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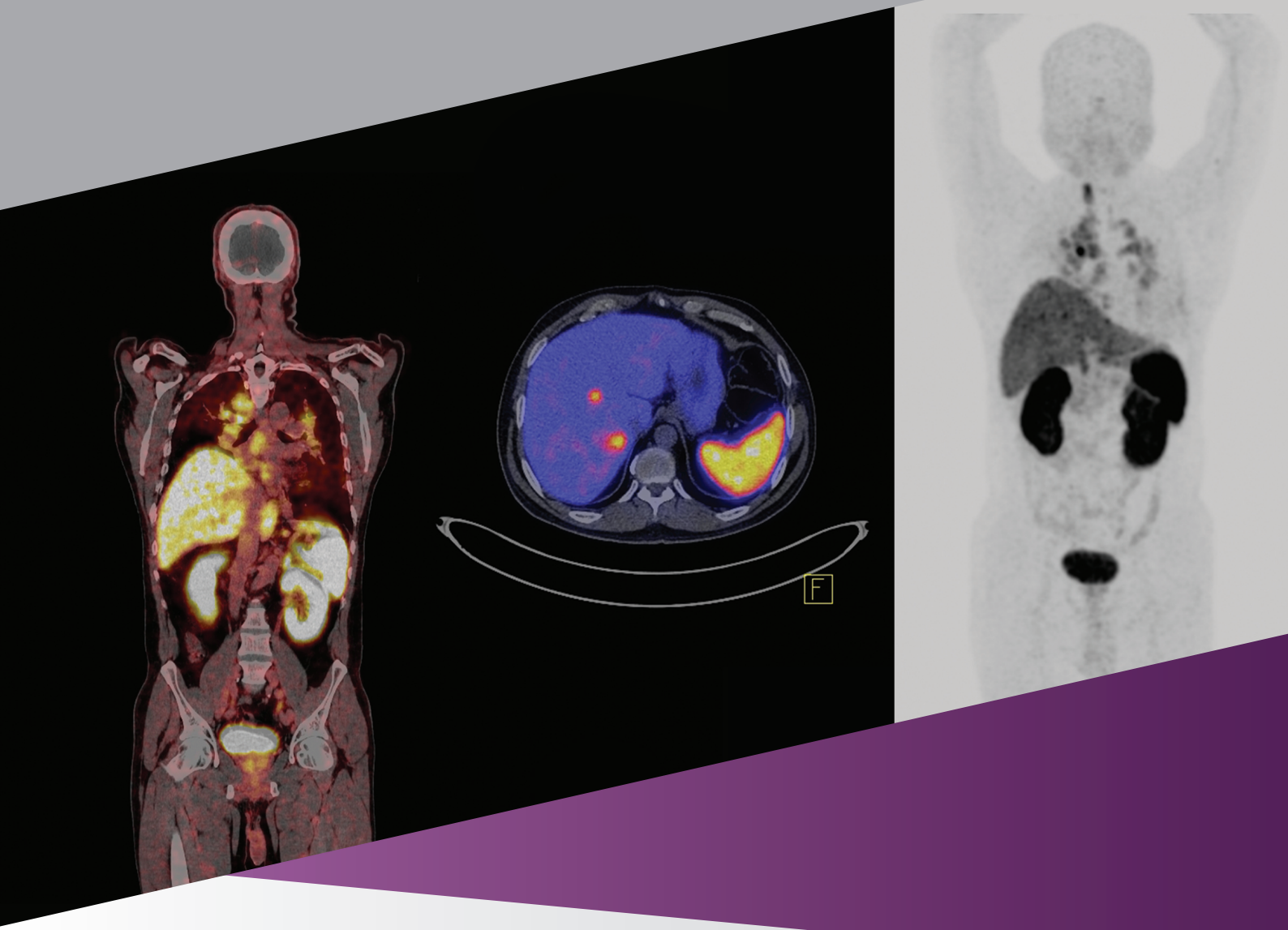
Neuroendocrine Tumor Diagnosis and Management



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Diagnosis and Management: The Role of ^{68}Ga-DOTATATE PET/CT

Neuroendocrine Tumors were first described in 1907 by Oberndorfer as small tumors of the intestine that he referred to using the German diminutive for cancer, Karzinoid, and thereby mistakenly implying a benign tumor. It is now apparent that this class of tumors, Neuroendocrine Tumors, exhibit a wide range of malignancy, are ubiquitous, rapidly increasing in incidence and have a greater prevalence in the gut than all other neoplasia, except for colon cancer. They have in the past been considered rare and were overall little understood as scientific and clinical attention and research sources were mostly focused on adenocarcinoma; however, based on Dasari et al. there is a 6.4 fold increase in age adjusted incidence of these Tumors from 1973 till 2012.

Neuroendocrine tumors are most commonly arising in the gastroenteropancreatic (GEP) tract and lungs.

