

NEUROENDOCRINE TUMORS

A PRIMER FOR
HEALTHCARE PROFESSIONALS
2nd Edition



Advocating for the Right Treatment,
by the Right Team, at the Right Time

OUR MISSION

*To optimize the care of those with
neuroendocrine cancer through
the education of and collaboration
among physicians, health care
providers, patients, and caregivers*





Faculty at the Healing NET International Summit in San Diego, CA, February 22-24, 2018

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This 2019 edition of the NET Primer is a free publication for medical providers funded through private contributions by The Healing NET Foundation, a 501(c)(3) organization. Multidisciplinary physicians provide fundamental concepts of neuroendocrine tumors (NETs) with recommendations on when to suspect, and how to diagnose and treat the disease and deliver patient care. This 2nd edition includes a new section on the importance of effective communication between physician and patient for a complicated disease that can vary widely among patients. We provide additional information through our website:

THEHEALINGNET.ORG.

NEUROENDOCRINE TUMORS

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NEUROENDOCRINE CANCER MAY NOT BE WHAT YOU THINK IT IS.

- *If a patient presents with symptoms suggestive of Irritable Bowel Syndrome (IBS), Crohn's Disease, or another common digestive disorder, but does not improve with appropriate treatment, should the possibility of a neuroendocrine tumor be excluded because of its rarity?*
- *If a patient is confirmed to have a neuroendocrine tumor, is it safe to assume this is a slow-growing, mostly benign tumor?*
- *If a patient has a neuroendocrine tumor resected with clear margins and no other evidence of disease, is the patient considered "cancer-free" and unlikely to need follow-up or monitoring?*
- *If a patient diagnosed with a neuroendocrine tumor has continued progression of disease, is there a standard protocol for clinical treatment?*

Among physicians who regularly treat people with neuroendocrine tumors, all of these questions would be answered with a resounding NO.

Michelle Kim, MD (Gastroenterology, Mount Sinai Medical Center): *"My patients have been told by other physicians that they had irritable bowel syndrome, inflammatory bowel disease, and even psychiatric disorders, when they in fact had a neuroendocrine tumor. While I understand that these conditions are much more common than NETs, an astute clinician who thinks of a NET may be instrumental in providing an earlier diagnosis."*

Eric Liu, MD (Surgery, The Neuroendocrine Institute at Rocky Mountain Cancer Centers): *"When I went to medical school there was about 45 minutes of neuroendocrine in four years of education. There's definitely a gap in the education and understanding of medical providers."*

Cindy Lovelace (Healing NET Executive Director): *"When I was initially diagnosed and had a small neuroendocrine tumor in my pancreas resected, I was told to go live my life, and there was no suggested protocol for followup treatment. When I sought out a neuroendocrine specialist, two metastasized tumors were found, and my path was completely changed."*

NEUROENDOCRINE TUMORS

BACKGROUND AND HISTORY

Diagnosing and treating neuroendocrine tumors (NETs) is complicated by the extreme variation in tumor behavior and tumor subtypes. Some patients are completely asymptomatic and diagnosed incidentally. Others have had symptoms for many years but remain undiagnosed because this malignancy is not considered. NETs are mostly diagnosed in the GI tract or lungs, but tumors of hormone-producing cells can occur almost anywhere. Also, the location of the tumor can lead to misdiagnosis based on the body part, i.e., pancreatic or lung cancer instead of a NET.

NETs have a reputation as slow-growing tumors, or “not cancer” due to the use of older terminology “carcinoid” (or cancer-like), but there are high-grade variations, such as the poorly differentiated neuroendocrine carcinomas (NECs), which are very aggressive and often recur. On the other hand, patients with indolent disease may get over-treated with aggressive therapy. Complicating the situation further is the lack of education about NETs in healthcare because it is classified as a rare disease.

NEUROENDOCRINE TUMORS

EPIDEMIOLOGY

Neuroendocrine tumors remain relatively uncommon. However, the most recent studies show that by 2012, the incidence in the United States had risen to approximately 7 in 100,000, which means more than 20,000 new cases a year. Survival rates have also increased over time. A retrospective review of the SEER data (Dasari, et al.) estimated the prevalence of neuroendocrine tumors in the United States at over 170,000 in 2014. The incidence of the tumors by primary site (2012 data) is approximately:

- 23%** lung
- 18%** small intestine
- 16%** rectum
- 12%** pancreas
- 17%** other gastroenteropancreatic or GEP-NETs
(*stomach, appendix, colon, cecum*)
- 14%** unknown primary site and rare sites

Rare sites include the uterus, ovary, testis, breast, adrenal glands and larynx.

