Iodine-131-Metaiodobenzylguanidine Scintigraphy in Preoperative and Postoperative Evaluation of Paragangliomas: Comparison with CT and MRI

Simone Maurea,* Alberto Cuocolo, James C. Reynolds, Sabah S. Tumeh, Martin G. Begley, W. Marston Linehan, Jeffrey A. Norton, McClellan M. Walther, Harry R. Keiser and Ronald D. Neumann

Nuclear Medicine and Diagnostic Radiology Departments, Warren G. Magnuson Clinical Center; Surgery Branch, National Cancer Institute; Hypertension-Endocrine Branch, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland

Iodine-131-metaiodobenzylguanidine (MIBG) scintigraphy, transmission computed tomography and magnetic resonance imaging were used to evaluate 36 patients with clinically suspected functioning paragangliomas. The patients were divided into two groups. In Group 1 (n = 21), studied before surgery, patients mainly had benign adrenal disease. In Group 2 (n = 15), studied after surgery, patients frequently had malignant or extra-adrenal tumors. In Group 1, transmission computed tomography and magnetic resonance imaging were more sensitive (100% for both) than MIBG scintigraphy (82%), which, however, was the most specific (100%). In Group 2, MIBG scintigraphy and magnetic resonance imaging were more sensitive (83% for both) than transmission computed tomography (75%), but MIBG was again the most specific (100%). Thus, all three were complementary modalities for localizing paragangliomas both preoperatively and postoperatively. MIBG imaging is indicated for both groups but it is especially recommended for postsurgical patients with recurrence because the disease is often malignant or extra-adrenal.

J Nucl Med 1993; 34:173–179

Paragangliomas, catecholamine-secreting tumors of chromaffin cells in either the adrenal medulla or sympathetic paraganglia, may cause sustained or paroxysmal hypertension (*1,2*). These tumors occur in sympathetic tissue that extends from the glomus jugulare to the adrenergic plexus of the urinary bladder. Most paragangliomas occur as sporadic unilateral adrenal lesions (pheochromocytomas), but the occurrence of bilateral, multiple, extra-adrenal, metastatic or familial disease is not uncommon. Each has an incidence approaching 10% (*3*). Familial paragangliomas may occur as a single disease or in syndromes such as multiple endocrine neoplasia (MEN), neurofibromatosis and Von Hippel-Lindau disease (VHLD) (*4–6*).

In patients with the clinical diagnosis and biochemical findings of functioning paraganglioma, precise localization of disease is essential for the planning and evaluation of treatment (*7*). A wide range of radiologic procedures has been used to locate paragangliomas (*3,8,9*). Cross-sectional imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), play a major role in detecting these tumors before surgery (*10*). However, such techniques may fail to detect tumor at sites of previous surgery or locate extra-adrenal or metastatic disease (*11,12*). Metaiodobenzylguanidine (MIBG) scanning provides an additional method of locating paragangliomas that can be effective even when anatomy has been distorted by tumor growth or previous surgery (*13–15*). In addition, MIBG whole-body surveys effectively detect tumors arising in unusual or unexpected locations. In this study, we compared MIBG imaging with CT and MRI in the preoperative and postoperative evaluation of patients with paragangliomas.

Received Apr. 10, 1992; revision accepted Sept. 2, 1992.

For Correspondence or reprints contact: James C. Reynolds, MD, National Institutes of Health, Building 10, Room 1C-401, 9000 Rockville Pike, Bethesda, MD, 20892.

* Current Address: Cattedra di Medicina Nucleare, Istituto di Scienze Radiologiche, II Facolta Di Medicine e Chirugia, Universitá degli Studi Di Napoli Federico II, via S. Pansini n. 5, 80131, Napoli, Italy.

MATERIALS AND METHODS

Patient Population

Thirty-six patients, 18 men and 18 women, mean age 37 ± 11 yr, with clinically suspected functioning paragangliomas were evaluated with MIBG, CT and MR imaging. The patients were divided into two groups. Group 1 consisted of 21 patients who had no previous surgery for paraganglioma. In Group 2, 15 patients were evaluated after previous surgery for adrenal or extra-

adrenal paragangliomas. A histopathologic diagnosis was made from the primary tumor in each case. Eight patients had familial syndromes frequently associated with paragangliomas; five patients had VHLD and three had multiple endocrine neoplasia type 2A (MEN 2A) (Tables 1, 2).

The clinical diagnosis of functioning paraganglioma was based on characteristic signs and symptoms of disease or abnormal levels of plasma or urinary catecholamines or metabolites (*1–3*) (Tables 1, 2). In some patients, a glucagon stimulation test, a clonidine suppression test (CST) or both were performed (*16,17*) (Tables 1, 2). Fifteen patients in Group 1 and seven patients in Group 2 had surgical confirmation of disease. In those patients with recurrent or metastatic disease, abnormal clinical, biochemical and imaging findings were considered diagnostic even when histologic proof was not obtained. Informed written consent was obtained from all patients.

Catecholamine Measurements

Plasma catecholamine concentrations were measured by liquid chromatography with electrochemical detection (*18*). The urinary excretion rates of catecholamines and their metabolites were determined by quantitative fluorometric analysis and spectrophotometry, respectively (*19–21*).

