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Utility of ¹¹¹Indium-pentetreotide Scintigraphy in Patients with Neuroendocrine Tumors

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Abstract

Background—Neuroendocrine (NE) tumors pose a diagnostic challenge with the need to utilize a combination of biochemical analysis, standard cross-sectional imaging, and more recently, nuclear medicine scans such as ¹¹¹indium–pentetreotide scintigraphy (somatostatin receptor scintigraphy, SRS; OctreoScan, Covidien Imaging Solutions, Hazelwood, MO). In this study we sought to evaluate the clinical utility of scintigraphy in the diagnosis and management of patients with NE tumors at a major university hospital.

Methods—A retrospective chart review was performed on all patients who underwent both ¹¹¹indium–pentetreotide scintigraphy and computed tomography/magnetic resonance imaging (CT/MRI) at a single institution between February 2001 and July 2008. Charts were reviewed for patient demographics, symptoms of NE disease, and results of biochemical testing, imaging studies, histopathologic diagnosis, and medical and/or surgical management.

Results—One hundred forty-five patients received ¹¹¹indium–pentetreotide scintigraphy (SRS) and concurrent cross-sectional imaging (CT/MRI) over the 7-year period studied. In the evaluation of primary disease, 60 % of tumors were localized by anatomic imaging, significantly greater than the 15 % detection rate achieved by SRS. In the evaluation of recurrent disease, 61 % of NE tumors were localized by cross-sectional imaging, significantly greater than the 31 % detection rate of SRS. Scintigraphy identified disease foci not seen on CT/MRI in just 8 of 74 of the cohort with evidence of disease and only altered the surgical management in 3 of 74 cases.

Conclusions—Cross-sectional CT/MRI imaging is sufficient for the localization of NE tumors. ¹¹¹Indium–pentetreotide scintigraphy does not significantly alter the surgical management of patients with NE tumors, and we suggest that it be selectively reserved for patients with disease that is occult to cross-sectional imaging.

Neuroendocrine (NE) tumors comprise a heterogeneous group of carcinomas which are thought to arise from amine precursor uptake and decarboxylation cells, which are widely disseminated throughout multiple organ systems. They include gastroenteropancreatic endocrine tumors such as carcinoids and pancreatic endocrine tumors, medullary thyroid cancers (MTCs), paragangliomas such as pheochromocytomas, and less commonly, small cell lung cancers and NE tumors of the anterior pituitary gland.^{1–3} NE tumors are rare, slow-

growing neoplasms that pose a diagnostic challenge because they are often innocuous at the time of presentation, and they are often only detected when metastases have developed, most commonly in the liver.^{4,5} Accurate localization of the primary tumor and metastatic foci, although frequently challenging, is essential because surgery remains the optimal treatment for locoregional, and in some cases distant, metastatic disease.^{6–9} Although it is clear that standard cross-sectional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI), as well as nuclear medicine studies such as somatostatin receptor scintigraphy (SRS), play an important role in the diagnosis, staging, and posttreatment follow-up of patients, the relative advantages of cross-sectional (CT and MRI) and functional (SRS) imaging remain unclear.

SRS, specifically ¹¹¹indium–pentetreotide scintigraphy, has been previously reported as an accurate tool for the detection of NE tumors, with reported sensitivities of 80–100 % depending on tumor type, location of primary tumor, size, and technique utilized.^{10,11} Compared with CT and MRI, SRS techniques have the advantages of whole-body visualization with high sensitivity and specificity, but radiolabeled peptides are frequently taken up in normal organs and SRS techniques have relatively low spatial resolution, potentially confounding accurate interpretation of the images.¹² Furthermore, by convention, the NE tumor has to be functioning with respect to the radiopharmaceutical utilized for SRS. As such, the aim of our study was to evaluate the additional clinical value of ¹¹¹indium–pentetreotide scintigraphy and its implication on surgical management as compared with cross-sectional imaging (CT and MRI) alone in patients with NE tumors at a major university hospital.

