



# NETs – Why this master of disguise needs careful handling

Rare, hard to recognise, with primaries occurring at many different sites and associated with a wide variety of symptoms, tumours of the neuroendocrine system (NETs) are often detected too late to cure, and can be a cruel burden to live with. **Sophie Fessl** hears from patients and experts about why specialist NET services are so important.

**“W**hen you hear hoof beats, do not only think of horses, but also zebras.” With this slogan, patient advocates are trying to raise awareness of one of the more uncommon cancer types – neuroendocrine tumours. “Doctors are taught that, usually, a more common disease – a horse – is the reason for a patient’s symptoms, rather than an uncommon disease – a zebra. But that is how rare diseases get overlooked. We are asking doctors to specifically consider zebras,” says Teodora Kolarova, Executive Director of the International Neuroendocrine Cancer Alliance (INCA), an umbrella organisation of 26 NET patient advocacy and research groups spread across six continents.

With only 7 in 100,000 people diagnosed a year with a neuroendocrine tumour, misdiagnosis and late diagnosis are big issues for patients with NETs. But that is often only the start of their problems, because these tumours occur at a wide range of sites (see box p 38) and their treatments are associated with a variety of burdensome symptoms and treatment side effect that require specialist management, which is often lacking due to the rarity of this cancer type.

“I’ve read your file, and I don’t know much about NETs. Will you tell me what your experience is?” is what Sally Jenkins, from south Wales in the UK, was asked when she first received her diagnosis, a few years ago. “Patients at diagnosis would be seen in an endocrinology clinic, by different people, none of whom knew anything about NETs,” says Jenkins, who went on to successfully campaign for the establishment of a specialist NET service for Wales.

The NET ‘experience’ is often at the heart of the late diagnosis problem. Depending on the tumour’s location and behaviour, it often mimics common conditions that physicians and clinicians are more used to encountering. Abdominal pain can be mistaken for irritable bowel syndrome, hot flushes for menopause, and breathing problems for asthma. Because of this, NETs are sometimes referred to as the ‘forgotten cancer’, and a global survey conducted by INCA and Novartis in 2014 found a mean patient-reported time from first symptoms to diagnosis of 52 months (*J Glob Oncol* 2017, 3:43–53).

Sabine Wagner lived with gastrointestinal problems on and off for several years until a diagnosis of NET was finally given in May 2012. “I was admitted as an emergency patient because of my acute abdominal pain. I told the emergency doctor about my problems and that I felt like I was pregnant as my abdomen was so swollen by ascites. When the doctor did the ultrasound, she said that it was no wonder I had lost so much weight recently – there were metastases on my liver. Only six weeks earlier, I had been

discharged as healthy from a different hospital.”

By the time a diagnosis of NET is given, many patients will have metastases, precluding curative treatment. In many cases, NETs are slow growing; however, they can be aggressive and resistant to therapy. Survival outcomes also depend on the primary site of the tumour, which most often is in the gastrointestinal tract, lungs or pancreas.

**“I’ve read your file. I don’t know much about NETs. Will you tell me what your experience is?”**

“NETs need to be recognised,” says Jenkins. “Not necessarily by GPs, but once patients are referred to a gastroenterologist, surgeon or oncologist, they should be able to recognise that the symptoms are probably from a neuroendocrine tumour – and then refer the patient to a specialist team. But this doesn’t necessarily happen.” She was initially referred to a surgeon, who did not realise she had a neuroendocrine tumour, says Jenkins, until she nearly died as an emergency patient. “For me, it is all about awareness among the medical community.”