NEUROENDOCRINE TUMORS

PATHOLOGY CLASSIFICATION, GRADING AND STAGING

In 2010 and 2017, the World Health Organization revised the nomenclature for neuroendocrine neoplasms with specific emphasis on the distinction between well-differentiated neuroendocrine tumors (WD-NET) and poorly-differentiated neuroendocrine carcinomas (PD-NEC), which are vastly different in tumor biology, clinical presentation, therapeutic strategies, and prognosis. Pathological grading of NETs is based on tumor proliferative activity, i.e., mitotic figures and Ki67 index (Table 1). PD-NECs are always high grade. However, proliferative activity alone may not be sufficient to determine whether the tumor is a WD-NET or a PD-NEC, particularly in small and suboptimal biopsies. Additional clinical information, immunohistochemical workup, and molecular testing may be necessary to confirm the correct diagnosis.

WHO (2017)

	MITOSES	Ki67
WD-NET G1	<2/10 HPF	<3%
WD-NET- G2	2-20/10 HPF	3-20%
WD-NET- G3	>20/10 HPF	>20%
PD-NEC <i>(small and large cell carcinoma)</i>	>20/10 HPF	>20%

(table 1)

Bronchial NETs have a slightly different classification system using the older terminology:

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

The standard pathology assessment of a neuroendocrine neoplasm should include:

- Clear definition of WD-NET or PD-NEC
- Immunohistochemical markers to confirm NET/NEC (synaptophysin and chromogranin)
- Mitotic activity: number of mitoses/10 high power fields for biopsies; and number of mitoses/50 high power fields for surgical specimens.
- Ki67 proliferative index by immunohistochemistry
- Presence or absence of tumor necrosis

In cases of unknown primary tumors, additional immunohistochemical markers may indicate possible primary sites. For example, TTF-1 expression is often associated with bronchial carcinoids; CDX2 is commonly seen in NETs of the gastrointestinal tract, etc. Some molecular tests of a biopsy specimen may also help determine the primary site (Cancer TYPE ID).

The American Joint Commission on Cancer (AJCC) has updated the staging system for NETs of the digestive tract and the pancreas in its 8th edition (2018).

It is important to recognize that tissue pathology gives information at only one point in time unless it is repeated as tumor grade may change. Tumor grade is indicative of the biologic behavior of NETs and can predict the clinical course and outcome of disease. Tumor stage (based on the TNM classification) reflects the extent of disease at the time of initial diagnosis, which can help physicians determine initial therapeutic strategies (local or systemic therapy).

NEUROENDOCRINE TUMORS

PRESENTATION AND SYMPTOMS

The presentation of NETs ranges from no symptoms to profound symptoms. With the increased frequency and availability of imaging scans (CT and MRI) and endoscopic procedures, NETs are increasingly being diagnosed incidentally in patients without symptoms or with symptoms unrelated to the diagnosis. In patients who develop symptoms, these are often vague gastrointestinal or respiratory symptoms such as cough, wheezing, abdominal pain, diarrhea, or flushing. Patients are often misdiagnosed with other more common conditions such as irritable bowel syndrome, reflux, inflammatory bowel disease, menopause, rosacea, or asthma. Delay in diagnosis can exceed five years from the onset of symptoms in numerous cases.

Rarely do patients present with the classic symptoms described in textbooks. Patients may present with only partial symptoms. **THE MAJORITY OF NETS ARE NON-FUNCTIONAL**, meaning they do not secrete systemic peptide or amines, so patients may suffer mostly from mechanical complications of the tumor, including obstruction and bleeding. These occur in both the digestive and respiratory tracts. In the small bowel, intermittent sub-acute small bowel obstructions may occur resulting from a desmoplastic reaction around the tumor that causes abdominal pain and kinking of the bowel. In the lungs, airway obstruction may result in recurrent bronchitis or pneumonia. Paragangliomas may cause mass effect in the neck or torso. Therefore, persistent symptoms without a clear cause warrant further investigation. Because NETs are difficult to diagnose, a thorough workup is required before completely ruling out the disease.



Image from upper endoscopy, demonstrating a large gastric NET with overlying ulceration.

Peptide and amine hormone induced symptoms are well-described and include:

CARCINOID SYNDROME

(usually small intestinal or pulmonary NETs)

- flushing
- night sweats
- diarrhea
- wheezing
- pellagra

Note: Carcinoid heart disease occurs in 50-70% of patients diagnosed with carcinoid syndrome.