MATERIALS AND METHODS

Patients

Approval was obtained from the institutional review board to undertake a retrospective review of patients who received ¹¹¹indium–pentetreotide scintigraphy for initial NE tumor evaluation or for metastatic surveillance of disease from February 2001 to July 2008 at a single institution. The following data were reviewed from the medical record: age, gender, symptoms of NE disease, results of biochemical testing, imaging studies, histopathologic diagnosis, and medical and/or surgical management. Clinical suspicion of NE disease was based on the constellation of clinical symptoms characteristic of excess hormone production, including sudden flushing, tachycardia, palpitations, hypertension, diarrhea, headaches, visual changes, and anxiety. For biochemical analysis, common NE tumor markers such as chromogranin A, urine 5-hydroxyindoleacetic acid, calcitonin, gastrin, plasma metanephrines/normetanephrines, and/or urinary catecholamines/metanephrines were analyzed and considered suggestive of NE disease if elevated above institutional normal parameters. The presence of any one of these biochemical markers elevated above institutional normal parameters was considered to be biochemical evidence of disease in our analysis. CT or MRI of the abdomen, chest, and/or neck were performed initially in all patients according to the specific clinical indication and were followed by ¹¹¹indium–pentetreotide scintigraphy, which was interpreted independently. To evaluate the additional value of SRS in patient management, patients were evaluated on the basis of the use of

imaging to localize primary or recurrent/metastatic disease. The data were analyzed to determine how often the results of SRS altered the treatment plan, e.g., the decision to proceed with surgical treatment, and the choice of operation.

SRS

Scintigraphy was performed after intravenous administration of ^{111}In -pentetreotide (mean dose 233 MBq; range 71–342 MBq) (OctreoScan kit; Covidien Imaging Solutions, Hazelwood, MO). Because the sensitivity of this mode of imaging is reduced in patients receiving therapeutic doses of octreotide acetate, octreotide therapy was discontinued 72 h before administration of SRS. Doses were adjusted for patients weighing under 45 kg per our institutional in-house nomogram. Images were obtained with the GE Infinia Nuclear Gamma Camera (GE Medical Systems, Waukesha, WI) equipped with a medium-energy collimator. After injection, patients were scanned at 4h for a quick whole-body survey (scan speed at 4 min per view), and a single-photon emission computed tomography (SPECT)/CT of the area of interest was obtained. At 24 h after injection, and occasionally 48 h after injection, a whole-body scan and SPECT/CT images of the area of interest were acquired again. Scintigraphic images were visually analyzed by one of three board-certified nuclear radiologists, and disagreements were resolved by consensus. The indication for scintigraphy was primarily to determine the extent of NE disease; however, in three cases, the indication also included evaluation for octreotide therapy.

Statistical Analysis

Statistical analysis was performed with StatPac, version 4, using the one-sample *t*-test. A *p*-value of <0.05 was considered statistically significant.

RESULTS

Patient Demographics and Clinical Characteristics

A total of 202 patients underwent ^{111}In -pentetreotide scintigraphy (SRS) over the 7-year period studied. Fifty-eight patients were excluded from the analysis because of the absence of corroborative cross-sectional imaging (CT/MRI) performed within 30 days of scintigraphy. Of the 144 patients with concurrent cross-sectional imaging and scintigraphy, 91 (63 %) were female, with a mean age of 50 years (Table 1). Thirty-seven patients were investigated in the primary staging of their NE tumors. The remaining 107 patients were evaluated for recurrent and metastatic disease.

Among the 37 patients evaluated for the presence of a new tumor who had both cross-sectional imaging and SRS for primary staging, 32 (86 %) had biochemical testing performed to facilitate diagnosis. Twenty (63 %) of these 32 patients had biochemical data that were suggestive of NE disease. Among the 107 patients evaluated for recurrence of previously diagnosed NE disease or for evaluation of lesions amenable to tumor-targeted somatostatin radiotherapy, 42 patients (39 %) were evaluated for recurrent carcinoid disease, 32 (30 %) were evaluated for recurrent islet cell tumors, and 23 (21 %) for recurrent MTC. The remaining 10 patients were evaluated for the recurrence of other tumors with NE features. Out of the total patients evaluated for recurrent disease, 42 patients (39 %)

presented with clinical signs or symptoms consistent with recurrent or metastatic NE disease, and 54 (72 %) of 75 of these patients in whom laboratory testing was performed had biochemical evidence NE disease.

