False-negative ^{123}I-MIBG SPECT is most commonly found in *SDHB*-related pheochromocytoma or paraganglioma with high frequency to develop metastatic disease

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Abstract

The purpose of this study was to present the characteristics and outcome of patients with proven pheochromocytoma or paraganglioma who had false-negative iodine-123 metaiodobenzylguanidine single photon emission computed tomography (^{123}I-MIBG SPECT). Twenty-one patients with false-negative ^{123}I-MIBG SPECT (7 males, 14 females), aged 13–55 years (mean: 41.40 years), were included. We classified them as nonmetastatic or metastatic according to the stage of the disease at the time of false-negative ^{123}I-MIBG SPECT study, the location and size of the tumor, plasma and urinary catecholamine and metanephrine levels, genetic mutations, and outcome in terms of occurrence and progression of metastases and death. Thirteen patients were evaluated for metastatic tumors, while the remaining eight were seen for nonmetastatic disease. All primary tumors and multiple metastatic foci did not show avid ^{123}I-MIBG uptake regardless of the tumor diameter. The majority of patients had extraadrenal tumors with hypersecretion of normetanephrine or norepinephrine. *SDHB* mutations were present in 52% ($n=11$) of cases, *RET* mutation in 4% ($n=1$), and the rest were apparently sporadic. Twenty-four percent ($n=5$) had metastatic disease on initial presentation. Fourteen patients were followed for 3–7 years. Of them, 71% ($n=10$) had metastatic disease and the majority had *SDHB* mutations. Nine are still alive, while five (four with *SDHB*) died due to metastatic disease. We concluded that false-negative ^{123}I-MIBG SPECT is frequently related to metastatic tumors and usually due to *SDHB* mutations with unfavorable prognosis. We therefore recommend that patients with false-negative ^{123}I-MIBG SPECT be tested for *SDHB* mutations and undergo more regular and close follow-up.

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Introduction

Pheochromocytoma (PHEO) and paragangliomas (PGLs) are tumors arising from chromaffin cells of the adrenal medulla or extraadrenal paraganglionic tissues respectively (DeLellis *et al.* 2004). These tumors express the cellular membrane norepinephrine transporter (NET), through which catecholamines can enter and be deposited into neurosecretory granules via vesicular monoamine transporter systems (VMATs). Metaiodobenzylguanidine (MIBG) is a guanethidine

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analogue resembling norepinephrine (NE) that can enter chromaffin cells through active uptake via NET or passive diffusion and is stored in catecholamine-containing neurosecretory granules (Sisson *et al*. 1981, Bomanji *et al*. 1987, Havekes *et al*. 2008, Vaidyanathan 2008). This characteristic makes MIBG very useful and extremely specific for the diagnostic localization of PHEO and PGL when labeled with radiotracers such as iodine-123 (^{123}I) or iodine-131 (^{131}I) (Sisson *et al*. 1981, Ilias & Pacak 2004, Havekes *et al*. 2008, Goldsmith 2009, Timmers *et al*. 2009*a*,*b*, Jacobson *et al*. 2010, Meyer-Rochow *et al*. 2010). In addition, ^{131}I-MIBG is also used for the treatment of metastatic PHEOs and PGLs that demonstrate avid MIBG uptake (Loh *et al*. 1997, Rose *et al*. 2003, Gonias *et al*. 2009, Castellani *et al*. 2010).

It was previously shown that $^{123/131}$I-MIBG scintigraphy has a sensitivity of about 78% in the detection of primary, sporadic, and nonmetastatic PHEO and PGL, which is comparable with other nuclear imaging studies such as 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG), [^{18}F]-fluorodopamine (^{18}F-FDA), and [^{18}F]-fluorodopa (^{18}F-DOPA) positron emission tomography (PET) that have sensitivities of 78–88% (Timmers *et al*. 2009*a*,*b*). However, the sensitivity of $^{123/131}$I-MIBG scintigraphy in the detection of metastatic tumors and familial PHEO and PGL is about 53–60.9%, which is somewhat suboptimal compared to other nuclear imaging studies (Shulkin *et al*. 1999, van der Harst *et al*. 2001, Ilias *et al*. 2003, Taïeb *et al*. 2004, Fiebrich *et al*. 2009, Goldsmith 2009, Kauhanen *et al*. 2009, Fottner *et al*. 2010). It is also less sensitive in the detection of extraadrenal and small PHEO and PGL (van der Harst *et al*. 2001, Bhatia *et al*. 2008, Wiseman *et al*. 2009). The uptake of MIBG was also shown to be well correlated with the presence of NET or VMATs (Bomanji *et al*. 1987, Eisenhofer 2001, Fottner *et al*. 2010). Thus, the number of neurosecretory granules and perhaps the degree of differentiation of tumor cells controlling the expression of NET may play an important role in a successful application of $^{123/131}$I-MIBG scintigraphy. Nevertheless, $^{123/131}$I-MIBG scintigraphy remains widely used because it is readily available and less expensive than ^{18}F-FDA PET/computed tomography (CT) and ^{18}F-FDOPA PET.

