Images in GEP-NETs – Diagnosis and Staging

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Images are very important for the diagnosis and staging in neuroendocrine tumors. Diagnosis and staging are critical in order to prescribe the proper treatment. The developments of the last few years include radioactive labeled material to diagnose, stage, and lately to treat neuroendocrine tumors.

The SRS, i.e.: the Somatostatin Receptors Scintigraphy, called in Latin America Octreoscan, which in fact is a brand name by Mallinckrodt Medical, does nothing else than express the distribution of somatostatin receptors subtype 2 and 5 (ss5-2 and sst-5), not only in normal tissue but also in pathological tissue.

Somatostatin receptor expression cannot be obtained with morphological imaging. That is why in the last few years we are working with molecular imaging and medications.

It started in late 1980s with Eric Krenning, who used this molecule octreotate and now there are others not only labeled with indium but with technetium. This helps get an image of the distribution of these receptors in the whole body.

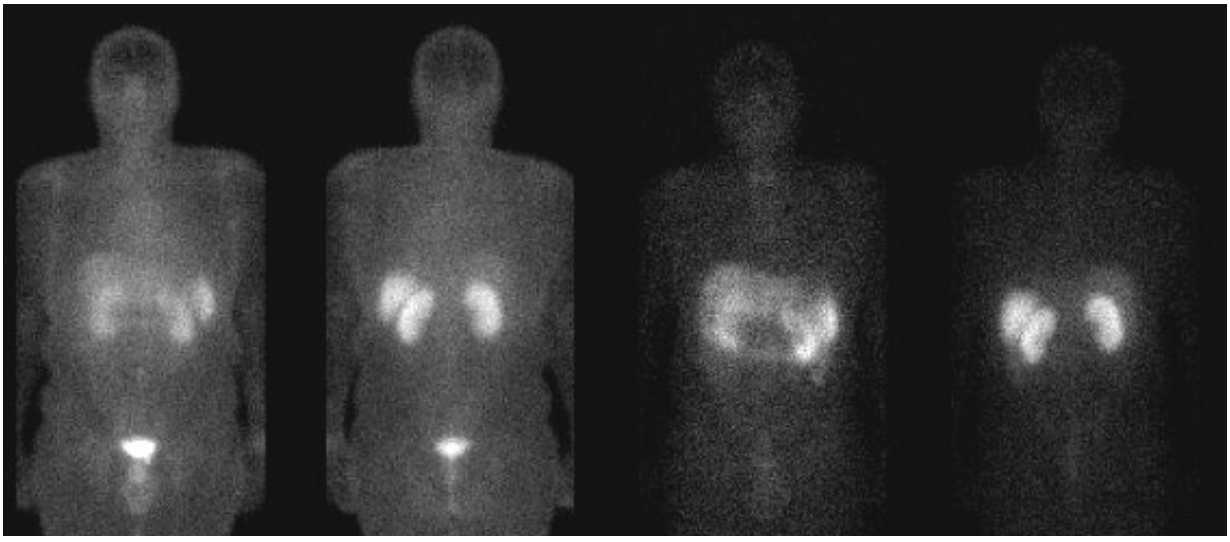
There are two technical things for clinicians and surgeons to be aware of. You can get planar and whole body images, but also tomographic images of this distribution.

Second, you have to withdraw unlabeled octreotide. Some of these patients are treated with somatostatin analogue due to symptoms or with the aim of tumor reduction. So you need to stop treatment for a short or a longer time, depending on the type of isotope used. For patients with severe symptoms, you can do the scanning without withdrawing the medication because probably there are enough receptor sites for everything, for labeled and unlabeled isotopes.

Just to give you an idea over whole-body distribution in a normal scan (Figure 1), you have normal concentrations in the liver, in the spleen, the kidneys because the excretion is done by these organs. Brazil has had a home-synthesized pentreotide for four years, In-Octreoscan. Here we have different views, axial, coronal, which will allow you to see the distribution. This scan shows even quite small tumors.

In the last few years, with specific peptides you can do much better than with CT or MRI. PET FDG is not the best way to get information about NET tumors, especially about slow-growing tumors, because they have a very low glucose metabolism. Depending on the type of tumor you have a different sensitivity. There is not a very good

Figure 1. *111 In-Octreoscan (Pentetreotide) Normal scintigraphic pattern Brazilian (IPEN-CNEN) pentreotide.*



correlation between in-vitro receptor status and what I call in-vivo receptor status of SRS images. It also depends on whether you are working with the edge or the center of the tumor. What pathologists do, is deal with a very small amount of tumor. If we can see the whole body, this would make a great difference for the patient. Tumor deposits as small as 6 mm can be seen with SPECT.