Iodine-131-MIBG Scintigraphy

For the MIBG study, thyroid iodine uptake was blocked with a saturated solution of potassium iodide (200 mg per day orally starting the day before tracer administration and continuing for 8 days). Reserpine, MAO inhibitors and tricyclic antidepressants were discontinued for 30 days or longer before the study. For these studies, 0.5 mCi of [^{131}I]MIBG, (University of Michigan Radiopharmacy, Ann Arbor, MI) was administered intravenously. Anterior and posterior whole-body scans, spot images (15 min preset time) or both were obtained at 24, 48 and 72 hr after radiopharmaceutical administration with a large field of view gamma camera (GE Maxicamera 500-Autotune ZS, General Electric, Milwaukee, WI) equipped with a high-energy collimator and using a 20% window centered at 364 keV. The MIBG scan was considered positive when adrenal or extra-adrenal foci of increased uptake were seen on the 24, 48 and 72 hr images.

Computed Tomography

CT was performed with a GE 9800 scanner (General Electric, Milwaukee, WI). Contiguous sections, 10 mm thick, of the head, chest and abdomen were obtained. Oral (Hypaque, Winthrop Pharmaceuticals) and intravenous contrast (Isovue 300, Squibb Diagnostics) were used in all patients.

TABLE 1
Preoperative Cases

Patient no.	Current diagnosis	Location	Previous diagnosis	PNE	PE	UCa	Met	VMA	GST	CLO	MIBG	CT	MRI	MIBG	CT	MRI
1	UA	R	None	425	371	531	18.9	39.7	+	+	+	+	+	TP	TP	TP
2	UA	R	None	2787	76	485	1.9	13.7	+	ND	O	+	+	FN	TP	TP
3	UA	R	None	13503	335	983	11.2	23.5	ND	+	+	+	+	TP	TP	TP
4	UA	L	None	9965	120	1072	5.0	20	+	+	O	+	+	FN	TP	TP
5	UA	R	None	630	213	70	33.6	145	O	+	+	+	+	TP	TP	TP
6	UA	R	None	537	99	58	6.3	21	+	+	+	+	+	TP	TP	TP
7	UA	R	None	1050	454	389	2.7	12.5	ND	+	O	+	+	FN	TP	TP
8	UA	L	None	3997	7	1108	2.6	14.9	+	+	+	+	+	TP	TP	TP
9	UA	L	VHLD	673	5	102	1.3	9.0	O	O	+	+	+	TP	TP	TP
10	UA	R	VHLD	1262	52	218	0.7	11.7	ND	O	+	+	+	TP	TP	TP
11	UA	L	None	613	358	161	2.4	12.3	O	+	+	+	+	TP	TP	TP
12	BA	L/R	MEN2A	195	48	87	1.8	22.7	+	+	+	+	+	TP	TP	TP
13	BA	L/R	None	7136	384	ND	ND	ND	+	+	+	+	+	TP	TP	TP
14	BA	L/R	VHLD	420	15	134	1.0	ND	O	ND	+	+	+	TP	TP	TP
15	MAL	Z	MAL	720	13	207	3.7	17.0	+	ND	+	+	+	TP	TP	TP
16	MAL	L	MAL	910	5	97	3.7	11.8	ND	ND	+	+	+	TP	TP	TP
17	MAL	L/Lu	None	6119	5	677	36.5	10.0	ND	ND	+	+	+	TP	TP	TP
18	AM	R	Colon Ca	395	32	93	0.5	12.9	O	ND	O	+	+	TN	FP	FP
19	AM	L	Cushing	797	5	47	0.6	7.9	O	O	O	+	+	TN	FP	FP
20	Hy		Hy	1555	116	155	1.5	16.2	O	+	O	O	O	TN	TN	TN
21	Hy		Hy	h	h	h	h	h	ND	ND	O	O	O	TN	TN	TN

Headings: PNE = plasma norepinephrine (normal: <910 pg/ml); PE = plasma epinephrine (normal: <5 pg/ml); UCa = urinary total catecholamines (normal: <115 ug/24 hr); Met = metanephrine (normal: <1.3 mg/24 hr); VMA = vanillylmandelic acid (normal: <10 mg/24 hr); GST = glucagon stimulation test; CLO = clonidine suppression test; MIBG = metaiodobenzylguanidine; CT = computed tomography; MRI = magnetic resonance imaging.

Test Results: + = positive for abnormality; O = negative for abnormality; TP = true-positive; TN = true-negative; FP = false-positive; FN = false-negative; h = elevated biochemical test; ND = test not done; – = no tumor found.

Diagnosis: UA = unilateral adrenal tumor; BA = bilateral adrenal tumors; MAL = malignant pheochromocytoma; AM = adrenal mass; Hy = hypertension.

Location: R = right adrenal; L = left adrenal; Z = organ of Zucherkandl; Lu = lung.

Previous diagnosis: None = no diagnosis before present illness; VHLD = Von Hipple Lindau disease; MEN2A = multiple endocrine neoplasia, Type 2A; Colon Ca = colon carcinoma; Cushing = Cushing's disease.