Initially, we observed that patients with PHEO and PGL, especially those growing rapidly, presented with false-negative ^{123}I-MIBG single photon emission computed tomography (SPECT). Some of these false-negative results were found to be associated with succinate dehydrogenase subunit B (*SDHB*) gene mutations. Therefore, we hypothesized that false-negative ^{123}I-MIBG SPECT in patients having either primary, recurrent, or metastatic disease would point toward the presence of *SDHB* mutations. Proving this hypothesis would alert physicians to initiate *SDHB* mutation testing in these patients, especially among those who have negative family history of this disease. Furthermore, we hypothesized that these ^{123}I-MIBG SPECT-negative tumors could reflect more aggressive behavior (as also commonly seen in *SDHB* patients) and should also alert physicians to perform more regular follow-up, including biochemical and imaging tests.

Materials and methods

Patients

Official results of ^{123}I-MIBG SPECT of patients seen at the National Institutes of Health (NIH) from 2002 through March 2011 for evaluation of PHEO and PGL were reviewed. Patients with false-negative ^{123}I-MIBG SPECT at any point from initial presentation to follow-up were identified and included in the present study if they were diagnosed with PHEO and PGL based on clinical presentation, specific biochemical tests (including measurement of catecholamine and metanephrines (MNs) in either plasma or urine), PHEO- and PGL-specific imaging studies, and histopathological confirmation of resected tumors. All patients were part of an Institutional Review Board-approved prospective study of patients with known or suspected PHEO and/or PGL at NIH. All patients provided informed consent.

Biochemical tests

Patients were asked to abstain from acetaminophen for 5 days and caffeinated and decaffeinated products, smoking, and alcohol for 24 h prior to blood extraction and 24-h urine collection. For plasma catecholamine and MN determination, a cannula was inserted in the forearm for i.v. access. Patients rested in the supine position without a pillow in a quiet room for 20–30 min before and during collection. As soon as blood was collected, it was placed on ice and stored at −80 °C until testing. Basal plasma levels of catecholamines and MNs were measured by HPLC. For urinary catecholamine and MN determination, total volume collected over 24 h was used and measured by HPLC or liquid chromatography–tandem mass spectrometry. Hypersecretion of plasma or urinary catecholamines or MNs was defined as any elevation above the upper reference limit.

Imaging tests

Computed tomography

Axial images of the neck, chest, abdomen, and pelvis were obtained after administration of oral and i.v. low-osmolar contrast. Multiple helical axial images at 2.5 and 5 mm thick were obtained in the neck and from the thoracic inlet to the symphysis pubis respectively.

Magnetic resonance imaging

Axial images of the head, neck, chest, abdomen, and pelvis were obtained. Axial T1, axial short time inversion recovery (STIR), and postcontrast fat-saturated axial T1-weighted images were obtained through the neck, while T1- and T2-weighted scans and STIR images were obtained in the chest. Scans were obtained before, during, and after i.v. injection of 14 ml Magnevist. In the abdomen, multiple sequences including axial T2-weighted (one without fat suppression with respiratory trigger; another one with fat suppression and suspended respiration) and two dimensional (2D) in- and out-of-phase T1-weighted images prior to, and multiphase three dimensional (3D) volume images in axial planes, single venous coronal following vascular contrast administration (18 cc Magnevist) were obtained at 3 T. If clinically indicated, magnetic resonance imaging (MRI) of the spine was obtained with sagittal T1-weighted and sagittal STIR images of the cervical, thoracic, and lumbar spine without administration of contrast material. Axial T2-weighted images were acquired at selected levels.

^{123}I-MIBG SPECT

Patients were required to discontinue medications that could potentially interfere with MIBG uptake (e.g. labetalol, monoamine oxidase inhibitors, phenylpropanolamine, tricyclic, and other antidepressants, or reserpine) at least 1 week before the procedure. To protect the thyroid from accumulation of free radioactive iodine, patients received 100 mg of saturated solution of potassium iodide by mouth twice a day for 4 days starting the night before ^{123}I-MIBG administration. Whole body planar and SPECT imaging were done in most cases 24 h, and in some 48 h, after i.v. administration of 8.4–11 mCi (mean: 10.18) ^{123}I-MIBG. Attenuation CT scans were available for three patients.

