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Octreoscan Radioreceptor Imaging

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With the in vivo demonstration of somatostatin-receptor-positive tumors in patients using a radiolabeled somatostatin analog, peptide receptor scintigraphy became available some 15 yr ago. Octreoscan® is a radiopharmaceutical with proven clinical importance in the visualization of somatostatin-receptor-positive tumors, and the overall sensitivity of somatostatin receptor imaging is high. In a number of neuroendocrine tumor types, as well as in Hodgkin's disease, inclusion of somatostatin receptor imaging in the localization or staging procedure may be very rewarding. The value of somatostatin receptor imaging in patients with other tumors, like breast cancer, or in patients with granulomatous diseases, has to be established.

Key Words: Analogs; octreotide; radionuclide imaging; somatostatin; spleen.

Introduction

With the in vivo demonstration of somatostatin receptor (SSTR)–positive tumors in patients using a radioiodinated somatostatin analog, peptide receptor scintigraphy became available in 1987 *(1)*. More recently, other radiolabeled somatostatin analogs were developed, of which two are commercially available. Because of the nearly worldwide availability of radiopharmaceuticals for SSTR imaging (SRI), most of this chapter focuses on this type of receptor scintigraphy.

SSTRs

Somatostatin is widely distributed in the human body, in particular in the central and peripheral nervous system, in endocrine glands, in the immune system, as well as in the gastrointestinal (GI) tract. In the nervous system, somatostatin acts as a neurotransmitter. Endocrine effects include the inhibition of the physiologic and tumorous release of growth hormone (GH), insulin, glucagon, gastrin, serotonin, and calcitonin *(2)*. Somatostatin also has antiproliferative effects in vitro, as has been found in cultured breast cancer cell lines, cultured small cell lung cancer (SCLC) cell lines, numerous animal tumor models, and in neuroendocrine tumors in humans. Finally, it has specific regulatory effects on immune responses *(3)*.

All known somatostatin actions are mediated through membrane-bound receptors, of which five have been cloned (SSTR1–SSTR5) *(4-8)*. These G protein–coupled receptors can be divided, on the basis of pharmacology and structure, into two subfamilies: one consisting of SSTR2, SSTR3, and SSTR5; and the other consisting of SSTR1 and SSTR4 *(4–8)*. All known receptors have a high affinity for the naturally occurring somatostatin-14 and somatostatin-28, as well as for the recently discovered cortistatin. However, only SSTR2; SSTR5; and, to some extent, SSTR3 have a high affinity for the commercially available synthetic octapeptides octreotide, lanreotide, or vapreotide *(4-8)*. SSTRs are expressed in many tissues, including brain, pituitary, GI tract, pancreas, thyroid, spleen, kidney, immune cells, vessels, and peripheral nervous system *(9-18)*.

SSTRs have been identified in vitro in a high incidence and density especially in neuroendocrine tumors, such as, GH-producing pituitary adenoma, nonfunctioning adenoma, pancreatic islet cell tumor, gut and lung carcinoid, pheochromocytoma, paraganglioma, medullary thyroid cancer (MTC), and small cell lung carcinoma *(19)*. Tumors of the nervous system including meningioma, neuroblastoma, and medulloblastoma also very often express a high density of SSTRs. Other types of tumors, such as lymphoma, breast cancer, renal cell cancer, hepatocellular cancer, prostate cancer, sarcoma, and gastric cancer can also express SSTRs *(19)*. In addition, it has been demonstrated in vitro that veins surrounding several human cancers express SSTRs, independent of the receptor expression in the tumor *(20)*. In the majority of tumors, the SSTR2 subtype is predominantly expressed, although low amounts of other SSTR subtypes may be concomitantly present *(21)*. Finally, it should be emphasized that selected nontumoral lesions may express somatostatin receptors. One example of this are active granulomas in sarcoidosis, in which the epithelioid cells express SSTRs *(22)*. Other examples are that inflamed joints in active rheumatoid arthritis express SSTRs, preferentially located in the proliferating synovial vessels *(23)*, and inflammatory bowel diseases *(24)*. The expression of SSTR is therefore not specific for tumoral pathologies, which has important clinical implications.

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Radiolabeled Somatostatin Analogs

