

Experience with Somatostatin Receptor Scintigraphy in the Management of Pulmonary Carcinoid Tumors

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Key words: carcinoid, lung, octreotide, scan, detection

Abstract

Background: Somatostatin receptor scintigraphy has been used widely for the evaluation of neuroendocrine tumors in the gastrointestinal tract. Its use for detecting and staging thoracic carcinoids is only sporadically reported.

Objectives: To evaluate the possible roles of SRS in the management of proven or suspected pulmonary carcinoids.

Methods: We conducted a retrospective study of all patients undergoing SRS for known or suspected pulmonary carcinoids in a tertiary referral center during a 10 year period. During this period 89 patients underwent resection of pulmonary carcinoids and SRS was used for detection, staging or localization purposes in 8 of them (9%). Scans were labeled true positive, true negative, false positive, or false negative in comparison with histologic or follow-up results.

Results: SRS was true positive in 6/6 lung locations; true positive in 2/8, true negative in 4/8 and false positive in 2/8 lymph node locations; and true positive in 1/8, true negative in 6/8 and false negative in 1/8 distant locations. The sensitivity, specificity, positive and negative predictive values and accuracy were 90%, 83%, 83%, 91% and 87% respectively. The scans were strongly positive in the tumors and involved lymph nodes. SRS correctly localized an occult secreting pulmonary carcinoid. Granulomatous and reactive lymph nodes showed increased uptake. SRS was accurate in ruling out distant metastases.

Conclusions: SRS is effective for visualizing and localizing pulmonary carcinoids. It assists in the staging of these tumors by detecting lymph node involvement and confirming or ruling out distant metastases. Inflammatory areas in the lung or lymph nodes may be falsely positive.

IMAJ 2005;7:712-716

Carcinoid tumors are rare neuroendocrine tumors (incidence 2.1 per 100,000) [1] that generally arise in the gastrointestinal tract. Pulmonary carcinoids comprise about 1% of primary lung neoplasms [2]. These tumors are thought to derive primarily from enterochromaffin cells possessing the specific ability to take up and decarboxylate amine precursors and to produce peptides and biogenic amines, the most prominent of which is serotonin (except for thymic carcinoid). Although surgery is the mainstay of treatment for localized disease, curative surgery is generally not possible when the disease has metastasized, leaving tumor

load reduction, inhibition of secretion, and symptom management as the remaining treatment options.

Biochemical measurement of secretory products and imaging studies are important investigations for diagnosing and staging carcinoid tumors. Analysis of metabolites from both the serotonin and catecholamine pathways is generally performed, particularly the measurement of urinary 5-hydroxy-indoleacetic acid, which is the main metabolite of serotonin.

The discovery of dense high affinity somatostatin receptors in membrane homogenates and tissue sections of these tumors [3,4] led to the use of radiolabeled somatostatin analogues for their *in vivo* scintigraphic imaging [5]. The *in vivo* technique provides whole-body screening and is associated with radiation exposure comparable to that of other imaging modalities [6]. This method has been used widely for gastrointestinal carcinoids and other neuroendocrine tumors, including small cell lung cancer, but has been reported only sporadically for the detection and staging of pulmonary and mediastinal carcinoids. The present report describes the diagnostic and therapeutic implications of somatostatin receptor scintigraphy in the management of patients with proven or suspected pulmonary carcinoid tumors.

