

Usefulness of ^{123}I -MIBG Scintigraphy in the Evaluation of Patients with Known or Suspected Primary or Metastatic Pheochromocytoma or Paraganglioma: Results from a Prospective Multicenter Trial

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Although ^{123}I -MIBG has been in clinical use for the imaging of pheochromocytoma for many years, a large multicenter evaluation of this agent has never been performed. The present study was designed to provide a prospective confirmation of the performance of ^{123}I -MIBG scintigraphy for the evaluation of patients with known or suspected primary or metastatic pheochromocytoma or paraganglioma. **Methods:** A total of 81 patients with a prior history of primary or metastatic pheochromocytoma or paraganglioma and 69 with suspected pheochromocytoma or paraganglioma based on symptoms of catecholamine excess, CT or MRI findings, or elevated catecholamine or metanephrine levels underwent whole-body planar and selected SPECT 24 h after the administration of ^{123}I -MIBG. Images were independently interpreted by 3 masked readers, with consensus requiring agreement of at least 2 readers. Final diagnoses were based on histopathology, correlative imaging, catecholamine or metanephrine measurements, and clinical follow-up. **Results:** Among 140 patients with definitive diagnoses (91, disease present; 49, disease absent), ^{123}I -MIBG planar scintigraphy had a sensitivity and specificity of 82%. For patients evaluated for suspected disease, sensitivity and specificity were 88% and 84%, respectively. For the subpopulations of adrenal (pheochromocytoma) and extraadrenal (paraganglioma) tumors, sensitivities were 88% and 67%, respectively. The addition of SPECT increased reader confidence but minimally affected sensitivity and specificity. **Conclusion:** This prospective study demonstrated a sensitivity of 82%–88% and specificity of 82%–84% for ^{123}I -MIBG imaging used in the diagnostic assessment of primary or metastatic pheochromocytoma or paraganglioma.

Key Words: ^{123}I -MIBG; scintigraphy; pheochromocytoma; paraganglioma; neuroendocrine tumors

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Uptake and retention of the norepinephrine analog metaiodobenzylguanidine (MIBG) or iobenguane are mediated primarily by the plasma membrane norepinephrine transporter system located on sympathetic neurons, ganglia, or chromaffin cells (1,2) and intracellular vesicular monoamine transporters (3). On the basis of this mechanism of uptake, MIBG has proven useful for the scintigraphic imaging of tumors that arise from the embryonic precursors of the sympathetic nervous system, particularly the neural crest cells (4,5). About 85% of pheochromocytomas arise in the chromaffin cells of the adrenal medulla, with the remainder, extraadrenal tumors commonly defined as paragangliomas, arising in chromaffin cells mainly along the aorta in the abdomen, pelvis, chest, and neck (6).

During the past 25 y, both ^{123}I -MIBG and ^{131}I -MIBG have been extensively used in research and clinical imaging of pheochromocytoma, even though in the United States before September 2008, only ^{131}I -MIBG was approved by the Food and Drug Administration (FDA) as a diagnostic imaging agent. ^{123}I -MIBG has nevertheless been available for clinical use for many years, both at sites with Investigational New Drug applications and in locations where the product could be obtained from radiopharmacies that

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compounded and supplied it for individual patient use. Most publications on MIBG imaging of pheochromocytoma, typically involving small numbers of patients and retrospective reviews of single-center experiences, have reported both sensitivity and specificity between 80% and 100% (7–16).

The objective of the present trial was to document the efficacy of ^{123}I -MIBG scintigraphy for confirming or excluding the diagnosis of pheochromocytoma. The trial was performed in support of a submission of a new drug application to the FDA, a process essential to making diagnostic imaging agents manufactured to regulatory standards generally available to patients and the medical community. For the purposes of the trial, paraganglioma was considered as extraadrenal pheochromocytoma and was included in the primary analysis. In this article, data are also presented for pheochromocytoma and paraganglioma separately.