TABLE 2
Postoperative Cases

Patient	Diagnosis	Location	PrDx	PNE	PE	UCa	Met	VMA	GST	CLO	MIBG	CT	MRI	MIBG	CT	MRI
1	UA	R	MEN2A	245	99	43	0.6	2.5	±	ND	+	+	+	TP	TP	TP
2	EA	PA	BPheo	32324	999	4029	11.4	45.5	ND	+	+	+	+	TP	TP	TP
3	EA	PT	VHLD	1533	0	581	4.0	9.9	ND	+	+	+	+	TP	TP	TP
4	MAL	SK	MAL	1375	5	139	0.9	8.6	ND	+	+	O	+	TP	FN	TP
5	MAL	Mlti	MAL	4399	336	607	36.9	62.4	ND	ND	+	+	+	TP	TP	TP
6	MAL	Mlti	MAL	4856	40	593	5.2	15.2	ND	ND	+	+	+	TP	TP	TP
7	MAL	Liv	MAL	6225	<5	1663	3.7	28.6	ND	+	O	+	+	FN	TP	TP
8	MAL	Und	MAL	1674	3	416	1.1	10.6	+	ND	O	+	+	FN	FN	FN
9	MAL	L	MAL	638	53	347	7.2	21.0	+	+	+	+	+	TP	TP	TP
10	MAL	L	BPheo	20600	5	2896	ND	8.5	O	ND	+	+	+	TP	TP	TP
11	MAL	Mlti	BPheo	2658	<5	423	2.5	13.6	+	+	+	+	+	TP	TP	TP
12	MAL	Mlti	BPheo	726	645	514	13.6	21.6	O	ND	+	O	O	TP	FN	FN
13	NT	—	VHLD	522	15	91	0.2	0.4	O	ND	O	O	O	TN	TN	TN
14	OT	Med	MEN2A	ND	ND	ND	ND	ND	ND	ND	O	+	+	TN	FP	FP
15	NT	—	AMH	588	5	71	0.6	7.3	±	±	O	O	O	TN	TN	TN

Headings: See Table 1.

Test results: + = positive for abnormality; O = negative for abnormality; ± = borderline abnormal; TP = true-positive; TN = true-negative; FP = false-positive; FN = false-negative; ND = test not done.

Diagnosis: UA = unilateral adrenal tumor; EA = extra-adrenal tumors; MAL = malignant pheochromocytoma; NT = no tumor; OT = other tumor.

Location: R = right adrenal; PA = para-aortic; PT = para-thoracic; SK = skull; Mlti = multiple tumors; Liv = liver; Und = undetermined location; L = left adrenal; Med = mediastinum.

Previous Diagnosis: MEN2A = multiple endocrine neoplasia, Type 2A; BPheo = benign pheochromocytoma; VHLD = Von Hipple Lindau disease; AMH = adrenal medullary hyperplasia.

Magnetic Resonance Imaging

MRI was performed with a 1.5 Tesla (Signa, General Electric, Milwaukee, WI) or a 0.5 Tesla (Picker International, Highland Heights, OH) superconducting magnet system. A spin echo technique was used to obtain 5-mm contiguous axial and coronal sections of the head, chest and abdomen. T1-weighted images (TR/TE 300/12 msec) and T2-weighted images (TR/TE 2000/80 msec) were obtained.

Data Analysis

CT and MRI images were independently reviewed by two radiologists, whereas MIBG studies were separately evaluated by three specialists in nuclear medicine. Images were categorized as positive or negative and the results compared with the final clinical and surgical findings. True-positive, true-negative, false-positive and false-negative findings were defined as described in Table 3. Sensitivity, specificity and accuracy values were calculated as well (*14*). To statistically determine whether the three imaging tests differed among themselves, Cochran's Q-test was performed (*22*).

RESULTS

The clinical, biochemical, pathologic and imaging findings of the two groups are shown in Tables 1 and 2.

Group 1

Eleven of 21 patients (nos. 1–11) in this group had unilateral (right, n = 7; left, n = 4) adrenal pheochromocytomas (Fig. 1). Eight were evident on MIBG scan, but all were detected by CT and MRI. Three patients (nos. 12–14) had bilateral adrenal tumors detected by all three imaging methods. Three other patients (nos. 15–17) had malignant disease. In all these patients, the tumors were large and easily detected by each method.

Two patients (nos. 18 and 19) had unilateral adrenal masses discovered by CT and MRI, but borderline or normal biochemical studies. In these, T2-weighted MRI

TABLE 3
Data Analysis

True-Positive: an abnormal imaging study with pathologic confirmation of the findings or, when pathologic examination was not available, (a) all three imaging tests are abnormal or (b) there are two abnormal imaging tests and clinical evidence of pheochromocytoma.
True-Negative: a normal imaging study with pathologic confirmation of the findings or, when pathologic examination was not available, (a) all three imaging tests are normal or (b) there is at least one other normal imaging test and no clinical evidence of pheochromocytoma.
False-Positive: An abnormal imaging study with no evidence of pheochromocytoma by pathology or, when pathologic examination was not available, an abnormal imaging study and no clinical or other imaging evidence of pheochromocytoma.
False-Negative: A normal imaging study with diagnosis of pheochromocytoma by pathology or, when pathologic examination was not available, a normal imaging study with clinical and imaging findings of pheochromocytoma.