A unique feature of these tumors is overexpression of somatostatin receptors (SSTRs) on their cell membrane, particularly type 2. Hence, SSTR-based ^{68}Ga-tetraazacyclododecatetraacetic acid (DOTA)-peptide PET/CT is an exciting imaging modality with significant advantages over conventional imaging modalities in diagnosis and management of NETs.

Molecular and Cellular Biology:

Gastroenteropancreatic neuroendocrine tumors (GEP) are now known as neuroendocrine neoplasms (NENs) and are derived from neuroendocrine cells in the pancreas and GI tract which themselves are derived from local tissue specific stem cells, probably through a committed precursor cell.

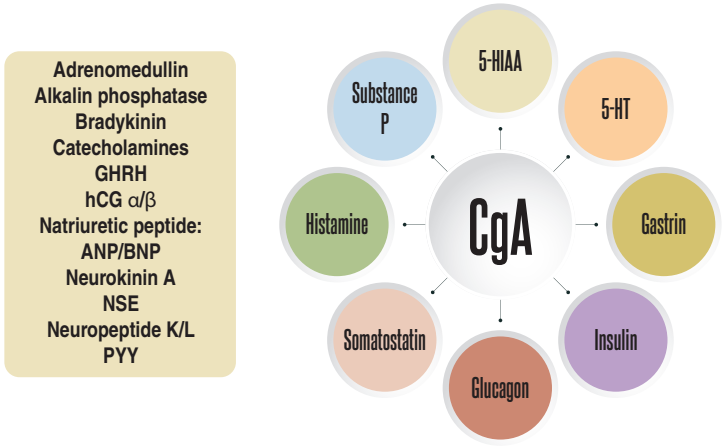
The majority of lesions (> 95%) are sporadic. Others, notably some gastric and pancreatic types are related to genetic defects, such as multiple endocrine neoplasia type 1 (MEN1), neurofibromatosis (NF-1), von Hipple Lindau (VHL) or tuberous sclerosis (TSC).

Overall, there are at least 13 different neuroendocrine cell types, distributed in the gastrointestinal tract and four in the pancreas with distinct anatomical localization and secretory products.

Cell type	Localization	Products
(D)δ	Entire GI tract	Somatostatin
Enterochromaffin (EC)	Entire GI tract	Somatostatin/Substance P/Guanylin/ Melatonin
Enterochromaffin-like (ECL)	Gastric Fundus	Histamine
Gastrin (G)	Gastric antrim and duodenum	Gastrin
Gherlin (Gr)	Entire GI tract	Gherlin
I	Duodenum	CCK
K	Duodenum/Jejunum	GIP
L	Small Intestine	GLP-1/PYY/NPY
Motilin (M)	Duodenum	Motilin
Nerotensin (N)	Small Intestine	Neurotensin
Serotonin (S)	Duodenum	Secretin
Vasoactive Intestinal peptide (VIP)	Entire GI tract	VIP
X	Stomach: Fundus and antrum	Amylin
β	Pancreas	Insulin
α	Pancreas	Glucagon
δ	Pancreas	Somatostatin
PP	Pancreas	PP

Although diverse in location, neuroendocrine cells share a number of common features, including:

1. Linear derivation (largely neuroendocrine 3 expressing secretory progenitor cells)
2. Production of specific proteins (e.g., chromogranin A [Cg A], involved in secretory granule formation, maturation and exocytosis)



Gastroenteropancreatic neoplasm biomarkers.

3. Transport (vesicular monoamine transporters-VMAT1 and VMAT2)
4. Amine synthesis through specific rate limiting enzymes (histamine and histidine decarboxylase in gastric ECL cells or serotonin and tryptophan hydroxylase in EC cells and amine uptake and decarboxylation (APUD))
5. Electron dense secretory granules (readily visible by electron microscopy)
6. Calcium and ERK1/2 signaling pathways for secretion
7. MAPK pathways for growth factor (e.g gastrin/TGF) mediated proliferation
8. ***Inhibitory receptors that can be targeted, for example somatostatin receptors***

The majority of these cell types can transform into tumors; which based on their origin, exhibit a wide range of clinical behavior that ranges from indolent (like gastric type 1 tumor or insulinomas) to highly aggressive (eg. glucagonomas and colon NET).

Histologic Classification and Staging of Neuroendocrine Tumors:

Neuroendocrine tumors are generally sub-classified by the site of origin, stage and histologic classification.

Histologic Classification:

Histologically, neuroendocrine tumors are classified based on tumor differentiation and tumor grade (G 1-3) and most of them fall into 3-4 broad histologic categories:

- Well differentiated; low grade (G1)
- Well differentiated; intermediate grade (G2)
- Poorly differentiated; high grade (G3)

And a forth category for pancreatic neuroendocrine tumors; well differentiated, high grade (G3).