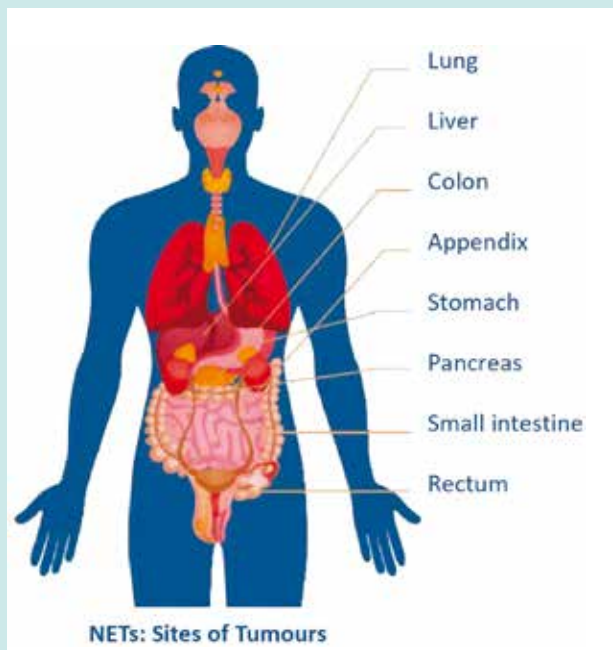
“No two patients with NETs are the same,” she adds, “because the disease is so heterogeneous. This makes supporting NET patients very difficult, and healthcare professionals need a lot of knowledge to do so.”

### Living with a chronic cancer

For patients with well-differentiated, slow-growing tumours, NETs often turn into a ‘chronic disease’ – a cancer they live with for many years. This does not make NETs a ‘good cancer’, however, says Nikie Jervis, former NET nurse specialist and now Patient Support Manager at the NET Patient Foundation in the UK. “No cancer is a good cancer. Just because it may not be imminently life-threatening does not mean it is good. Patients have to live with no cure, often experiencing lifelong symptoms, with acute phases that can occur at any moment. They are not in remission, but living with cancer day in, day out. Their fear is not so much recurrence as progression, and the uncertainty of not knowing when this may happen.”

These lifelong symptoms can have a significant impact on quality of life, depending on the patient, their tumour and the care they receive. Mohid Khan, consultant in gastroenterology and neuroendocrine tumours at the University

### NETs – the Nearly Everywhere Tumour



Neuroendocrine tumours (NETs) arise from specialised neuroendocrine cells, either from glands containing neuroendocrine cells or, more commonly, from neuroendocrine cells scattered throughout the body (diffuse neuroendocrine system). These cells can sometimes produce and release hormones into the bloodstream. Most NETs are slow growing. Survival varies from a few years to decades, even with widespread metastases, including in the liver. The most common sites for primary neuroendocrine tumours are shown in the

figure, but they can also be located on ovaries, the adrenal gland (and paraganglia), the thymus gland, the thyroid gland and others.

Because they affect such a wide variety of organs, specialist NET services require a broad range of specialists, including specialists in: gastroenterology, gastrointestinal and hepatobiliary surgery, endocrinology, medical and/or clinical oncology, radiation oncology, nuclear medicine, cardiology, thoracic medicine/surgery, gynaecology, as well as NET nurse specialist, nutritionist/dietician, psycho-oncology and palliative care.

The quality of care for NETs patients is currently being held back by very patchy access to specialist physicians, surgeons, multidisciplinary teams and nurses, says Mohid Khan, consultant in gastroenterology and neuroendocrine tumours at the University Hospital of Wales, in Cardiff.

Access to specialist treatments and equipment can also be a problem in some cases, he adds. Gallium PET scanning, for instance, is difficult to access for many patients, but only in a small proportion of patients does it result in changing management. Likewise, peptide receptor radionuclide therapy is indicated in only a very small proportion of patients with metastatic NETs, but access is a problem in some areas of Europe.

*Information about consensus guidelines for managing NETs and about accredited NET Centres of Excellence can be found on the website of the European Neuroendocrine Tumors Society [www.enets.org](http://www.enets.org)*

Hospital of Wales, conducted a patient-reported outcomes (PROMs) survey asking about the impact of NETs on quality of life, as part of an effort to improve the NET service by listening to patients. Top of the list, he says, were gastrointestinal symptoms, such as diarrhoea, bloating and abdominal pain. “Lethargy and fatigue also scored quite highly,” he adds. “The NET medical community’s clinical knowledge in these areas is low.”

Some of the problems that affect patients’ quality of life may also affect the care they are able to access. Sabine Wagner, who lives in Stuttgart, says she would have to travel three hours to reach the next accredited NET centre of excellence. “Despite treatment, I need to go to the toilet three to five times a day. How am I meant to travel? This is a challenge.”