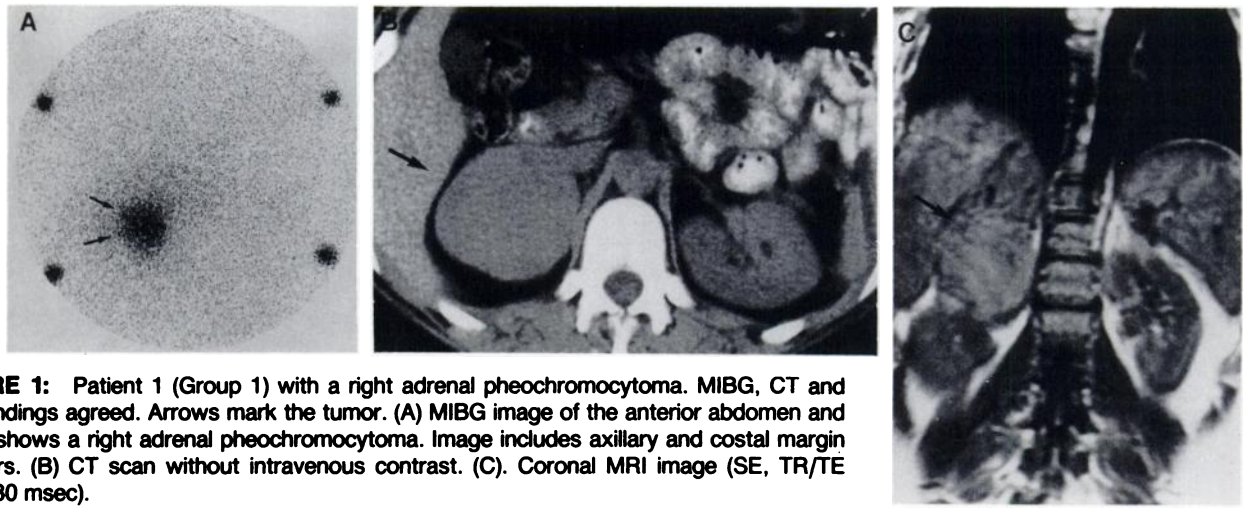

FIGURE 1: Patient 1 (Group 1) with a right adrenal pheochromocytoma. MIBG, CT and MRI findings agreed. Arrows mark the tumor. (A) MIBG image of the anterior abdomen and chest shows a right adrenal pheochromocytoma. Image includes axillary and costal margin markers. (B) CT scan without intravenous contrast. (C). Coronal MRI image (SE, TR/TE 2000/80 msec).

signal intensity was increased, suggestive of pheochromocytoma. MIBG scans were normal.

In Patient 18, the right adrenal mass was found to be a colon carcinoma metastasis (Fig. 2). In Patient 19, a left adrenal mass had shrunk after pituitary surgery for Cushing's disease and was considered a macroadenoma that developed from excess adrenocorticotrophic hormone. Two patients (nos. 20 and 21) with essential hypertension and abnormal biochemical tests were also studied. In these, all three imaging tests were normal. Abnormalities of plasma and urinary catecholamines were apparently related to antihypertension medication.

Thus, in the 17 patients in Group 1 with paraganglioma, CT and MRI detected all the lesions (sensitivity 100%), whereas MIBG imaging had a sensitivity of 82%. MIBG, however, had 100% specificity, whereas CT and MRI were false-positive in two cases (Table 4).

Group 2

Three of the 15 patients in this group (nos. 1–3) had benign disease. A patient with MEN 2A and a prior left adrenalectomy had recurrent pheochromocytoma in the contralateral adrenal. Bilateral para-aortic paragangliomas were found in another patient who earlier had carotid body paragangliomas resected. A patient with VHLD and a previous bilateral adrenalectomy for pheochromocytoma returned with a thoracic paraganglioma. All three imaging methods detected lesions in these patients.

Nine patients in the group (nos. 4–12) had malignant tumors. In six, the nature of the disease was known from prior surgery or imaging. In two, MIBG did not detect disease because of poor uptake (Patient 7) or small lesions (Patient 8). In Patient 4, postsurgical changes made CT imaging ineffective, however, both MIBG and MRI detected this tumor.

Three patients (nos. 10–12) with a history of benign pheochromocytoma had recurrences that proved to be malignant. In Patient 10, surgery was needed to confirm the infiltrative nature of the tumor which was detected by all three imaging methods. In Patient 11, all three imaging modalities showed evidence of tumors but only MRI and CT showed disease in the liver. In Patient 12, the diagnosis of malignant paraganglioma was first made with MIBG (Fig. 3). Four years earlier, this patient had a single large pheochromocytoma resected. Recurrent symptoms and abnormal biochemical tests led to CT and MRI imaging of the adrenal areas but they were negative. MIBG images