MATERIALS AND METHODS

Patient Selection

This was an open-label, phase 3 scintigraphy study performed at 12 centers in the United States and 6 centers in Europe. Subjects were enrolled between August 2005 and September 2006. The primary inclusion criterion was a clinical indication for ^{123}I -MIBG imaging to evaluate for the presence, extent, or status of pheochromocytoma, and each center attempted to recruit as many of the patients referred for such examinations as possible. Primary exclusion criteria were history of renal insufficiency (serum creatinine level > 3.0 mg/dL [$265 \mu\text{mol/L}$]) and inability to be withdrawn from medications known to interfere with ^{123}I -MIBG uptake, primarily inhibitors of norepinephrine transporter system-dependent uptake such as antidepressants and labetalol and sympathomimetic drugs (4). The protocol was approved by the local ethical committees or Institutional Review Boards, and all patients provided written informed consent before performance of any study procedures.

Imaging Procedures

After the administration of thyroid blockade (potassium perchlorate, potassium iodide, potassium iodate, or Lugol solution), all patients received 370 MBq (10 mCi) of ^{123}I -MIBG (AdreView; GE Healthcare). At 24 h (± 6 h) after administration, total-body planar imaging (anterior and posterior whole-body or multiple overlapping spot images extending from the head to below the knees) was performed, followed by SPECT of the thorax or abdomen/pelvis (17). The imaging parameters (camera, collimator, and image matrix) used were as per standard clinical practice at the investigational center.

Image Interpretation

The 3 readers were experienced nuclear imagers who were unaware of all clinical data and were not affiliated with any of the investigational centers. All reviews were performed independently and included an assessment of image quality (diagnostic or nondiagnostic) and of presence or absence of pheochromocytoma on a patient level.

For each patient, the reader reviewed all planar images first and recorded whether the findings were consistent with active tumor. SPECT images were then presented and the procedure was

repeated. The reader then recorded whether the SPECT images had clarified the location or etiology of an abnormality seen on the planar images and had provided additional diagnostic value above that of the planar images alone.

On the basis of the independent results for each reader, a derived consensus regarding the presence or absence of pheochromocytoma (agreement of at least 2 readers) was obtained for the planar and planar + SPECT interpretations.

Standard of Truth

In this study, the presence or absence of tumor reflected the disease status of the patient on the day of ^{123}I -MIBG injection. For patients with a history of previously diagnosed and treated pheochromocytoma or paraganglioma, categorization of tumor as present required current evidence of active disease.

The presence or absence of tumor was established in 1 of 2 ways. The primary standard of truth was histology results from biopsy or surgical specimens. The secondary standard involved the combination of data from available histology (e.g., posttherapy biopsy or surgery), results of recent imaging procedures (CT, MRI, scintigraphy [bone, octreotide, ^{18}F -FDG PET, ^{131}I -MIBG]), blood and urine catecholamine and metabolite measurements, and clinical follow-up. Patients with data judged insufficient to establish the diagnosis (usually because of equivocal imaging or biochemistry results and incomplete follow-up) were classified as indeterminate and removed from the efficacy analysis.

Statistical Analysis

Both the imaging (derived reader consensus) and standard-of-truth data were analyzed on a patient level for sensitivity and specificity, defined as follows:

Sensitivity =

$$\frac{\text{Number of patients with true-positive } ^{123}\text{I-MIBG assessments}}{\text{Number of patients with tumor present}}$$

Specificity =

$$\frac{\text{Number of patients with true-negative } ^{123}\text{I-MIBG assessments}}{\text{Number of patients with tumor absent}}$$

Secondary analyses were performed on the readers' assessments of the incremental value of SPECT and to determine the sensitivity and specificity of ^{123}I -MIBG imaging in the subsets of patients with a prior history of disease and those with suspected disease at study entry (no prior histopathologic confirmation or treatment for pheochromocytoma or paraganglioma).

