EDITORIAL

Making the Best of Imperfect Tumor-Localizing Radiopharmaceuticals

The somatostatin receptor agent pentetreotide has greatly improved the localization of endocrine neoplasms bearing somatostatin receptors. An extensive spectrum of tumor types has been imaged using pentetreotide, ranging from neuroendocrine neoplasms to a variety of non-endocrine tumors and processes involving tissues that express somatostatin receptors (Table 1) (*1*). This broad application has expanded the clinical usefulness of nuclear medicine but has come with a catch: A biochemical or tissue-based diagnosis must be confirmed before imaging. Somatostatin receptor scintigraphy (SRS) for neuroendocrine tumor localization encompasses such a wide variety of endocrine and non-endocrine neoplasms and other conditions that scan interpretation may be confounded. This dilemma, of course, reflects the distribution of somatostatin receptors and the important role that somatostatin plays in the regulation of many endocrine and non-endocrine functions. Without adequate pre-scintigraphic diagnosis, however, the presence of pentetreotide uptake may indicate any one of many differential diagnoses that do more to confound than to facilitate management (*2,3*). Previous studies have focused on SRS in the localization of neoplasms where sensitivity is of primary concern but have generally ignored other conditions that might affect SRS biodistribution.

The article by Gibril et al. (*4*) marks a significant advance in the evaluation of the true clinical usefulness of SRS for gastrointestinal pancreatic neuroendocrine tumors and, specifically, gastrinomas. Gastrointestinal pancreatic neuroendocrine tumors are, in general, challenging and difficult to diagnose lesions, and gastrinomas are among the most elusive and difficult subtypes to manage (*1,5*). The study by Gibril et al., however, is a model of how such evaluations of clinical usefulness should be performed. A number of features lend strength to this study:

1. The series was large because the National Institutes of Health is a major referral center, drawing patients from all over the U.S. and the world (480 studies in 146 patients).
2. The series was consecutive, including all patients referred with the diagnosis of gastrinoma (at the time of the study or before the study).
3. The criteria for diagnostic classification were prospective and rigidly defined.
4. The results of scintigraphy were classified as true- or false-positive or -negative on the basis of established biochemical, radiological and histological criteria.
5. An adequate follow-up period was allowed for the full investigation of suspect foci and for their natural history to be revealed.
6. The data were analyzed to yield the usual parameters of performance, such as sensitivity, specificity, positive predictive value and negative predictive value. Unlike most researchers, Gibril et al. (*4*) have analyzed in detail the false-positive studies. These studies are relatively common and by no means insignificant, accounting for 59 of 296 (20%) of the positive studies. The fraction was particularly high (80%) in the category of patients believed by all the standard biochemical and radiological criteria to be disease-free after surgery. The large series, which makes it possible to observe and describe a wide range of false-positive localizations, is a useful aid to those struggling with the complexities of SRS interpretation. Many of the false-positive locations of uptake in these gastrinoma patients arose from unrelated pathologies. This is not surprising, given the many functions that somatostatin is believed to subserve (acting through its family of five receptor subtypes). These functions include: a hormone in the hypothalamic pituitary portal, enterohepatic portal and perhaps the general circulatory systems; neurotransmitter in the brain, spinal cord and peripheral nervous systems; paracrine transmitter in pancreatic islets, stomach and gut; and an autocrine modulator of its own secretion and inflammatory processes. Many of the false-positive foci were at sites of various inflammatory processes, presumably because of receptors on lymphocytes and other inflammatory cells (*6–10*).
7. Rather than merely list the false-positive rate and break it down into various categories, Gibril et al. (*4*) analyzed the rate of false-positive studies that led to alterations in management. The authors carefully interpreted SRS with a knowledge of the various potential causes of false-positive studies. Only 2.7% of studies overall (or 22% of the false-positive studies) had false-positive results that led to alterations in management, which is an encouraging but not ideal result.

The growing experience with ^{111}In-diethylenetriamine pentaacetic acid oc-

Received Nov. 3, 1998; accepted Dec. 18, 1998.
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TABLE 1
Pathologic Processes Expressing Somatostatin Receptors Imaged with Pentetreotide

Organ/tissue	Neoplasm/pathologic process
Anterior pituitary	Adenoma (GH, TSH)*
Pancreas islet cell	Islet cell tumors*
Gastrointestinal endocrine cells	Carcinoid*
Bronchopulmonary	Small cell lung cancer*
Ovary	Adenocarcinoma
Cervix	Adenocarcinoma
Endothelium	Adenocarcinoma
Breast	Adenocarcinoma
Kidney	Adenocarcinoma
Larynx	Adeno/squamous carcinoma
Paranasal sinuses	Adenocarcinoma
Salivary glands	Adenocarcinoma
Colon	Adenocarcinoma
Meninges	Meningiomas
Glial cells	Tumors of glial origin
Adrenal medulla	Pheochromocytoma*
	Neuroblastoma*
	Ganglioneuroma*
	Ganglioblastoma*
Paraganglia	Paraganglioma*
Thyroid	Thyroid cancer
	Papillary
	Follicular
	Anaplastic
	Medullary*
	Thyroid adenomas
Skin	Merkel cell*
	Melanoma*
Leukocytes	Lymphoma
	Tuberculosis
	Sarcoidosis
	Wegener's granulomatosis
	Sjörgen's syndrome
	Rheumatoid arthritis
	Graves' ophthalmopathy
	Other granulomatous processes

*Neuroendocrine neoplasms
GH = growth hormone; TSH = thyroid-stimulating hormone.
Modified with permission (*1*).

treotide and the more recent development of many additional ligands for SRS suggest that we have yet to find the "ideal" imaging agent. Indeed, it is certain that there will be no single ideal radiopharmaceutical for SRS; instead, various agents with different spectra of affinity for the various subclasses of somatostatin receptors will be chosen, depending on the nature of the pathology suspected. Further correlation of in vivo SRS imaging with carefully conducted in vitro characterization of the receptor subclass distribution is needed. The work of Reubi et al. (*11*) is a model of this approach. Full in vivo characterization of somatostatin receptor status might even require a cocktail of two (or more) ligands with different radiolabels and different patterns of receptor subtype affinity to classify the lesion fully (*12*).

The article by Gibril et al. (*4*) teaches two important lessons. First, functioning endocrine neoplasms are suspected on the basis of clinical symptoms and signs (and, in the case of many endocrine tumors, on family history) and are confirmed by screening biochemistry (designed to be sensitive if not entirely specific) and confirmatory biochemistry (designed to be even more specific) (*2,3*). Second, only after solid clinical suspicion and biochemical diagnosis should localization be attempted (*2,3*). This lesson reminds us that there are many pitfalls to SRS imaging that, if not appreciated, may affect the diagnostic usefulness of SRS for endocrine tumor localization.

We look forward to SRS studies that apply the scientific rigor of Gibril et al. (*4*) to other types of gastroenteropancreatic neuroendocrine tumors and other lesions. We would all do well to apply the same principles to work with other tumor-seeking radiopharmaceuticals.

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