

# NEUROENDOCRINE TUMORS

A PRIMER FOR  
HEALTHCARE PROFESSIONALS



*Advocating the Right Team,  
the Right Treatment, at the Right Time*  
for Neuroendocrine (NET)  
patients and physicians

**educating | funding | supporting**



## DEAR COLLEAGUE,

Thank you for your interest in Neuroendocrine Tumors (NETs) and the Healing NET Foundation. There are many people suffering from this complicated disease and having you as a partner in their care is vital. In this short document, we will describe the fundamental concepts of neuroendocrine tumors with a basic description of the disease, some recommendations on how to recognize, diagnose, and treat it, and some pearls in patient care.

The Healing NET Foundation is eager to send you more information and guidelines, and more resources are available at our website [www.thehealingnet.org](http://www.thehealingnet.org). Please do not hesitate to partner with someone who treats neuroendocrine tumors on a regular basis. There are subtleties to NETs that are different from the far more common adenocarcinomas and they require a different care path. The nuances of the disease and the treatment decisions we make can have a tremendous influence on the quality and quantity of our patients' lives.

Thank you.

The Medical and Scientific Advisory Board of the  
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Dr. Eric Liu with Dr. Kjell Oberg, founder of NET research at Uppsala University, Sweden

# NEUROENDOCRINE TUMORS

## BACKGROUND AND HISTORY

Neuroendocrine tumors (NETs) derive from cells of the diffuse neuroendocrine system scattered throughout the body, but mostly in the respiratory and digestive tracts. These tumors develop from hormone/neuropeptide producing cells that regulate physiology and maintain homeostasis. The types of hormones produced have specific functions often leading to specific syndromes, but others still remain to be discovered. The classical hormones include: serotonin, insulin, gastrin, glucagon, histamine, dopamine, vasoactive intestinal peptide, and somatostatin. However, some less well known ones include Ghrelin, pancreatic polypeptide, and pancreastatin. Still other classes of peptides include bradykinins and tachykinins. Therefore, an appreciation for the vast hormonal repertoire of NETs and the realization that we cannot measure all of them are important in NET care.

The natural history of this disease is complicated by the extreme variation in tumor behavior and tumor subtypes. Some patients are completely asymptomatic and diagnosed incidentally. Some have had vague symptoms for years that go undiagnosed because a peptide producing malignancy is not considered. Also, NETs have a reputation as slow-growing tumors, so some patients do not receive adequate treatment even once diagnosed, whereas other patients with extremely indolent disease may get over-treated.

The term “carcinoid” was originally given to this class of tumors in 1907 when Siegfried Oberndorfer first described the bland pathological features of these tumors. Because it was not the same as the more common adenocarcinoma, he called it “Karzinoide” (Carcinoma-like). Unfortunately, subsequent cases demonstrated that this was often a highly metastatic and lethal malignancy, albeit at a slower pace than most carcinomas. The term carcinoid has been used for nearly a century with the false understanding that it is a benign disease. This class of tumors has gone through many names including Amine Precursor Uptake and Decarboxylase Tumors (APUDomas) and Islet Cell Tumors. The lack of common terminology led to confusion. However, in 2000 the World Health Organization devised a new nomenclature that classified all these tumors as “Neuroendocrine Tumors” and each is named by its primary site (e.g. pancreatic neuroendocrine). In general, NETs are divided into their embryological sites of origin (foregut [including lung], midgut, and hindgut). These groupings have provided some distinction to the behavior and treatment responses of tumors. However, we are moving towards classifying NETs according to their primary organ site. Another important criterion used to classify NETs is the “grade” determined from the pathologist’s analysis of the tumor specimen or biopsy. Grade is discussed later in a separate section.