Other functional imaging studies

^{18}F-FDG PET/CT, ^{18}F-FDA PET/CT, and ^{18}F-FDOPA PET were performed. The patients were asked to fast for at least 6 h prior to i.v. injection of ^{18}F-FDA (1 mCi), ^{18}F-FDG (15.9 mCi), and ^{18}F-FDOPA (12 mCi). Patients were also asked to refrain from caffeine, tobacco, and alcohol for at least 12 h. Capillary blood glucose was measured before ^{18}F-FDG PET/CT. A low-dose, noncontrast, nondiagnostic CT was obtained for attenuation correction and anatomic localization. For ^{18}F-FDOPA PET, patients received 2 mg/kg carbidopa orally as pretreatment 1 h before radiotracer injection.

Genetic testing

Genetic testing was performed at the Department of Human Genetics of the Pittsburgh University Medical Center Clinic, Pennsylvania, and at Mayo Clinic Laboratories, Minnesota, USA. A stepwise approach to genetic testing was performed based on the most likely gene mutation based on the clinical presentation, biochemical phenotype, and the location of tumor(s). Patients were tested for von Hippel–Lindau, MEN2, *SDHB*, and *SDHC* and *SDHD* gene mutations (Maher & Eng 2002). Not all currently known susceptibility genes for PHEO and PGL were tested in our patients if a specific gene mutation causing the disease was already found. Furthermore, testing for *TMEM127*, *SDHA*, *SDHAF2*, and *MAX* gene mutations was not performed (Comino-Méndez *et al*. 2011, Hensen & Bayley 2011).

Statistical analysis

^{123}I-MIBG studies were reviewed separately by two experienced nuclear medicine physicians (C C and J R) who were blinded to any anatomic imaging studies and clinical history of patients. Physiologic uptake in the adrenal gland was carefully distinguished from abnormal uptake using the widely accepted four-point visual scale: (0) no increased activity demonstrated in one or both adrenal glands; (1) faint increased activity demonstrated in one or both adrenal glands; (2) moderate increased activity in one or both adrenal glands less than or equal to that of the liver; and (3) intense increased activity in one or both adrenal glands greater than the liver. Scores of 0–2 were classified as negative or physiologic uptake, while a score of 3 was classified as positive for PHEO or PGL.

All patients with adrenal tumors had histopathological confirmation of PHEO. Thus, a false-negative ^{123}I-MIBG scan among these patients was defined as the absence of uptake or radiotracer uptake in the adrenal gland less than that of the liver (score 0–2). On the other hand, patients with multiple metastatic lesions or inoperable tumors may not have pathologic confirmation of metastatic PHEO or PGL. Therefore, a false-negative ^{123}I-MIBG scan in this group was defined as the absence of radiotracer uptake in a

tumor of a patient who had clinical, biochemical, and anatomical and specific nuclear imaging studies clearly consistent with PHEO and PGL.

Metastatic PHEO or PGL was defined as the presence of tumors at sites where chromaffin tissues, such as the bones, liver, lungs, and lymph nodes, are not normally located. Multifocal disease was defined as the presence of multiple tumor foci, presenting synchronously or metasynchronously (new primary) to the original tumor, whereas recurrence was defined as reappearance of the disease as documented at reintervention or by combined biochemical and radiological tests after previous complete eradication of the tumor.

Results

Patient characteristics

Of the 245 patients who underwent ^{123}I-MIBG SPECT, we identified 21 patients (7 males, 14 females) aged 13–55 years (mean: 41.40 years) with false-negative ^{123}I-MIBG SPECT. Seven of these patients were referred for evaluation and management of possible PHEO and PGL, while the remaining 14 patients were referred after previous surgery of their primary tumor (adrenal PHEO, $n=4$; urinary bladder PGL, $n=3$; retroperitoneal and extraadrenal PGL, $n=6$; and carotid body tumor, $n=1$) (Table 1). After a thorough evaluation, eight patients were found to have nonmetastatic tumors and thirteen were found to have metastatic disease.

Plasma MNs were elevated in 17 patients (81%) (5 had both normetanephrine (NMN) and MN elevated, 12 had elevated NMN only), while 4 had normal levels. Plasma catecholamines were elevated in 15 patients (71%) (one had elevated NE, epinephrine (EPI), and dopamine (DA); one had elevated NE and EPI; five had elevated NE and DA; six had elevated NE only; one had elevated EPI only; and one had elevated DA only). Urinary MNs and catecholamines were available only in 13 patients. Eleven patients (85%) had elevated urinary MNs (two had elevated total MNs, NMN, and MN; nine had elevated total MNs and NMN). Ten patients (83%) had elevated urinary catecholamines (one had elevated NE and EPI; two had elevated NE and DA; and seven had elevated NE only).