Neuroendocrine Neoplasm Classification Systems:

The World Health Organization (WHO) uses mitotic count and the level of the nuclear protein Ki-67, which is associated with cellular proliferation, to classify GEP neuroendocrine tumors. NEN of the lungs, also called pulmonary carcinoids, are classified according to their mitotic count rate and the presence of necrosis. In 2010, The WHO updated its classification of GEP NENs. Pancreatic NENs are classified into three grading subgroups on the basis of mitotic activity and Ki-67 index. Regardless of size and anatomic extent

of the tumor, G1 and G2 NENs with well differentiated morphology were designated as NETs; G3 NENs were poorly differentiated neuroendocrine carcinoma (NECs) of small or large cell type.
Poorly differentiated GEP NENs show poorer outcome than well differentiated tumors. Poorly differentiated NENs respond to Cisplatin in more than 50% of cases versus less than 15% of well differentiated tumors. The new WHO classification, NEC are further divided into well-differentiated G3 NETs and poorly differentiated NECs on the basis of Ki-67 index and concordance between mitotic count and Ki-67 index.

Background to the Updates in the 2017 WHO Grading System:

Ambiguity of Grade 3 NEC in the 2010 WHO Grading System

The 2010 WHO classification categorizes NEN as a NET grade 1, NET grade 2, and NEC grade 3. In general, a well-differentiated NEN is composed of cells showing minimal to moderate atypia, lacks necrosis, expresses general markers of neuroendocrine differentiation, i.e., diffuse and intense synaptophysin or chromogranin A staining, and produces hormones. In contrast, poorly differentiated NEN is composed of highly atypical small cells or cells of large to intermediate size that express general markers of neuroendocrine differentiation, i.e., faint synaptophysin or chromogranin A staining. The histologic grading is based on the Ki-67 index or mitotic index that should be counted in tumor hot spots. Ki-67 is an excellent marker of cell proliferation. The fraction of Ki-67-positive tumor cells (the Ki-67 labeling index) is often correlated with the clinical course of cancer and its prognosis. If there is a discrepancy between the Ki-67 index and the mitotic index, the higher grade should be used.
In the 2010 WHO grading system, there was confusion regarding the discrepancy between grade and differentiation. “Differentiation” refers to the morphologic resemblance of the tumor cells to islets of Langerhans. In contrast, “grade” refers to the aggressiveness of the tumor cells in terms of their potential for rapid tumor growth and spread. Based on the definition in the 2010 WHO classification, it was possible that morphologically well-differentiated NETs could show a high Ki-67 level and be technically classified as grade 3 NEC. These well differentiated NETs, which are technically classified as grade 3 NEC, may not be sensitive to the chemotherapy regimen used in poorly differentiated grade 3 NEC. This finding suggested that the definition of grade 3 NEC based simply on the Ki-67 level and/or mitotic index was too broad to distinguish the differentiation and grade, and could lead to inappropriate treatment and an unsatisfactory clinical outcome.

The WHO grading system was revised in 2017 and the above-mentioned issues have been reflected in the changes as follows:

2010Classification:

WHO 2010	Mitosis/10 HPF	Ki-67 index
Well differentiated NENs		
NET grade1	**< 2**	**< 2**
NET grade 2	**3-20**	**2-20**
Poorly differentiated NENs		
NEC grade 3 Small cell type Large cell type	**>20**	**>20**
MANEC		

MANEC = mixed adenoneuroendocrine carcinoma

2017 Classification:

WHO 2017	Mitosis/10 HPF	Ki-67 index
Well differentiated NENs		
NET grade1	**< 2**	**< 3**
NET grade 2	**2-20**	**3-20**
NET grade 3	**>20**	**>20**
Poorly differentiated NENs		
NEC grade 3 Small cell type Large cell type	**>20**	**>20**
MiNEN		

MiNEN = mixed endocrine non-endocrine neoplasm, ***NEC*** = neuroendocrine carcinoma, ***NEN*** = neuroendocrine neoplasm, ***NET*** = neuroendocrine tumor, ***WHO = World Health Organization***

MiNENs may have non-endocrine component other than adenocarcinoma, e.g., squamous cell carcinoma or acinar cell carcinoma. To qualify as MiNEN, each component must be at least 30%.

The 2017 American Joint Cancer Committee classification (AJCC 2017) adopts such a classification for all digestive sites.

Background to the Updates in the 8th AJCC Staging System:

