High Grade Neuroendocrine Cancer

Overview / Tests / Follow Up

NET Patient Foundation

NET Patient Foundation (NPF) is a UK wide charity solely dedicated to providing support and information to those affected by Neuroendocrine Cancer.

The Neuroendocrine System

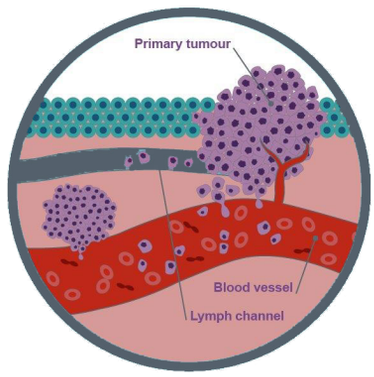
The Neuroendocrine System is made up of specific cells, found throughout the body, that help regulate normal bodily functions such as breathing and digestion.

Neuroendocrine Cancer

Neuroendocrine Cancer is a term used to cover a group of cancers that start in neuroendocrine cells. These cancers may also be referred to as NETs, NECs, **NENs (Neuroendocrine Neoplasms) or even Carcinoids.** Neuroendocrine Cancer occurs when neuroendocrine cells stop working normally and start to grow or behave abnormally.

Further information about Neuroendocrine Cancer, including videos and support services can be found at **www.netpatientfoundation.org**

High Grade NEN



The assessment of malignant Neuroendocrine Neoplasms (NET and NEC) is made by reviewing the appearance and activity of abnormal neuroendocrine cells under a microscope (histological review). NET/NEC can behave very differently depending on where they originate, how abnormal the cells have become and a what rate they divide and grow (Ki67). Histological review is vital to decision-making with regards to best treatment / care planning and follow up. It includes, amongst others, looking at:

- Cell type - does the cancer originate from a neuroendocrine cell?
- Differentiation - to what degree has cancerous change occurred and how disorganised have the cells become. Normal cells tend to be uniform in shape and size and appear organised.
- Proliferation rate (Ki67) - what percentage of cancerous cells are actively dividing and growing
- Grading - G1 is where Ki67 is less than (<) 3%, G2 is between 3 and 20%, G3 is greater than (>) 20%

Neuroendocrine Tumours (NET):

- Originate in neuroendocrine cells
- Are well-differentiated
- Have octreotide sensitive receptors on their surface
- Can be graded as G1, 2 or 3.

Neuroendocrine Carcinomas (NEC):

- Originate in neuroendocrine cells
- Are poorly-differentiated
- Tend to have lost their octreotide sensitive receptors
- Have a Ki67 >20% - therefore G3.

Symptoms of High Grade NET/NEC, if present, may be related to tumour position/size, excess hormone production and / or a para-neoplastic syndrome. Less than 10% have hormone excess related symptoms. NB may be similar to para-neoplastic syndrome.

Para-neoplastic syndromes are rare disorders triggered by an altered reaction of the immune system to the presence of a cancer - they are not specific to Neuroendocrine Cancer - and may include elevated calcium (hypercalcaemia), Cushings syndrome +/- SIADH (Syndrome of Inappropriate ADH secretion).

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Diagnosis for High Grade NEN

Blood / Urine Tests

- Full blood count
- (B12 + serum Iron)
- Liver and kidney function
- Biochemical :
- Chromogranin A (and B)
- NSE
- Gut Hormone profile
- Calcium
- Thyroid function tests
- LDH, Ca125, CEA, Ca19-9 - site specific ‘tumour markers’
- Urinary 5HiAA
- NT-Pro-BNP
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- Assess for presence of Cushing Syndrome, SIADH, Hypoglycaemia, Carcinoid Syndrome and hypercalcaemia
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- Echocardiogram : as a baseline in the presence of carcinoid syndrome / raised U5HiAA and / or elevated NT-Pro-BNP +/- clinical signs of heart valve impairment/R sided heart failure