κ -coefficients were calculated for each pair of independent masked reviewers using SAS software (SAS Institute) (18). κ -values greater than 0.60 were considered to represent good agreement between readers (19).

RESULTS

A total of 157 patients consented to participate in the study, but 6 withdrew consent (because of scheduling or other conflicts) and 1 was withdrawn because of the continued use of the sympathomimetic albuterol. The demographic information for the 150 study patients who received ^{123}I -MIBG is summarized in Table 1.

TABLE 1. Demographic Characteristics of Study Patients

Patient characteristic	<i>n</i>
Age (y)	
Mean ± SD	49.2 ± 14.7
Range	17–88
Sex	
Male	62 (41%)
Female	88 (59%)

At study entry, 79 patients (53%) had a prior histologic diagnosis of pheochromocytoma (including 23 with paragangliomas), and 2 patients (1 paraganglioma) had previously undergone treatment empirically based on imaging findings and highly elevated catecholamine levels. Of these 81 patients, 15 (19%) had reported a history of at least 1 previous MIBG scintigraphy examination.

All readers judged the planar ^{123}I -MIBG images diagnostic in all 150 patients. For the 149 patients who underwent SPECT, the SPECT images were judged diagnostic by all 3 readers in 121 patients (81%) and by 2 readers in 16 patients (11%). SPECT images for 12 patients (8%) were judged nondiagnostic by at least 2 readers, and these patients were not included in the ^{123}I -MIBG SPECT data analyses.

The presence of pheochromocytoma was confirmed in 91 patients and was excluded in 49 patients; final diagnosis was indeterminate in 10 patients. The evaluable efficacy population of 140 patients included 79 with a prior history of pheochromocytoma or paraganglioma and 61 with suspected disease. Of the 91 patients with the presence of tumor, this diagnosis was established on the basis of definitive histology in 45 (49%) and recent imaging and catecholamine (or catecholamine metabolite) results in 46 (51%). In the 49 patients in whom tumor was not present, the diagnosis was based on histology in 10 (19%) and imaging, catecholamine determinations, and clinical follow-up in 39 (81%). Eight patients with indeterminate results had suspected disease based on elevated catecholamine determinations or abnormal imaging findings but inadequate follow-up data to confirm a diagnosis. The other 2 patients with indeterminate results had previously treated paraganglioma and no tissue confirmation of the etiology of new imaging findings suspected of reflecting recurrent disease.

The ^{123}I -MIBG planar imaging results are summarized in Table 2. Overall, sensitivity and specificity were both 82%. Sensitivity was similar for the subpopulations with suspected and known prior disease (88% vs. 81%) and was similar for those with known prior and suspected adrenal pheochromocytoma (87% vs. 90%). Among those with known prior disease, the sensitivity of ^{123}I -MIBG planar imaging was lower for those with paraganglioma (67% vs. 87% for pheochromocytoma). The higher sensitivity in pheochromocytoma patients, compared with paraganglioma patients, was also seen in the subgroup with confirmed

metastatic disease. Specificity was lower in patients with known prior disease than in those with suspected disease (75% vs. 82%, respectively).

Of the 140 patients with a standard-of-truth diagnosis, 130 had consensus diagnostic SPECT examinations for inclusion in the analyses. The results for the planar + SPECT interpretations in these patients are summarized in Table 3. Compared with the planar interpretations, the addition of SPECT resulted in small improvements in sensitivity in the total population and most subgroups. Specificity was slightly decreased in the same populations.

For most patients for whom there was disagreement between scan interpretations and final diagnoses, it was not possible to establish an explanation for the discrepancies. Among the patients with negative image interpretations, 5 had treated but persistent metastatic disease and 5 had small or atypical paragangliomas. Four patients with positive image interpretations had adrenal adenoma or hyperplasia but no evidence of pheochromocytoma on subsequent surgeries. Examples of study images are presented in Figures 1 and 2 and Supplemental Figures 1 and 2 (supplemental materials are available online only at <http://jnm.snmjournals.org>).

