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evaluation of head and neck lesions.**

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¹¹¹In Octreotide Scintigraphy in the Evaluation of Head and Neck Lesions

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PURPOSE: To evaluate indium 111 octreotide scintigraphy for the detection of suspected neuroendocrine lesions of the head and neck. **METHODS:** After receiving 6 mCi of ¹¹¹In octreotide, 22 patients with suspected lesions of the head and neck were examined with both planar and single-photon emission CT (SPECT). Static images, obtained at 4 hours, included the head/neck, chest, abdomen, and pelvis. Additional SPECT images were obtained at 4 or 24 hours. Studies were compared with available conventional radiologic examinations (12 CT, 11 MR, and three angiographic studies) as well as with clinical and pathologic findings. **RESULTS:** Eighteen of the 22 patients had abnormal findings at scintigraphy. Eleven paragangliomas were seen in 10 patients, metastatic medullary thyroid carcinoma in three patients, thyroid adenoma in two patients, and Merkel cell tumor, carcinoid, and plasmacytoma in one patient each. Surgical confirmation was available in 13 patients. The smallest lesion detected was 1.5 cm. There was one false-positive and one false-negative examination. **CONCLUSION:** ¹¹¹In octreotide scintigraphy is a useful imaging tool for the detection of primary and metastatic neuroendocrine tumors of the head and neck that are larger than 1.5 cm. This technique enables distinction of glomus tumors from other masses (such as neuromas) and can be used in the postoperative setting to distinguish scar from recurrent paraganglioma. Since it is an examination of the entire body, it has great utility for detecting multicentric paraganglioma and for screening patients with familial paraganglioma.

Index terms: Radionuclide imaging; Neck, neoplasms

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Neuroendocrine cells produce peptides and amines that act as hormones or as neurotransmitters throughout the body. These cells have previously been referred to as *APUD* (amine precursor uptake and decarboxylation) cells. Tumors of neuroendocrine origin have cell surface receptors with a high affinity for somatostatin. Somatostatin is a naturally occurring cyclic neuropeptide composed of 14 linked amino acids. It is naturally present in the brain

stem, hypothalamus, cerebral cortex, and gastrointestinal tract. Somatostatin has a myriad of physiological effects and is a universal inhibitor of hormone release from a variety of organs. It inhibits the release of growth hormone and thyrotropin from the anterior pituitary gland and prevents release of insulin, gastrin, glucagon, and vasointestinal peptide from the gastrointestinal tract. Many tumors have been reported to have a high density of somatostatin receptors, including carcinoids, paragangliomas, medullary thyroid carcinomas, islet cell tumors, pheochromocytomas, and other neuroendocrine and nonneuroendocrine tumors (1).

Octreotide is an octapeptide analogue of somatostatin that can bind to somatostatin receptors. Octreotide, with a half-life of 90 to 120 minutes, is of greater clinical utility than natural somatostatin, with a half-life of 2 to 3 minutes. This analogue has been labeled with both iodine 123 and indium 111 and is recommended for use in the scintigraphic location of primary and

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metastatic neuroendocrine tumors, which bear somatostatin receptors.

The purpose of this study was to evaluate the use of ^{111}In pentetretotide, a DTPA conjugate of octreotide, using a commercially available product recently approved by the Food and Drug Administration (Octreoscan, Mallinkrodt Medical, St Louis, Mo) for the detection of suspected neuroendocrine lesions of the head and neck.

Materials and Methods

Twenty-two patients with suspected lesions of the head and neck were examined with ^{111}In octreotide scintigraphy. The group included 15 women and seven men, ranging in age from 30 to 85 years (average age, 59 years). Octreotide was administered intravenously as ^{111}In pentetretotide, a DTPA conjugate of octreotide, in a dose of 6 mCi. Patients were imaged with both planar and single-photon emission computed tomography (SPECT). For planar imaging, a medium energy collimator was used with energies centered at 20% of the two primary photopeaks (171.3 and 245.4 keV) of indium III. Static images at 4 hours were obtained for 10 to 15 minutes per view, which included the head and neck, chest, abdomen, and pelvis. SPECT scans of the area of interest were obtained at either 4 or 24 hours. For most patients, the SPECT studies were obtained on a dual-detector ADAC (Milpitas, Calif) system, with 64 steps at 40 seconds per step over 360° using a 64×64 matrix.