Results of anatomical and functional imaging studies are presented in Table 2. All patients had tumors (primary or metastatic) that failed to accumulate ^{123}I-MIBG at first presentation to NIH, except patients nos 11, 15, 18, and 19, in whom false-negative scans were observed on follow-up (second ^{123}I-MIBG SPECT) when they developed metastatic disease

Table 1 Characteristics of patients at the time of false-negative ^{123}I-MIBG SPECT

Patient	Age (years)/sex	Reason for consult at NIH	Hypersecretion in plasma		Hypersecretion in urine		Gene mutation
			Metanephrines	Catecholamines	Metanephrines	Catecholamines	
1	13/F	P	NMN, MN	NE, E, DA	–	–	Apparently sporadic
2	47/F	P	NMN, MN	E	NMN, MN, T	None	*RET*
3	51/F	P	NMN, MN	NE, E	NMN, MN, T	NE, E	Apparently sporadic
4	61/M	P	None	DA	–	–	*SDHB*
5	49/F	P	NMN	NE	NMN, T	NE	Apparently sporadic
6	46/F	P	NMN, MN	None	–	–	Apparently sporadic
7	36/F	New P	NMN	NE	NMN, T	NE	*SDHB*
8	40/F	R	NMN	NE	NMN, T	NE, DA	Apparently sporadic
9	55/M	Met + New P	NMN	NE, DA	NMN, T	NE	Neg for *SDHx*
10	54/M	Met + New P	NMN	NE, DA	NMN, T	NE, DA	*SDHB*
11	42/F	Met + New P	NMN	NE, DA	NMN, T	NE	*SDHB*
12	36/F	Met	NMN	NE	NMN, T	NE	*SDHB*
13	32/M	Met	NMN, MN	None	None	None	Apparently sporadic
14	47/F	Met	None	None	–	–	*SDHB*
15	43/F	Met	NMN	NMN	NMN, T	None	*SDHB*
16	34/M	Met	NMN	NE, DA	–	–	*SDHB*
17	37/M	Met	NMN	NE, DA	–	–	*SDHB*
18	43/F	Met	None	None	–	–	*SDHB*
19	45/F	Met	NMN	NE	None	NE	Apparently sporadic
20	33/M	Met	None	None	–	–	*SDHB*
21	22/F	Met	NMN	NE	NMN, T	NE	Apparently sporadic

Adr, adrenal gland; DA, dopamine; E, epinephrine; F, female; M, male; Met, metastasis; MN, metanephrine; NE, norepinephrine; Neg, Negative; NMN, normetanephrine; P, primary tumor; R, recurrence; *RET*, rearranged during transfection; *SDHB*, succinate dehydrogenase subunit B; *SDHD*, succinate dehydrogenase subunit D; T, total metanephrines; –, not available.

Table 2 Comparative imaging studies of patients with false-negative ^{123}I-MIBG SPECT

Patient	CT	MRI	^{123}I-MIBG	^{18}F-FDA	^{18}F-FDOPA	^{18}F-FDG-PET
1	R adr	NA	Neg	NA	NA	R adr
2	R+L adr	R+L adr	Neg	Neg	NA	R parietal skull[a], R upper posterior neck[a], R mediastinum[a]
3	L adr	L adr	Neg	L adr	NA	L adr
4	L paraaortic, L renal mass[b]	L paraaortic	Neg	Neg	Neg	L paraaortic, and L kidney
5	R adr	R adr	Neg	R adr	NA	NA[c]
6	R+L adr	R+L adr	Neg	Neg	R adr	NA
7	Paraesophageal	Paraesophageal	Normal adr uptake	Neg	NA	Paraesophageal
8	R adr	NA	Neg	Neg	NA	Neg
9	Liver, lung, LN, B, bilateral carotid	Liver, LN, B, bilateral carotid	Neg	B	B, liver, LN	R carotid, soft tissues adjacent to C2 and C3 cervical vertebrae, B, liver, LN
10	B, LN, lungs, R adr	NA	Normal adr uptake	LN	NA	NA
11	B, lungs, liver, periaortic	R adr, B, liver, retroperitoneal L periaortic	Normal adr uptake	Liver, B, LN, soft tissues in the abdomen	NA	B, L upper abdomen in the region of the pancreas and toward the L side of the upper abdomen, liver, LN and soft tissues in the abdomen
12	Lung, pelvic LN	Lung, pelvic LN	Normal adr uptake	Neg	NA	Lungs, pelvic LN[d]
13	B	B	Normal adr uptake	B	NA	B
14	Lung, LN, B	B[e]	Normal adr uptake	Neg	Neg	B, lungs
15	B, liver, LN, Infrasplenic	B, liver, LN	Normal adr uptake	B, infrasplenic	NA	R posterior medial lung, B, L lateral abdomen, liver
16	B, lungs, LN, liver, L paraaortic mass, intrathoracic prevertebral mass	B, liver, LN, L paraaortic mass, intrathoracic prevertebral mass[e]	Normal adr uptake	Neg	NA	Lungs, LN, B, liver, L lower abdomen extending to the midline
17	LN, lungs, B, liver	B, LN, liver	Normal adr uptake	LN	Neg	LN, B, liver
18	LN	LN	Normal adr uptake	Neg	NA	B, LN
19	Lungs, LN	Lungs, LN	Normal adr uptake	R mediastinum at the hilar area, L lung, LN	NA	Lungs, LN
20	R carotid LN in the chest	R carotid LN in the chest	Neg	Neg	R carotid	LN in the chest
21	LN	LN	Normal adr uptake	LN	LN	LN