ZOLLINGER ELLISON SYNDROME/ GASTRINOMA

(usually duodenal or pancreatic)

- diarrhea
- severe small bowel ulceration
- heartburn
- abdominal pain

GLUCAGONOMA

(usually pancreatic)

- diabetes
- cachexia (severe weight loss)
- necrolytic migratory erythema (severe migrating skin rashes)
- deep venous thrombosis

INSULINOMA

(almost always pancreatic)

- symptoms of hypoglycemia (neuroglycopenia, sympathetic overdrive)

VIPOMA

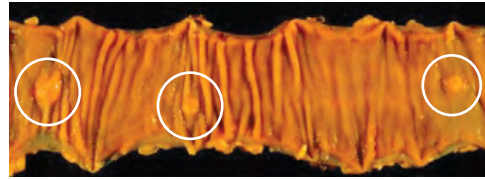
(usually pancreatic)

- watery secretory diarrhea
- electrolyte disturbances

PHEOCHROMOCYTOMA

(adrenal)

- hypertension
- headaches
- sweating
- palpitations



Specimen of surgical resection of small bowel, demonstrating multiple small NETs.



Cross section of a small bowel NET, demonstrating invasion through the deep muscle layer.

NEUROENDOCRINE TUMORS DIAGNOSTICS

BIOMARKERS

A high index of suspicion is the most important step towards making a diagnosis of NET, but there are many serum and urine markers that are used to help refine the diagnosis. Hormonally active tumors enable us to measure peptide or amine concentrations as a disease marker supporting a diagnosis, refining the tumor type, and helping predict disease recurrence or progression. Functional small intestinal tumors that produce carcinoid syndrome usually produce serotonin, which can be measured in the serum, and its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA) in the urine. A plasma test for this marker, 5-HIAA, is also commercially available. False positive 5-HIAA results occur when foods rich in serotonin are eaten (in particular tropical fruits, chocolate and nuts). These functional small intestinal tumors also produce tachykinins, and recently a neurokinin A (NKA) assay has become

available. While highly specific for small intestinal NETs, many patients do not produce the hormone, so a negative result does not exclude the diagnosis.

Other peptides produced by functional pancreatic NETs such as gastrin, glucagon, insulin (and C-peptide) and VIP can be measured and tend to correspond with symptoms and tumor burden for these tumors. For pheochromocytomas, catecholamines are produced, and standard biochemical evaluation includes serum catecholamines and metanephrines, as well as urinary metanephrines and vanillylmandelic acid (VMA).

General tumor markers can be used as a measure of NET tumor activity. These include chromogranin A (CgA), pancreatic polypeptide (PP) and neuron-specific enolase (NSE). NSE is an older marker that has been replaced by CgA, which is the most commonly used marker and corresponds well with tumor burden, but not all NETs secrete CgA. In patients with benign NETs or some Grade 3 (more aggressive) NETs and many neuroendocrine carcinomas (NECs), CgA is not raised. There is significant laboratory variation in the measurement of CgA, so tests from different laboratories may give different results. It is best therefore to use only one laboratory when following a patient's progression. The greatest weakness for CgA is that it is elevated in other circumstances, by proton pump inhibitors, in autoimmune atrophic gastritis, inflammatory bowel disease, and in renal injury. PP can be produced by pancreatic NETs that may not be overtly hormonal (non-functional tumors). PP may also be raised occasionally in lung or rectal NETs. Other newer markers include pancreastatin, CgA fragments, chromogranin B, and a multi-array RNA analysis (the NETest). Some of these tests are commercially available and may be suitable markers for some NETs. A potential issue with the biomarkers is lack of sensitivity and specificity. For example, because of the frequency of CgA unreliability, recent studies support the substitution of the pancreastatin test; pancreastatin, the breakdown product of Chromogranin A, is more sensitive and specific for NETs.

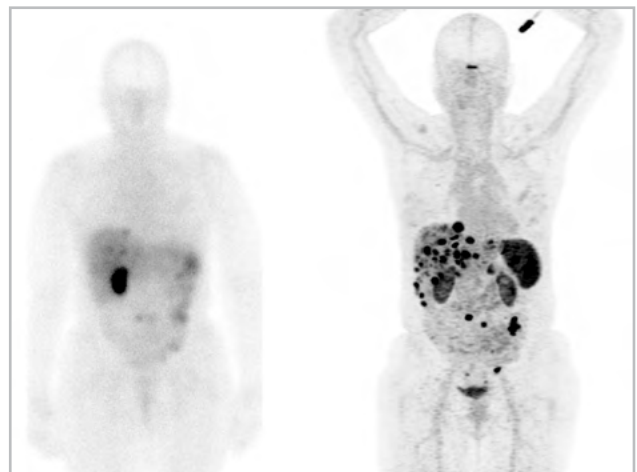
IMAGING

Both anatomical and functional imaging techniques are important for the workup of NETs. Typically, the initial and most common evaluation is by contrast-enhanced CT of the chest, abdomen, and pelvis, which is used to try and identify the primary tumor as well as metastases. While CT has many strengths, its weaknesses for visualizing NETs are a lack of sensitivity in