# NEUROENDOCRINE TUMORS

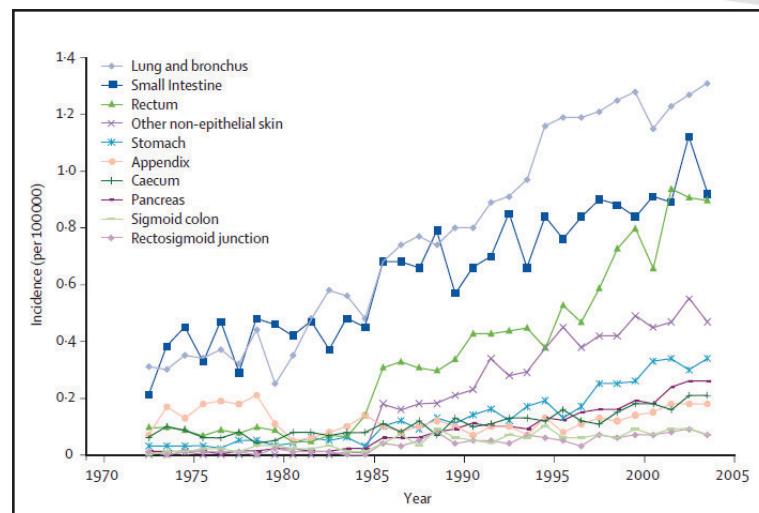
## EPIDEMIOLOGY

Neuroendocrine tumors are still relatively uncommon malignancies, but the number of cases has been increasing over the past 30 years. In 2008, the incidence in the United States was approximately 5/100,000 population. However, because of their general indolence early on, their prevalence is high (at least 112,000). The distribution of primary tumors is approximately: lung (27%), small intestine (19%), pancreas (7%), rectum (16%), stomach (5%), and other (26%).

# NEUROENDOCRINE TUMORS

## PRESENTATION AND SYMPTOMS

The presentation of NETs is quite broad and depends largely on the type of amine-peptide hormone produced by the tumor. The presentations are usually very vague abdominal and respiratory symptoms that the patient either ignores or are easily confused with other more common conditions. In addition, they may only be intermittent or triggered by environmental/emotional cues because early on most NETs are non-autonomous. Therefore, persistent symptoms without a clear cause warrants further investigation. Because NETs are difficult to diagnose and may elude particular tests, a thorough workup is required before completely ruling out the disease.



An increasing incidence of NETs, especially in the lung, small intestine, and rectum. Modlin, et al.

Neuroendocrine induced symptoms are classically reported in textbooks, but rarely do they present classically in clinical practice. Patients may only present with a partial combination of symptoms, and others are asymptomatic. Thus, accurate diagnosis often takes between 5-7 years from the time of symptom onset. Since many tumors do not secrete

systemic peptide, patients may suffer mostly from mechanical complications of the tumor, including obstruction and bleeding. These occur in both the digestive and respiratory tract. In the small bowel, intermittent partial small bowel obstructions causes abdominal pain. In the lungs, airway obstruction results in recurrent bronchitis/pneumonia. Peptide induced symptoms are well-described and include:

### CARCINOID SYNDROME

(SMALL INTESTINAL NETS)

- flushing
- diarrhea
- wheezing
- pellagra

### ZOLLINGER ELLISON SYNDROME

(GASTRINOMA)

- diarrhea
- persistent foregut ulceration
- heartburn
- abdominal pain

### GLUCAGONOMA

- diabetes
- cachexia
- necrolytic migratory erythema
- DVT

### INSULINOMA

- symptoms of hypoglycemia (neuroglycopenia, sympathetic overdrive)

### VIPOMA

- watery secretory diarrhea
- electrolyte disturbances

## NEUROENDOCRINE TUMORS

### DIAGNOSTICS / BIOMARKERS

A high index of suspicion is the most important step towards making a diagnosis of NETs, but there are many serum and urine markers that are used to help refine the diagnosis. Luckily, hormonally active tumors allow us to measure hormone levels as a disease marker. Markers may support a diagnosis, refine the tumor type, and help determine disease recurrence or progression. Small intestinal tumors usually produce serotonin; however, since the serum measurement can fluctuate and be unreliable, the urine metabolite 5-hydroxyindolacetic acid (5-HIAA) is usually used (a plasma form of this marker is commercially available). Its strength is determining the risk of carcinoid heart disease and being very specific for small intestine NETs, but its weakness is false positives when high serotonin foods are eaten (banana, avocado, chocolate, walnuts). Other hormones such as gastrin, glucagon, C-peptide, insulin tend to correspond with symptoms and tumor burden.