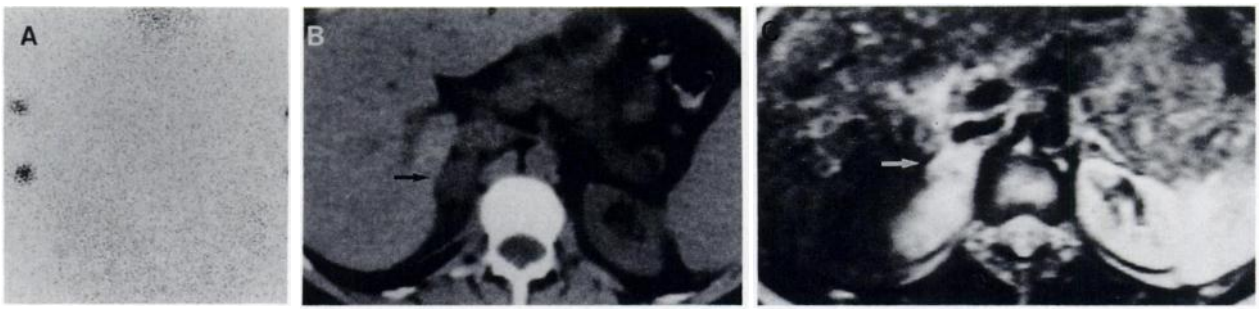

FIGURE 2. Patient 18 (Group 1) with a right adrenal mass: metastatic colon carcinoma. The tumor did not accumulate MIBG but was detected by CT and MRI (intense T2-weighted image). Arrows, when present, mark the tumor. (A) MIBG image of the posterior abdomen. Lateral markers are on costal margins and iliac crests. (B) CT scan without intravenous contrast. (C) Transaxial MRI image (SE, TR/TE 2000/80 msec).

TABLE 4
Results from Imaging Studies

	Group 1			Group 2		
	MIBG	CT	MRI	MIBG	CT	MRI
Sensitivity (%)	82*	100*	100*	83	75	83
Specificity (%)	100	50	50	100	67	67
Accuracy (%)	86	91	91	87	73	80

* p value = 0.05. Groups were analyzed with Cochran's Q-test (*22*).

showed multiple metastatic lesions in the chest, abdomen, and pelvis. CT and MRI later confirmed the multifocal nature of the disease. In Group 2, three patients (nos. 13–15) did not have pheochromocytomas. Patient 14 is discussed in more detail below.

Thus, in 10 of the 12 patients with recurrent paraganglioma, MIBG and MRI demonstrated tumor for a sensitivity of 83%. CT failed to detect abnormalities in three patients (a sensitivity of 75%). Again, MIBG specificity in this group was 100%, whereas MRI and CT detected a lesion that probably was not a paraganglioma (Table 4).

DISCUSSION

Previous studies have suggested that MIBG, CT and MRI are complementary techniques for localizing adrenal pheochromocytoma and extra-adrenal paragangliomas (*23–28*), but the specific role of these three modalities is currently under debate. Velchik et al. (*23*) proposed MIBG as the initial imaging technique especially for extraadrenal or recurrent disease. Van Gils et al. (*28*) recommended that whole-body MRI be used as the primary imaging method for patients with clinical symptoms of catecholamine excess and suggested that MIBG could be used in cases with equivocal MRI findings. Quint et al. (*27*) suggested that because of better tissue characterization, MIBG and MRI were superior and should be used for patients with suspected pheochromocytoma.

To further explore the utility of these techniques in various clinical situations, we assigned patients to two groups based on whether they had prior surgery for paraganglioma. The results differed considerably. Of the patients undergoing their initial evaluation, 82% (Group 1) had benign disease, whereas 75% of those with recurrent or residual tumors (Group 2) had malignant disease. In addition, only two patients in Group 1 (11.8%) had extra-