the liver and its high dependency on the timing of the contrast injection. **A CT scan is usually not diagnostic of the FULL EXTENT OF DISEASE.** Most liver metastases only appear in the arterial phases when contrast is used. A non-contrast study may miss all but the largest liver metastases. A more sensitive test for the liver and bone is 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. Endoscopic procedures including endoscopic ultrasound can be useful in identifying gastrointestinal NETs.

Functional (nuclear) imaging also has an important role in diagnosing NETs by utilizing the expression of somatostatin receptors (SSTRs) to identify tumor sites. This technology has been available for many decades with gamma-camera imaging or single photon emission computed tomography (SPECT), using the radiopharmaceutical 111-Indium-pentetreotide (OctreoScan), which has limited resolution, but the tracer and the scanner are widely available. Since 2016, a newer generation radiopharmaceutical 68-Gallium-DOTATATE (NETSPOT®) has been FDA-approved for this same indication, using positron emission tomography (PET) coupled with CT or MRI. It has many advantages over an OctreoScan, including much higher resolution, better sensitivity, a shorter scan time and a lower radiation dose. **Where the ⁶⁸Ga-DOTATATE scan is available, it is the much preferred scan for visualizing extent of disease.** There remain issues with access and insurance

approvals for this scan though this is decreasing. Recently, Appropriate Use Criteria for ⁶⁸Ga-DOTATATE were published in the Journal of Nuclear Medicine; in brief, SSTR-imaging has a role in diagnosis, identification of the primary, staging, restaging and selection of patients for peptide receptor radionuclide therapy (PRRT) with 177-Lutetium-DOTATATE (LUTATHERA®). Its role in assessment of response to treatment remains under investigation. In general, SSTR-imaging is most effective for well-differentiated tumors, since poorly-differentiated tumors may not express SSTRs at a sufficiently high concentration. For patients with NECs and some with Grade 3 NETs the standard PET radiopharmaceutical 18F-fluorodeoxyglucose (FDG) is preferred. For tumors with a proliferation index in the middle-ground, Ki67 of 20-55%, both ⁶⁸Ga-DOTATATE and FDG PET may be required for full staging.



A comparison in the same patient between a In111-pentetreotide scan (OctreoScan, left) and Ga68-DOTATATE PET (NetSpot, right). Images courtesy of Hong Song, MD, PhD (Stanford University).

NEUROENDOCRINE TUMORS

TREATMENT

Over the past decades many treatment options for NETs have emerged. They should 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, their slower rate of growth can still result in long survival times. Therefore, a scan showing widespread disease is not immediate cause for alarm; even widely metastatic disease can often be considered chronic disease. **Clinical trials should not be overlooked as an option for any NET patient.** In general, therapy can be divided into systemic and local treatments.



SYSTEMIC TREATMENTS

HORMONAL TREATMENTS— SOMATOSTATIN ANALOGS (SSAS)

Biotherapy with SSAs is the mainstay of maintenance treatment for NETs. Not only are these agents effective in reducing functional symptoms, but they also retard growth in lower grade tumors. Two preparations are available, octreotide (short-acting SANDOSTATIN[®] and long-acting SANDOSTATIN[®] LAR) or lanreotide (long-acting SOMATULINE[®] DEPOT). The two medications have similar biological effects on the somatostatin receptors (predominantly receptor subtypes 2 and 5). Short acting SANDOSTATIN[®], also known as “rescue injection,” is a water-soluble preparation given subcutaneously and lasting 4-6 hours, so it must be administered 2-4 times daily. Rescue injection is immediately bioavailable and can reduce symptoms within a few minutes. This is the option of choice for back-up for patients prone to carcinoid crisis. The longer acting formulations are particularly suited to chronic maintenance therapy and are generally well tolerated.

OCTREOTIDE (SANDOSTATIN[®] LAR) has the longest history in NETs. It is formulated as a polymer that slowly releases octreotide, given as an IM injection into the gluteus muscle. It comes in doses of 10, 20, and 30 mg given every 28 days, though individual differences may require a change in

dosing or scheduling. The major side effects include gallstones, pain at the injection site, abdominal pain, and changes in thyroid or glucose metabolism. Subclinical fat malabsorption from pancreatic insufficiency also results after long term use of SSA. Mixing and administering the drug can be difficult. Octreotide is FDA-approved for carcinoid syndrome, VIPoma, and acromegaly. However, the PROMID Trial 2009 demonstrated that maintenance treatment also slows tumor growth.