Adr, adrenal gland; B, bones; L, left; LN, lymph nodes; NA, not available; Neg, negative; R, right; ^{18}F-FDA, ^{18}F-fluorodopamine; ^{18}F-FDOPA, ^{18}F-dihydroxyphenylalanine; ^{18}F-FDG PET, 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography. Normal adr uptake means a score of 1–2 and was considered to be physiologic uptake in the adrenal gland.
[a]Medullary thyroid cancer-related.
[b]Left renal mass: renal cell carcinoma by histopathology.
[c]Available from outside prior to referral to NIH with increased uptake in the right adrenal gland.
[d]Outside scan not available for review.
[e]MRI of the chest not done.

(patient no. 18) or progression of known metastatic disease (patients nos 11, 15, and 19). Of the eight patients with nonmetastatic tumors (patients nos 1–8), anatomical and nuclear imaging studies other than ^{123}I-MIBG SPECT/CT showed adrenal gland PHEO ($n=6$; five unilateral, one bilateral), paraesophageal PGL ($n=1$), and paraaortic PGL ($n=1$), which were confirmed by histopathology after surgery. In patient no. 2 with MEN2 syndrome, ^{18}F-FDG PET/CT further showed increased uptake of radiotracer in the skull, neck, and mediastinum, which was proven to be related to medullary tumor of the thyroid gland after excision. None of them were found to have multifocal or metastatic disease, as proven by multiple imaging studies, together with normalization of plasma MNs and catecholamines postoperatively.

Among the 13 patients with metastatic disease, metastases were noted in the lungs ($n=8$), multiple bony sites ($n=9$), lymph nodes ($n=12$), liver ($n=5$), and other soft tissues ($n=3$). Despite multiple tumor sites found per patient, none showed avid ^{123}I-MIBG uptake. Patient no. 10 with metastatic disease was concomitantly found to have another primary tumor in the right adrenal gland, while patient no. 9 developed additional primary tumors bilaterally in the carotid bodies with metastatic disease in the liver, lungs, lymph nodes, and bones, as shown in Fig. 1, after removal of a urinary bladder PGL. In these patients, both the primary and metastatic tumors had no uptake of ^{123}I-MIBG.

Of the seven patients with adrenal PHEO (five primary and nonmetastatic; one recurrence; and one new primary with metastases), the mean largest diameter of the tumor was 4.3 cm (range: 1.5–7 cm). In one patient with a primary tumor in the right carotid body and in another patient with a left paraaortic PGL, the tumors measured 0.8 and 1.5 cm respectively.

Eleven (52%) patients were found to have an *SDHB* mutation and one (4%) was found to have MEN2 syndrome, while the remaining patients presented with apparently sporadic PHEO and/or PGL. Among *SDHB*-related tumors, nine were associated with metastatic disease, one had multifocal tumors, and one had a nonmetastatic tumor.

Outcome analysis

Patients with false-negative ^{123}I-MIBG SPECT performed before 2008 were included for outcome analysis ($n=19$). Five patients were excluded due to lack of follow-up ($n=4$) and infection with human

