# Single-Photon Emission Computed Tomography Tracers in the Diagnostics of Neuroendocrine Tumors

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**KEYWORDS**

• mIBG • Somatostatin • Somatostatin analogues • Pentetreotide

**KEY POINTS**

- Neuroendocrine tumors constitute a multisided, complex world, which has long been challenging for physicians.
- Different imaging strategies have been developed targeting the unique features of this group of rare diseases.
- Efforts have been made to study metabolic characteristics and receptor expression on the tumor surface, with knowledge still growing as a result of the implementation of fusion imaging and development of more detailed positron emission tomography tracers for NETs.
- In many countries, the scintigraphic study of NETs is still the most diffused and convenient technique to evaluate patients.

## INTRODUCTION

Under the term neuroendocrine tumors (NETs), several types of epithelial neoplasms with predominant neuroendocrine differentiation are grouped. These almost uncommon tumors, however heterogeneous, share their origin from neuroendocrine cells from the neural crest. On one hand, this is the reason why NETs can arise from different anatomic regions and tissues, given the broad distribution in the body of the neuroendocrine-derived cells. Thus, the common origin, because these tumors are part of the amine precursor and decarboxylation system (APUD), is why they produce hormones, despite their localization. As a consequence of this characteristic, different hormonal syndromes causing nonspecific symptoms may feature in the clinical presentation of these neoplasias.[1,2]

More often characterized by slow growing patterns and well-differentiated histologic features that correlate with a better prognosis, these tumors can also present with a range of poorly differentiated and more aggressive diseases.[3]

The incidence of this group of tumors accounts for about 5/100,000 cases, although it seems to have increased in the last 3 decades,[4] probably as a result of a greater awareness and new emphasis on its diagnostic-related issues.

The diagnosis of NETs has always been challenging, because of the wide range of clinical presentations and demonstrating the lesions

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has always been problematic mainly because of their small size, low rate of metabolism. and variable anatomic distribution. Conventional imaging sometimes shows results of nonunivocal interpretation.

However, functional imaging of NETs has become possible as a result of 2 fields of interest: the APUD metabolic features of the neuroendocrine cells and the discovery that most human NETs overexpress somatostatin (SS) receptors,[5] leading to the development of receptor-based imaging of NETs.

In this scenario, the contribution of nuclear medicine is essential for the in vivo detection of NETs.

The development of adrenomedullary radiopharmaceuticals took place mostly in the United States, in particular, at the University of Michigan; in Europe, most effort was given to the development and radiolabeling of SS analogues.

In this article, the origin and evolution of single-photon emission radiopharmaceuticals and diagnostic tools for the study of NETs are discussed.

## THE RADIOPHARMACEUTICALS

### *A Metabolic Probe for the Study of NETs: Meta-$^{131}$I-Benzylguanidine*

The first synthesis of aralkylguanidines with an antiadrenergic effect dates back to 1967,[6] but it was between the end of the 1970s and the early 1980s that the successful radioiodination of these amines led to the first scintigraphic visualization of the adrenals in dogs[7] and later to the first imaging results in humans.[8,9]

The radiopharmaceutical used was meta-$^{131}$I-benzylguanidine ($^{131}$ImIBG), which derives from the combination of the benzyl group of bretylium and the guanidine group of guanethidine.

mIBG is an analogue of norepinephrine, sharing with this adrenergic hormone some characteristics of its molecular structure and the ability to enter the same metabolic pathway.

Norepinephrine is synthesized by normal adrenergic cells and stored in intracellular granules. Excretion follows an exocytosis mechanism. Reuptake is also possible via the vesicular monoamine transporters ($VMAT_1$ and $VMAT_2$).

Radiolabeled mIBG is taken up by VMAT and then stored in the secretory granules of the neuroendocrine cells[10] without being further metabolized significantly. The result is a specific concentration in these cells, which allows their visualization in contrast to nonadrenergic tissues.

Moreover, mIBG does not show relevant binding activity for postsynaptic receptors, hence the absence of a pharmacologic response.[11]

Both isotopes of iodine ($^{123}$I and $^{131}$I) commonly available in nuclear medicine diagnostic imaging are used for radiolabeling mIBG.

### *SS and Its Analogues*

SS, first described by Brazeau and colleagues,[12] is a cyclic hormone, a peptide naturally occurring in 2 forms (either 14 or 28 amino acids) in humans, with a short half-life of about 2 minutes. Its synthetic analogues, the octapeptides, octreotide and lanreotide, have a longer half-life (about 2 hours) and, therefore, have been developed for clinical use for both diagnostic and therapeutic purposes.[13,14]

SS and its analogues bind some specific receptors that belong to a family of G-protein coupled receptors; 5 subtypes have been identified: sstr1, sstr2, sstr3, sstr4, and sstr5[15]; their selective affinity toward native peptide and synthetic analogues is shown in **Table 1**.

Several studies have assessed the expression of these receptors on the tumor surface, and the results suggest that sstr2 is mostly represented on the surface of NETs, whereas ssrt3 is more widely diffused in human tumors.[16,17]

The possibility of radiolabeling the SS analogues enabled the in vivo investigation of the SS receptor distribution and, therefore, the imaging of NETs.

### *Nuclear Medicine Receptor Imaging: an Outline*

Toward the end of the 1980s, Krenning and the Rotterdam group[18] were the first to describe NETs in humans using scintigraphic planar images obtained with $^{123}$I-Tyr3-octreotide, a radioiodinated SS analogue with a TYR substitution.[19,20] However, this tracer showed some weak points: high biliary excretion, leading to an accumulation in the bowel, making interpretation of the images more difficult; the high costs of $^{123}$I production;

**Table 1**
**sstr subtype selectivity to endogenous SS and SS analogues**

| | *Ki* (nM) | | | | |
|---|---|---|---|---|---|
| Agonist | sstr1 | sstr2 | sstr3 | sstr4 | sstr5 |
| SS-14 | 1.1 | 1.3 | 1.6 | 0.53 | 0.9 |
| SS-28 | 2.2 | 4.1 | 6.1 | 1.1 | 0.07 |
| Octreotide | >1000 | 0.6 | 34.5 | >1000 | 7 |
| Lanreotide | >1000 | 0.8 | 107 | >1000 | 5.2 |
| Vapreotide | >1000 | 5.4 | 31 | 45 | 0.7 |
| Pasireotide (SOM-230) | 9.3 | 1.0 | 1.5 | >100 | 0.2 |