LANREOTIDE (SOMATULINE® DEPOT)

is an aqueous nanotubule that is given as a deep sub-cutaneous injection. It is indicated for syndrome control and also is FDA-approved for tumor control with improvement in progression-free survival (PFS) (CLARINET Trial 2013). Lanreotide comes in doses of 60, 90, or 120 mg and is pre-packaged, making administration somewhat easier. Side effects are similar to octreotide.

Patients treated with octreotide LAR or lanreotide have reduced likelihood of experiencing a carcinoid crisis when undergoing invasive procedures. Intravenous infusion of octreotide is the standard treatment.

TELOTRISTAT ETHYL (XERMELO®) is the first oral medication that can be used to control diarrhea in carcinoid syndrome (CS) by inhibiting tryptophan hydroxylase, the rate-limiting enzyme involved in the production of serotonin. It is FDA-approved for the treatment of diarrhea in patients sub-optimally treated with a somatostatin analog alone. Telotristat is not indicated for

tumor control. The drug is well tolerated with minor elevations in liver enzymes. Some patients may require dose reductions because of constipation and/or abdominal pain. Telotristat does not enter the central nervous system and is not thought to be associated with depression.

CHEMOTHERAPY

Chemotherapy is used for patients with neuroendocrine carcinomas (Grade 3, well-differentiated and poorly-differentiated NEC). This aggressive malignancy grows rapidly, and while it is typically responsive to chemotherapy and targeted radiation, rapid recurrence after treatment is common. Platinum doublets such as cisplatin or carboplatin with etoposide, are most commonly used frontline. Based on limited data, many clinicians empirically employ second-line fluoropyrimidine combination regimens, such as FOLFIRI, FOLFOX, or FOLFIRINOX (NCCN 2018).

For well-differentiated Grade 1 and 2 NETs, alkylating chemotherapy is less frequently a suitable option. However, chemotherapy has its most established role in patients with NETs originating in the pancreas. Streptozocin- and temozolomide-based regimens are both supported by randomized data, with many clinicians using capecitabine/temozolomide (CAPTEM). The dosing is usually capecitabine 750 mg/m² twice daily, day 1-14, and temozolomide 200mg/m² once daily, day 10-14, then two weeks off, repeated on monthly cycles. Though

data are limited, some clinicians use temozolomide-based chemotherapy empirically for patients with rapidly-progressing disease, even when the NET arises outside of the pancreas.

MOLECULARLY TARGETED AND BIOLOGICAL THERAPIES

Molecularly targeted agents have proven beneficial for patients with well-differentiated NETs. For patients with pancreatic NETs, both the mTOR inhibitor everolimus (AFINITOR[®], 10 mg daily) and the tyrosine kinase inhibitor sunitinib (SUTENT[®], 37.5 mg daily) have shown delays in progression or death in randomized studies. For patients with GI or pulmonary NETs, everolimus also delays progression or death. Additional regimens with less clear data include bevacizumab/octreotide and interferon/octreotide and are used less commonly in clinical practice.

NUCLEAR MEDICINE— PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT)

Peptide receptor radionuclide therapy with ¹⁷⁷Lu-DOTATATE (LUTATHERA[®]) is a novel treatment approved in 2018 that utilizes an injectable, radioactive form of the somatostatin analog DOTATATE to deliver internal, targeted radiation therapy.



It is approved for all gastroenteropancreatic (GEP)-NET patients with inoperable, metastatic disease who progress on first-line somatostatin receptor therapy with octreotide or lanreotide. It is the therapeutic analog of ⁶⁸Ga-DOTATATE and similarly utilizes the somatostatin receptors to target the NET cells directly but utilizes the isotope lutetium-177, which causes DNA damage, destroying the cell over time. Proper patient selection is primarily based on NET grade and stage, confirmation of high SSTR-expression based on functional imaging, progression of disease based on conventional imaging and/or clinical parameters, and renal function. PRRT is administered intravenously, usually over 4 cycles once every 2 months. Toxicity is quite low and primarily involves bone marrow suppression. Other potential toxicities include renal (reduced with co-administration of amino acids) and liver (which is typically transient but requires ongoing monitoring before, during, and after the therapy).