Patients and Methods

Scan methodology

Twenty-four and 48 hours after administration of 200 MBq ¹¹¹In-octreotide (Octreoscan®, Mallinckrodt, Petten, The Netherlands), planar whole-body scans of 30 minute duration (1,000 Kcount) were obtained using a large field-of-view, dual-head gamma camera (Helix®, Elscint/Elgem, Israel) equipped with a medium-energy, all-purpose collimator and a 15% window centered for each of the 173 and 247 keV photopeaks of ¹¹¹In. Single photon emission CT imaging acquisition and processing was performed with 120 projections on a 128 x 128 matrix. Filtered back projection with a Metz filter and Chang attenuation correction was performed. All scans but one were done at the Sheba Medical Center. All the patients with SRS underwent surgery at this center

Background information

SRS was introduced into routine use at the Sheba Medical Center in 1992. From 1992 to May 2002, 89 patients underwent resection for pulmonary carcinoid in two medical centers in Israel

SRS = somatostatin receptor scintigraphy

by the same surgical team. In about half the patients the diagnosis was established intra- or postoperatively. Because SRS is a high cost study, it was used for specific indications only and not as a routine preoperative examination. Our indications included: a) detecting and localizing an occult neuroendocrine tumor, b) ruling out more than one pulmonary mass, c) ruling out metastases in suspected cases, and d) planning reoperation.

Patients

SRS was performed in eight patients (seven male, one female) aged 18–61 years [Table 1]. Six of them had typical carcinoid and two had atypical carcinoid tumors. Of the six with typical carcinoid, two had neuroendocrine syndromes: Cushing in one and carcinoid in the other. Chest and abdominal computed tomography scans were performed in all patients, and bronchoscopy in six that revealed the precise proximal location of the tumor and the histologic diagnosis in all six. In six patients SRS was performed preoperatively. In one case only, reported previously [7], SRS was performed to detect a secreting tumor. In five patients SRS was aimed to evaluate tumor spread: in two the CT scan suggested that there were two separate bronchial masses (one also had a pleural effusion), one patient had a splenic lesion the nature of which was not determined by other studies (ultrasound, red blood cell scan), in one CT showed hilar and mediastinal lymphadenopathy, and in one patient with carcinoid syndrome SRS was done to rule out liver metastases. In two patients SRS was done postoperatively: to plan reoperation in one with a malignant positive surgical margin determined on final histologic examination, and to detect suspected metastases in the other.

All patients underwent at least one operation and were followed at intervals of 6 months with physical examination and CT scans. The follow-up was complete for all patients until September 2002 (median 76 months).

Octreoscanning was defined as true positive if confirmed by histology (lung and lymph nodes) or follow-up data (distant spread as proved by CT scan, bone scan, hepatic ultrasound, or positron emission tomography scan), true negative if a negative scan was supported by a negative histologic finding or follow-up information, false positive if an area of pathologic uptake did not contain tumor, and false negative if a location deemed negative proved on surgery or follow-up to contain tumor. Altogether, 10 histologically proven lesions were evaluated

Results [Table 2]

SRS successfully detected and localized the tumor and involved lymph node in patient #1. It accurately showed the presence of only one mass in two patients (#5 and #7). In three cases (#4, #6, #8) in whom distant spread was considered, STS did not reveal any metastatic disease, allowing the patients to undergo resection. Patient #4 had a known mass in the lower lobe and later developed a carcinoid syndrome. Since this syndrome is uncommon in patients with isolated pulmonary carcinoid, a search for metastases was necessary [Figures 1 and 2]. The lack of metastases was confirmed by clinical and radiologic evidence during follow-up of 4–76 months. In two patients SRS was performed postoperatively: in one to confirm the presence of mediastinal and systemic spread suggested by CT and carcinoembryonic antigen scans (#2), and in the other to support a decision of completion pneumonectomy in a patient with a