The radioiodinated somatostatin analog that was first used in patients is [^{123}I,Tyr^3]octreotide. However, [^{123}I,Tyr^3] octreotide has several drawbacks: The labeling of [Tyr^3]octreotide with ^{123}I is cumbersome and requires special skills. In addition, Na^{123}I of high specific activity is expensive and not available worldwide. Moreover, the moment of the labeling and scanning procedures is dependent on the logistics of the production and delivery of Na^{123}I. Finally, substantial accumulation of radioactivity is seen in the intestines, since a major part of [^{123}I-Tyr^3]octreotide is rapidly cleared via the liver and biliary system. This makes the interpretation of planar and single photon emission computed tomographic images of the upper abdomen difficult. Most of these problems can be solved by replacing ^{123}I with ^{111}In, which also improves scintigraphy 24–48 h after application by virtue of its longer half-life. However, for binding of ^{111}In to the somatostatin analog octreotide, it has to be complexed with a diethylenetriaminepentaacetic acid (DTPA) group coupled to the αNH_2 group of the N-terminal D-Phe residue *(25)*. The result of this is [^{111}In-DTPA^0]octreotide (Octreoscan®), which is commercially available and is the most commonly used agent for SRI. The preferred dose of [^{111}In-DTPA^0]octreotide (with at least 10 μg of the peptide) is about 200 MBq. With this dose, it is possible to perform single photon emission computed tomography (SPECT), which may increase the sensitivity to detect SSTR-positive tissues and gives a better anatomic delineation than planar views.

^{99m}Tc-Depreotide (Neotect®) is another commercially available somatostatin analog that has been approved specifically for the detection of lung cancer in patients with pulmonary nodules *(26)*. Because of the relatively high abdominal background and the impossibility of performing delayed imaging owing to the short half-life of the tracer, it is less suited for the detection of abdominal neuroendocrine tumors *(27)*.

[^{111}In-DOTA]Lanreotide is another SRI agent with a slightly different sst affinity profile than [111In-DTPA^0]octreotide *(28)*. In comparison with Octreoscan, it has a lower sensitivity to demonstrate neuroendocrine tumor, but it may have advantages in other tumors, such as in differentiated thyroid cancer *(29)*.

Technique and Normal Findings

Scanning Protocol of [^{123}I,Tyr^3]Octreotide

Because of its relatively long effective half-life, [^{111}In-DTPA^0]octreotide is a radiolabeled somatostatin analog that can be used to visualize SSTR-bearing tumors efficiently after 24 and 48 h, when interfering background radioactivity is minimized by renal clearance. A higher lesion detection rate of 24-h planar imaging over 4-h acquisition was reported by Jamar et al. *(30)*, as well as the additional value of SPECT imaging. Planar studies after 24 and 48 h can be carried out with the same protocol. Repeat scintigraphy after 48 h is especially indicated when 24-h scintigraphy shows accumulation in the abdomen, which may also represent radioactive bowel content.

Normal Scintigraphic Findings

Normal scintigraphic features of SRI include visualization of the thyroid; spleen; liver; kidneys; and, in some patients, pituitary. Additionally, the urinary bladder and the bowel are usually visualized to a variable degree *(31)*. Visualization of the pituitary, thyroid, and spleen is owing to receptor binding. During octreotide treatment, the uptake of [^{111}In-DTPA^0]octreotide in SSTR-positive tumors and the spleen is diminished. Yet, neuroendocrine tumors may remain visible during treatment with octreotide, although the tumor uptake of [^{111}In-DTPA^0]octreotide may be less (up to 50%) than without octreotide treatment *(32)*.

Imaging Results

Pituitary Tumors

On virtually all GH-producing pituitary adenomas SSTRs are present *(25,26)*, but other pituitary tumors, parasellar meningiomas, lymphomas, or granulomatous diseases of the pituitary may be positive as well. However, SRI does not seem to have a role in deciding whether or not to treat an acromegalic patient with octreotide *(33,34)*.

Because of the limited effect of octreotide on hormone secretion by clinically nonfunctioning pituitary tumors, there is no role for SRI in treatment selection *(35-37)*.

Endocrine Pancreatic Tumors

The majority of the endocrine pancreatic tumors can be visualized using SRI. Reported data on the sensitivity of SRI in patients with gastrinomas vary from about 60 to 90% *(38,39)*, and part of the discrepancy in results is likely owing to insufficient scanning technique (especially short acquisition time), not performing SPECT studies, or injection of relatively low doses of [^{111}In-DTPA^0]octreotide, all of which lead to a poorer performance of SRI.

Using ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and/or angiography, endocrine pancreatic tumors can be localized in about 50% of cases. Studies comparing the value of endoscopic ultrasonography with SRI in the same patients point to more favorable results for SRI *(38,40,41)*. Gibril et al. *(39)* found that in 80 patients with Zollinger-Ellison syndrome, SRI was as sensitive as all of the other imaging studies combined, and, therefore, they advocated its use as the first imaging method to be used in these patients because of its sensitivity, simplicity, and cost-effectiveness. Several groups reported the results of SRI in patients with gastro-entero-pancreatico (GEP) tumors. SRI modified patient classification and surgical therapeutic strategy in a significant proportion of patients *(42–44)*. Results in

patients with insulinomas are disappointing, because these tumors frequently either are SSTR negative or contain SSTRs that do not bind octreotide.