Radiographic Detection Rate in Patients with Biochemical Evidence of NE Disease

Out of the 37 total patients evaluated for primary NE tumors by cross-sectional and SRS, 20 patients had biochemical evidence of disease. This group contained initial clinical diagnoses of carcinoid tumors, pancreatic NE tumors, and pituitary adenomas. Among the 20 patients with biochemical evidence of NE disease, 12 (60 %) primary NE tumors were localized by cross-sectional imaging, which is significantly greater than the 3 (15 %) primary NE tumors localized by SRS (Table 2).

Fifty-four patients of the total 107 evaluated for recurrent NE tumors had biological evidence of disease. Cross-sectional imaging localized disease in 12 (67 %) of 18 cases of recurrent carcinoid, 13 (77 %) of 16 cases of recurrent MTC, and 8 (42 %) of 19 cases of recurrent pancreatic NE tumors. In contrast, SRS localized disease in 6 (33 %) of 18 cases of recurrent carcinoid, 5 (31 %) of 16 cases of recurrent MTC, and 6 (32 %) of 19 of recurrent pancreatic NE tumors (Table 3). Among the total 54 cases of recurrent NE tumors with biological evidence of disease, cross-sectional imaging localized disease in a total of 33 cases (61 %), which is significantly greater than the 17 cases (31 %) in which disease was localized by SRS.

Comparison of SRS and Cross-sectional Imaging on Disease Management

Out of the 20 patients with biochemical evidence of primary NE tumors, 2 (10 %) had disease localized by SRS that was not seen on cross-sectional imaging (Table 4). Surgical management was necessitated in one of these cases as a direct result of the SRS results.

Out of the 54 patients with biochemical evidence of recurrent or metastatic NE disease, 6 (11 %) had disease identified only as result of SRS. Among these 6 cases, 1 case was in the evaluation of recurrent carcinoid, 2 cases were in the evaluation for recurrent MTC, and 3 cases were in the evaluation of recurrent pancreatic NE tumors (Table 4). Nodal disease was the most common SRS identified foci of disease not seen in cross-sectional imaging in patients evaluated of recurrent or metastatic NE tumors. The management of 2 (33 %) of these 6 cases was dictated by the SRS results, necessitating surgery.

Imaging Characteristics in Cases with Surgical Management

Surgery was performed on a total of 9 (24 %) out of the entire cohort of 37 patients evaluated for a primary NE tumor. Among these 9 patients, 5 (56 %) had biochemical evidence of NE disease, 4 (44 %) had signs and symptoms consistent with NE disease, and 3 (33 %) had neither biochemical evidence nor signs and symptoms consistent with NE disease. Among these 9 patients with surgical management, cross-sectional imaging localized the site of disease in 7 (78 %). This is in contrast to SRS, which localized the site of disease in 2 patients (22 %) (Table 5). Of note, none of these patients with primary NE tumors managed with surgery had their disease site localized by both SRS and cross-sectional imaging (Table 5). Additionally, among the 3 patients in whom there was no initial

evidence of NE disease, cross-sectional imaging localized the disease in all 3 cases, whereas SRS found no evidence of disease in all 3 cases.

In the patients evaluated for recurrent NE tumors, 43 (40 %) out of the total 107 cases evaluated were surgically managed. Out of these 43 cases, signs and symptoms of NE disease were present in 16 (37 %), and biochemical testing was suggestive of disease in 28 (65 %); 11 (26 %) of these patients in whom surgery was necessitated had neither biochemical nor clinical signs and symptoms of NE disease. Among the 43 patients with surgical management for their recurrent NE tumors, cross-sectional imaging localized the disease focus in 33 (77 %), which is significantly greater than the 19 (44 %) in which SRS localized the site of disease. In all cases with surgical management for recurrent NE disease, 15 (35 %) had the disease site localized by both SRS and cross-sectional imaging. Additionally, among the 11 patients in whom there was no initial evidence of disease, cross-sectional imaging localized the disease focus in 9 (82 %), whereas SRS localized the disease focus in 1 (9 %).