Table 1. Data relating to patients under octreoscanning

Pt	Age/ Gender	Symptoms	NE syndrome	CT scan	Bronchoscopy	Tumor location/ size (cm)	OS timing related to first surgery	Role of octreoscanning	Results of OS Lung LNs distant
1	22/F	Cushing's	Cushing's	Negative	NA	LUL/1	Preoperatively	Detection & localization	+ - -
2	40/M	SOB, cough, weight loss	None	Positive	Positive*	Br. Inter/NA	Postoperatively	Detection of metastasis (on follow-up)	NA ++
3	24/M	Rec. pneumonia	None	Positive	Positive*	Br. Inter/NA	Postoperatively	Plan redo surgery (positive margin)	- + -
4	61/M	Hot flashes, diarrhea, PAF	Carcinoid	Positive	NA	LLL/5	Preoperatively	Rule out liver metastases	+ - -
5	26/M	SOB	None	Positive (suspected 2 masses)	Positive*	Br. Inter/3.5	Preoperatively	Rule out additional tumor	+ - -
6	45/M	Rec. pneumonia, hemoptysis	None	Positive (+ splenic lesion)	Positive*	Lt main branch/4	Preoperatively	Rule out splenic metastasis	+ - -
7	21/M	Chest pain	None	Positive + effusion + additional mass	Positive*	Br. Inter/2	Preoperatively	Rule out additional tumor & pleural spread	+ - -
8	18/M	Pers. pneumonia atelectasis	None	Positive + hilar lymphadenopathy	Positive*	RUL+RMB/2	Preoperatively	Rule out lymph node & distal spread	+ + -

OS = octreoscanning, SOB = shortness of breath, PAF = paroxysmal atrial fibrillation* including histology, LUL = Lt upper lobe, LLL = Lt lower lobe, RUL = Rt upper lobe, RMB = Rt main bronchus, Br. Inter = bronchus intermedius, NA = not applicable, Rec. = recurrent, Pers. = persistent, LN = lymph node.

Table 2. Operative and postoperative data

Pt	Date of surgery	Type of tumor	Type of resection	Lymph node status (first surgery)	Accuracy of octreoscanning lung lymph node metastasis	Outcome (months)
1	Sept 1993	TC	Lobectomy	+	TP(P) TP(P) TN(C)	NED, 108 NES resolved
2	Aug 1994	AC	Pneumonectomy	+	NA TP(C) TP(C)*	DOD (12)
3	April 1996	TC	Upper & middle lobectomy	+	TP(P) FP(P) TN(C)	NED (97)
4	May 1996	TC	Lobectomy	-	TP(P) TN(P) TN(C)	NED (76) NES resolved
5	June 1997	TC	Lower & middle lobectomy	-	TP(P)** TN(P) TN(C)	NED (63)
6	Dec 1999	TC	Lobectomy	-***	TP(P) TN(P) TN(C)	NED (33)
7	Oct 2000	AC	Bronchial sleeve resection	-	TP(P) TN(P) FN(C)****	Systemic metastasis (24), Carcinoid syndrome
8	May 2002	TC	Lobectomy plus sleeve resection	-	TP(P) FP(P)***** TN(C)	NED (4)

* Confirmed by carcinoembryonic antigen scan, CT and outcome.

** Octreoscanning correctly showed one mass.

*** Patient was found to have multiple lung metastases of papillary thyroid carcinoma.

**** Octreoscanning was positive for metastases when carcinoid syndrome developed.

***** This false positive result was expected; octreoscanning probably not indicated.

TC = typical carcinoid, AC = atypical carcinoid, (P) = pathologic confirmation,

(C) = clinical validation, NED = no evidence of disease, NES = neuroendocrine syndrome,

DOD = dead of disease.

positive surgical margin and involved hilar lymph node (#3). In the former the positive SRS prompted the administration of systemic chemotherapy. In the latter, the pathologic uptake in the mediastinum coupled with no uptake elsewhere helped the patient to decide positively on redo surgery. In this case as well as in case #8, SRS was falsely positive owing to reactive changes (postoperative in one and secondary to infection in the second) in the corresponding lymph nodes. The false positive result in case #3 probably led to an unnecessary operation as the resected lymph nodes and the remaining lobe and bronchus contained no tumor deposits. One patient (#6) was found intraoperatively to have multiple lung metastases of papillary thyroid carcinoma. These, as well as the primary tumor in the thyroid gland, were SRS-negative as expected. This patient presented with systemic metastases and elevated 5-HIAA 24 months later. Some of these metastases were positive on a follow-up SRS but were negative on the original scan.