The WHO 2010 classification recommended use of the AJCC TNM staging system (7th edition) but also acknowledged use of the ENETS staging system proposed in 2006. Historically, the AJCC/Union for International Cancer Control (UICC) system has used the same staging system for NETs and exocrine pancreatic adenocarcinomas, while ENETS has developed a dedicated staging system for foregut NETs . In the 7th AJCC/UICC TNM staging, there is a difference in T staging between the AJCC/UICC and ENETS systems that may be a source of confusion for clinicians. Specifically, T3 is controversial in that it is defined in the AJCC/UICC system as peri-pancreatic tumor spread without major vascular invasion, but in the ENETS system, it is defined as tumor confined to the pancreas, greater than 4 cm in size, or invading the duodenum or bile duct. Recognition of peripancreatic tumor spread in pathological examinations is very complicated because the pancreas has irregular lobules and fatty degeneration/replacement, both of which may hamper the reproducibility of the criteria. Furthermore, the majority of NENs, even when small and/or well-differentiated, protrude from the surface of the pancreas, which may lead to false classification of a small and well-marginated tumor as T3 disease according to the AJCC/ UICC system, i.e., overestimation of T staging. In contrast, the ENETS system relies primarily on tumor size, which is a factor related to the malignant potential of NENs and is much more reproducible than peri-pancreatic fat infiltration. Indeed, a previous study of post-surgical NEN showed that the ENETS system was superior to the AJCC/UICC system as a predictor of patient survival. In the 7th AJCC/UICC staging system, there was significant overlap of survival between stage II and III disease, with survival in patients who had stage III disease being better in some time periods. The recently modified ENETS system has maintained the ENETS T, N, and M definitions and adopted the AJCC staging definitions, as well as demonstrated a significantly improved ability to stratify the survival outcome based on stage when compared with the 7th AJCC/UICC staging system. These inconsistencies and limitations are addressed in the 8thv edition of the AJCC/UICC staging system, which is now modified so as to be consistent with the ENETS system for well-differentiated NETs. The criterion of peri-pancreatic soft tissue invasion has been removed and NETs are now staged mainly on the basis of size.

Differences between AJCC/UICC TNM Staging System and ENET staging System (For well-differentiated neuroendocrine tumors of the pancreas):

T stage	7th AJCC/UICC	ENETS	8TH AJCC/UICC
T1	Confined to the pancreas, < 2 cm	Confined to pancreas, < 2 cm	Confined to pancreas, < 2 cm
T2	Confined to pancreas, > 2 cm	Confined to pancreas, 2-4 cm	Confined to pancreas, 2-4 cm
T3	Peri-pancreatic spread; without major vascular invasion	Confined to pancreas, >4cm, or invades duodenum or bile duct	Confined to pancreas, >4 cm or invades duodenum or bile duct
T4	Tumor invades celiac axis or superior mesenteric artery	Invasion of adjacent organs or major vessels	Invasion of adjacent organs or major vessels

Confined to pancreas means there is no invasion of adjacent organs or wall of large vessels. Extension of tumor into peripancreatic adipose tissue is NOT basis for staging. AJCC = American Joint Committee on Cancer, ENETS = European Neuroendocrine Tumor Society, UICC = Union for International Cancer Control

Lung Neuroendocrine tumors:

In the 2015 WHO classification, neuroendocrine tumors of the lungs are categorized into small cell lung carcinoma (SCLC), large cell neuroendocrine carcinoma (LCNEC), typical and atypical carcinoids, and they are all malignant.

Term	Mitosis (/2mm2)	Necrosis	Ki-67 index
Carcinoid	< 2	No	< 5%
Atypical carcinoid	2-10	Focal	< 20%
Small cell NEC	>10	Yes	50-100%
Large cell NEC	>10	Yes	40-80%

Role of Diagnostic Imaging in NENs:

The localization of a NEN and the assessment of the extent of disease are two critical requirements to ensure optimal management. As a consequence, every effort should be undertaken to ensure accuracy and thereby facilitate the interface of the diagnostic and therapeutic components necessary for disease staging and application of appropriate therapeutic modalities.

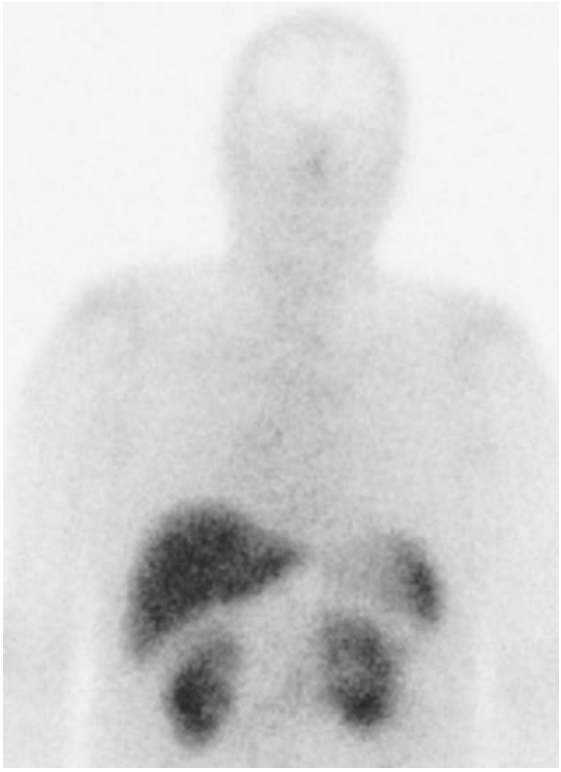
The aims of diagnostic imaging embrace a number of inter-related areas but primarily, this is used to lo-

calize the tumor lesion and define its relation to adjacent structures as well as to evaluate the extent of disease at both loco-regional and distant levels (staging) and to guide the patients for specific therapy. Diagnostic strategies that are available include morphologic modalities, such as CT, MRI, trans-abdominal ultrasound (US), endoscopic (EUS) and intra-operative US (IOUS) and selective angiography with or without hormonal sampling. Nuclear medicine imaging consists of ^{111}In-Pentreotide (Octreoscan), ^{123}I-MIBG or more recently PET with ^{68}Ga-labled octreotides, ^{18}F-DOPA and ^{11}C-hydroxytryptophan (^{11}C-HTP).