These studies were compared with conventional imaging examinations, when available, including 12 CT, 11 magnetic resonance (MR) (including one with MR angiography), and three angiographic studies. The octreotide studies were also compared with clinical and surgical pathologic findings, when available.

Results

Review of medical records of the 22 patients revealed a variety of clinical indications for the study, including a palpable or visible mass ($n = 13$), hearing loss/or tinnitus ($n = 5$), history of paraganglioma resection ($n = 4$), Cushing syndrome ($n = 1$), and medullary thyroid carcinoma with elevated serum calcitonin levels ($n = 3$) (see Table).

Eighteen patients had evidence of abnormal radiotracer uptake on octreotide scintigraphy (see Table). In four of these patients, abnormal uptake was noted at more than one site. Eleven paragangliomas were identified in 10 patients (one patient had bilateral carotid body tumors) (Fig 1). Three patients had metastatic medullary thyroid carcinoma; two patients had thyroid adenoma (surgically confirmed); one patient had a Merkel cell tumor of the skin; one patient

had a carcinoid tumor; and one patient was found to have a plasmacytoma of the skull base. Surgical confirmation was obtained in 13 patients. The smallest lesion detected was 1.5 cm.

Of the 11 paragangliomas, seven were carotid body tumors, three were glomus jugulare tumors, and one was a glomus vagale. Of the four patients who had a history of paraganglioma resection, two had normal studies and two had abnormal uptake. In the latter two, both patients showed uptake in sites different from the location of their previous tumors. Thus, none of the four patients who had had resection of a paraganglioma showed evidence of recurrent disease at the surgical site. One patient (case 2) had had complete resection of a left glomus jugulare tumor and a tumor of the right carotid body. The new lesion detected on this octreotide study was consistent with a tumor of the left carotid body by both MR imaging and MR angiography, with splaying of the carotid bifurcation (Fig 2). Another patient (case 20) had had a left glomus vagale tumor removed several years earlier. Octreotide scintigraphy showed uptake on the right and MR imaging revealed a 1.5-cm mass, consistent with a right glomus intravagale tumor. Conventional angiography confirmed the hypervascular nature of the lesion, consistent in location and appearance with a right glomus intravagale tumor. Thus, both patients (cases 2 and 20) had multicentric (although not synchronous) paragangliomas. Two patients (cases 12 and 20) had a familial history of paragangliomas.

One patient (case 8) underwent extensive medical evaluation, which could have been limited had the octreotide study been obtained early on. This 41-year-old woman had symptoms of severe Cushing syndrome, with swelling of the face and ankles, weight gain, facial hair growth, easy bruising, hypokalemia, and, ultimately, steroid psychosis. A clinical diagnosis of Cushing syndrome was established and a CT examination of the chest and abdomen were obtained, which were interpreted as negative at an outside institution except for bilateral symmetric enlargement of the adrenal glands. MR findings of the sella were also within normal limits. The symptoms persisted and the patient underwent an invasive procedure, venous sampling of the petrosal sinus, which did not suggest any focality. An octreotide study was eventually obtained, which showed uptake in the anterior aspect of the chest. Reevaluation of the