Concordance among the masked readers was good, with the κ -statistic greater than 0.60 (range, 0.65–0.71) among each pair of readers. With regard to the contribution of SPECT among the 3 readers, the study clarified the location of findings on planar images in 35%–41% of patients and provided additional diagnostic value in 33%–36% of studies examined.

DISCUSSION

After the first reports of MIBG (labeled with ^{131}I) results in pheochromocytoma in 1981 (20,21), similar descriptions of experience using ^{123}I -MIBG appeared within the next few years (7,22,23). The value of the new MIBG imaging tool for diagnosis and follow-up of pheochromocytoma was such that clinicians in both Europe and the United States quickly began to incorporate the procedure into their clinical practices, even though prospective controlled trials had not been performed. Although the present study is the largest prospective validation of the performance characteristics of ^{123}I -MIBG imaging in pheochromocytoma and paraganglioma of which we are aware, these results arrive long after most clinical decision-makers concluded that the method was efficacious based on published data and individual experience (5).

Sensitivities for detecting primary pheochromocytoma using ^{123}I -MIBG and ^{131}I -MIBG have almost always been reported as greater than 80% (7–16). In the largest published experience using ^{123}I -MIBG (315 patients), Miskulin et al. (24) reported a sensitivity of 98% in 48 patients with confirmed pheochromocytoma but did not provide details on the results for the 267 patients who presumably were ruled out for the disease. Similar high-

TABLE 2. ¹²³I-MIBG Planar Imaging Results in 140 Patients with Diagnostic Images and Standard-of-Truth Diagnoses

Patient category	No. of patients	Tumor present		Tumor absent		Sensitivity (%)	Specificity (%)
		Scan positive	Scan negative	Scan positive	Scan negative		
Prior known...							
Pheochromocytoma*	57	40	6	3	8	87	73
Paraganglioma*	22	14	7	0	1	67	100
Disease total*	79	54	13	3	9	81	75
Suspected...							
Pheochromocytoma/paraganglioma [†]	61	21	3	6	31	88 [‡]	84
Total	140	75	16	9	40	82	82
Metastatic disease subpopulation [§]							
Pheochromocytoma	27	25	2	—	—	93	—
Paraganglioma	14	10	4	—	—	71	—
Total	41	35	6	—	—	85	—

*Prior histologic diagnosis ($n = 77$) or previously treated based on imaging and catecholamine findings ($n = 2$).

[†]No disease confirmation before study with ¹²³I-MIBG.

[‡]For 21 patients with pheochromocytoma, sensitivity was 90%; for 3 patients with paraganglioma, sensitivity was 67%.

[§]Metastatic disease standard-of-truth diagnosis based on histopathology and imaging results (exclusive of study ¹²³I-MIBG imaging).

sensitivity values were presented in reports by Mozley et al. (88%) (11), Mannelli et al. (90%) (25), and Van Der Horst-Schrivers et al. (92%) (16). Larger clinical experiences with ¹³¹I-MIBG have yielded comparable findings (8,26,27). High specificity has been the rule in most published MIBG data (8,12,14), but this often reflected inclusion of many low-likelihood patients who might not have been scanned if adequate measurements of plasma metanephrines had been available to rule out disease (6). Although selection bias may have exaggerated the apparent performance of both ¹³¹I-MIBG and ¹²³I-MIBG imaging in various publications, most clinicians accept the reliability of the information provided by this scintigraphic method (6,28).