Then there is the psychological impact, which can be immense, says Jenkins. “We live with uncertainty. We are given a death sentence, and know how we will probably die, but not when. This needs to be recognised.” Jervis adds that the long-term, chronic character of NETs can lead to problems in the social sphere. “Because NET patients don’t always look sick, there is less sympathy, it is assumed that things are OK. This is a huge issue, a hidden issue. But patients don’t necessarily want sympathy, they want better awareness and understanding of what they are experiencing – some acknowledgement that they’re not alone, unsupported, in this.”

Jenkins sought support by going to support groups for patients with other types of cancer, including a colorectal

## Sabine Wagner – diagnosed with neuroendocrine tumour in 2012, living in Germany

“In March 2012, I was seen in a small hospital for my severe symptoms. I had abdominal pain and had lost weight massively. Nothing showed up on the ultrasound, and the ward physician recommended a biopsy of the small intestine. But the senior physician declined, saying it would go away – I should eat chicken and potatoes only. Six weeks later, I was diagnosed with a neuroendocrine tumour.

I was overwhelmed. If I had been diagnosed with breast cancer or cervical cancer, I could have understood the diagnosis better. But NET? There is no reference frame for this.

My tumour progressed in 2014 and I received peptide receptor radionuclide therapy, which stopped the progression.

Since 2015, I'm again taking somatostatin analogues. When I once couldn't receive my monthly injection promptly because of bureaucratic problems, I felt worse than I had for many years. Now I know again that I'm ill.

In the first two years after my diagnosis, I didn't want to know that much about my disease. But through Netzwerk NETS [a self-help organisation], I help newly diagnosed patients by also giving them more background about the disease. In Germany, we do not have nurse specialists for NETs, but it would be desirable. There is case management in some clinics, but if not, you receive no information about follow-ups and have to organise your own scan appointments. Also, the case management does not answer questions you may have.”



cancer support group. “But I didn't fit into the stereotype of a cancer patient: immediate death is not probable, but I will also never get over the disease. However, that is what the counsellor there was used to dealing with, and so they were not able to give me any help other than being sympathetic. I am now seeing a clinical psychologist, and it was a learning process for her as well. NET patients need specialist support in all areas.”

### Multidisciplinary specialist care is essential

The global survey of patients with NETs conducted by INCA and Novartis showed that patients in the US who visit specialist centres felt more satisfied with treatment than those who were cared for in other settings (*Pancreas* 2017, 46:639–47). This is backed up by an analysis of the SEER database, which showed that the median overall survival in patients with distant metastatic disease was higher in patients cared for in specialised NETs centres (*JCO* 2008, 26:3063–72). To promote centralised care, the European Neuroendocrine Tumor Society (ENETS) established criteria for the certification of NET centres of excellence. Since 2009, 50 such centres have been accredited worldwide ([enets.org/coe\\_map.html](http://enets.org/coe_map.html)).

Sally Jenkins experienced what a big difference specialist

care can make. “When I was diagnosed, NET patients in south Wales were dealt with by a group of well-intentioned endocrinologists who didn't have expertise about what patients with NETs needed.” A survey conducted by the NET Patient Foundation, commissioned by Wales Health Specialised Services Committee (NHS Wales), found an overall satisfaction score of just 18%. This was later followed by consultant Mohid Khan's PROMs assessment, which demonstrated a high burden of unaddressed gastrointestinal symptoms even in those patients who had lived with a NET for years without specialist care.

“We raised awareness with the Welsh government that our treatment did not meet the criteria that patients with cancer in Wales should expect – including access to specialist care,” says Jenkins. “This led to the funding for a specialist NET service.” The service is now gastroenterology-led, with Khan as the clinical lead, and oversees the treatment of all patients diagnosed with NETs in south Wales. “Patients with stable disease previously often led a miserable life with diarrhoea and other symptoms. But now, with the gastroenterology-led service, these symptoms are managed very well, as all relevant issues are being addressed,” (see p 41).

The objective of this turnaround is clear, says Khan. “We want to give patients a decent quality of life and confidence in their disease management as part of value-based healthcare. We remeasured patients' burden of symptoms and have

## Quality of Life



### Mark McDonnell – diagnosed with a neuroendocrine tumour in 2011, living in Ireland

“ I was diagnosed by accident. In an ultrasound, doctors saw clouds on the liver, which the hospital then confirmed as tumours. Initially, I was diagnosed in a private hospital, which did not have great expertise on NETs. I received a call from my consultant, telling me I have a neuroendocrine tumour. I got off the phone and my wife asked me: ‘Is that cancer?’ I replied: ‘I don’t really know.’