Functional imaging of neuroendocrine tumors:

Functional imaging of NETs exploits the fact that the vast majority express somatostatin receptors on their cell membrane. Somatostatin is a cyclic hormone expressed in the central and peripheral nervous system, inhibiting the release of hormones such as glucagon and insulin by binding to G-coupled somatostatin receptors. Five human somatostatin receptors (hSSTR1-5) have been identified, of which hSSTR2 is the most commonly expressed on NET cell membranes.

A number of synthetic peptides such as octreotide have somatostatin agonist activity through the mechanism of receptor binding and are used to treat NETs. In the early 1990s, a radiolabelled version of octreotide, indium-111-DTPA-DPhe1-octreotide (^{111}In-octreotide), which has a high affinity for hSSTR2 and hSSTR5, was introduced for somatostatin receptor imaging (SSRI). ^{111}In-octreotide is injected intravenously (iv) and whole-body images obtained four and 24 hours later, with additional single photon emission tomography (SPECT) over areas of interest. Physiological uptake is seen in the spleen, kidneys and liver, with minimal uptake in pituitary and thyroid glands. The bowel and gallbladder may accumulate tracer in late images and are major pitfalls in the search for gut primary or metastatic liver lesions.



Normal distribution of In-Octreotide

The largest body of experience with ^{111}In-octreotide is from the Rotterdam group which performed SSRI in over 1,000 patients with NETs. They demonstrated 100% sensitivity for gastrinoma and glucagonoma, 96% for carcinoid and 69% for insulinoma. Subsequently, ^{111}In-octreotide was established as the imaging method of choice for diagnosis and follow-up of NETs, aided by parallel developments in gamma camera hardware and a wider use of SPECT to improve image resolution.

Inevitably, cumulative experience of imaging with ^{111}In-octreotide showed several drawbacks adversely affecting its diagnostic accuracy. Despite the universal use of SPECT, image resolution was not adequate to pick up lesions smaller than 1 cm due to the inherent physical qualities of ^{111}In. This, coupled with the realization that the affinity of octreotide to hSSTR2 is limited, means that lesions adjacent to areas of physiological uptake such as the spleen and kidneys are difficult to detect. In addition, the two-day imaging protocol is inconvenient for both patients and doctors.

An alternative radiopharmaceutical, iodine-123 metaiodobenzylguanidine (^{123}I-mIBG) is also used in the detection of gastroenteric NETs that express the noradrenaline transporter. In addition to the imaging drawbacks listed above, however, it exhibits a lower sensitivity than ^{111}In-octreotide (49% vs 91%) and uptake may be compromised by drug interference.

PET/CT imaging of neuroendocrine tumors:

To overcome the limitations of SPECT radiopharmaceuticals, radionuclide NET imaging is now undertaken by hybrid PET/CT which offers higher spatial resolution and better anatomical localization. PET/CT imaging has revolutionized the management of cancer by improving resolution to approximately 5 mm, allowing detection of small lesions and by fusing functional data with simultaneous CT for accurate localization. PET/CT is currently an essential diagnostic and follow-up tool for a vast number of cancers, particularly lymphoma, melanoma, lung and colorectal cancer.

The first PET radiopharmaceutical to be used for detecting NETs was ***fluorine-18 fluorodeoxyglucose (^{18}F-FDG)***, which accumulates in lesions with high metabolic rates and glucose utilization.^{18}F-FDG was found to be useful in detecting NETs but is limited to the minority of tumors that are undifferentiated and behave aggressively. Several studies have shown that ^{18}F-FDG is more sensitive than ^{111}In-octreotide in the detection of poorly differentiated NETs but less sensitive for well-differentiated tumors.

Fluorine-18-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) has also been used in NET, based on its biochemical pathway in dopamine synthesis, uptake being proportional to tumor cell metabolism. Hoegerle et al found a high (65%) sensitivity for ^{18}F-DOPA in detecting NETs compared with 29% sensitivity for ^{18}F-FDG and 57% sensitivity for ^{111}In-octreotide. However, ^{18}F-DOPA has a major drawback of physiological uptake in the pancreas, making it less sensitive for the detection of small pancreatic lesions. It is also difficult and expensive to produce, and remains a research tool in the UK.

Carbon-11-hydroxytryptophan (^{11}C-5-HTP) targets the serotonin production pathway and was shown to be superior to ^{111}In-octreotide, CT and ^{18}F-DOPA in the detection of NETs. Unfortunately, the short half-life of ^{11}C (20 min) restricts its use to facilities with an on-site cyclotron for radioisotope production.