Patients examined with octreotide scintigraphy

Case	Age, y/ Sex	Presenting Signs/Symptoms	Findings at Octreotide Study	Surgical Confirmation	Diagnosis
1	62/M	R neck mass	R neck and thyroid masses	Yes	R carotid body tumor and R thyroid adenoma
2	34/M	L neck mass, prior paragangliomas resected	L neck mass	No	L carotid body tumor
3	33/F	L neck mass	L thyroid mass	Yes	L schwannoma and thyroid adenoma
4	67/F	R ear mass, tinnitus, decreased hearing on R	R neck mass	Yes	R glomus jugular tumor
5	55/F	R ear mass, pain R ear, decreased hearing on R	R neck mass	No	R glomus jugular tumor
6	73/M	Bilaterally decreased hearing, bilateral tinnitus	None	No	None
7	85/F	L ear pressure	None	No	Presumed glomus tympanicum tumor
8	41/F	Cushing syndrome	Retrosternal mass	Yes	Carcinoid tumor in anterior mediastinum
9	73/F	L neck mass	L neck	Yes	Merkel cell tumor
10	55/F	L neck mass	L neck	No	Glomus jugular tumor
11	58/M	2-cm parapharyngeal space mass (incidental MR finding)	None	No	Unknown
12	57/M	Bilateral neck masses	R and L neck masses	Yes	Bilateral carotid body tumors
13	69/F	Past medullary thyroid carcinoma, rising calcitonin levels	Mediastinum mass	No tumor found at surgery	False positive finding
14	66/M	Past medullary thyroid carcinoma, rising calcitonin levels	Multiple sites	Yes	Metastatic medullary thyroid carcinoma
15	65/F	15-year history of L neck mass	L neck mass	Yes	L carotid body tumor
16	60/F	Past medullary thyroid carcinoma, rising calcitonin levels	Multiple sites	Yes	Metastatic medullary thyroid carcinoma
17	67/F	L neck mass	L neck mass	Yes	L carotid body tumor
18	70/F	Past removal of L glomus vagale tumor	None	No	No recurrence
19	66/F	Past removal of L glomus tympanicum tumor	No mass at surgical site, R thyroid mass	No	No recurrence, questionable lesion of R thyroid
20	30/F	Past removal of L glomus vagale tumor	R neck mass	No	R glomus vagale tumor
21	49/M	Tinnitus	R skull base mass	Yes	Plasmacytoma
22	68/M	L neck mass	L neck mass	Yes	L carotid body tumor

chest CT scan revealed a small soft-tissue density in the anterior mediastinum, which had the appearance of a lymph node and measured less than 2 cm. At surgery, a 2- to 3-cm mass was found in the expected location and was confirmed to be a carcinoid tumor, which was responsible for ectopic production of corticotropin. Had the octreotide study been obtained earlier, the invasive venous sampling procedure might have been avoided.

One patient (case 13) had a false-positive study. This 69-year-old woman had a history of thyroidectomy for medullary carcinoma of the thyroid. Her calcitonin levels became elevated, and an octreotide study suggested uptake in the mediastinum. However, exploration of the mediastinum showed no evidence of tumor, although her calcitonin levels remain elevated.

Another patient (case 7) had a false-negative study. This 85-year-old woman was noted on physical examination to have a reddish mass behind the left tympanic membrane. CT of the temporal bones revealed a small, less than 1-cm, mass near the cochlear promontory, consistent with a glomus tympanicum. The lesion was not surgically confirmed, owing to the patient's advanced age. This lesion was not detected by the octreotide study; however, a lesion smaller than 1 cm is likely to be below the threshold of the examination.

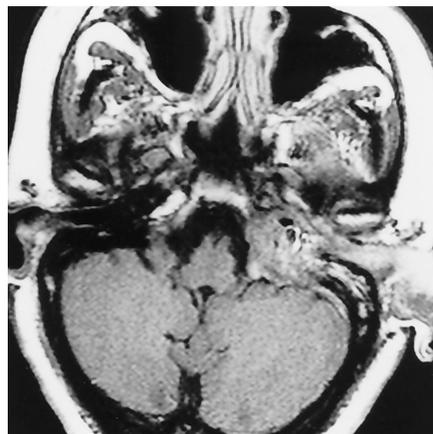
Discussion

¹¹¹In octreotide, a somatostatin analogue, has been available in Europe since 1989 and has been available commercially in the United