DISCUSSION

The principal finding of this study is that cross-sectional CT/MRI imaging is a sufficient imaging modality for the localization of NE tumors, both in the evaluation of primary and recurrent disease. In evaluating the clinical utility of cross-sectional imaging SRS, we focused our analysis on the role these imaging modalities played on influencing surgical management by delineating the extent of NE disease. Through this retrospective review, we found that cross-sectional imaging had a significantly greater detection rate of NE tumors compared to SRS in the evaluation of both primary and recurrent NE tumors. Specifically, in patients with biochemical evidence of primary NE tumors, cross-sectional imaging detected disease in 60 % of cases, versus the 15 % detection rate achieved via SRS. Similarly, in the evaluation of patients with biochemical evidence of recurrent NE tumors, cross-sectional imaging localized the disease in 61 % of cases, which was significantly greater than the 31 % detection rate achieved by SRS.

These results are in contrast with some previous work reporting that SRS is highly sensitive in localizing NE tumors, with reported sensitivities ranging 80–90 %.^{10,11,13} However, our results are similar to more recent studies evaluating the utility of ¹¹¹indium–pentetreotide scintigraphy on the therapeutic decision making in patients with NE tumors. In a study reporting the utility of SRS in the management of adrenocorticotrophic hormone-producing tumors, similar findings were reported in that octreotide scintigraphy did not significantly alter the management of NE disease compared to CT or MRI.¹⁴ Furthermore, it has been reported that even in occult disease, repeat CT/MRI scanning was more beneficial at locating initially occult disease than SRS.¹⁴ It has been previously reported that SRS may facilitate radiologic interpretation of cross-sectional imaging.¹⁵ However, among the patients in our study with surgical management, none of the patients in evaluation for primary disease had disease localized by both SRS and cross-sectional imaging, and only 15 % of recurrent cases of NE disease managed with surgery had disease localized by both SRS and cross-sectional imaging. Therefore, we report that only in a minority of cases were SRS and cross-sectional

imaging both positive, allowing for both imaging modalities to be used jointly for image analysis and surgical planning.

Although our data suggest that cross-sectional imaging is sufficient for the localization of NE tumors, the scintigraphic findings did discover disease not localized by cross-sectional imaging in 8 patients out of the total 74 patients with biochemical evidence of primary or recurrent disease. The majority of these 8 cases were in the setting of recurrent NE disease in patients with a history of NE tumors. Furthermore, although SRS localized disease not seen by cross-sectional imaging in 8 cases out of the entire cohort with biochemical evidence of disease, in only 3 of these cases did the SRS results directly affect the patient's management by leading to surgery. Therefore, even though SRS did discover new tumor sites in a minority of cases, the final impact on therapeutic decisions was even more minimal. Similar to previously reported data, we also found false-positive SRS results in that 1 of the 3 cases in which SRS localized disease occult to cross-sectional imaging was identified as a benign lesions on final pathology.^{13,15}

However, our data do support the utility of SRS as a second-line method for the evaluation of patients with biochemical diagnosis of disease in which cross-sectional imaging is inconclusive. The early detection of primary NE tumors can affect the survival of patients; therefore, SRS may be warranted to localize disease not seen on cross-sectional CT/MRI imaging.¹⁶ It has been reported that SRS had a detection rate of 39 % in the setting of localizing NE tumors, which are not found on cross-sectional imaging.¹⁷ Similarly, as described, we found 8 cases of disease localized only by SRS, which eventually led to surgical resection of NE tumors in 2 cases.

Our study was limited by the inability to fully investigate every potential disease site by surgical pathology because in patients with metastatic lesions, histological confirmation of these lesions would not change the patient's management, and thus surgery would be unethical. Surgical pathological evaluation is the gold standard for diagnosing NE tumors, and although we find cross-sectional imaging to be far more useful in diagnosing NE tumors than SRS, it is accepted that even cross-sectional imaging may not fully delineate the extent of NE disease. Furthermore, as a total of 52 patients underwent surgery for treatment out of the 144 patients evaluated, there may be some inherent recall bias in our data set. Also, we did not directly determine the cost-benefit implications, but it is well accepted that reducing the number of diagnostic procedures will lower financial cost, patient discomfort, and potential morbidity. Although not included in this report, future studies evaluating the clinical utility of emerging imaging technologies using positron emission tomography tracers are warranted.