LOCAL TREATMENTS

SURGERY

Surgery is a powerful diagnostic and therapeutic modality in NETs; however, its application is different in NETs than in adenocarcinoma. **For NETs, relatively early surgical intervention is encouraged to prevent future complications.** Primary tumors (especially of the small intestine) are associated with morbidity, such as obstruction and bleeding. Surgical debulking is particularly helpful as it can help prevent mechanical issues and decrease the hormone-producing tumor load that may be associated with carcinoid or other hormonal syndromes. Mesenteric metastases from the small intestines can cause a desmoplastic reaction and chronic or acute small bowel obstruction if not resected early. Pancreatic lesions can cause venous thrombosis, left-sided varices, and biliary duct obstruction. Lung lesions may obstruct the airway and cause bleeding, pneumonia, and persistent symptoms. Absolute eradication of disease is not necessary to obtain benefits of NET surgery. Because NETs tends to be a systemic disease, surgery should be considered a method of wide local-regional control that provides safe and significant long-term benefit to the patient by improving symptoms and delaying the requirement for more toxic systemic treatments.

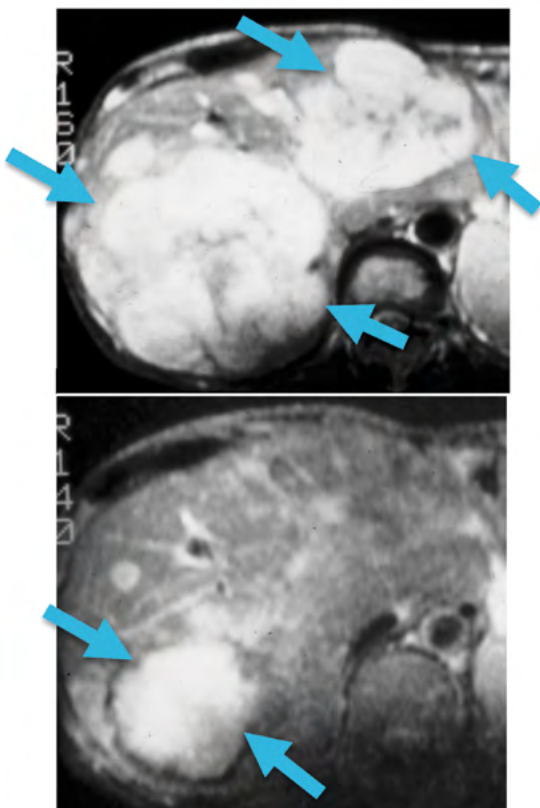
Special precautions must be taken during surgical procedures for NET patients. Massive hormone release can cause hemodynamic instability and major morbidity (also known as carcinoid crisis). In addition to standard anesthetic care, intravenous octreotide should be considered to help suppress hormone production. For very low blood pressure, intravenous Solucortef can be considered to inhibit tumor release of bradykinin, a potent vasodilator. Intraoperative carcinoid crisis is currently under investigation because no well-established protocol exists.

EXTERNAL BEAM RADIATION THERAPY (SBRT OR SABR)

External beam radiation therapy is used to treat localized metastases causing symptoms, most commonly painful bone metastases. Techniques that focus the radiation such as stereotactic radiotherapy (SBRT or SABR, sometimes called gamma knife or CyberKnife) and proton therapy can be used for localized tumors deeper in the body, most commonly paragangliomas or pheochromocytoma, and also for liver metastases not amenable to other forms of liver-directed therapy.

LIVER-DIRECTED THERAPY (LDT)

Ninety percent of NET patients with malignant disease will develop liver metastases. These metastases are a leading cause of eventual death due to liver failure. Therefore, LDTs are commonly used in the setting of liver dominant disease. Embolization is a liver-directed therapy where a catheter is placed into the hepatic artery to the liver, which is selectively embolized in the areas of metastatic deposit. This technique is based on the fact that tumors in the liver derive their blood supply from the hepatic arterial system, while the normal liver tissue receives most of its blood from the portal venous system.



MRI of the liver before and after Chemoembolization. The large white tumors (blue arrows) are markedly reduced in size after TACE.

BLAND EMBOLIZATION cuts off the arterial supply to the tumors by the introduction of oil, gelatin, or tiny particles into the selected branch of the hepatic artery.

CHEMOEMBOLIZATION (transarterial chemoembolization, TACE) utilizes one or more chemotherapeutic drugs added to the embolic material, causing the drugs to be trapped in the tumors at a high concentration.

RADIOEMBOLIZATION utilizes microscopic resin or glass particles with yttrium 90 (Y90), a beta-radioisotope which emits radiation that can travel only a few millimeters inside the body, radiating the tumors specifically.