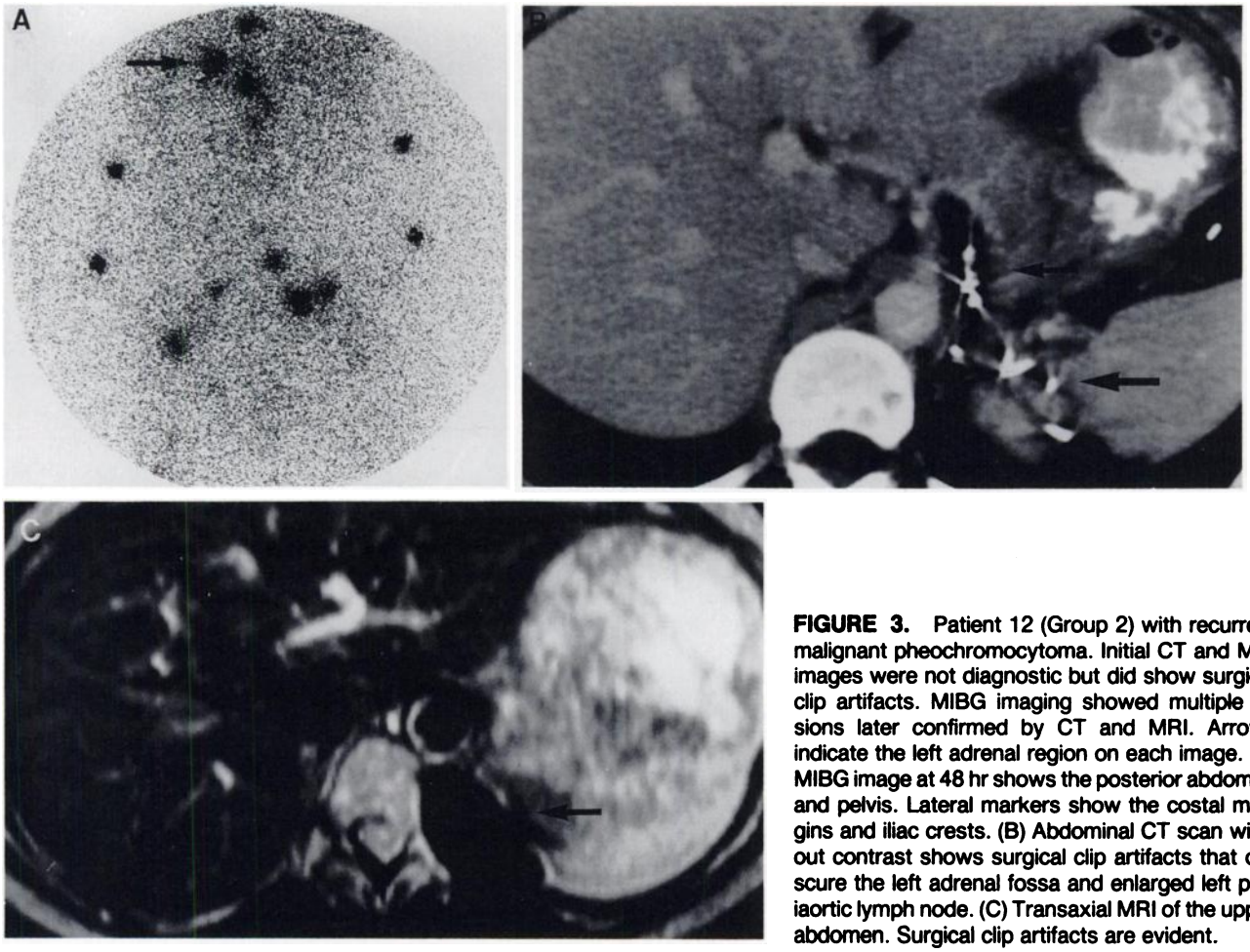

FIGURE 3. Patient 12 (Group 2) with recurrent malignant pheochromocytoma. Initial CT and MRI images were not diagnostic but did show surgical clip artifacts. MIBG imaging showed multiple lesions later confirmed by CT and MRI. Arrows indicate the left adrenal region on each image. (A) MIBG image at 48 hr shows the posterior abdomen and pelvis. Lateral markers show the costal margins and iliac crests. (B) Abdominal CT scan without contrast shows surgical clip artifacts that obscure the left adrenal fossa and enlarged left periaortic lymph node. (C) Transaxial MRI of the upper abdomen. Surgical clip artifacts are evident.

adrenal paragangliomas and both tumors were malignant. In Group 2, 11 of 12 patients with paraganglioma had extra-adrenal disease and 9 had malignancies.

Accurate diagnosis and localization of tumor are essential. Using a combination of biochemical and (if necessary) provocative tests, the diagnosis of functioning paraganglioma can be made with an accuracy of over 95% (*29*). The role of imaging is to localize disease for possible surgical removal. Some high sensitivity tests are most desirable. Clearly, for patients presenting for the first time with disease (Group 1), CT and MRI should be the initial choices. Here, paragangliomas are most often found in the adrenal gland or at least in the abdomen.

For patients with recurrent disease (Group 2), malignancy and extra-adrenal locations are more common. In our study of this second group, MRI and MIBG were equally sensitive (83% for both) with CT less so (75%). At our institution, both MRI and MIBG are used to locate paragangliomas. However, because of the experience with Patient 12 in Group 2, where both MRI and CT initially failed to detect lesions while MIBG was positive, we now prefer MIBG as the initial imaging method for recurrent disease. MIBG is also superior in ruling out adrenal bed recurrences where clip artifact and anatomical distortion make interpretation difficult. In one patient in Group 2, however, MRI rather than MIBG showed a metastatic lesion in the liver.

In this study, the MIBG sensitivity was similar to previous reports (*13,28*) and equally sensitive for benign (82%) and malignant lesions (83%). An important question is whether MIBG should always be used before initial surgery to rule out extra-adrenal or malignant tumor. Because of the seriousness of this rare disorder, the time required to prepare patients for surgery with alpha adrenergic blockade and fluid expansion and the availability of whole body images with MIBG, we favor this approach. However, we have no data to suggest that using CT or MRI alone for these patients would be inadequate. Certainly, MIBG must be used for those patients with recurrent disease before any further surgery for paraganglioma.

Although MIBG is most often used to locate paraganglioma, its high specificity and reasonably high sensitivity also make it useful when the diagnosis is in doubt. Despite the sophistication of catecholamine measurement techniques, values from normal and paraganglioma patients often overlap. As shown in this study, MIBG imaging may be diagnostically useful in the following situations: (a) in patients with familial syndromes such as MEN 2A or VHLD where paragangliomas are present, but catecholamine levels are only mildly abnormal or normal (*30,31*); (b) in patients with hypertension, where medications may affect catecholamine measurements (*32*); or (c) in patients with adrenal or extra-adrenal tumors that have intense signals on T2 weighted MRI images. Although a high T2 signal intensity may be characteristic of paraganglioma (*33–38*), other lesions, including adrenal adenoma and necrotic metastases, give similar findings (*38*).

The three imaging modalities gave very similar results. Statistical analysis of our studies showed a significant difference only for the sensitivity of imaging in Group 1 (Table 4). However, as suggested earlier, the clinical features of the cases seem to play a role in the success of these imaging procedures.

Our study is limited because only 22 of the 36 patients had surgical confirmation of the imaging findings. In three patients who did not have surgery, the three imaging modalities did not show tumors and the patients were considered disease free. In one patient with elevated catecholamines, all three imaging studies were negative, possibly due to small tumor deposits. In other patients who had both abnormal imaging studies and catecholamine tests, the overall results were considered sufficient evidence of disease. In three patients who did not have surgery, the imaging studies disagreed. A composite of the clinical, laboratory and imaging data was used to assign these patients who deserve special comment.