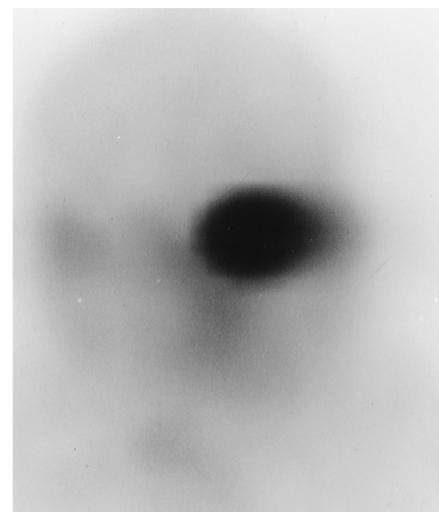
Fig 1. Large left glomus jugulare tumor in a 55-year-old woman with a mass protruding from the left external auditory canal.

A, Postcontrast (gadopentetate dimeglumine, 0.1 mmol/kg) MR image (550/20/2 [repetition time/echo time/excitations]) shows prominent enhancement of the mass with residual areas of signal void, compatible with enlarged vascular structures.

B, Coronal planar image of the head/neck from the octreotide study shows intense uptake in the region of the left side of the skull base. Findings are consistent with a glomus jugulare tumor.

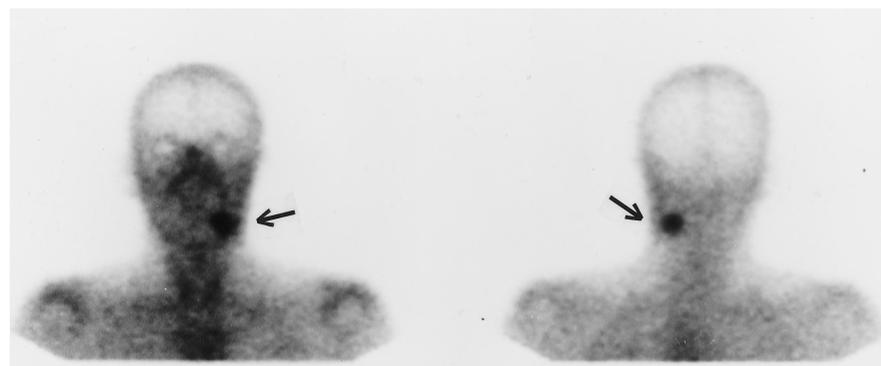


A



B

Fig 2. Left carotid body tumor in a 34-year-old man who had had a left glomus jugulare tumor removed and a right carotid body tumor resected several years earlier. He presented with a new left-sided neck mass. Coronal octreotide scintigraphic image reveals uptake in the left side of the neck, corresponding to the site of a palpable mass (arrows). An MR angiogram (not shown) confirmed splaying of the carotid bifurcation, consistent with a left carotid body tumor.



States since 1993. Large European clinical trials have determined that octreotide uptake by somatostatin receptors can be seen in a number of neuroendocrine and nonneuroendocrine tumors (1). Those lesions that have the greatest affinity for octreotide include carcinoid tumor, paraganglioma, medullary thyroid carcinoma, oat cell carcinoma, islet cell tumors, pituitary adenoma, pheochromocytoma, and neuroblastoma (1). However, many other tumors have shown octreotide uptake as well, although not as consistently as those just named. These other tumors include astrocytoma, lymphoma, breast carcinoma, meningioma (1), and Merkel cell tumors (2). Octreotide uptake can also be seen in some autoimmune and granulomatous diseases (1).

The longer half-life of octreotide (90 to 120 minutes) compared with that of native somatostatin (2 to 3 minutes) makes it a more clinically useful compound. This utility not only enables radiolabeled octreotide to detect neuroendocrine tumors but cold (unlabeled) oc-

treotide has also been used to treat the debilitating symptoms associated with endocrine-secreting tumors, such as flushing and secretory diarrhea (Sandostatin, Sandoz, Basel, Switzerland). This somatostatin analogue has also been reported to slow the growth of certain tumors by interfering with growth-hormone release (3).

