Molecular Imaging and Neuroendocrine Tumors

SNMMI SOCIETY OF NUCLEAR MEDICINE & MOLECULAR IMAGING

What are neuroendocrine tumors?

A neuroendocrine tumor (NETs) occurs when cells of the body's neuroendocrine system grow in an uncontrolled, abnormal manner. Neuroendocrine cells have traits similar to nerve cells and to the hormone-producing cells of the endocrine glands. Neuroendocrine cells are located in organs throughout the body and perform specific functions, such as regulating air and blood flow and controlling the speed at which food is moved through the gastrointestinal tract.

NETs are relatively rare and develop most commonly in the lungs, appendix, small intestine, rectum, and pancreas. Many NETs start in the digestive tract, as it has more neuroendocrine cells than any other part of the body. Some tumors grow slowly while others can be very aggressive and spread to other parts of the body (metastasize), most often to the liver or bone.

NETs may secrete higher-than-normal amounts of hormones, which can cause conditions and symptoms including diabetes, flushing, and diarrhea. Because these symptoms resemble those of other diseases, such as irritable bowel syndrome (IBS) or Crohn's disease, they are often misdiagnosed. Special blood tests and imaging tools and sometimes specialized pathologists are necessary to help accurately diagnose these tumors.

There are several types of NETs, including Gastro Intestinal (GI NETS), Pancreatic (PNETS), Lung NETS, medullary thyroid carcinomas (MTCs), pheochromocytomas, and neuroendocrine carcinomas of the skin (Merkel Cell Cancer). Treatment depends on the type of tumor and its location, whether it produces excess hormones, how aggressive it is, and whether it has spread. Advances in treatment have improved the length of survival for patients with NETs.

While relatively rare, NETs are the second most common of all GI cancers (colon cancer is the most common), because many people continue to live with the disease. Over the last several decades the incidence (number of new diagnoses) has also been rising, which might be due to increased awareness, improved diagnostic tools, or a change in definition.

What is molecular imaging?

Molecular imaging is a type of medical imaging that provides detailed pictures of what is happening inside the body at the molecular or cellular level (e.g. PET scans). Where other diagnostic imaging procedures—such as x-rays, computed tomography (CT) and ultrasound— predominantly offer anatomical pictures, molecular imaging allows physicians to see how the body is functioning and to measure its chemical and biological processes.

Molecular imaging offers unique insights into the human body that enable physicians to personalize patient care. In terms of diagnosis, molecular imaging is able to:

- provide information about the molecular characteristics that is unattainable with other imaging technologies or that would require more invasive procedures such as biopsy or surgery
- identify disease in its earliest stages and determine the exact location of a tumor, by detecting small volumes of disease before symptoms occur or abnormalities can be detected with other diagnostic tests or conventional imaging

As a tool for evaluating and managing the care of patients, molecular imaging studies help physicians:

- determine the extent or severity of the disease, including whether it has spread elsewhere in the body
- select the most effective therapy based on the unique biologic characteristics of the patient and the molecular properties of a tumor or other disease
- determine a patient's response to specific drugs
- accurately assess the effectiveness of a treatment regimen
- adapt treatment plans in response to changes in cellular activity
- assess disease progression
- identify recurrence of disease and help manage ongoing care

Molecular imaging procedures are noninvasive, safe, and painless.

How does molecular imaging work?

When disease occurs, the biochemical activity of cells begins to change. For example, some cancer cells multiply at a much faster rate and are more active than normal cells. Brain cells affected by dementia consume less energy than normal brain cells. Heart cells deprived of adequate blood flow begin to die.

As disease progresses, this abnormal cellular activity begins to affect body tissue and structures, causing anatomical changes that may not be seen on CT or MRI scans. For example, cancer cells may form a mass or tumor. With the loss of brain cells, overall brain volume may decrease or affected parts of the brain may appear different in density than the normal areas. Similarly, the heart muscle cells that are affected stop contracting and the overall heart function deteriorates.

Molecular imaging excels at detecting the cellular changes that occur early in the course of disease, often well before structural changes can be seen on CT and MR images.

Most molecular imaging procedures involve an imaging device and an imaging agent, or probe. A variety of imaging agents are used to visualize cellular activity, such as the chemical processes involved in metabolism, oxygen use, or blood flow. In nuclear medicine, which is a branch of molecular imaging, the imaging agent is a radiotracer, a compound that includes a radioactive atom, or isotope. Other molecular imaging modalities, such as optical imaging and molecular ultrasound, use a variety of different agents. Magnetic resonance (MR) spectroscopy is able to measure chemical levels in the body, without the use of an imaging agent.

Once the imaging agent is introduced into the body, it accumulates in a target organ or attaches to specific cells. The imaging device detects the imaging agent and creates pictures that show how it is distributed in the body. This distribution pattern helps physicians discern how well organs and tissues are functioning.

How is molecular imaging helping people with NETs?