In the present prospective trial, sensitivity was 82% for the total population and 88% for those with suspected disease, the latter result being the most concordant with published experiences and the least likely to have been affected by patient selection bias. Sensitivity of ¹²³I-MIBG imaging for identification of adrenal pheochromocytoma was somewhat higher than for extraadrenal paraganglioma, consistent with prior reports for the latter pathology (29,30). The somewhat lower-than-expected specificity likely reflects effects of 2 attributes of the trial design: the readers interpreted abdominal planar and SPECT images without anatomic information and previous surgical history (increasing the potential for false-positive interpretations), and

TABLE 3. ¹²³I-MIBG Planar + SPECT Results in 130 Patients with Diagnostic SPECT Images and Standard-of-Truth Diagnoses

Patient category	No. patients	Tumor present		Tumor absent		Sensitivity (%)	Specificity (%)
		Scan positive	Scan negative	Scan positive	Scan negative		
Prior known...							
Pheochromocytoma*	53	38	5	3	7	88	70
Paraganglioma*	21	15	5	0	1	75	100
Total*	74	53	10	3	8	84	73
Suspected...							
Pheochromocytoma/paraganglioma [†]	56	21	2	8	25	91 [‡]	76
Total	130	74	12	11	33	86	75
Metastatic disease subpopulation [§]							
Pheochromocytoma	26	24	2	—	—	92	—
Paraganglioma	14	9	5	—	—	64	—
Total	40	33	7	—	—	83	—

*Prior histologic diagnosis ($n = 72$) or previously treated based on imaging and catecholamine findings ($n = 2$).

[†]No disease confirmation before study with ¹²³I-MIBG.

[‡]For 20 patients with pheochromocytoma, sensitivity was 90%; for 3 patients with paraganglioma, sensitivity was 100%.

[§]Metastatic disease standard-of-truth diagnosis based on histopathology and imaging results (exclusive of study ¹²³I-MIBG imaging).

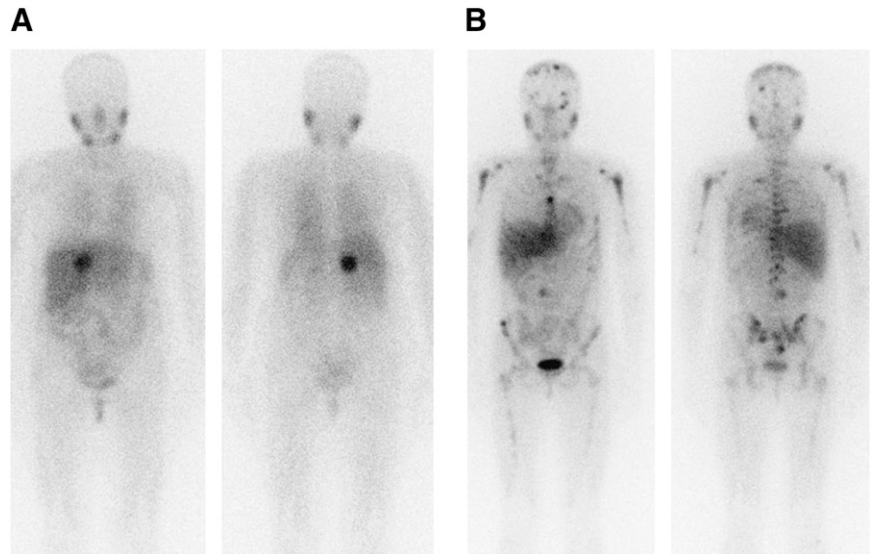


FIGURE 1. (A) Anterior (left) and posterior (right) whole-body images of 51-y-old woman with right adrenal tumor on CT, confirmed as pheochromocytoma at surgery. (B) Anterior (left) and posterior (right) whole-body images of 28-y-old woman with paraganglioma metastatic to bone.

the study included few low-likelihood patients (limiting the number of true-negative patients). SPECT had only a small effect on reader performance, producing a slight increase in sensitivity (82%–86%) and a small drop in specificity (82% to 75%). The limited impact of SPECT in part reflects the good performance of planar imaging for patient-based (rather than lesion-based) diagnosis of pheochromocytoma and the challenges of judging the significance of adrenal asymmetry without anatomic and clinical information. Although SPECT increased reader confidence, this imaging only changed the consensus interpretation for 10 patients (7%).