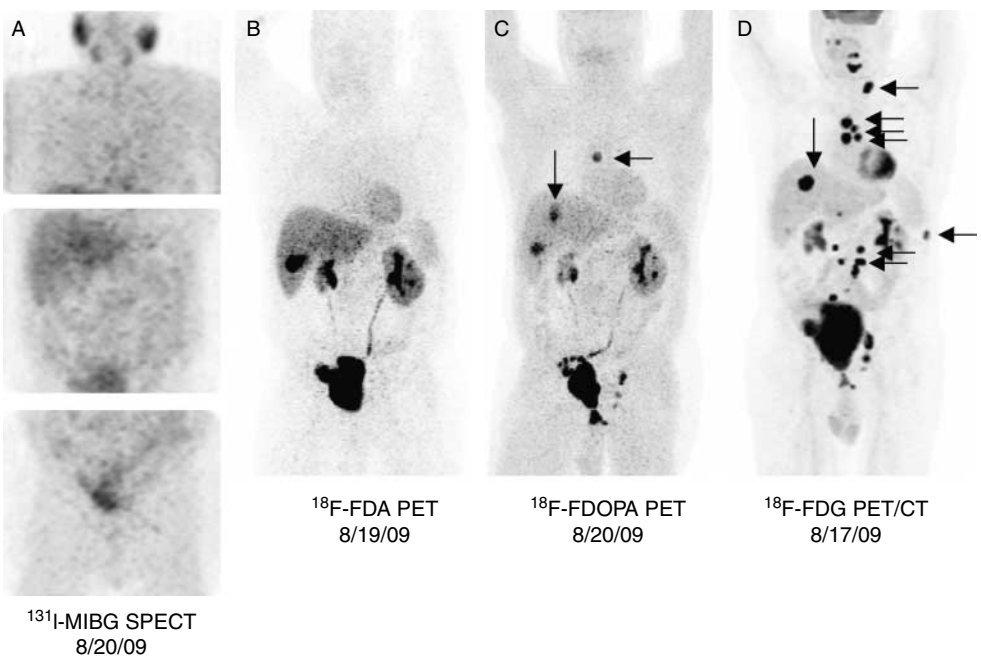

Figure 1 Nuclear imaging studies of a 55-year old male with metastatic pheochromocytoma who tested negative for succinate dehydrogenase B, C, and D mutations. The primary tumor was found in the urinary bladder and was removed with en bloc cystectomy, prostatectomy, with lymphatic node dissection and creation of ileal neobladder in 2005. In 2009, he was diagnosed with metastatic disease with false-negative ^{123}I-MIBG SPECT/CT. At NIH, (A) ^{123}I-MIBG SPECT/CT was also negative, but other nuclear imaging such as (B) ^{18}F-FDA, (C) ^{18}F-FDOPA, and especially (D) ^{18}F-FDG PET showed multiple metastatic foci in the lymph nodes, lungs, and liver. He underwent radiofrequency ablation of liver lesions. A repeat ^{18}F-FDG PET/CT after 3 months showed evidence of progression.

immunodeficiency virus ($n=1$). A total of 14 cases were analyzed with a mean follow-up period of 5 years (range: 2–7) after the first documented false-negative ^{123}I-MIBG SPECT at NIH (Table 3). On initial presentation at NIH, four (29%) of these patients had no metastases, while ten (71%) had metastatic disease.

Of the four patients with nonmetastatic PHEO or PGL, none developed metastatic disease until March 2011, when one patient (patient no. 7) developed another primary tumor in the left carotid body and a paraesophageal PGL about 6 years after a false-negative ^{123}I MIBG SPECT. Two of the nonmetastatic cases were due to *SDHB* mutations, while the other two were apparently sporadic. All the patients are still alive.

Of the ten patients with metastatic disease, nine (90%) had *SBHB* mutations, while the remaining case had apparently sporadic PHEO or PGL. Patient no. 12 had multiple metastases in the lungs and left paraaortic lymph nodes, which were excised. Patient no. 15 had multiple metastases to the bones, liver, and lymph nodes and was given chemotherapy with cyclophosphamide + vincristine + dacarbazine (CVD), sunitinib, bortezomib, 17-DMAG, and external beam radiotherapy. Patient no. 16 who had multiple metastases to the bones, lungs, liver, and lymph nodes received chemotherapy with CVD and underwent radiofrequency ablation of liver metastases. Patients nos 11 and 17 who had metastases to the bones, liver, lungs, and lymph nodes were treated with CVD and 17-DMAG respectively. Patient no. 18 had gamma knife radiotherapy of a carotid body tumor invading the skull, which was later resected. She also received CVD chemotherapy. Patient no. 19 developed metastatic lesions with avid uptake on subsequent ^{123}I-MIBG SPECT and therefore underwent ^{131}I-MIBG treatment, but due to persistent disease, she also received temozolomide. Patient no. 21 had resection of the periaortic lymph node and hilar metastases and developed another primary tumor in the left adrenal gland 6 years after the initial diagnosis, which was also resected. Five (55%) (four *SDHB* + one sporadic) died due to overwhelming metastases after a mean of 10.4 years (range: 3–17 years) after the initial diagnosis of PHEO or PGL and a mean of 5.2 years (range: 3–7 years) after development of metastatic disease. Sixty percent of deaths occurred within 5 years of the diagnosis of metastatic disease. Four other patients (two *SDHB* and two sporadic) had progressive disease within a mean follow-up of 7.25 years (range: 6–9 years), while one other patient had stable metastatic disease.

Table 3 Outcome of patients with false-negative ^{123}I-MIBG SPECT

	Living	Dead
n	9	5
Tumor type		
Nonmetastatic	4	0
Metastatic	5	5
Primary tumor location		
Adrenal	2	2
Extraadrenal	7	3
Gene mutation		
SDHB	5	4
Sporadic	4	1

Discussion

The present study shows detailed characteristics and outcomes of patients with false-negative ^{123}I-MIBG SPECT. The majority had primary tumors of extra-adrenal chromaffin tissues, noradrenergic biochemical phenotype, and metastases, and over half had mutations in *SDHB*. The latter comprise 25 and 69% of patients with nonmetastatic and metastatic PHEO or PGL respectively. To our best knowledge, this is the first paper to show that PHEOs or PGLs in patients with false-negative ^{123}I-MIBG SPECT follow a more aggressive course and are frequently linked to the presence of *SDHB* mutations.