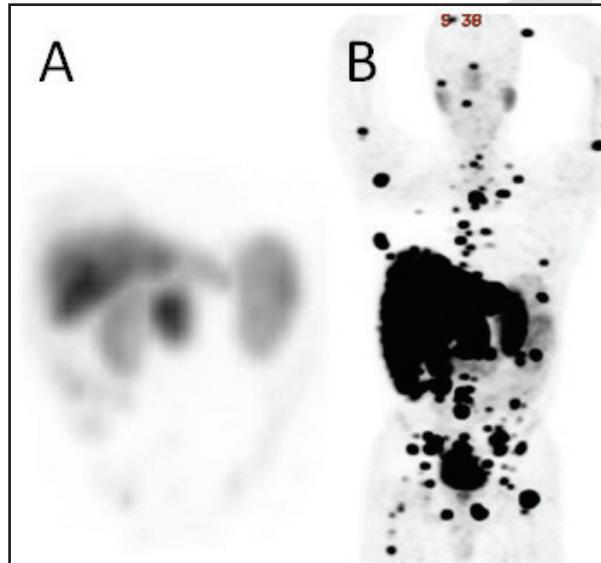
Other non-hormonal markers include Chromogranin A (CgA), Pancreatic Polypeptide (PP), and Neuron Specific Enolase (NSE). Chromogranin A is the most commonly used marker and corresponds well with tumor burden, but not all NETs secrete CgA. Also, there is significant laboratory variation, so tests from different places may give different CgA results. The greatest weakness for CgA is it is falsely elevated by Proton Pump Inhibitors. Pancreatic Polypeptide can be produced by pancreatic NETs that may not be overtly hormonal

(sometimes referred to as “Non-Functional”). Neuron Specific Enolase is an older marker that has been mostly replaced by CgA. Other newer markers include Pancreastatin, Neurokinin A, Chromogranin B, and multiarray RNA analysis. These tests are also commercially available and may be suitable for some NETs.

## NEUROENDOCRINE TUMORS IMAGING

Cross-sectional and functional imaging are the essential aspects of the work-up. Most disease is discovered on CT scans. Depending on the symptom pattern, CT of either the chest, abdomen/pelvis, or both may give you the fastest opportunity of diagnosis. CT is generally best suited to discover metastatic disease, especially in the liver, lung, or mesentery. While CT is a universal test, its weakness for NETs is a lack of sensitivity in the liver and its high dependency on the timing of the contrast dye injection. Most NETs in the liver only appear on arterial phases (early or late) and so the protocol is critical. Moreover, a non-contrast study will miss nearly all NETs in the liver. A more sensitive test for the liver and bones is the MRI. With liver specific contrast, it can detect up to 20% more disease. Diffusion weighted protocols are particularly sensitive as NETs have a unique water pattern in relationship to the normal liver parenchyma. Other tests, such as ultrasound and endoscopy are useful, especially in combination, but are user dependent. Colonoscopy and upper endoscopy are useful for identifying NETs of the colon/rectum and stomach/duodenum while enteroscopy or video capsule endoscopy are important if the clinical suspicion is high in small intestinal primaries. Endosonography is of value in the diagnosis of pancreatic NETs and fine needle aspiration permits a tissue diagnosis.

Functional imaging with nuclear scans has a strong role in NETs. The standard test is OctreoScan, an older imaging tracer that uses the somatostatin receptor with single photon emission tomography (SPECT). It is usually a whole body scan with moderate sensitivity for NETs. Unfortunately, OctreoScan is well known to miss large deposits of disease and it is extremely reader dependent. FDG-PET is another option, but is mostly



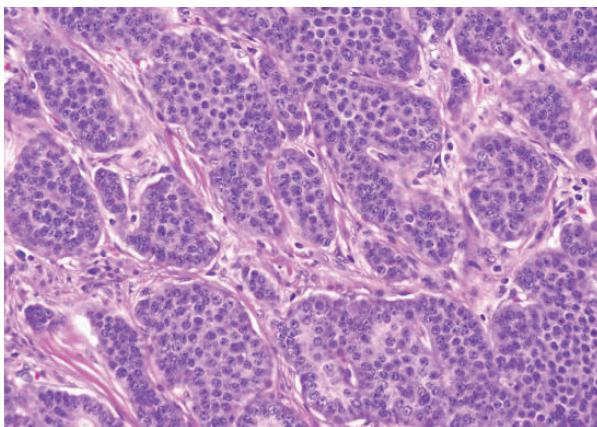
A comparison in the same patient between Octreoscan (A) and 68-Gallium-DOTATATE PET/CT (B)

useful for high-grade disease, as they tend to be glucose dependent. A newer imaging tracer for the somatostatin receptor is the 68-Gallium-DOTA-SSA PET-CT. The 68-Gallium PET-CT is more sensitive with higher resolution than the OctreoScan. **The FDA has approved a version of the 68-Ga (NETSPOT) for use in the United States. See update on last page for details.**