Current guidelines recommend embolization therapy for liver metastases that are symptomatic or progressive despite octreotide or lanreotide therapy, without recommendation among the available embolization techniques. On average, embolization results in control of hormonal symptoms in 85% of patients, substantial reduction in tumor burden in 55%-60%, and prevents disease progression in the liver for one and a half years.

NEUROENDOCRINE TUMORS

SPECIAL CONSIDERATIONS

CARCINOID HEART DISEASE

Carcinoid heart disease (CaHD) is a consequence of the effects of excess hormone production (usually from liver metastases of small intestinal NET). Serotonin in high concentrations entering the heart from the liver causes fibrosis, particularly in the tricuspid and pulmonic valves, resulting in right-sided heart failure. **Fifty to seventy percent of patients with carcinoid syndrome (CS) will develop CaHD in time.** Therefore, every patient with CS should have an echocardiogram performed by an experienced echocardiographer. Progressive CaHD has a high morbidity and should be considered life-threatening requiring surgical valve replacement. The most appropriate sequencing of surgical procedures should be considered carefully within a multidisciplinary team.

LUNG NETS

Lung NETs represent at least 25% of all NETs. **Small cell lung cancer, a type of neuroendocrine carcinoma, accounts for approximately 20% of lung cancers.** Lower grade carcinoid tumors only make up about 2% of all lung cancer. Diagnosis is confirmed by tissue sampling either by needle biopsy or surgical resection. Increasing incidence is likely multifactorial, based on better awareness and improved imaging modalities. Traditionally the classification of lung NETs has been aligned to lung carcinomas and not to neuroendocrine tumors, thus the care of these patients has fallen to thoracic surgeons and oncologists rather than to NET specialists.

The primary treatment is surgical resection. Following the principles of surgery for resection for non-small cell lung cancer, however, parenchymal sparing approaches are sometimes used in typical carcinoids. Lymph node examination is considered the standard of care. There are no prospective data showing that adjuvant treatment for pulmonary carcinoids produces a survival benefit. Patients are generally followed with physical exams and chest CTs postoperatively. Disease may recur many years later.

The only FDA-approved treatment for advanced disease (RADIANT 4 trial) is the mTOR inhibitor everolimus (AFINITOR®). Other options for therapy include somatostatin analogs (octreotide LAR and lanreotide), PRRT, and CAPTEM. Other options for advanced disease may also follow that of gastroenteropancreatic NETs, including liver directed therapy and cytoreductive surgery.

POST-TREATMENT FOLLOW-UP

Despite its reputation as an indolent disease, NETs can be 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 with subsequent 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.

NEUROENDOCRINE TUMORS **PHYSICIAN/PATIENT RELATIONSHIP**

MULTIDISCIPLINARY TEAM APPROACH

Neuroendocrine tumors may present a broad range of disease manifestations in primary site, grade, stage and systemic secretions. The NET patient does not have to look very far to learn that NETs are rare and that the experience level of the treating physician is very important. This is emphasized in nearly every patient online site and support group. Experience in the treatment and care of these patients is hugely important for best practices and a patient's confidence in care. **The importance of a multidisciplinary care team cannot be overstated.**

There are many guidelines in place such as those from NCCN, NANETS and ENETS that can help practitioners better understand the disease pathways to consider in the surveillance, treatment and management of the disease. Physicians who are not highly experienced with NETs may effectively manage NET patient care by engaging a knowledgeable team, having a commitment to being current in the field, and seeking consultation when appropriate. It is important to be forthcoming with patients regarding personal experience and to express the readiness to research on patients' behalf. Physicians are encouraged to reach out for guidance and collaboration to their closest large academic center that has an interest in NETs or a regional expert physician. A willingness to engage others will reassure patients, promote a trusting relationship and ensure that the optimum management plan is designed.

Management of these patients is complex. Treatment by a multidisciplinary team may include radiologists, gastroenterologists, medical oncologists, endocrinologists, cardiologists, nuclear medicine specialists and surgeons. This can create questions about who is truly managing the NET patient's care. Without established lines of communication, the multiple points of care can be overwhelming to patients who may start to feel lost in the system and unsure of who governs what. It is important to establish who ultimately serves as "quarterback" of the multidisciplinary team. That physician will then take the lead and help coordinate with the patient how to best approach



management and treatment. This will allow patients to feel more secure that someone is leading the charge of their care. This is especially important when it pertains to decisions regarding the proper sequencing of multiple diagnostic and therapeutic interventions.