The present study establishes the utility of ^{111}In octreotide scintigraphy in the detection of neuroendocrine tumors in the head and neck region that are larger than 1.5 cm. Our one false-negative result (a glomus tympanicum tumor less than 1 cm in diameter) indicates that this test may be unreliable for masses smaller than 1 cm. In the abdomen, octreotide scintigraphy appears to have a 90% sensitivity for neuroendocrine tumors greater than 2 cm in diameter, but only a 50% sensitivity for tumors smaller than 2 cm (4).

Octreotide scintigraphy is particularly useful in confirming or excluding paraganglioma in selected cases (Fig 3). For many skull base

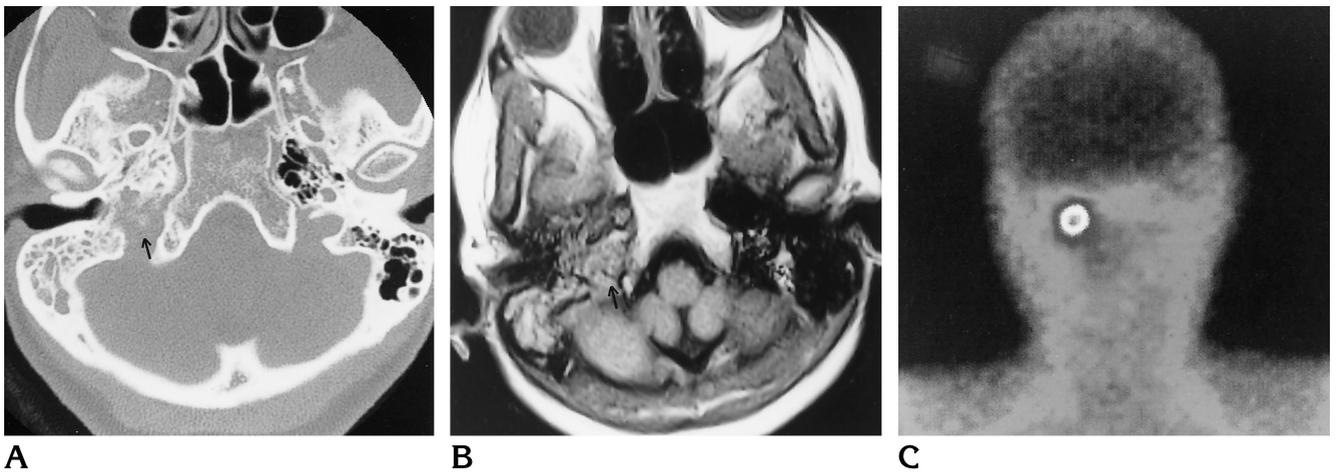


Fig 3. Right glomus jugulare tumor in a 52-year-old woman who had pain in the right ear and loss of hearing on the right.
A, CT scan reveals extensive bone destruction on the right side of the skull base with expansion of the jugular foramen (*arrow*).
B, T1-weighted MR image (550/30) shows the right skull base lesion (*arrow*). Inflammatory changes are seen more laterally in the right mastoid.
C, Coronal scintigraphic image from the octreotide examination reveals focal radiotracer uptake in the same location.