Carcinoids

Reported values for the detection of known carcinoid tumor localizations vary from 80 to nearly 100% *(45-47)*. SRI, regarding its ability to demonstrate SSTR-positive tumors, can be used to select those patients who are likely to respond favorably to octreotide treatment. On the other hand, only for those patients who have SSTR-negative tumors is chemotherapy effective *(48,49)*. Furthermore, SRI may detect resectable tumors that would be unrecognized with conventional imaging techniques. Therefore, it may prevent surgery in patients whose tumors have metastasized to a greater extent than can be detected with conventional imaging.

Paragangliomas

In virtually all patients with paragangliomas, tumors are readily visualized *(50)*. Unexpected additional paraganglioma sites are frequently found. Multicentricity and distant metastases are each reported to occur in 10% of patients *(50)*. One of the major advantages of SRI in the case of a paraganglioma is that it provides information on potential tumor sites in the whole body. It could thus be used as a screening test, to be followed by CT scanning, MRI, or ultrasound of the sites at which abnormalities are found.

(Medullary) Thyroid Carcinoma

In patients with MTC, the sensitivity of SRI to detect tumor localizations has been shown to be 50–70% *(51,52)*. The ratio of serum calcitonin over carcinoembryonic antigen levels seems to be significantly higher in patients in whom SRI can be successfully applied. This may imply that SSTRs can be detected in vivo on the more differentiated forms of MTC. Furthermore, SRI is more frequently positive in patients with high serum tumor markers and large tumors *(52)* and therefore seems less suitable to demonstrate microscopic disease *(52,53)*.

Although all other thyroid carcinomas do not belong to the group of classic neuroendocrine tumors, the majority of patients with these cancers show uptake of radiolabeled octreotide during SRI *(54,55)*. Interestingly, differentiated thyroid cancers that do not take up radioactive iodine may show radiolabeled octreotide accumulation *(54)*.

Lung Cancer

Primary tumors can be demonstrated in virtually all patients with SCLC with SRI *(56-58)*. Part of the known metastases may be missed, however *(59)*. Of special interest are patients in whom the additional information provided by SRI may have therapeutic consequences, especially those in whom unexpected cerebral metastases are found, and those in whom the additional information leads to upstaging from limited disease to extensive disease. Adding SRI to the staging protocol in patients with SCLC led to an upstaging in 5 of 14 patients (36%) out of a group of 26 untreated patients *(56)* who seemingly had limited disease with conventional imaging alone.

Breast Cancer

SRI localized 39 of 52 primary breast cancers (75%) *(60)*. A special remark has to be made with respect to the observation of bilateral and diffuse, physiologic breast uptake in normal females. This faint uptake is present in about 15% of patients 24 h after administration and is clearly different from the more localized accumulation at the site of breast cancer. At present, the basis for this finding is unknown. SRI may be of value in selecting patients for clinical trials with somatostatin analogs or other medical treatments. Furthermore, SRI is sensitive for detecting recurrences of SSTR-positive breast cancer.

Malignant Lymphomas

In vitro, SSTRs can be detected in the majority of lymphomas. However, their density is often very low *(15)*. Although in many patients with non-Hodgkin lymphoma one or more lesions may be SSTR positive, receptor-negative lesions also occur in a substantial number of patients *(61)*.

Pheochromocytomas

In a large retrospective study in patients undergoing surgery for pheochromocytoma, the overall preoperative detection rate for tumors >1 cm in diameter was 90% for ^{123}I-MIBG, and only 25% for SRI *(62)*. Most of the patients had primary benign pheochromocytomas. In patients with metastases, SRI detected lesions in seven of eight patients, including ^{123}I-MIBG-negative cases. Therefore, it can be concluded that SRI should be tried in suspicious metastatic, ^{123}I-MIBG-negative pheochromocytomas.

Cushing Syndrome

In a study of 19 patients with Cushing syndrome, none of the pituitary adenomas of eight patients with Cushing disease or the adrenal adenoma of another patient could be visualized with SRI *(63)*. In 8 of the other 10 patients, the primary ectopic corticotropin or corticotropin-releasing hormone (CRH)–secreting tumors were successfully identified with SRI *(64,65)*. Therefore, SRI can be included as a diagnostic step in the work-up of Cushing syndrome with a suspected ectopic corticotropin or CRH-secreting tumor.

Sarcoidosis

In a crosssectional study in 46 patients with sarcoidosis, known mediastinal, hilar, and interstitial diseases were recognized in 36 of 37 patients *(66)*. To determine the value of SRI in the follow-up of patients with sarcoidosis, a prospective longitudinal study will have to be performed.

Conclusion

[^{111}In-DTPA^{0}]Octreotide is a radiopharmaceutical with proven clinical importance in the visualization of SSTR-positive tumors. The overall sensitivity of SRI to localize neuroendocrine tumors is high. In a number of neuroendocrine tumor types, as well as in Hodgkin disease, inclusion of SRI in the localization or staging procedure may be very rewarding. The value of SRI in patients with other tumors, such as breast cancer, or in patients with granulomatous diseases, has to be established.

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