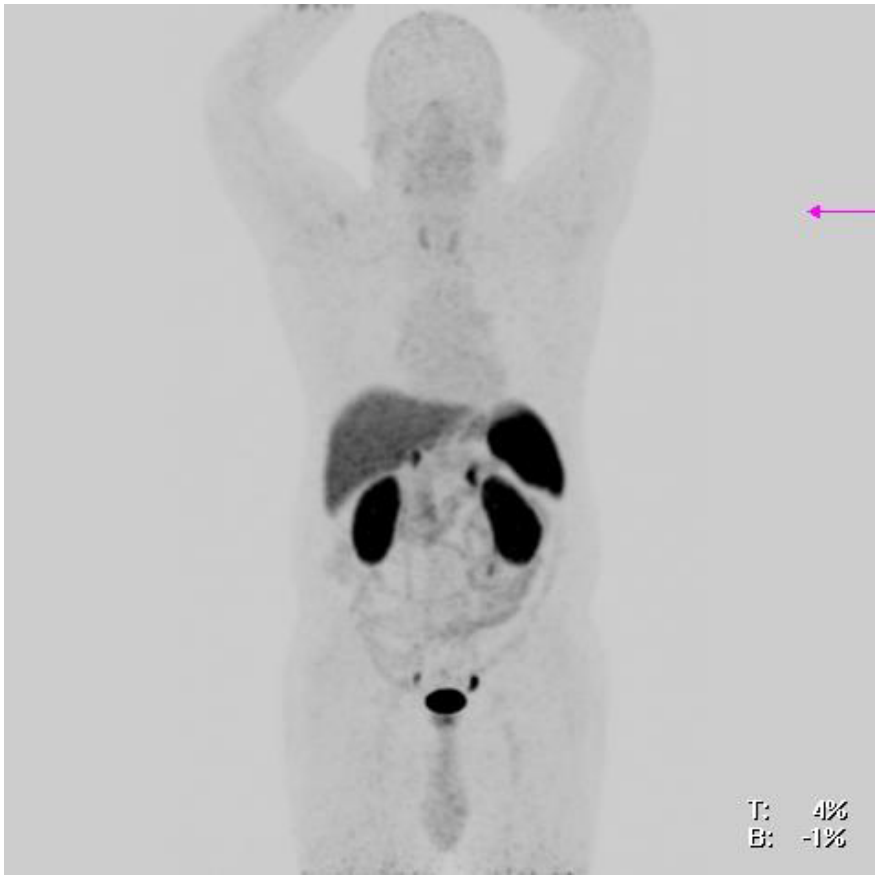
PET/CT with Gallium-68 peptides

The success in imaging NETs with PET/CT reached its climax with the introduction of gallium-68-peptides in 2001. The two major factors contributing to this breakthrough were the development of a gallium-68 (^{68}Ga) generator and the introduction of new somatostatin agonist peptides with very high affinity to hSSTR. The small size of the ^{68}Ga generator eliminates the need for a costly cyclotron facility, while its long half-life of 270 days ensures a daily supply of ^{68}Ga for at least one year. This provided an opportunity for departments with standard radiopharmacies to exploit this advanced imaging approach.