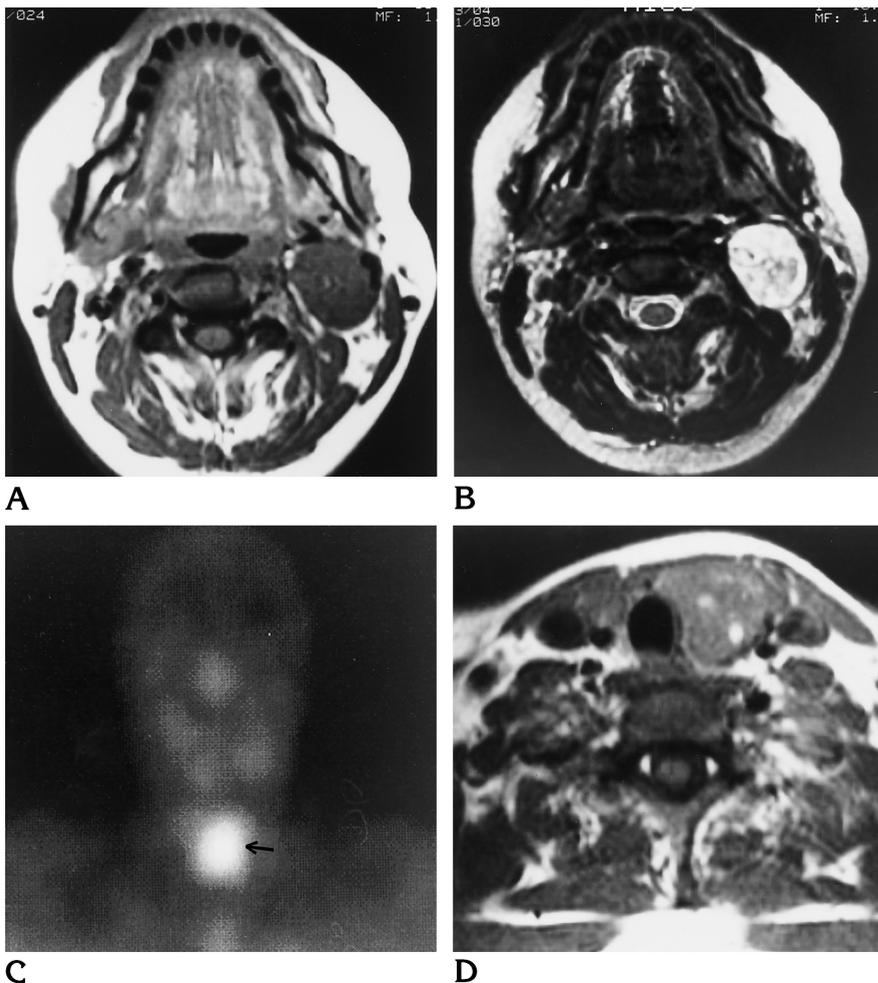


Fig 4. Neuroma/thyroid adenoma in a 33-year-old woman who had a palpable mass in the upper left part of the neck.

A, Axial T1-weighted MR image (500/11) reveals a fairly homogeneous mass in the left poststyloid parapharyngeal space with splaying of the carotid and jugular vessels.

B, T2-weighted image (2400/80) shows increased signal within the mass, which is slightly inhomogeneous.

C, Coronal scintigraphic image shows radiotracer accumulation, but not at the site of the palpable mass. The uptake is lower in the neck and more midline (*arrow*). No uptake is seen in the upper left part of the neck.

D, Axial T1-weighted MR image (500/11) at the level of the thyroid gland reveals enlargement of the left lobe of the thyroid, which is heterogeneous in appearance. This had not been clinically apparent. The location of uptake on the octreotide study correlated well with this thyroid lesion. At surgery, the mass in the left upper part of the neck was found to be a neuroma, while the thyroid lesion was an adenoma.