Initially, my oncologist recommended to take a wait and see approach, which I agreed with, as I had no symptoms. But she urged me to get a second opinion from a NET specialist in another Dublin hospital. I thank her to this day that she did this, as the specialist saw my scans and decided we should take a proactive approach including surgery and treatment with somatostatin analogues.

It took me a full year trying to recover from surgery, both physically and psychologically. After taking somatostatin analogues, I got all the symptoms of NETs, including flushing, sweating, diarrhoea, which caused a lot of problems and led to me retiring from work. My doctor was very dismissive of these symptoms, and he really didn’t acknowledge that they were coming from the medication. But when the NET specialist returned from a stint working abroad, we revised this approach and decided that I should stop taking SSAs [somatostatin analogues].

Eight years down the road from diagnosis, do I see a long-term future? Maybe. I know it will be problematic, but now I think about it in terms of years. I have changed my lifestyle around eating and drinking, as I know that I need to stay healthy.”

achieved a significant difference in QoL compared to previously, which is reflected by the positive feedback demonstrated in a repeat patient experience survey.” In addition to providing centralised specialist care, Khan believes that the new service has also raised awareness of NETs among the medical community in the region, reflected in a reduction in the median time to diagnosis, which has decreased from nine months in the old service to four months in the new service. “We give individual feedback on cases, but in addition, gastroenterologists and surgeons are educated about NETs and become more aware of the disease in south Wales.”

Patients and patient advocates emphasise that all NET patients have to be seen by a specialist to receive best care. “Hanging on to a patient because it is an interesting case is not good medicine,” argues Jervis. “Care should be patient-

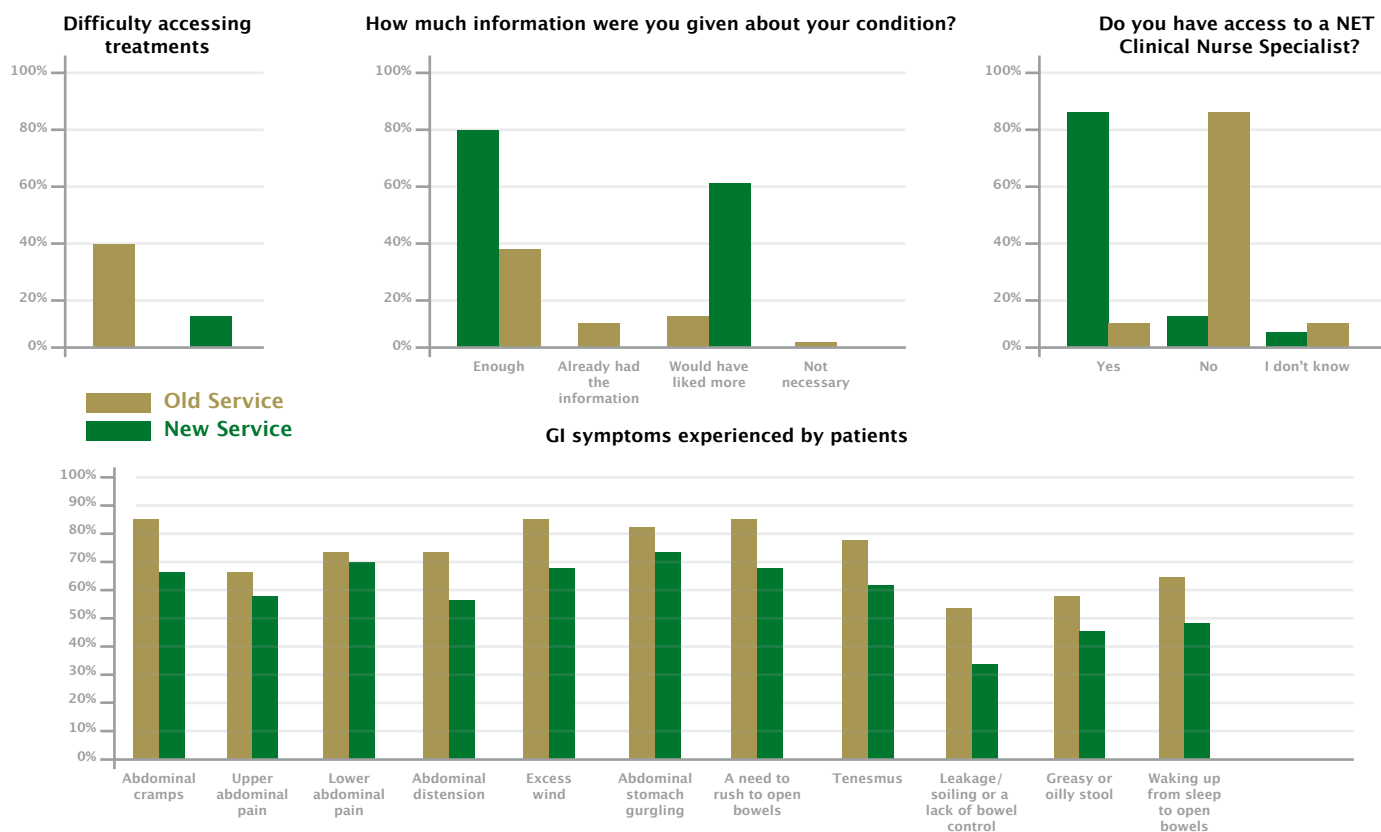
**“When they have a patient with a NET, they just give somatostatin analogues, even if it may not really help”**