Patient 19 of Group 1 had a diagnosis of pituitary Cushing's disease that had previously been treated with radiotherapy and transphenoidal surgery. The patient had a history of flushing. Biochemical tests were negative for pheochromocytoma, but MRI showed an extremely "bright" left adrenal mass on T2-weighted images. An enlarged right adrenal gland was consistent with adrenal cortical hyperplasia. A CT scan found a left adrenal mass and an enlarged right adrenal but the MIBG study was normal. Adrenal surgery was not performed. After 6 mo of clinical follow-up, a repeat MRI scan showed that the left adrenal mass had become smaller. Normal biochemical tests, the negative MIBG scan and the decrease in adrenal size with time suggested that the left adrenal lesion was not a pheochromocytoma but more likely a cortical adenoma related to Cushing's disease.

Patient 4 of Group 2 had a right norepinephrine-secreting glomus jugulare tumor. The extracranial portion had already been removed and the intracranial portion had been treated with radiotherapy. Brain CT showed bony destruction at the base of the skull on the right side attributed to the tumor resection. MRI revealed a mass in the same area and MIBG showed abnormal uptake in the same region. In addition, the basal plasma norepinephrine level was high (1108 pg/ml), and a CST was consistent with a norepinephrine-secreting tumor. According to both clinical and laboratory findings, for this patient, CT was false-negative, while MIBG and MRI were true-positive for the residual intracranial chromaffin-tissue tumor.

Patient 14 of Group 2 with MEN 2A previously had a total thyroidectomy and a left radical neck dissection for medullary thyroid carcinoma (MTC). A bilateral adrenalectomy was performed for pheochromocytoma. The patient was known to have residual MTC with basal plasma calcitonin levels of 770 pg/ml (normal value <50 pg/ml). CT and MRI scans showed a retroaortic mediastinal nodule. The T2-weighted MRI image showed the lesion to be very bright similar to a paraganglioma. Plasma calcitonin

levels on two successive days were abnormal: 766 and 770 pg/ml. A pentagastrin stimulation test was also abnormal and showed increased calcitonin levels. These data supported the diagnosis of MTC metastatic to the mediastinum but the lesion was not histologically confirmed. From the combined data, we concluded that MIBG was true-negative while CT and MRI were false-positive for paraganglioma.

SUMMARY

This study shows that MIBG, CT and MRI are complementary modalities in evaluating patients with functioning paragangliomas. CT and MRI provide the best anatomic detail but are not easily used for whole-body screening. Furthermore, they can be difficult to interpret when there are anatomical changes or metal clips from surgery. MIBG, which depends on the active transport of radiopharmaceutical into viable tumor cells, is the most specific test both in the preoperative and postoperative evaluation of disease. However, MIBG scanning can fail to detect some pheochromocytomas.

For patients who have a clearly abnormal biochemical test at initial presentation, CT and MRI are the best choices. For these patients, tumors are often located in the adrenal and the CT and MRI sensitivity is very high. When biochemical tests are not clearly diagnostic, MIBG can be helpful in confirming or ruling out pheochromocytoma. MIBG is also useful for assessing extra-adrenal or unexpected disease. In patients with recurrent disease who are more likely to have malignant and extra-adrenal tumors, we favor MIBG as the initial modality followed by MRI and CT for better anatomic detail.

ACKNOWLEDGMENT

We thank Dr. Robert Wessley for help with the statistical analysis.