Treating the NET patient can involve challenges that go well beyond treatment decisions. Patients often interact with the medical system for years before a correct diagnosis is made. This can result in patients presenting with greatly impaired quality of life and with significant trust issues in medical systems and practitioners. Couple this with a rare diagnosis that is hard to understand, and the situation becomes confusing and overwhelming for patients and their families. Understanding and attending to these issues can help guide physician strategies for a successful initial consultation.



OPEN COMMUNICATION AND TRUST

NET patients with indolent disease will be followed over many years, even decades. Trust and open communication will help when addressing the medical issues that emerge during this period, which may be varied and unexpected. NETs are one of a few tumor types that need to be managed not only for control of tumor bulk but also for control of excess functional hormone production and secretion. Additionally, as with many long-term, chronic diseases, there may be quality of life issues related to their illness, such as: insurance and financial issues, psychological and emotional distress, caregiving and social network deficiencies, and palliative care needs. These will often necessitate the involvement of ancillary services and/or referrals during the course of treatment. As with all chronic disease, other health issues NOT related to NETs may emerge that need attention.

Over the course of the treatment period, patients will be making treatment decisions that are often less than clear-cut and for which they will rely heavily on the judgment of their physician. Establishing a trusting relationship is imperative in NET patient care, and establishing effective communication is a cornerstone of that trust.

TIPS ON BUILDING COMMUNICATION AND TRUST

- Allow extra time for the initial visit and a comprehensive history to determine the extent of the issues and evaluation of functional disease.
- Provide clear directions for how to communicate with the office and practitioner between appointments for questions, scheduling, prescriptions, etc., and set expectations for timely responses.
- Allow ample time for explanation of the disease and what is being discussed as well as patient questions. Consider having the patient work more closely with advanced practice providers and nurses to give them ample time to discuss their symptoms and concerns.
- Ask what the patient understands about what you have covered in the appointment so you can tell if the patient has comprehended what you have spoken about. A nervous or stressed patient may have great difficulty remembering what has been said. Guide patients and their families to trusted resources and provide supportive materials for patient and families to review at home. It is often helpful if the patient is accompanied by a family member or a friend at appointments.
- Regularly ask if patients have any concerns that have not been addressed, and provide a safe environment and receptive demeanor to elicit concerns regarding sensitive subjects. Excess hormones can create embarrassing issues that may be uncomfortable to discuss; these can be addressed with proper intervention. Encourage patients to share their concerns/issues even if they are unsure of the relation to their disease.
- Treatment paradigms can differ dramatically from patient to patient depending on many things. Be honest about what is known and not known about NETs and the efficacies of specific treatments. This helps establish reasonable expectations of care and trust. It is important to take time to explain why certain treatments and interventions are offered or not suitable at each point of care for the NET patient. Answer questions as fully as possible and offer to further investigate unknowns. Facilitate consultations and second opinions as appropriate. Help patients weigh the risks and benefits of treatments.



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RESOURCES

GUIDELINES

ASCO Patient-Clinician Communication Guideline

<https://connection.asco.org/blogs/asco-patient-clinician-communication-guideline-fostering-relationship-centered-care>

European Neuroendocrine Tumor Society (ENETS) Guidelines

https://www.enets.org/enets_guidelines.html

National Comprehensive Cancer Network Guidelines (as of March 2019)

https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

National Comprehensive Cancer Network NET Guidelines for Patients (2018)

<https://www.nccn.org/patients/guidelines/neuroendocrine/index.html>

North American Neuroendocrine Tumor Society (NANETS) Guidelines

<https://nanets.net/net-guidelines-library>

NET VITALS TOOL *for patients to track their NET care*

<https://www.lacnets.org/netvitals/>

ORGANIZATIONS PROVIDING INFORMATION AND ADVOCACY

The Carcinoid Cancer Foundation

<https://www.carcinoid.org/>

Los Angeles Carcinoid Neuroendocrine Tumor Society

<https://www.lacnets.org/>

Neuroendocrine Cancer Awareness Network

<https://www.netcancerawareness.org/>

Neuroendocrine Tumor Research Foundation

<https://netrf.org/>

Northern California CarciNET Community

<https://norcalcarcinet.org/>

CO-PAY ASSISTANCE PROGRAMS

Advanced Accelerator Applications, a Novartis Company— LUTATHERA®

<https://aaapatientconnect.com/cap/>

Ipsen— SOMATULINE® DEPOT

<https://www.ipsencares.com/somatuline-patient-support>

Lexicon Pharmaceuticals— XERMELO®

<https://www.xermelo.com/xermelo-cost-assistance>

Novartis— AFINITOR® & SANDOSTATIN®

<https://www.copay.novartisoncology.com/>

Note: These are working links at the time of publication and may become outdated before the next print edition of the Primer.

NOTES



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