centred. All patients with neuroendocrine cancer should be referred to a specialist centre for review – an expert opinion – and then triaged. Any treatment that can only be given at a specialist centre should be done there. But if the recommended treatment can be safely and effectively delivered locally then, yes, with good communication and collaboration, care should be given locally.”

Mark McDonnell, who was diagnosed with a NET in 2011, and is Chairperson of the Irish NET Patient Network, is campaigning for such a model of care in Ireland. “We are pushing the message that patients need to see a NET specialist. Patients cannot accept to be handled solely by an oncologist without specialist NET knowledge. If a patient is not treated at a centre of excellence, he or she needs at least to be seen by a NET specialist, or their care should be overseen by a NET multidisciplinary team. Unfortunately, that doesn’t always happen.”

Vera Megdanova, a doctor in Bulgaria who completed her medical oncology training last year, is seeking to improve care for NET patients in her home country. An ENETS fellowship will allow her to do fellowship training at centres of excellence in Dublin and Manchester. The current situation is dire, she says: “Patients with NETs are treated everywhere and by everyone. All doctors know

## Transforming the NET service in south Wales: measures of success



Source: M Khan et al. (2019) Turning it around: The South Wales Neuroendocrine Cancer Service, developing a patient-centred service through co-production <http://patientexperiencenetwork.org/wp-content/uploads/2013/11/WINNER-Turning-it-around-Cardiff-and-ValeUHB-Developing-a-patient-centred-service-for-NET-cancer-across-South-Wales.pdf>

The radical improvement in NET care in south Wales, led by consultant gastroenterologist Mohid Khan, won Cardiff & Vale University Health Board the UK Patient Experience 2019 Award for 'Turning it Around'. The service was commissioned across seven National Health Service boards or trusts, covering 16 hospitals in south Wales. In designing the service, Khan used quality-of-life assessments and patient-reported outcome measures, including the EORTC QLQ-GINET21 and gastrointestinal symptom rating scales (GSRs). The GI symptom scores were significantly lower in the new service ( $P=0.006$  for GINET21 and  $P=0.004$  for GSRs), and the reduction was felt across all symptom categories. Overall patient satisfaction with the service improved from 18% to 99%. "At the heart of it, our turnaround came from listening to patients. We involved patients throughout the process through stakeholder meetings and by going to patient group meetings," says Khan.

The service for NET patients now works collaboratively across the region. Any patient diagnosed with a NET in south Wales is referred to the NET service, regardless of geography or organisational boundary. Scan and laboratory reports and other documents are accessible electronically to the specialists, through a national Wales Clinical Portal, who give initial advice and guidance to the referring hospital before the multidisciplinary team meeting, and request additional tests or scans. The referring doctor/nurse also provides initial feedback to the patient. "After the MDT, we confirm the diagnosis and bring the patient to the clinic to provide ongoing management. Any aspects of care that can be done locally are done there, e.g. basic tests and imaging, but we still see most patients centrally, on a regular basis, if needs be through a phone consultation." Critically, the MDT brings together specialists from different areas of expertise to cover the very varied needs of NET patients.