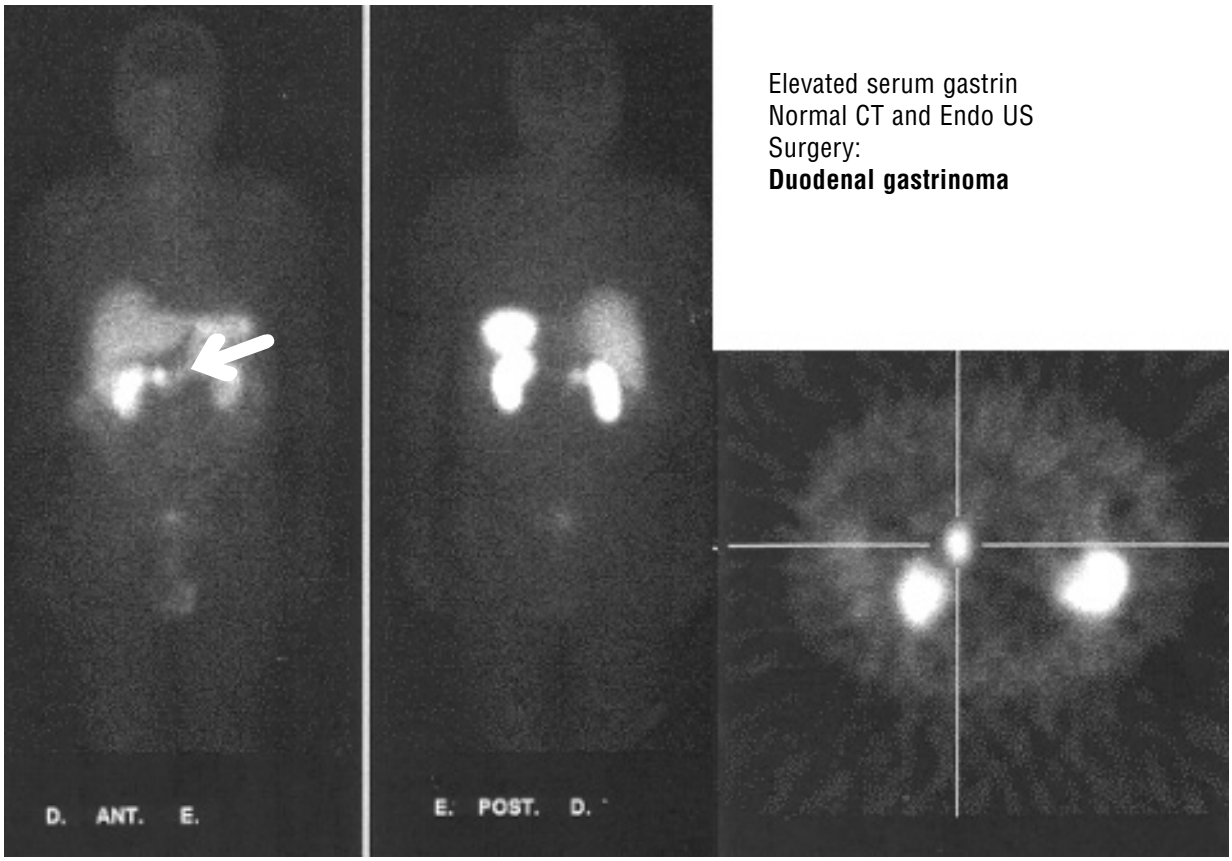
What is the role of SRS in clinical situations? Regarding foregut GEP-NET tumors, especially for those located in the respiratory tract and the stomach, SRS is not used to locate them and produce a diagnosis but rather endoscopy, bronchoscopy and CIMs are used. The real role for SRS is that it lets you study the whole body and produce the staging for the surgeon.

In duodenum and pancreatic tumors, again SRS is not used for location and diagnosis. Endoscopic US can see very small tumors, not only in the pancreas but also in the duodenum. Some conventional imaging methods can deliver a lot of information. The role of SRS is the detection of primary tumors when endo-US fails. These cases include pancreatic tail; depending on the size and shape of the pancreas it may be difficult to reach the area. This is also the case when dealing with duodenal-wall gastrinoma, where you cannot see small tumors from inside the tube. SRS is very size-depending. One third of small tumors, < 1cm, which cannot be seen by endoscopic US methods, can be seen by SRS.

Just an example of a patient with elevated gastrin normal CT, normal endo-US, who had a duodenal gastrinoma that can be seen here in this SPECT images (Figure 2), and also in the planar view. It was a duodenal-wall gastrinoma, confirmed at the time of surgery. You can see there is no other evidence of tumor. There is no need to have this patient scanned by MRI, CT or any other test because there is little probability that this study could show a false negative for this tumor.