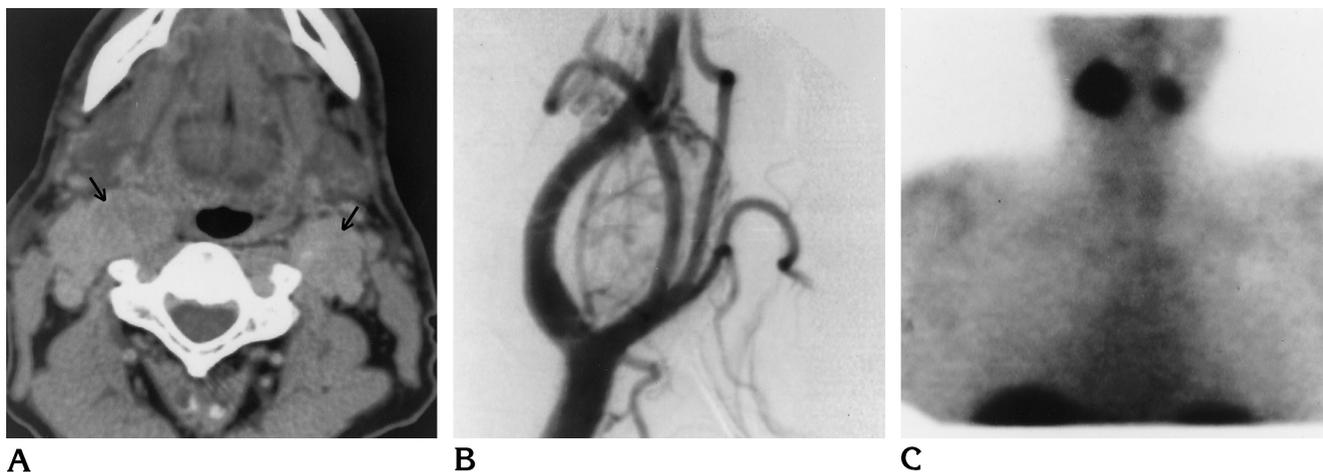


Fig 5. Bilateral carotid body tumors in a patient with familial paraganglioma.
 A, Axial CT scan reveals bilateral neck masses, right larger than left (*arrows*).
 B, Right common carotid angiogram reveals splaying of the carotid bifurcation, compatible with a carotid body tumor. Later images showed a dense tumor stain at this site. A similar appearance was present at the left carotid bifurcation.
 C, ^{111}In octreotide scintigraphic image reveals intense uptake bilaterally, greater on the right. The larger, right-sided lesion was removed and confirmed to be a carotid body tumor.

lesions, the primary differential is neuroma versus paraganglioma (Fig 4). The MR appearance of paraganglioma has been described as "salt and pepper." On T2-weighted images, the lesion appears bright with multiple signal voids caused by the intense vascularity of these lesions (5). However, not all paragangliomas have this appearance, particularly the smaller ones (6). In the past, suspected paragangliomas were evaluated by angiography, which clearly differentiated the vascular paraganglioma from the relatively avascular neuroma. Octreotide scintigraphy is a noninvasive procedure that can aid in this differentiation. An additional benefit over angiography is that ^{111}In octreotide scintigraphy is an examination of the entire body whereas angiography is limited to a specific site. Thus, with one examination, a paraganglioma can be differentiated from a neuroma, and any other coexistent paragangliomas can be identified and localized. Octreotide scintigraphy is thus an excellent alternative to an invasive angiographic procedure.

Angiography is not only diagnostic for paraganglioma but is helpful in preoperative planning, as it clearly delineates the vascular supply. Embolization can also be performed at the time of angiography. Yet even for those patients undergoing angiography, octreotide scintigraphy is a useful adjunct, providing such addi-

tional information as the presence of multiple tumors, which are seen in 10% of patients with paraganglioma and even more frequently in familial tumors (7, 8) (Fig 5). Angiography, MR imaging, and CT do not cover the entire body on a single examination.

Octreotide can also be used to screen family members of patients with known paraganglioma, as approximately 9% of patients with paraganglioma have a familial history of this disease (7). In our study, two of the 22 patients had a positive family history for paraganglioma, and we are attempting to screen other family members.

Octreotide scintigraphy can also be used to identify recurrent disease in patients with a history of neuroendocrine tumor. Recurrent medullary thyroid carcinoma was suggested by the octreotide study in all three patients who had a history of medullary thyroid carcinoma and rising calcitonin levels. However, one of these findings appears to be a false-positive result. Although none of the four patients in this study with prior paraganglioma resection had tumor recurrence at the surgical site, octreotide scintigraphy has documented recurrent paragangliomas in other studies (9). ^{111}In octreotide could also prove extremely useful in the examination of patients with multiple endocrine neoplasia syndromes, who are prone to incur a variety of neuroendocrine tumors (pheochromocytoma,

