caused by any tumour at a particular anatomical site (e.g. small bowel obstruction)
- General symptoms associated with a metastatic tumour (e.g. weight loss, fatigue)

USEFUL INVESTIGATIONS FOR DIAGNOSING NEUROENDOCRINE NEOPLASMS

- For people with persistent, troublesome, particularly watery diarrhoea for whom the standard tests have not confirmed a diagnosis, consider a functional NET and arrange a Gut Hormone Profile and measurement of plasma/urinary 5-HIAA. Ensure these are taken correctly. (11)
- Chromogranin A is the most useful general biomarker for NENs but is not completely sensitive or specific. It is helpful for patients with confirmed NEN but shouldn't be used as a screening test. Review of the assays used and interpretation of the results in the context of the patient is important.
- Unusual looking polyps in the stomach, duodenum or rectum that could potentially be NENs should initially be biopsied rather than being removed at the time of the initial endoscopy. If a NEN is histologically confirmed, full tumour characterisation and staging is required to determine the optimal treatment plan.
- CT and MR imaging are useful for patients with persistent abdominal pain and diarrhoea and will often detect previously undiagnosed NENs. However, they will not necessarily demonstrate the full extent of disease.
- Nuclear medicine scans (e.g. 68Ga DOTATATE PET/CT and FDG-PET/CT), whilst not available in every hospital, can be very useful for determining the full extent of the disease and the optimal treatment plan and these should be considered before proceeding to treatment, unless it is an emergency.
- Refer patients with a confirmed or highly suspected diagnosis of NET/NEC or multiple endocrine neoplasia or MEN on to your local NET MDT or Centre of Excellence.
- Multidisciplinary working is the bedrock of management for patients with NEN.

SPOTLIGHT ON NEUROENDOCRINE CANCER IS A COLLABORATION BETWEEN UKINETS & NEUROENDOCRINE CANCER UK

Clinical guidelines are available - alongside expert advice from any one of 14 UK accredited European Centres for Neuroendocrine Cancer - should NENs be suspected/diagnosed: UKINETs: www.ukinets.org ENETs: www.enets.org

Patient-facing and HCP information, education and support is available from Neuroendocrine Cancer UK Office: 01926 883487 I Helpline: 0800 434 6476 Registered charity number: 1092386

THE LACK OF A NATIONAL PATHWAY AND NON-INCLUSION IN NG12 DIFFERENTIALS HAS HAMPERED THE DIAGNOSIS OF NENS, HOWEVER, A COLLABORATIVE MULTI-STAKEHOLDER WORKING GROUP – INCLUDING NHS EARLY DIAGNOSTIC LEADS – HAS ADDRESSED THIS DISPARITY. THE **NEUROENDOCRINE CANCER PATIENT CARE PATHWAY** WAS LAUNCHED MAY 2023. IT IS AVAILABLE TO VIEW HERE: WWW.NEUROENDOCRINECANCER.ORG.UK

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