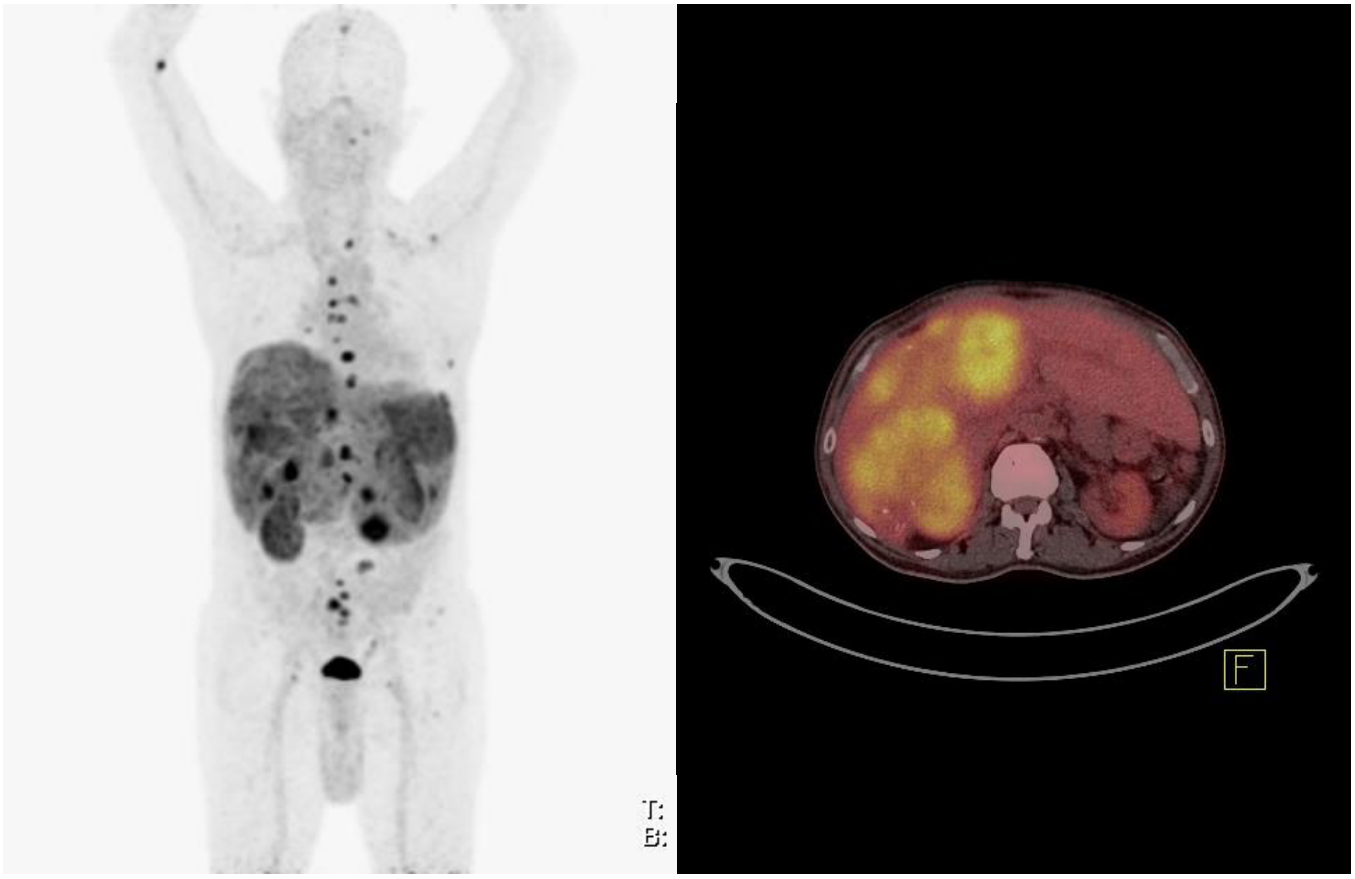
Different ^{68}Ga-labelled peptides (^{68}Ga-Dotatate,^{68}Ga-Dotatoc and ^{68}Ga-Dotanoc) were soon introduced into clinical practice and proved to have very similar efficacies. The images are of high clarity and sensitivity due to early washout of surplus peptides from the body, allowing a short imaging time of about 25 min. NETs that are easily missed or appear equivocal on ^{111}In-octreotide show clearly on ^{68}Ga-Dotatate. In a study by Gabriel et al on 84 patients with NETs comparing ^{68}Ga-Dotatoc, ^{111}In-octreotide and CT, ^{68}Ga-Dotatoc showed 97% sensitivity, 92% specificity and 96% accuracy and had a major impact on management.

^{68}Ga-peptides are also useful in neuroectodermal tumors; a group of related conditions that includes phaeochromocytoma and paraganglioma, which also demonstrate hSSTR on their cell membrane.

One of the interesting aspects of ^{68}Ga-peptides PET/CT imaging is their ability to detect early bone involvement not discernible using CT or MRI. Early imaging with ^{68}Ga-peptides could therefore have a significant positive impact on NET staging and consequent management.



Physiologic Distribution of Ga-DOTATATE



Metastatic NET with unknown primary (possibly from small intestine)

Appropriate Use of Ga PET/CT in neuroendocrine tumors Based on NCCN Guideline versoin 1.2019:

A: *Duedonal*, *Jejunal*, *Ileal* and ***colon*** NEN: Multi-phasic contrast enhanced abdominal and pelvic CT or MRI;

When appropriate, Somatostatin-based imaging (i.e ^{68}Ga-DOTATATE PET/CT or PET/MRI or Somatostatin receptor scintigraphy)

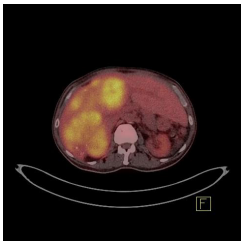
B: *Appendix*: When the primary tumor is > 2 cm or there is evidence of incomplete resection; including nodes or margins: Multi-phasic contrast enhanced abdominal and pelvic CT or MRI;
When appropriate Somatostatin-based imaging (i.e ^{68}Ga-DOTATATE PET/CT or PET/MRI or Somatostatin receptor scintigraphy)

C: *Rectal*: T2-T4: *Colonoscopy, Multi-phasic contrast-enhanced CT scan or MRI is recommended; If appropriate Somatostatin-based imaging (i.e ^{68}Ga-DOTATATE; PET/CT, PET/MRI or Somatostatin receptor scintigraphy)*

D: *Gastric:*

a. Hypergastrinemia type 2 (Zollinger Ellison, No atrophic gastritis, low gastric PH)

b. Normal Gastrin /Type 3; which are unifocal, sporadic and unassociated with either atrophic gastritis or Zollinger Ellison syndrome