## NEUROENDOCRINE TUMORS PATHOLOGY AND STAGING

In 2000, the WHO revised the nomenclature for NETs and structured it around pathological grading based mostly on proliferation. The most important part of the pathological diagnosis is correctly identifying the tumor as a NET, which is often mistaken for a poorly differentiated tumor of unclear type.

Immunohistochemical markers are important for verifying the NET; synaptophysin and



Well-differentiated neurendocrine tumor by H&E staining

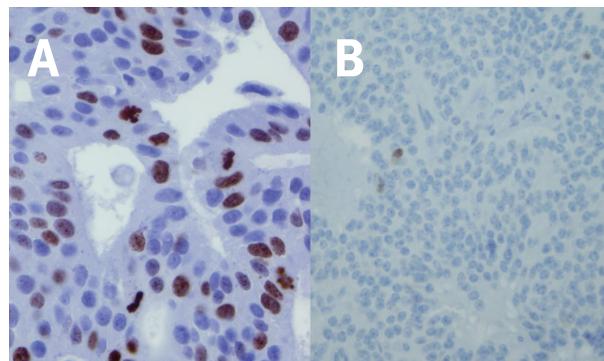
Chromogranin are standard. TTF-1 has some association with bronchial carcinoids. CDX2 is also helpful for NETs of the GI tract.

NETs are currently divided into Grades 1 – 3 based on proliferation (*Table 1*).

	Mitotic Index (mitoses/HPF)	Ki67 (%/2000 cells)
Grade 1	0-2	0-2
Grade 2	3-10	2-20
Grade 3	>10	>20

Table 1 – Tumor Grade based on proliferation.  
There is some variation based on primary site.

The easiest proliferative marker that can be assessed on any pathological slide is the mitotic index. Another proliferative marker is Ki67, an immunohistochemical stain.



Ki67 staining of high-grade NET (A) and low-grade NET (B)

It is divided into three grades also:

- Grade 1 = 0–2%
- Grade 2 = 3-20%
- Grade 3 = greater than 20%

Not all pathology labs routinely provide these data, so it is important to ask for them. This system only applies to digestive NETs; bronchial NETs have a slightly different system using the older terms

- Typical Carcinoid (Grade 1)
- Atypical Carcinoid (Grade 2)
- Poorly-Differentiated (Grade 3)

The grade of the tumor is predictive of survival. Staging is a more complicated issue because it is somewhat less standardized. The American Joint Commission on Cancer (AJCC) currently has a staging system for NETs of the digestive tract, but not for the pancreas.

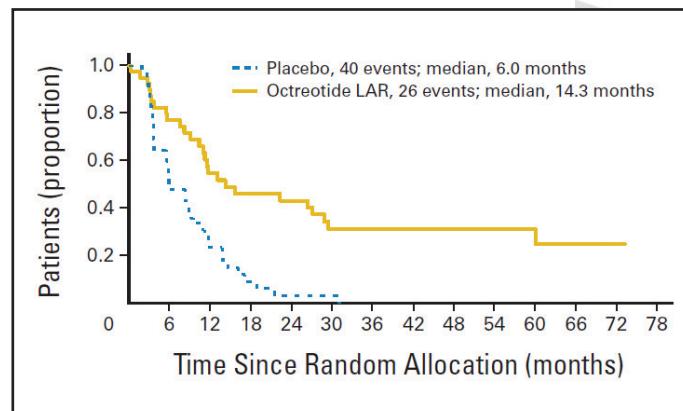
# NEUROENDOCRINE TUMORS TREATMENT

We are fortunate to have many treatment options for NETs, but they must be used with a careful weighing of benefit and risk and applied to the appropriate variant of disease. Despite the fact that NETs are frequently diagnosed with metastatic disease and Stage IV, its slower growth rate can still result in longer survivals. Therefore, a scan showing wide-spread disease is not immediate cause for alarm. We should also always consider clinical trials for our NET patients. Even when they are doing well, enrolling them in clinical studies helps us better understand the disease and develop new tools for diagnosis and treatment.