This study has several limitations. The sample size was smaller than in many prospective phase 3 imaging trials, and the masked reading procedures did not reflect standard multimodality interpretation commonly used in clinical practice. Interpretation of scintigraphic images in isolation also eliminated any potential impact of SPECT/CT, which recent experience suggests can improve the diagnostic

accuracy of ^{123}I -MIBG imaging (31,32). Although every effort was made to recruit all eligible patients, the possibility of selection and ascertainment bias (e.g., known prior disease status or results of past MIBG imaging used as a basis for recruiting or not recruiting a patient) cannot be excluded. Potential relationships between ^{123}I -MIBG imaging results and genetic abnormalities associated with pheochromocytoma could not be explored because the trial did not include the collection of relevant historical and histopathology data. Finally, because the collection of plasma normetanephrine results was neither an element of the protocol nor a standard procedure at many centers, it was not possible to assess the complementary value of this parameter in conjunction with ^{123}I -MIBG imaging (6).

CONCLUSION

This prospective multicenter clinical trial confirmed the performance characteristics of ^{123}I -MIBG scintigraphic

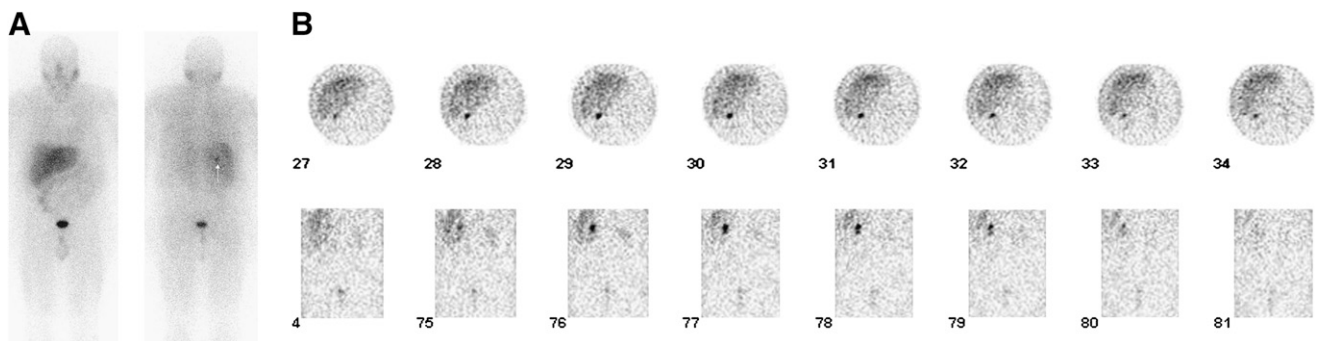


FIGURE 2. (A) Anterior (left) and posterior (right) whole-body ^{123}I -MIBG images of 59-y-old man with remote history of neck paraganglioma excised at age 25. As part of routine follow-up, abdominal CT scan was acquired and showed no abnormalities. Increased uptake in right upper abdomen is apparent on posterior ^{123}I -MIBG image (arrow). (B) Selected axial and coronal SPECT images demonstrate discrete increased uptake corresponding to abdominal finding on planar images. All 3 readers identified this uptake as in right adrenal gland, uptake that presumably reflected asymmetry in otherwise normal gland. Knowledge of history and CT findings might have altered readers' conclusion that uptake was pathologic.

imaging in a contemporary population of patients referred for assessment of known prior or suspected pheochromocytoma and paraganglioma, with sensitivities of 87%–90% for the former and 67%–100% for the latter. Specificity ranged from 70% to 84%. As these results were achieved with fully masked image interpretation, it is likely that sensitivity greater than 90% and specificity between 80% and 90% would be achieved for interpretations performed in combination with correlative anatomic data.

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