## Quality of Life

about somatostatin analogues, so when they have a patient with a NET, they just give somatostatin analogues, even if it may not really help. We have no specialist NET centres in Bulgaria and few specialists interested in that area.” As elsewhere, patients frequently turn to the internet for more information. “Sometimes, patients know more about their disease than the doctor.”

### Wanda Geilvoet, a NET specialist nurse practitioner in Rotterdam, describes her role as ‘the bridge between cure and care’

Economic challenges also hamper efforts to help NET patients. “In most places, it is difficult to give a diagnosis, as patients have to pay for immunohistochemistry themselves. Tumour markers in NETs are also not covered by health insurance.” According to Megdanova, Gallium-DOTATATE PET/CT – highly effective in detecting NETs with high levels of somatostatin receptor 2 – should soon be available in the capital Sofia. So should peptide receptor radionuclide therapy – a molecular targeted therapy used in a small proportion of patients with NETs, which binds to somatostatin receptors and delivers high doses of radiation. Coverage of the imaging or treatment by health insurance, however, is so far unclear. “The money problem is exhausting,” says Megdanova. We want to help patients, but it can be very frustrating as it takes such an effort in money and time to give the right diagnosis and treatment.” As EU citizens, Bulgarian patients are often sent to be treated in other countries – once a diagnosis is finally given.

### Nurse specialists provide vital information and support

Mohid Khan attributes the success of the south Wales NET service in part to the recruitment and training of two clinical nurse specialists with expertise in caring for patients with NETs. “The clinical nurse specialist provides crucial support at the time of diagnosis, and coordinates care at the start and throughout the pathway. In a nurse-led clinic, the nurse specialist carries out simple procedures, clinical review including holistic assessment, signposting, education and simple management under supervision of a doctor. For example, a nurse specialist gives the first injection of soma-

tostatin analogues and then provides follow-up and virtual consultations on how patients are doing,” he says.

Importantly, dedicated nurse specialists may fill a major gap identified in the global survey on unmet needs of NET patients, which was carried out by the advocacy group INCA in 2017 – namely the need for high-quality information.

Wanda Geilvoet, chair of the ENETs nurse group ([enets.org/net\\_nurse\\_group.html](http://enets.org/net_nurse_group.html)) and a NET specialist nurse practitioner at the Erasmus Medical Center in Rotterdam, describes her role as “the bridge between cure and care”.

“I’m the main contact person for patients and their families when they have questions, both about medical and non-medical issues. I do triage when patients are referred to our hospital – this avoids duplicating diagnostic tests, and patients have a point of contact before their first outpatient visit. I’m also the care coordinator for new patients, and they know that they can call me if necessary.”

Geilvoet also screens patients to assess their need for psychosocial support or whether they need to see a physiotherapist or a dietician. She’s in contact with the home nurses about somatostatin analogue injections, and sees patients in the outpatient clinic and during follow-up. As a prescribing nurse, she prescribes medications to treat side effects, as well as ordering CT scans or additional lab tests. “I think it is a must for hospitals treating patients with NETs to have someone specialised to deal with all non-medical aspects around NETs,” she says.

Kolarova, from INCA, agrees. “Specialist nurses make a huge difference as they can give information, follow up and stay in touch with patients,” but she adds that, unfortunately, “in many systems this role is not recognised.” One reason for this may be linked to one of the more surprising results from INCA’s 2017 survey, which showed that almost 90% of the health professionals who responded felt they were able to meet patients’ information needs about treatment options at diagnosis, while only 36% of patients indicated that all their information needs were met ([bit.ly/NETs-UnmetNeeds](http://bit.ly/NETs-UnmetNeeds)).

As it happens, 36% is very close to the proportion of NET patients in south Wales who reported their information needs were met before care of NET patients in the region was reorganised. Under the new NET specialist service, that figure has risen to 80%, while the overall patient satisfaction score has risen from 18% to 99% – rock hard evidence, for anyone who has yet to be convinced, of the benefits of establishing a specialist service to care for patients with this rare, very varied disease which, without expert care and support, can put such a burden on quality of life.

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