**SOMATOSTATIN ANALOGUES** (SSA) Hormone therapy is the mainstay of treatment for NETs. Not only are these agents effective in reducing functional symptoms, but they also retard growth in lower grade tumors. The two widely available agents include octreotide (short-acting and long-acting Sandostatin LAR) or lanreotide (long-acting Somatuline Depot). The two medications have similar biological effects on the specific somatostatin receptor (subtype 2A). The short acting version of octreotide (also known as “rescue injections”) is a water soluble form that is given subcutaneously and lasts 4-6 hours, so it must be administered 2-4 times per day. It is immediately bioavailable and can help with symptoms within a few minutes.

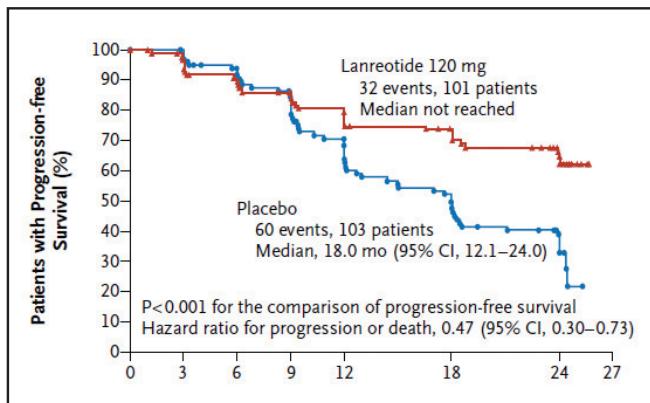
**OCTREOTIDE** (Sandostatin LAR) is the oldest version with the longest history in NETs. It is formulated as a polymer that slowly releases octreotide, but must be given as an IM injection into the gluteus muscle. It comes in doses of 10, 20, and 30 mg and is given every 28 days, though individual differences may require a change in dosing or scheduling. The major side-effects include gallstones, injection site pain,



Octreotide slows tumor growth in small intestine NETs. Rinke et al.

abdominal pain, and changes in thyroid or glucose metabolism. Subclinical fat malabsorption also results after long term use of SSA. Mixing and administering the drug can be difficult. Octreotide is FDA-approved for the carcinoid syndrome, VIPoma, and acromegaly. However, recent studies indicate that maintenance treatment has an effect in slowing tumor growth.

**LANREOTIDE** (Somatuline Depot) is an aqueous nanotubule that is given as a deep sub-cutaneous injection. It is indicated for syndrome control as well, but also is FDA approved for tumor control with improvement in progression free survival (PFS). Lanreotide comes in doses of 60, 90, 120 mg and is pre-packaged, making administration somewhat easier. The side effects are very similar to octreotide.



Lanreotide slows tumor growth in all GEP-NETs. Caplin et al.



A primary small intestinal neuroendocrine tumor (midgut carcinoid). The very small tumor has a classic white fibrotic appearance.

## SURGERY

Surgery is a powerful diagnostic and therapeutic modality in NETs; however, its application is different in NETs than in traditional adenocarcinoma. For NETs, we encourage early surgical intervention to prevent future complications. In retrospective studies, resecting the primary tumor has favorable outcomes even in the setting of metastatic disease. This observation is likely due to the fact that primary tumors (especially of the small intestines) are associated with morbidity, such as obstruction and bleeding. Surgical debulking is particularly helpful as it can help prevent mechanical issues as well as decrease the hormone-producing tumor load that may be associated with NET syndrome. Mesenteric metastases from the small intestines can cause a desmoplastic reaction and chronic small bowel obstruction if not resected early. A totally complete debulking is not necessary to obtain the benefits of NET surgery. For pancreatic NETs surgical approaches include: enucleation, distal pancreatectomy, partial pancreatectomy,

or pancreaticoduodenectomy, depending on patient risk, tumor size, location, and relation to other structures.