The sensitivity of SRS in our study was 90% (6/6 primary tumors, 2/2 involved lymph node, 1/2 metastatic disease). Octreoscanning was true negative in 10 stations, false positive in two and false negative in one. Thus, the specificity was 83% and the positive and negative predictive values 83% and 91% respectively.

Discussion

Somatostatin is an endogenous neuropeptide comprised of 14 amino acids produced in the hypothalamus and pancreas and

5-HIAA = 5-hydroxy-indoleacetic acid

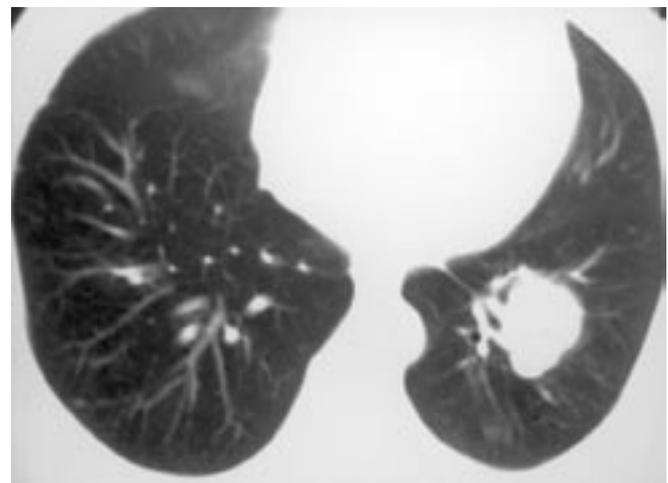


Figure 1. Computed tomography of the chest, axial cut 5 cm above the diaphragm (lung window). A 4 cm mass with lobulated borders is seen near the bifurcation of the lower lobe bronchus to the basal segments.

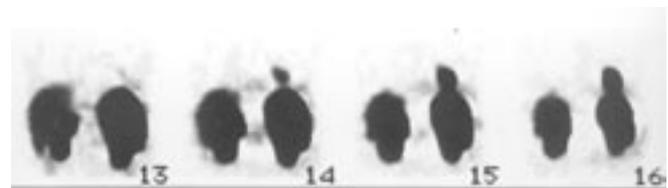


Figure 2. Coronal SPECT clearly defines the mass.

whose actions include regulation of growth hormone, insulin, glucagon, and gastrin secretion. A high density of somatostatin receptors is found on many cells of neuroendocrine origin, as well as on many endocrine-related tumors including carcinoid. Imaging of carcinoid tumors has dramatically improved with the introduction of somatostatin receptor scintigraphy with ¹¹¹In-labeled (diethylenetriaminepentaacetic acid-D-Phe)-octreotide (¹¹¹In-octreotide).

Ocreotide, a somatostatin analogue consisting of eight amino acids, has been proven to bind to somatostatin receptors on both tumor and non-tumor sites. Its biological half-life of 2–3 hours is relatively long because it is resistant to enzyme degradation. This binding capacity allows whole-body planar imaging as well as SPECT imaging.

The use of somatostatin receptor imaging of neuroendocrine tumors has been validated [8]. Bronchial carcinoid tumor is the most frequent occult source of ectopic ACTH-dependent Cushing's syndrome, but its initial localization as well as the postoperative follow-up may be difficult. Several individual case reports describing the contribution of In111-pentetreotide in such clinical settings have been reported [7,9–11].