A majority of NETs produce an abundance (called overexpression) of a specific cell feature called somatostatin receptors. Molecular imaging technologies use this cell feature to detect cancerous cells throughout the body and as a target for the delivery of therapy.

Physicians are using molecular imaging to:

- **diagnose and stage:** used to find NETS throughout the body. The patient is injected with a drug called octreotide — a synthetic form of the naturally occurring hormone somatostatin — that is chemically bound to a radioisotope, either indium-111, 68Ga-DOTATOC (NETSPOT) or 64CU Dotatate. The radioactive octreotide attaches to tumor cells that have somatostatin receptors and is detected by either a SPECT, PET/CT or PET/MR machine that creates pictures showing where the tumor cells are in the body. Nearly 90 percent of NETs can be identified with 68Ga-DOTATATE (NETSPOT), 68Ga-DOTATOC or 64Cu Dotatate which are tracers used with PET/CT or PET/MR machines.
- **deliver treatment:** radiopharmaceutical therapy (RPT) is a systemically administered, targeted therapy for cancer that delivers radiation at the cellular and molecular levels. In contrast to chemotherapy, wherein all proliferating cells are affected, RPT delivers radiation to only those cells that express cancer markers.

Protocols in the US do not change unless you are on a clinical trial. Local protocols may vary though, as to the radiopharmaceutical therapy (RPT) using ^{177}Lu or Y-90 or peptide (e.g. DOTATOC, DOTATATE), define number of treatments and dosage per treatment.

Peptide receptor radionuclide therapy (PRRT) is a highly targeted and effective form of RPT with minimal side effects for treating NETs with an abundance (or overexpression) of somatostatin receptors. In PRRT, the patient receives an intravenous injection of a drug such as octreotide that is chemically bound to (or radiolabeled with) a radioactive material, mainly lutetium-177. Other radiopharmaceuticals include yttrium-90, or indium-111. The radioactive octreotide attaches to somatostatin receptors on tumor cells, which are destroyed by the radiation.

In the US, Canada and European Union ^{177}Lu-Dotatate is approved for the treatment of neuroendocrine tumors. There are ongoing trials featuring other isotope, peptides and combinations with other therapies.

For detailed information on PRRT, go to: Fact Sheet: What is Peptide Receptor Radionuclide Therapy (PRRT)? - SNMMI

What are the advantages of molecular imaging technologies for people with NETs?

- localization of disease (identifying the source of the primary)
- accurate evaluation of the extent of disease
- evaluation of somatostatin receptors status prior to PRRT
- information complementary to anatomic imaging is provided
- In using PRRT, although rarely curative it has been shown to help relieve symptoms, shrink tumors, and slow the progression of the disease with minimal long-term side effects

Is nuclear imaging (PET or SPECT) safe?

Many medical procedures have side effects and risks; the same is true for nuclear medicine diagnostic tests such as PET (Positron Emission Tomography) and SPECT (Single Photon Emission Computerized Tomography). Each procedure takes a certain amount of radiation to perform

appropriately. Used in the right way for the right patient at the right time, nuclear medicine is very safe—the benefits of the procedure far outweigh the potential risks.

Is PRRT safe?

All medical therapies involve risks and can have both short- and long-term side effects. Please discuss with your treating physician the safety profile of PRRT treatments compared to other options you may be considering. For more of nuclear medicine and radiation go to, Radiation Safety Factsheet

Are molecular imaging technologies covered by insurance?

Check with your insurance company for specific information on your plan coverage.

What is the future of molecular imaging and NETs?

In January 2018, the Federal Drug Administration approved PRRT using ^{177}Lu-Dotatate, commercially known as Lutathera, for patients with NETS that are positive for the hormone receptor somatostatin, including GEP-NETs in the foregut, midgut, and hindgut. Currently there are several clinical trials that are evaluating the use of different peptides, isotopes and combinations to further enhance the efficacy of PRRT for neuroendocrine tumor patients.

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) has patient presentations regarding NETs on our website at http://www.snmmi.org/Patients/Videos/Content.aspx?ItemNumber=21804&navItemNumber=21816

For a more detailed understanding of the incidence and prevalence of NETS, please refer to Dasari, Arvind, Chan Shen, Daniel Halperin, Bo Zhao, Shouhao Zhou, Ying Xu, Tina Shih, and James C. Yao. "Trends in the Incidence, Prevalence, and Survival Outcomes in Patients with Neuroendocrine Tumors in the United States." JAMA Oncology (2017).

About SNMMI

The Society of Nuclear Medicine (SNMMI) is an international scientific and medical organization dedicated to raising public awareness about nuclear and molecular imaging and therapy and how they can help provide patients with the best health care possible. With more than 18,000 members, SNMMI has been a leader in unifying, advancing and optimizing nuclear medicine and molecular imaging since 1954.

The material presented in this pamphlet is for informational purposes only and is not intended as a substitute for discussions between you and your physician. Be sure to consult with your physician or the nuclear medicine department where the treatment will be performed if you want more information about this or other nuclear medicine procedures.