*Special precautions must be taken during a procedure for NET patients. Massive hormone release can cause hemodynamic instability and major morbidity (also known as carcinoid crisis). In addition to standard anesthetic care, high dose intravenous octreotide should be considered whenever the patient has hemodynamic complications.*

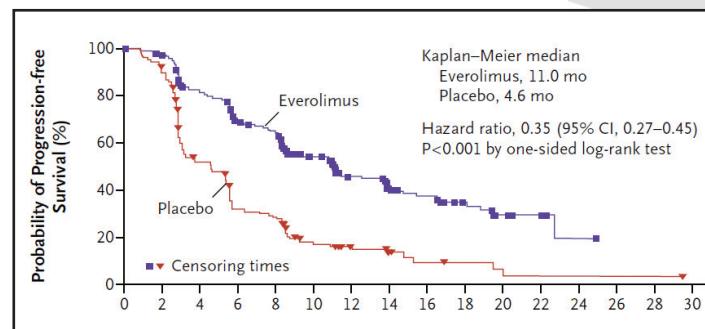
## MOLECULARLY TARGETED AND BIOLOGICAL THERAPIES

New treatments with molecularly targeted agents have proven effects for pancreatic NETs. Everolimus and Sunitinib are indicated for the treatment of metastatic, non-resectable pancreatic NETs. There is an improvement in PFS for both agents (Everolimus 11.0 vs 4.6 months; Sunitinib 11.4 vs. 5.5 months).

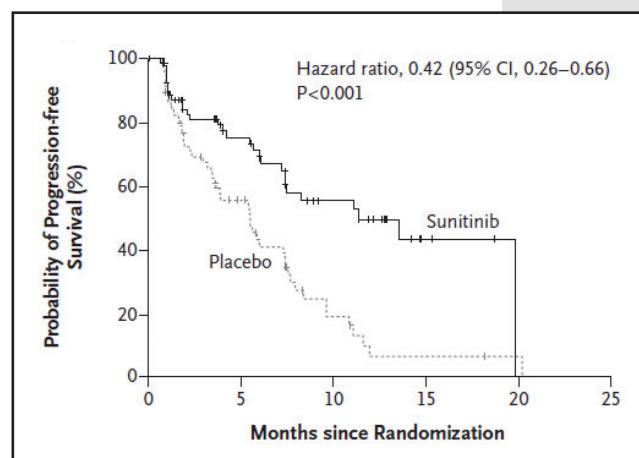
**EVEROLIMUS** (Afinitor) is given at a dose of 10 mg daily, though dose adjustment is frequent given the side effects of oral ulcers, impairment of wound healing, edema, changes in lipid and glucose metabolism, and edema.

**SUNITINIB** is given as 37.5 mg daily (lower than the dose for other malignancies such as renal cell carcinoma) with the major side effects of fatigue and hypertension.

**INTERFERON-A** has been shown to have some effect in small intestine NETs and is given at a dose of 10,000 units/week. The major side effect is flu-like symptoms.



Everolimus slows tumor growth in pancreatic NETs. Yao et al.



Sunitinib slows tumor growth in pancreatic NETs. Raymond et al.

## CHEMOTHERAPY

While traditionally less effective in low-grade NETs, chemotherapy does have a role in fast growing disease with a high proliferation index. Cytotoxic therapy based on platinum and etoposide are most effective in disease with Ki67 staining > 55% (Grade 3, small-cell). When this combination is effective, it typically shows a rapid response, but subsequent recurrence. The oral alkylating agent temozolomide is also frequently used in NETs, especially pancreatic, bronchial, and as a second-line therapy in high grade NETs. In pancreatic NETs, temozolomide plus capecitabine produced response rates of up to 70%. The dosing is usually capecitabine 1500mg/m<sup>2</sup>/day, d 1-14, temozolomide 200mg/m<sup>2</sup>/day, d 10-14, and then two weeks off with monthly cycles. The major side effects include bone marrow suppression and hand-foot disease.

## LIVER DIRECTED THERAPY (LDT):

Most NETs cause death due to liver failure secondary to hepatic metastases. Therefore, LDTs are commonly used in the setting of liver dominant disease. Liver directed therapies come in three major types:

- Radioembolization
- Chemoembolization
- Bland Embolization

In all three types, a catheter is placed through the femoral artery into the hepatic artery which is selectively embolized. This technique works because tumors in the liver tend to selectively derive their blood supply from the hepatic arterial system, rather than the portal system. Radioembolization utilizes resin or glass

particles coated with 90-Yttrium, a beta-emitting radioisotope. Chemoembolization consists of therapeutic loaded drug eluting beads. Bland embolization cuts off arterial supply to the tumors. Generally, a liver tumor burden greater than 20% lends itself well to LDT.