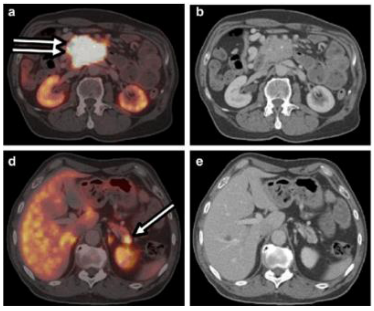
EUS, abdominoplevic CT or MRI and ***Somatostatin-based imaging is recommended.***

E: *Bronchopulmonary*: Chest/Mediastinal CT with contrast and abdominal multiphasic CT or MRI is recommended.

However, Somatostatin receptor imaging (i.e ^{68}Ga-DOTATATE PET/CT ,PET/MRI or Somatostatin receptor scintigraphy should be considered.

F: *Pancreatic tumors:*

A- ***Non-functional pancreatic NENs:*** Abdominal multi-phasic CT/MRI is recommended. Somatostatin receptor based imaging (i.e ^{68}Ga-DOTATATE PET/CT ,PET/MRI or Somatostatin receptor scintigraphy should be considered.



B- ***Gastrinoma:*** In appropriate cases, Somatostatin receptor imaging should be considered.

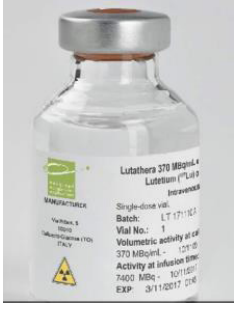
C- ***Insulinoma:*** In appropriate cases, Somatostatin receptor imaging should be considered.

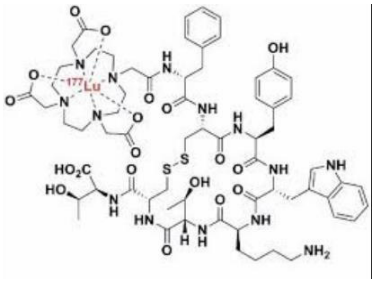
D- ***Glucagonoma:*** In appropriate cases, Somatostatin receptor imaging should be considered.

E- ***Vipoma:*** In appropriate cases, Somatostatin receptor imaging should be considered.

G: *Biopsy proven neuroendocrine of unknown primary:* Somatostatin receptor imaging should be considered during initial work-up. FDG PET/CT should be considered in poorly differentiated neuroendocrine carcinomas.

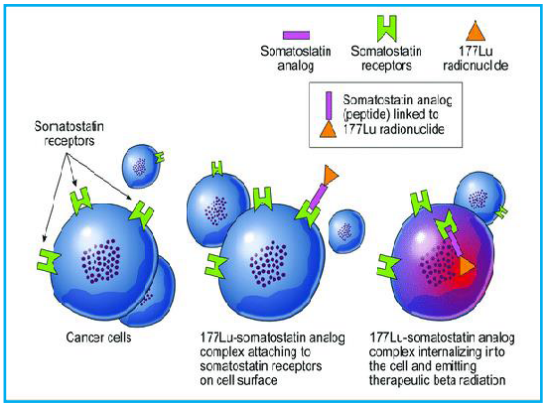
H: Management of Advanced Loco-regional Disease and/ or Metastatic Disease: Multiphasic abdominopelvic CT/MRI + chest CT scan with or without contrast based on clinical indication as well as ***Somatostatin-based imaging (i.e ^{68}Ga-DOTATATE PET/CT or PET/MRI or Somatostatin receptor scintigraphy and biochemical evaluation as clinically indicated***





PRRNT

PRRNT with ^{177}Lu-DOTATATE was approved by FDA in January 2018 for the treatment of adults with unresectable, low-to-intermediate grade locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors. NCCN recommends considering PRRNtT with ^{177}Lu-DOTATATE as a treatment option for some patients with advanced and/or metastatic GI tract, bronchopulmonary and thymic neuroendocrine tumors that are somatostatin receptor positive with imaging.



Treatment with ^{177}Lu-DOTATATE is recommended for patients with un-resectable GI neuroendocrine tumors that have progressed if there was somatostatin positive receptor imaging (category 1 for mid-gut tumors).

Treatment with Lu-DOTATATE may also be considered for patients with bronchopulmonary or thymic neuroendocrine disease and disease progression despite Octreotide or Lanreotide consumption.

Principles of Peptide Receptor Radionuclide Therapy (PRRNT) WITH 177Lu-DOTATATE:

Eligibility Criteria:

1. ***Low to intermediate grade Neuroendocrine tumors (Ki67 < 20%)***
2. ***Somatostatin receptor expression of NET as detected by Somatostatin receptor based imaging (means Ga-DOTATATE PET/CT or Octreotide SPECT)***
3. ***Adequate function of bone marrow, liver and kidneys***

PRRNT

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