In general, it is estimated that the rate of malignancy among patients with PHEO and PGL is about 10–30%, and that ~10% have metastatic disease upon initial presentation (Goldstein *et al*. 1999). It is also estimated that at least one-third of PHEOs and PGLs have a defined genetic cause (Amar *et al*. 2005, Erlic *et al*. 2009, Mannelli *et al*. 2009). However, we have shown in the present study that among patients with false-negative ^{123}I-MIBG SPECT, the rate of malignancy was higher, at 62% (13 out of 21), and 24% (5 out of 21) had metastatic disease on initial presentation. Furthermore, 57% (12 out of 21) were due to a genetic mutation, with 92% (11 out of 12) of these cases linked to *SDHB* mutations.

It is well established that PHEO or PGL due to *SDHB* mutations is associated with shorter survival (Amar *et al*. 2007) and higher incidence of malignancy (Brouwers *et al*. 2006, Burnichon *et al*. 2009, Timmers *et al*. 2009*a*,*b*). It is estimated that the malignancy rate of *SDHB*-related PHEO or PGL is at least 30% and often much higher; the 5-year probability of survival after the diagnosis of first metastasis among these patients drops to 36%, in contrast to 67% among patients without *SDHB* mutations (Amar *et al*. 2007). In our study, *SDHB* mutations accounted for 69% of metastatic disease and 80% of mortality. In the present study, 44% (four out of nine) of patients with

apparently sporadic PHEO and PGL were found to have metastatic disease, resulting in death of one patient within 6 years of the diagnosis of metastasis. In contrast to these data, it was previously shown that the rate of malignancy among apparently sporadic tumors is only 9% (Bravo & Tagle 2003). It should be further emphasized that of the five patients who had metastatic disease upon initial diagnosis, three had apparently sporadic tumors. These results suggest that negative ^{123}I-MIBG SPECT points toward an unfavorable outcome that may be independent of *SDHB* mutations. Thus, patients with false-negative ^{123}I-MIBG SPECT should be tested for *SDHB* mutations because a larger percentage of patients, as shown in this paper, harbor *SDHB* mutations. Screening for *SDHB* mutations is important not only because it is independently associated with higher rates of malignancy and mortality, but also because it allows for the identification of family members with the mutation for early diagnosis and treatment. Furthermore, it will guide clinicians in terms of which treatment to use, with CVD being the treatment of choice for *SDHB*-related metastatic disease (unpublished observations); which biochemical markers to use in the follow-up, with plasma methoxytyramine as the preferred test (Eisenhofer *et al*. 2011); and lastly, the imaging test of choice, with ^{18}F-FDG PET/CT having the highest sensitivity in detecting metastatic tumors (Timmers *et al*. 2007*a*,*b*).

There are several factors that can cause a false-negative ^{123}I-MIBG study. Medications such as labetalol, reserpine, calcium channel blockers, and antidepressants may interfere with MIBG uptake (Solanki *et al*. 1992, Havekes *et al*. 2008). $^{123/131}$I-MIBG scintigraphy has been shown to have lower sensitivity for small tumors (van der Harst *et al*. 2001, Bhatia *et al*. 2008, Wiseman *et al*. 2009). However, two of our patients had adrenal PHEOs measuring 7 cm with false-negative scans by ^{123}I-MIBG SPECT. The sensitivity of $^{123/131}$I-MIBG scintigraphy is also generally suboptimal for extra-adrenal PGLs; this was demonstrated in the present study by the inclusion of a patient with a mediastinal PGL measuring 8 cm with a false-negative ^{123}I-MIBG SPECT. The suboptimal sensitivity of $^{123/131}$I-MIBG for metastatic PHEO and PGL has also been shown in previous studies and is related to the dedifferentiation that results in loss of NET among these tumors (Ilias *et al*. 2003, Timmers *et al*. 2009*a*,*b*). The limited sensitivity of $^{123/131}$I-MIBG scintigraphy for familial cases of PHEO and PGL has also been documented (van der Harst *et al*. 2001, Ilias *et al*. 2003, Taïeb *et al*. 2004, Bhatia *et al*. 2008, Timmers *et al*. 2009*a*,*b*, Fottner *et al*. 2010). Thus, ^{123}I-MIBG scintigraphy is not recommended for these patients and negativity may reflect aggressive behavior. Studies have also shown that a predominantly NE and NMN secretion predicts negative ^{123}I-MIBG scintigraphy that was also observed in our study (van der Harst *et al*. 2001, Fottner *et al*. 2010). However, only 81% of our patients had elevated plasma NMN, which is known to have a sensitivity of about 97–99% in detecting PHEO and PGL in general (Lenders *et al*. 2002, Sawka *et al*. 2003). This may be due to the fact that the majority of our patients had *SDHB*-related tumors, and it was previously demonstrated that plasma NMN was elevated in only about 82% of patients with *SDHB* mutations (Timmers *et al*. 2007*a*,*b*). These results raise important questions whether other biochemical markers, including chromogranin A and plasma methoxytyramine, could be of a diagnostic value in these patients, in whom early diagnosis and treatment is paramount. However, one study showed that the uptake of MIBG was not correlated with plasma or urinary catecholamine levels, but with the amount of neurosecretory granules within the tumor (Bomanji *et al*. 1987). Recently, it was shown that VMAT-1 expression is lacking in a cohort of patients with false-negative MIBG scintigraphy, the majority of whom had familiar PHEOs or PGLs, with two patients having *SDHB* gene mutations (Fottner *et al*. 2010).