The cases presented here delineate the role of this scintigraphic technique in decision making and management of patients with pulmonary carcinoid tumors. In those with a peptide-producing tumor, SRS may help localize the primary lesion and identify its neuroendocrine characteristics. The sensitivity of SRS does not depend exclusively on tumor size, but rather on a high target-to-background ratio associated with dense, high affinity receptors on the tumor surface compared with adjacent tissue [7,12]. Venous sampling in case #1 correlated with scan findings of a secreting tumor, and provided additional *in vivo* validation of the pathology. In this case the scan was more sensitive than conventional modalities, namely CT and magnetic resonance imaging. Patient #4 was known to have a "silent" pulmonary mass and then developed carcinoid syndrome, which is unusual in the absence of liver metastases. The scan confirmed that the source of secretion was indeed in the lung and ruled out other lesions. SRS is not required in the evaluation of a "silent" lung carcinoid, but if the patient is symptomatic and there are no liver findings on CT, SRS may be helpful. Due to the added contribution it may be wise to do the scan for preoperative planning (as in case #3, although it was ultimately found to be false positive in this case) even in cases where the diagnosis is established prior to surgery. This would allow all affected lymph nodes to be detected prior to surgery, thus enabling improved procedure planning. Case #7 also supports the role of SRS for preoperative planning, particularly regarding penetration into the mediastinum.

Local recurrence may be difficult to diagnose with anatomic imaging alone. The optimal time for postoperative imaging (case #3) may be quite delayed. Pitfalls in the interpretation of SRS may include postoperative inflammation, necrotizing as well as non-necrotizing sarcoid-like granulomatous reactions, and occasionally also reactive lymph node changes. Thus, SRS was falsely positive in case #3 and with the positive surgical margin led to completion pneumonectomy. In case #8 the increased uptake in the regional lymph nodes was correctly interpreted as originating from reactive lymph nodes. While its use has been validated for the diagnosis and staging of

thoracic tumors with neuroendocrine differentiation, e.g., bronchial carcinoid and small cell lung cancer, the uptake is not specific. Somatostatin receptors exist on white blood cells, leading to false positive scans in the presence of active sites of infection and inflammation. Benign lesions including pleural plaques due to asbestosis or tuberculosis can be visualized *in vivo*.

Metastatic spread is more likely to be detected by scintigraphic whole-body screening. Scan results can influence patient management by either supporting curative surgery if metastases are not detected, or obviating unnecessary surgery in other cases [13,14] (case #2 had true positive lesions in the liver). Patient #6 had a preoperative diagnosis of carcinoid. The SRS was true positive for this lesion, and true negative as expected for multiple minute pulmonary metastases of papillary thyroid carcinoma. A splenic lesion was negative on SRS but not confirmed by any invasive test, except for the clinical course and repeat CT scan.

Although this retrospective study intended to clarify the indications for and the contribution of SRS in patients with proven or suspected pulmonary carcinoids, additional data emerged. In the present series, 111In-labeled pentetreotide detected pathologic uptake in the lung consistent with tumor in all the patients studied preoperatively (100% sensitivity for pulmonary parenchymal location). This is consistent with the literature reporting an 82–92% overall detection rate [6,15,16], albeit for gastroenteropancreatic endocrine tumors in general. The specificity (83%) and positive and negative predictive values (83% and 91% respectively) were also very high, although metastatic true negative values were supported in five patients by follow-up clinical and radiologic data only (in two of them the complete resolution of the neuroendocrine syndrome is a stronger support).

Pulmonary carcinoid tumors, especially typical carcinoid, rarely present with distal metastases, and nodal involvement occurs in about 10% of cases [17]. The presence of affected hilar or mediastinal lymph nodes would not change the therapeutic approach. Since SRS is a high cost study, we concur that it should not be part of the routine workup in patients with typical carcinoid tumors, but should rather be performed for the specific indications mentioned above.

Conclusions

111In-octreotide scintigraphy is a reliable and effective method for visualizing carcinoid tumors throughout the body. This non-invasive diagnostic technique has imaging capabilities even in the clinical setting of a non-secreting carcinoid and seems to be particularly beneficial in the presence of negative or doubtful endoscopic and radiographic findings. In our series of thoracic carcinoid patients, SRS was contributory in the detection of both primary tumors and metastatic lesions and exclusion of disease in regions suspected by other modalities. The scan was found to be complementary to anatomic imaging (CT/MRI). It is effective for localization of occult primary carcinoids and staging of known disease.