REFERENCES

1. Engelman K. Pheochromocytoma. *J Clin Endocrinol Metab* 1977;6: 769–797.
2. Manger WM, Gifford RW. Hypertension secondary to pheochromocytoma. *Bull NY Acad Med* 1982;58:139–158.
3. Manger WM, Gifford RW. *Pheochromocytoma.* New York: Springer-Verlag; 1977:31–37.
4. Sizemore GW, Heath H III, Carney JA. Multiple endocrine neoplasia. *J Clin Endocrinol Metab* 1980;9:299–315.
5. Brasfield RD, Das Gupta TK. Von Recklinghausen's disease: a clinicopathologic entity. *Ann Surg* 1972;175:86–91.
6. Lamiell JM, Salazar FG, Hsia YE. Von Hippel-Lindau disease affecting 43 members of a single kindred. *Medicine* 1989;68:1–29.
7. Sjoerdsma A, Engelman K, Waldmann TA, Cooperman LH, Hammond WG. Pheochromocytoma: current concepts of diagnosis and treatment. Combined clinical staff conference at the National Institutes of Health. *Ann Intern Med* 1966;65:1302–1326.
8. Harrison TS, Seaton JF, Cerny JC, Bookstein JJ, Barlett JD. Localization of pheochromocytomata by caval catheterization. *Arch Surg* 1967;95: 339–343.
9. Bowerman RA, Silver TM, Jaffe MH, Stuck KJ, Hinerman DL. Sonography of adrenal pheochromocytoma. *AJR* 1981;137:1227–1231.
10. Demas BE, Hricak H. Adrenal glands. In: Stamathis G, ed. *Magnetic resonance imaging,* 1st edition. St Louis: C.V. Mosby, 1988;1178–1180.
11. Freier DT, Eckhauser FE, Harrison TS. Pheochromocytoma: a persistently problematic and still potentially lethal disease. *Arch Surg* 1980;115: 388–391.
12. Stewart BH, Bravo EL, Haaga J, Meaney TF, Tarazi R. Localization of pheochromocytoma by computed tomography. *N Engl J Med* 1978;299: 460–461.
13. Sisson JC, Frager MS, Valk TW, et al. Scintigraphic localization of pheochromocytoma. *N Engl J Med* 1981;305:12–17.
14. Shaprio B, Copp JE, Sisson JC, Eyre PL, Wallis J, Beierwaltes WH. Iodine-131 metaiodobenzylguanidine for the locating of suspected pheochromocytoma: experience in 400 cases. *J Nucl Med* 1985;26:576–585.
15. McEwan AJ, Shapiro B, Sisson JC, Beierwaltes WH, Ackery DM. Radioiodobenzylguanidine for the scintigraphic location and therapy of adrenergic tumors. *Semin Nucl Med* 1985;15:132–153.
16. Lawrence AM. Glucagon provocative test for pheochromocytoma. *Ann Intern Med* 1967;66:1091–1096.
17. Bravo EL, Tarazi RC, Fouad FM, Vidt DG, Gifford RW. Clonidine-suppression test. A useful aid in the diagnosis of pheochromocytoma. *N Engl J Med* 1981;305:623–626.
18. Goldstein DS, Feuerstein G, Izzo JL, Kopin IJ, Keiser HR. Validity and reliability of liquid chromatography with electrochemical detection for measuring plasma levels of norepinephrine and epinephrine in man. *Life Sci* 1981;28:467–475.
19. Crout JR. Catecholamines in urine. In: Seligson MD ed. *Standard methods of clinical chemistry.* New York: Academic Press; 1960;62–80.
20. Pisano JJ, Crout JR, Abraham D, Determination of 3-methoxy-4-hydroxymandelic acid in urine. *Clin Chim Acta* 1962;7:285–291.
21. Pisano JJ. A simple analysis of normetanephrine and metanephrine in urine. *Clin Chim Acta* 1960;5:406–414.
22. Fleiss JL. *Statistical methods for rates and proportions,* 2nd edition. New York: Wiley; 1981.
23. Velchik MG, Alavi A, Kressel HY, Engelman K. Localization of pheochromocytoma: MIBG, CT and MRI correlation. *J Nucl Med* 1989;30: 328–336.
24. Francis IR, Glazer GM, Shapiro B, Sisson JC, Gross BH. Complementary roles of CT and ^{131}I-MIBG scintigraphy in diagnosing pheochromocytoma. *AJR* 1983;141:719–725.
25. Chatal JF, Charbonnel B. Comparison of iodobenzylguanidine imaging with computed tomography in locating pheochromocytoma. *J Clin Endocrinol Metab* 1985;61:769–772.
26. Falke THM, te Strake L, Shaff MI, et al. MR imaging of the adrenals: correlation with computed tomography. *J Comput Assist Tomogr* 1986; 110:242–253.
27. Quint LE, Glazer GM, Francis IR, Shapiro B, Chenevert TL. Pheochromocytoma and paraganglioma: comparison of MR imaging with CT and I-131-MIBG scintigraphy. *Radiology* 1987;165:89–93.
28. van Gils AP, Falke THM, van Erkel AR, et al. MR imaging and MIBG scintigraphy of pheochromocytomas and extraadrenal functioning paragangliomas. *Radiographics* 1991;11:37–57.
29. Grossman E, Goldstein DS, Hoffman A, Keiser HR. Glucagon stimulation and clonidine suppression tests in the diagnosis of pheochromocytoma. *Hypertension* 1991;17:733–741.
30. Nakajo M, Shapiro B, Copp J, et al. The normal and abnormal distribution of the adrenomedullary imaging agent m-[I-131]iodobenzylguanidine (I-131-MIBG) in man: evaluation by scintigraphy. *J Nucl Med* 1983;24: 672–682.
31. Sheps SG, Jiang N-S, Klee GG. Diagnostic evaluation of pheochromocytoma. *Endocrinol Metab Clin North Am* 1988;17:397–414.
32. Moon KL, Hricak H, Crooks LE, et al. Nuclear magnetic resonance imaging of the adrenal gland: a preliminary report. *Radiology* 1983;147: 155–160.
33. Fink IJ, Reinig JW, Dwyer AJ, Doppman JL, Linehan WM, Keiser HR. MR imaging of pheochromocytoma. *J Comput Assist Tomogr* 1985;9: 454–458.
34. Glazer GM, Woolsey EJ, Borrello J, et al. Adrenal tissue characterization using MR imaging. *Radiology* 1986;158:73–79.
35. Reinig JW, Doppman JL, Dwyer AJ, Johnson AR, Knop RH. Adrenal masses differentiated by MR. *Radiology* 1986;158:81–84.
36. Reinig JW, Doppman JL, Dwyer AJ, Frank J. MRI of indeterminate adrenal masses. *AJR* 1986;147:493–496.
37. Gross MD, Shapiro B, Sandler MP, Falke THM, Shaff MI. Adrenal gland imaging. In: Grayson T, ed. *Correlative imaging,* 1st edition. Baltimore: Williams & Wilkins; 1989:400, 413.
38. Choyke PL. MR imaging of the kidneys and retroperitoneum. *Syllabus special course: MR 1990.* 76th scientific assembly and annual meeting of the Radiological Society of North America, Chicago, November 25–30, 1990:166–167.