Midgut is a different situation. The incidence is higher than for foregut or hindgut. Frequently you will find liver and adjacent lymph node metastasis. For the location and diagnosis of the primary tumor

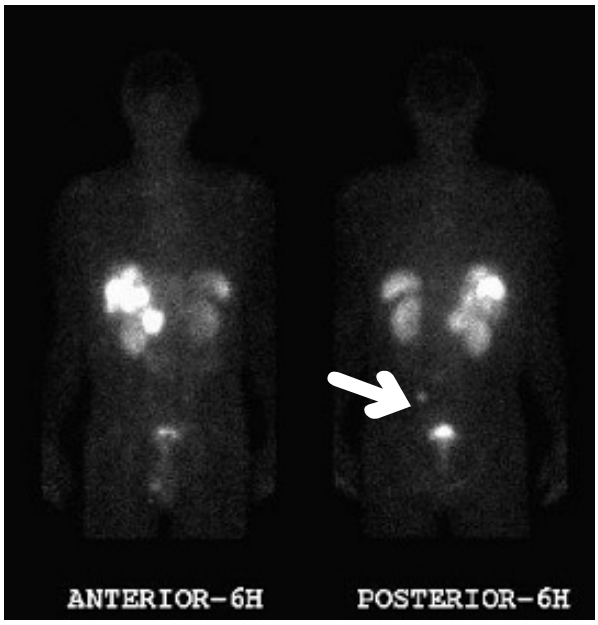
Figure 2. *Detection of primary tumor: male, 51 y, with unknown primary tumor.*



you can use any method, conventional, not conventional. SRS has a very important role with this type of patient.

This is an example (Figure 3) of a patient with liver metastasis, a patient with a tumor in the ileum, easily detectable. Tumors smaller than 1 cm can be seen in the endoscopy, not only for diagnosis but also for therapeutic reasons.

Figure 3. *Male, 72y. Detection of unknown primary tumor.*



If you have a larger tumor, SRS has a major role in staging those tumors because there are more chances of having metastasis, like this case (Figure 4), where you do not only have liver metastasis with a very high uptake, but you can also see bone metastasis. That is to say, in one exam you can do a very good staging procedure. SRS is a whole-body imaging system. Thus, with one injection at one time you can really see the whole body. As you have a much better opportunity if you can take the primary tumor out, it is very important to have a comprehensive view.

There is a difference in the methods to be used if you are dealing with hepatic or extra-hepatic lesions. In extra hepatic lesions, you have the advantage of looking at the whole body by using SRS.

If you compare per-lesion sensitivity, SPECT is much better than the planar imaging, and that is very important. SPECT imaging many times can modify the classification done by conventional imaging (CIP). SRS SPECT together with conventional imaging are the best methods to stage your patients before a surgery.

We can now say, based on literature and on our own experience, that SRS modifies management in 25-53% of the patients. This has a lot of implications even, economic consequences.

Regarding response evaluation of any oncologic therapy, if you want to analyze tumor response, in my own opinion, shared by many other colleagues, the morphological evaluation approaches are not the best methods, We should follow the "functional response". There is now a new movement in Europe, they call it "desist-resist".

One of the most recent clinical indications of SRS is before PRRT (i.e.: Peptide Receptor Radionuclide Therapy), where you can see receptor distribution and density to ascertain whether the patient is a candidate or not.