In conclusion, patients with a clinical history suggestive of NE disease, biochemical testing should be used to confirm the diagnosis, and cross-sectional imaging is sufficient for tumor localization. In the absence of hereditary disease or a history of NE tumors, ¹¹¹indium-pentetreotide scintigraphy does not significantly alter the surgical management of these patients. We therefore suggest that this method of imaging be selectively reserved for patients with a biochemical diagnosis of a NE tumor in whom no tumor can be localized on extensive cross-sectional imaging.

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TABLE 1

Demographic and clinical characteristics of patients receiving corroborative CT/MRI and ¹¹¹indium–pentetreotide scintigraphy for the evaluation of primary or recurrent neuroendocrine disease

Characteristic	Evaluation of primary disease	Evaluation of metastatic/recurrent disease	All patients
No. of patients	37	107	145
Age (y), mean ± SEM	44 ± 18	52 ± 16	50 ± 17
Sex, M:F	12:25	41:66	53:92
Patients with biochemical testing	32	75	107
Positive biochemical evidence of disease	24	69	93

TABLE 2

Detection rates of primary NETs by cross-sectional imaging and SRS 20 patients with biochemical evidence of neuroendocrine disease

NET classification	<i>n</i>	Cross-sectional imaging localized	SRS localized
All	20	12 (60 %) *	3 (15 %)

NET neuroendocrine tumor, *SRS* somatostatin receptor scintigraphy

* Statistically significant difference between detection rates of imaging modalities ($p < 0.05$)

TABLE 3

Detection rates of recurrent NETs by cross-sectional imaging and SRS in patients with recurrent or metastatic neuroendocrine disease

NET classification	<i>n</i>	Cross-sectional imaging localized	SRS localized
All	54	33 (61 %) *	17 (31 %)
Carcinoid	18	12 (67 %)	6 (33 %)
MTC	16	13 (81 %)	5 (31 %)
PET	19	8 (42 %)	6 (32 %)

NET neuroendocrine tumor, *SRS* somatostatin receptor scintigraphy, *MTC* medullary thyroid cancer, *PET* pancreatic neuroendocrine tumors

* Statistically significant difference between detection rates of imaging modalities ($p < 0.05$)

TABLE 4

Cases in which SRS detected disease that was not observed on CT/MRI

Sex/age (y)	Indication	SRS-identified foci of disease	Surgical histopathologic diagnosis	Altered surgical management?
M/79	Primary NET	Temporal lobe	NA	No
F/33	Primary NET	Pancreatic head lesion	Pancreatic islet cell tumor	Yes
F/42	Recurrent/metastatic carcinoid	Nodal disease	Metastatic carcinoid disease	Yes
M/70	Recurrent/metastatic MTC	Nodal disease	NA	No
M/56	Recurrent/metastatic MTC	Nodal disease	NA	No
F/61	Recurrent/metastatic PET	Hepatic and vertebral metastases	NA	No
F/52	Recurrent/metastatic PET	Appendiceal lesion	NA	No
M/63	Recurrent/metastatic PET	Pancreatic head lesion	Benign disease	Yes

¹¹¹Indium–pentetreotide scintigraphy (SRS) identified foci of disease not seen on cross-sectional imaging in just 8 (11 %) of 74 of the cohort with biochemical evidence of neuroendocrine disease, and ¹¹¹indium–pentetreotide scintigraphy altered the surgical management of only 3 (4 %) of 74 of this cohort

SRS somatostatin receptor scintigraphy, *CT* computed tomography, *MRI* magnetic resonance imaging, *NET* neuroendocrine tumor, *NA* not available, *MTC* medullary thyroid cancer, *PET* pancreatic neuroendocrine tumors

TABLE 5

Imaging characteristics of all cases with surgical management of neuroendocrine tumors

Indication	Total no. of surgical cases	Disease localized by		
		Both SRS and cross-sectional imaging	Cross-sectional imaging only	SRS only
Primary disease	9	0 (0 %)	7 (78 %)	2 (22 %)
Recurrent disease	43	15 (35 %)	18 (42 %)*	4 (9 %)

SRS somatostatin receptor scintigraphy, *CT* computed tomography, *MRI* magnetic resonance imaging* Statistically significant difference between detection rates of cross-sectional imaging (CT/MRI) versus SRS ($p < 0.05$)