The evaluation of patients with biochemically proven PHEO or PGL commences with anatomical imaging studies, such as CT and MRI scans, followed by nuclear imaging studies. For patients with adrenal tumors <5 cm, especially those associated with increased MN or EPI, nuclear imaging studies may not be done because the likelihood of metastatic disease or multifocal tumors is low. In patients with adrenal tumors more than 5 cm, extraadrenal tumors, and those associated with increases in NMN and NE, nuclear imaging studies should be done to prove that the tumor is indeed PHEO or PGL and to look for possible metastatic or multifocal tumors. The role of ^{123}I-MIBG SPECT in the evaluation of PHEO and PGL is currently debatable. Clearly, there is benefit for patients who will have to undergo ^{131}I-MIBG treatment for metastatic tumors. However, it has a limited role in the localization of extraadrenal and metastatic tumors, and as shown in the present study, *SDHB*-related tumors. ^{18}F-FDA PET/CT is the imaging technique of choice for extraadrenal primary tumors (Ilias *et al*. 2003), while ^{18}F-FDOPA PET/CT is most optimal for head and neck PGL, especially *SDHB*- and *SDHD*-related tumors (Fiebrich *et al*. 2009, Fottner *et al*. 2010, King *et al*. 2011). For patients with metastatic disease, ^{18}F-FDA PET/CT is the imaging

technique of choice, especially for those with unknown gene mutations (Timmers *et al*. 2009*a*,*b*). However, for those related to *SDHB*, ^{18}F-FDG PET/CT is the best imaging modality (Timmers *et al*. 2007*a*,*b*, 2009*a*,*b*). In centers where these imaging modalities are not available, patients who present with extraadrenal and possible metastatic tumors in anatomical imaging studies but have probable false-negative ^{123}I-MIBG SPECT should be referred to specialty centers where ^{18}F-FDA PET/CT, ^{18}F-FDOPA PET, and ^{18}F-FDG PET/CT are available. Testing for *SDHB* mutations should also be carried out, especially for patients with metastatic disease, and as observed in this study, may also be done in patients with nonmetastatic tumors with false-negative ^{123}I-MIBG SPECT.

The present study has some limitations. Most patients who were referred to NIH due to metastatic disease did not have preoperative $^{123/131}$I-MIBG scintigraphy. Furthermore, the data may be affected by referral bias, and the follow-up period for some patients seen at NIH for their primary tumors was relatively short to definitively exclude nonmetastatic disease. It is also recommended that a head-to-head comparison be made of the outcomes of *SDHB*-related tumors with avid and false-negative ^{123}I-MIBG SPECT. We also recommend a multicenter study to increase the number of patients to be evaluated with this rare disease of PHEO and PGL and in this even rarer subset of patients with false-negative ^{123}I-MIBG SPECT.

In conclusion, we have shown that a false-negative ^{123}I-MIBG SPECT is frequently related to metastatic tumors, usually due to *SDHB* mutations, with unfavorable prognosis. We therefore recommend that patients with false-negative ^{123}I-MIBG SPECT be tested for *SDHB* mutations and undergo more regular and close follow-up.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

All authors were involved in conceptualizing this research paper and contributed in the writing and editing of the final manuscript. Furthermore, J S Fonte, MD and J F Robles, MD were involved in data gathering. J S Fonte, MD, K Pacak, MD, PhD, DSc, C C Chen, MD, J Reynolds, MD, and M Whatley reviewed the nuclear imaging studies of the patients. J S Fonte, MD, K Pacak, MD, PhD, DSc, and A Ling, MD reviewed the CT scans and MRIs of the patients. K Pacak, MD, PhD, DSc, T Fojo, MD, K Adams, J S Fonte, MD, and J F Robles, MD were involved in the management of the patients included in the present study. J S Fonte, MD and K Pacak, MD, PhD, DSc wrote the initial manuscript.

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