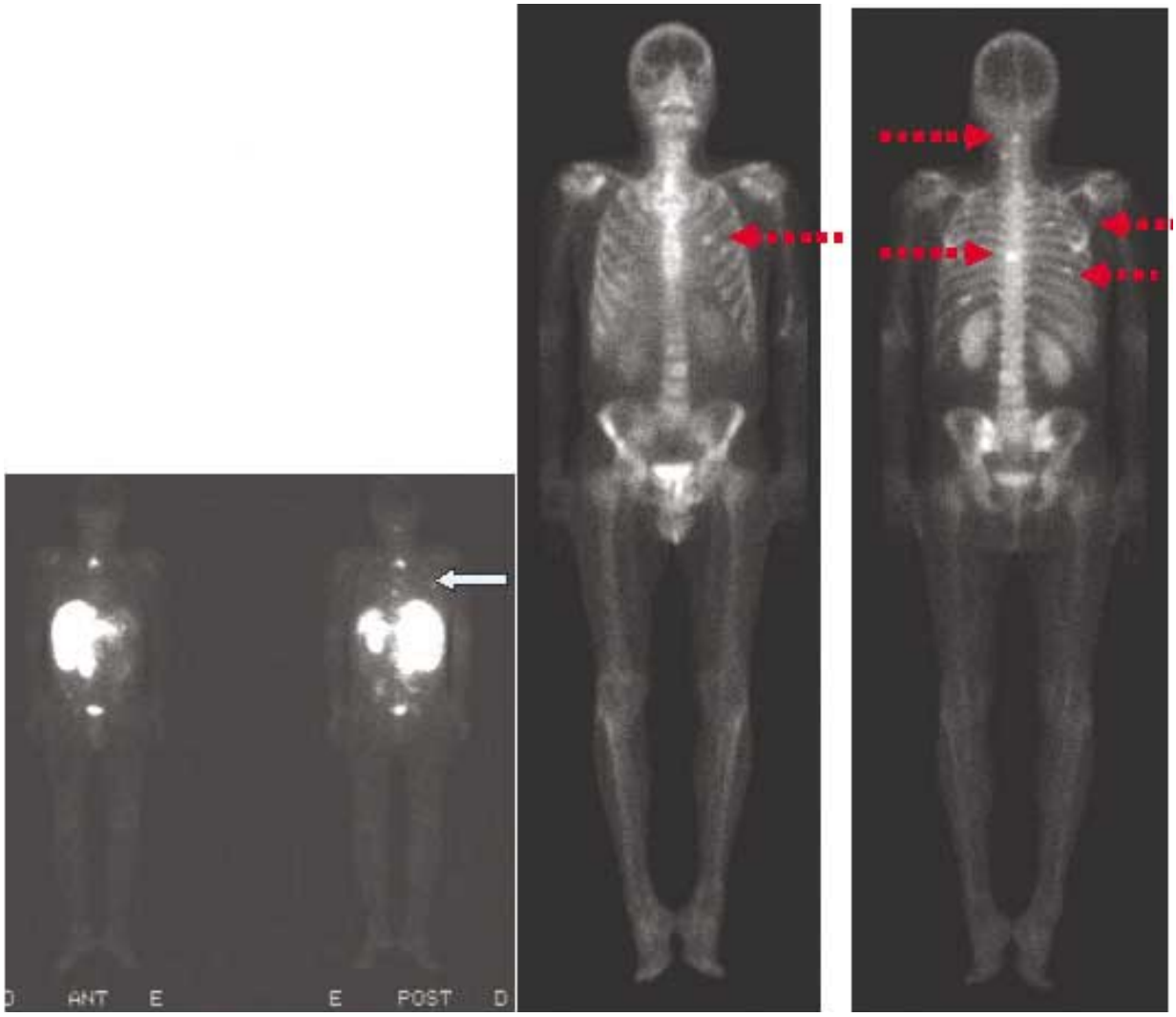
What will be the future of SRS? There are new somatostatin analogues that can be labeled with new isotopes. There are new peptides and new equipment. New equipment combines CT and new morphological imaging. The fusion gives you both morphological and anatomical information.

One very important thing that is happening this last year is new pharmaceuticals, labeled not with gamma radiation but with pulse emitting radiation like ^{18}F-FDG or ^{11}C-hydoxytryptophan.

One interesting thing about this PET imaging method is that you can study different metabolic pathways. So we are in the stage of helping the oncologist and the surgeon see what they want to see. So we do not use glucose metabolism, which you know already, but hormone precursors, like tryptophan, like phenylalanine, like F-DOPA, for example. So we are not only looking at diagnosis but in the future at therapeutically possibilities too.

Something that is starting in Brazil before the end of the year is a ^{68}Galium generator. I think this is the technique of the future. And you can also label somastotatin analogues, which have a better sensitivity.

I don't want to suggest that you use other methods in your daily routine, but from the literature, this is the way to go. If you have a PET camera, do not attempt to synthesize other peptides, labeling them with indium, go directly to this generator. It is very expensive but has many advantages. Apart from its high sensitivity and specificity, you can use



semi-quantitative data, the SUV index. A big advantage is that it has a very fast protocol. It is completed in one hour and a half. With other studies you need at least 24 hours, and the patient would need to stay in. Also, as you have the generator, you can perform daily exams. For instance, in Brazil we perform octreoscan or peptide SRS every two weeks. With this, you can do it daily in an hour and a half. You can see the difference from the practical point of view. If you use it this way, the cost of this generator is probably much lower than that of the conventional equipment.

A long time ago I learned that surgical ablation is the only curative modality in GEP-NET.

Early detection of all sites is very important for the surgical planning.

SRS based on somatostatin analogues and PET or serotonine peptide scintigraphy and amine precursors have an excellent detection rate of metastatic sites and primary lesions.

SRS and PET images based on functional aspects of GEP-NET tumors can guide the conventional morphological imaging (like MRI and CT) methods for a better surgery planning.

There is no doubt that SRS and PET/CT have an important role in diagnosis, staging and follow-up in the different clinical situations in GEP-NET, so complicated and heterogeneous.