Endoscopy

- Dependent on primary site - +/- biopsy depending on operability

Scans

- CT chest/abdomen/pelvis
- MRI Liver
- Functional imaging : Gallium-Dotatate PET/CT (SRS SPECT/CT if Dotatate PET n/a) - nb tumour heterogeneity
- FDG-PET – especially in High Grade NEC/ rapidly progressing disease.
- Bone scintigraphy - if bone metastases present/ suspected

Pathology

- Differentiation and cellular morphology
- Synaptophysin
- Chromogranin
- Ki67
- SSTR 2a - optional
- *NSE*
- *CD56*

*nb if a non-neuroendocrine component, such as adenocarcinoma, is present and exceeds 30%, it should be considered a mixed cell neoplasm = MiNEN *(mixed*

Diagnosis for High Grade NEN

Grade 1 : Well-differentiated cells, with a Ki67 less than 3%
Grade 2 : Well-differentiated cells, with a Ki67 between 3 and 20%
Grade 3a : Well-differentiated cells, with a Ki67 more than 20%
Grade 3b : Poorly differentiated cells, with a Ki67 more than 20%

MiNEN* : mixed neuroendocrine / non-neuroendocrine carcinoma

Neuroendocrine Tumours (NET) are more commonly seen in organs of the digestive system, that is, stomach, pancreas and bowel.

Neuroendocrine Carcinomas (NEC) are more commonly seen in the lungs and organs of the reproductive system, that is, testicles, ovaries, uterus, cervix, vaginal and vulva.
But this is no simple divide - not all lung NENs will be NECs and not all digestive tract NENs will be NETs - which is why it is important to be able to assess each NEN individually and avoid assumptions.

Treatment for High Grade NEN

For all patients, there are many things to consider in planning treatments. Your treatment will be personalised to you and the type of NEN you have. Even if you have a diagnosis that sounds the same as another patient, your treatment and follow up plan may be different.

If you are diagnosed with a Grade 3 NET or NEC, or MiNEN*, your specialist care team may recommend treatment that is more often used in other, more common cancers, for example, in High Grade Lung NEN, you may be offered a treatment usually used in Lung Cancer.

Chemotherapy may be given either before or after surgery or as the primary treatment if surgery is not possible. Platinum-based chemotherapy regimens including Etoposide are, historically, the first-line treatment of choice - however increased understanding of Ki67/ differentiation and evidence emerging about the efficacy of newer agents of treatment may influence which regimen best suits your specific NET/NEC.

Your care team will discuss your treatment options with you - giving you both written and verbal information - to help you make an informed choice. Together you can agree on the most appropriate treatment for you.

There is consensus agreement that all Neuroendocrine Cancer patients should be reviewed by a Specialist Neuroendocrine Cancer MDT. Information about the treatments that are used in NET and NEC can be found in the ‘NPF Handbook - your guide to living with Neuroendocrine Cancer’ - available online at: www.netpatientfoundation.org

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Follow up for High Grade NEN

As per expert opinion cited in ENETs guidance (2016)

G3 NEC who have undergone R0 / complete resection:
3 - 6mthly for first 3 years, then 6 - 12mthly up to 5 years post-op. with CT and/or MRI + relevant tumour markers*

G3 NET/NEC on active therapy : 2 - 3monthly during treatment.

Receptor appropriate functional imaging may be indicated if equivocal findings are identified on CT / MRI and / or if surgery is being considered

Advanced disease: frequent clinical assessment - further intervention should be guided by prognosis, expected treatment efficacy and treatment related toxicity considerations (assess performance status and clinical indication for active intervention) -

* is only indicated if elevated at diagnosis

NET or Neuroendocrine Tumour is neuroendocrine cancer with cells, that are described as well-differentiated - and usually has a slow to moderate growth rate.

NEC or Neuroendocrine Carcinoma is the term for neuroendocrine cancer that grows more rapidly and has cells, that under a microscope, are described as poorly-differentiated.

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