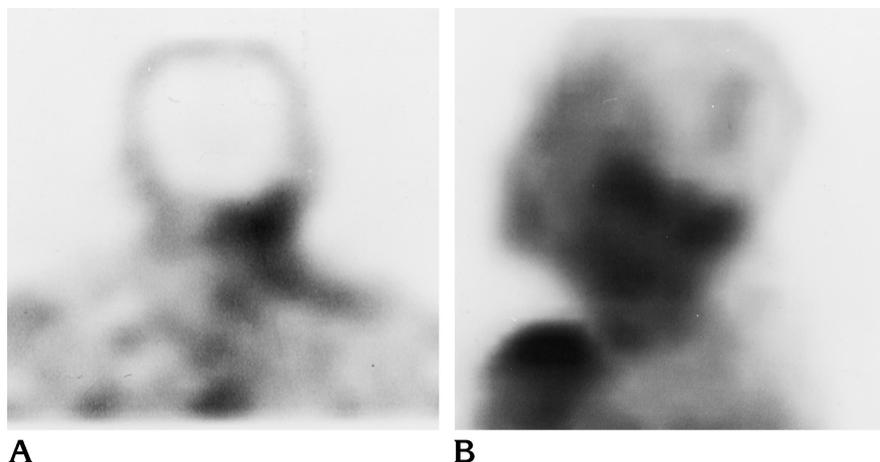


Fig 6. Merkel cell tumor. Coronal (A) and oblique sagittal (B) scintigraphic images from the octreotide study show extensive uptake on the left, denoting the full extent of this cutaneous neuroendocrine neoplasm.

pituitary adenoma, medullary thyroid carcinoma, pancreatic islet cell tumors, and so on).

Merkel cell tumors are aggressive neuroendocrine tumors of the skin with a propensity for nodal spread and local recurrence (Fig 6). While physical examination and biopsy sampling are usually diagnostic for the primary site, octreotide scintigraphy can be extremely helpful in the detection of local nodal disease, which occurs in 50% to 60% of patients (10), as well as of distant metastatic disease, which is seen in more than 33% of patients (10).

In two patients (cases 1 and 3), thyroid adenomas were identified at octreotide scintigraphy and subsequently confirmed at surgery. These lesions were not clinically symptomatic and were incidental findings. Scintigraphic uptake in the thyroid can also indicate a medullary thyroid carcinoma or an intrathyroidal paraganglioma (11), and thus focal activity in the thyroid bed on octreotide scanning warrants either biopsy or close clinical and radiologic follow-up.

One patient (case 21) had a plasmacytoma that showed abnormal radiotracer accumulation on ^{111}In octreotide examination. This patient, who presented with a skull base mass, had no history of myeloma. The octreotide study was obtained to evaluate a possible paraganglioma. Although focal uptake was seen, the activity was much less intense than that associated with known paragangliomas and was seen better on the delayed images, whereas all paragangliomas are quite evident on the 4-hour scans. The MR findings were not typical of either plasmacytoma or paraganglioma; however, surgical resection revealed a plasmacytoma, and further laboratory studies were consistent with multiple myeloma. It is noteworthy that the

pattern of uptake in this patient was significantly different from that seen with paragangliomas of the skull base. Nonneuroendocrine tumors (as well as some autoimmune and granulomatous diseases) have been reported to show uptake on octreotide scintigraphy. There are a number of different somatostatin receptor subtypes and these have different degrees of affinity for octreotide. The uptake in the case of plasmacytoma may thus be explained by the presence of somatostatin receptor subtypes that have a lesser affinity for octreotide than the subtypes associated with paragangliomas or that are present in far smaller numbers than those in paragangliomas.

In conclusion, ^{111}In octreotide scintigraphy is a useful examination for the detection of primary and metastatic neuroendocrine tumors. In the postoperative setting, octreotide can be used to distinguish recurrent or residual disease from postoperative changes. It is quite useful in detecting multicentric paraganglioma and in screening family members of patients with familial paragangliomas.

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