SPECT = single photon emission CT

References

1. Oberg K. Expression of growth factors and their receptors in neuroendocrine gut and pancreatic tumors, and prognostic factors for survival. *Ann NY Acad Sci* 1994;733:46–55.
2. Carter D, Eggleston JC. Tumors of the lower respiratory tract. In: Atlas of Tumor Pathology. 2nd series, fascicle 17. Washington, DC: Armed Forces Institute of Pathology, 1980.
3. Reubi JC, Kvols L, Krenning EP. The visualization of gastroenteropancreatic endocrine tumors. *Metabolism* 1992;41(Suppl 2):111–15.
4. Reubi JC, Krenning EP, Lamberts SWJ, Kvols L. In vitro detection of somatostatin receptors in human tumors. *Metabolism* 1992;41(Suppl 2):104–10.
5. Krenning EP, Kwekkeboom DJ, Reubi JC, et al. In 111-octreotide scintigraphy in oncology. *Metabolism* 1992;41(Suppl 2):83–6.
6. Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [^{111}In -DTPA-D-Phe1] and [$^{1123}\text{Tyr}3$]octreotide: the Rotterdam experience with more than 1000 patients. *Eur J Nucl Med* 1993;20:716–31.
7. Weiss M, Yellin A, Huszar M, Eisenstein Z, Bar-Ziv J, Krausz Y. Localization of adrenocorticotrophic hormone secreting bronchial carcinoid by vasomatostatin receptor scintigraphy. *Ann Intern Med* 1994;121:198–9.
8. Lamberts SW, Reubi JC, Krenning EP. Validation of somatostatin receptor scintigraphy in the localization of neuroendocrine tumors. *Acta Oncol* 1993;32:167–70.
9. Fernandez-Fernandez F, Halperin I, Manzanares JM, et al. Localization and postoperative follow-up of a bronchial carcinoid tumor causing Cushing's syndrome by ^{111}In -DTPA labeled octreotide scintigraphy. *J Endocrinol Invest* 1997;20:327–30.
10. Oliaro A, Filosso PL, Casadio C, et al. Bronchial carcinoid associated with Cushing's syndrome. *J Cardiovasc Surg (Torino)* 1995;36:511–14.
11. Matte J, Roufosse F, Rocmans P. Ectopic Cushing's syndrome and pulmonary carcinoid tumor identified by [^{111}In -DTPA-D-Phe1]octreotide. *Postgrad Med J* 1998;74:108–10.
12. Pauwels S, Leners N, Fiasse R, Jamar F. Localization of gastroenteropancreatic tumors with ^{111}In -pentetreotide scintigraphy. *Semin Oncol* 1994;21(Suppl 13):15–20.
13. Jamar F, Fiasse R, Lener N, Pauwels S. Somatostatin receptor imaging with ^{111}In -pentetreotide in gastroenteropancreatic neuroendocrine tumors: safety, efficacy and impact on patient management. *J Nucl Med* 1995;36:542–9.
14. Krausz Y, Pfeffer MR, Glaser B, Lafair J. Somatostatin-receptor scintigraphy of subcutaneous and thyroid metastases from bronchial carcinoid. *J Nucl Med* 1996;37:1537–9.
15. Joseph K, Stapp J, Reinecke J, et al. Receptor scintigraphy with ^{111}In -pentetreotide for gastroenteropancreatic tumors. *Horm Metab Res Suppl* 1993;27:28–35.
16. Lamberts SWJ, Krenning EP, Reubi JC. The role of somatostatin and its analogs in the diagnosis and treatment of tumors. *Endocr Rev* 1991;12:450–82.
17. Fink G, Krelbaum T, Yellin A, et al. Pulmonary carcinoid: presentation, diagnosis and outcome in 142 cases in Israel and review of 640 cases from the literature. *Chest* 2001;119:1647–51.

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