**RADIATION THERAPY:** In general, external beam radiation is not highly effective in NETs except for some bone lesions. The more targeted radiation based therapy for NETs is Peptide Receptor Radionuclide Therapy (PRRT or PRRNT). This therapy is currently not widely available in the United States, but is often used in Europe, Australia, and India. It targets somatostatin receptors with somatostatin analogue to carry a radioactive isotope directly into the tumor. An intravenous injection, the conjugated analogue and isotope can specifically target the tumors and continually irradiate them. PRRT (isotope 177-Lutetium) is usually given 200 mCi per treatment every 2 months for 2-8 cycles depending on the dosimetric tolerance of the individual patient. In a large retrospective trial from the Netherlands, disease response or stabilization occurs in up to 80% of patients with a PFS of 44 months. The major side effects are bone marrow suppression, renal impairment, and myelodysplastic disorder. Usually, OctreoScan or 68Ga-DOTA-SSA PET are companion diagnostics to determine if PRRT is a viable treatment option.

# NEUROENDOCRINE TUMORS

## FOLLOW-UP

Despite its reputation as an indolent disease, NETs are highly malignant and nearly all disease recurs. In some settings of local disease and complete resection, the patient may be cured; however, the more frequent situation is a disease free period and ultimate distant recurrence. Therefore, close follow-up is imperative for early detection. There is no fixed protocol for follow-up in surveillance or restaging; it is done with a combination of biomarkers, cross-sectional scanning, and functional imaging. Depending on the tempo of disease, the evaluations can vary from every 3–24 months.



*Digital version with latest updates can be found at  
[www.thehealingnet.org/resources/](http://www.thehealingnet.org/resources/)*

This booklet is provided as a service from the Healing NET Foundation, a 501-c3 charitable organization dedicated to furthering the education and training of physicians and health care professionals about neuroendocrine cancer, and supporting programs to upgrade NET patient care.

## SELECTED READING

Caplin et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. NEJM, 371(3):224-33, 2014.

Kvols et al. Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. NEJM, 315(11):663-6, 1986.

Gabriel et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J Nucl Med, 48(4):508-18, 2007.

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Rinke et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. JCO, 27(28): 4656-63, 2009.

Yao et al. Everolimus for advanced pancreatic neuroendocrine tumors. NEJM, 364(6):514-23, 2011.

### Update on NETSPOT Imaging Test:

**In 2016, the FDA approved the 68GalliumDOTATATE PET/CT for use in imaging in the United States for Neuroendocrine Tumors in patients of all ages. Commercialized by Advanced Accelerator Applications (AAA), the new name of the scan is “NETSPOT”. Currently it is still only limited to a few areas around the country, but it is expanding.**

**Currently, AAA is partnering with radiopharmacies around the country and placing a GALLIUM generator in the pharmacy. The pharmacy then uses the AAA kit and produces the radiotracer. Unfortunately, because of the short halflife of the 68gallium, it requires that the radiopharmacy be in relatively close proximity to the imaging center. Because of the high cost of the generator and its limited lifespan of one year, the generators are being placed in areas of high demand usually associated with regional expertise in the field of neuroendocrine.**

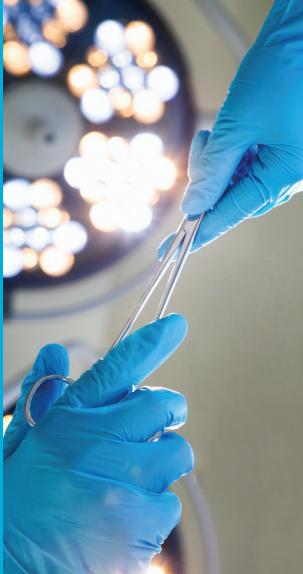
### More NETSPOT resources:

**AAA News Release on first NETSPOT in U. S:**

<http://www.adacap.com/wpcontent/uploads/2016/08/20160803PRFirstDoseNETSPOTHolyNameENGFINAL1.pdf>

### SNMMI report and Patient Resource for Locations:

<http://prrtinfo.org/62ga68petct/115ga68map>



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