Added Value of SPECT/CT for Correlation of MIBG Scintigraphy and Diagnostic CT in Neuroblastoma and Pheochromocytoma

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OBJECTIVE. In pheochromocytoma and neuroblastoma, pathologic findings on metaiodobenzylguanidine (MIBG) scintigraphy (planar and SPECT) and on diagnostic CT are sometimes difficult to correlate. Furthermore, CT reading may be impaired by anatomic distortion after surgery or irradiation and if contrast agent is not injected. The present study evaluates the impact of SPECT/CT fusion images on correlation and image analysis of both techniques.

MATERIALS AND METHODS. Eleven patients, three adults (age range, 27–64 years) with pheochromocytoma and eight children (age range, 16–72 months) with neuroblastoma, underwent 15 ^{123}I-MIBG scintigraphy (whole body and SPECT/CT) and diagnostic CT during follow-up after treatment, with a time interval of 2 to 30 days (mean, 12 days) between MIBG scintigraphy and diagnostic CT. The diagnostic CT scans were read twice: blindly and with knowledge of the SPECT/CT findings. The scintigraphic and anatomic data were subsequently compared and were verified by clinical outcome.

RESULTS. Of 15 imaging studies, there were nine cases of discordance between SPECT/CT and diagnostic CT, whereas concordant findings of planar MIBG and diagnostic CT were observed in six studies. Overall, SPECT/CT provided additional information in eight of the 15 cases (53%) and in eight of nine discordant studies (89%). In one case of pheochromocytoma in which anatomy was distorted by previous surgery and contrast agent was not injected, SPECT/CT findings guided the diagnostic CT that had initially misinterpreted the right adrenal gland as the inferior vena cava. In three of 11 studies performed for neuroblastoma, SPECT/CT facilitated the diagnostic CT reading: in one study, a small paravertebral thickening was overlooked at blind CT reading and in another case, SPECT/CT localized and characterized a soft-tissue mass medial to the iliac bone, which was missed on diagnostic CT in an area of difficult differential anatomy (bowel loops and eventual involved lymph nodes). In the third case, SPECT/CT directed the diagnostic CT to the MIBG abnormality after multiple surgical procedures. In these four cases, MIBG SPECT/CT allowed for localization of the pathologic site that was difficult to visualize on diagnostic CT. In four additional neuroblastoma studies in which a residual mass was present on diagnostic CT, planar MIBG scintigraphy was negative. SPECT/CT, focused on the area of the diagnostic CT abnormality, showed no focal MIBG uptake, thus increasing the diagnostic certainty of remission.

CONCLUSION. In cases of equivocal diagnostic CT, SPECT/CT bridges the gap between MIBG scintigraphy and diagnostic CT, with guidance of the diagnostic CT and characterization of its findings. In this small series, MIBG SPECT/CT increased the diagnostic certainty in 89% of discordant studies.

Keywords: CT, MIBG, neuroblastoma, pheochromocytoma, SPECT/CT

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Neuroblastoma and pheochromocytoma are the two most common tumors of the adrenal medulla and the sympathetic and parasympathetic systems. Both are derived from the primitive neural crest and have the histologic characteristics of the amine precursor uptake and decarboxylation (APUD) system.

Neuroblastoma is one of the most common childhood solid tumors. Up to 55% of neuroblastomas appear in the abdominal cavity; about 33% arise in the adrenal medulla, and the rest occur anywhere along the sympathetic chain, most often in the paravertebral region of the posterior mediastinum and the neck. Clinical symptoms and signs at diagnosis are usually nonspecific and include a large abdominal mass, diffuse abdominal pain, and fever. Paravertebral localization may cause neurologic symptoms. Neuroblastoma can

spread locally and involve regional and distant lymph nodes and its most frequent sites of hematogenic metastases are bones, liver, lungs, and skin [1]. All those factors have significant influence on the clinical outcome and prognosis [1–5].

Pheochromocytoma is an uncommon neoplasm that most often occurs in adults and rarely in children. About 85% of pheochromocytomas arise in the medulla of the adrenal glands; the rest come from any of the extraadrenal paraganglia, more often below the diaphragm. About 10% of intraadrenal pheochromocytomas are malignant. The risk of malignant development is higher in the extraadrenal tumors (20–40%). The main clinical feature is catecholamine-induced hypertension. A broad spectrum of clinical presentations is possible, from chronic, sustained high blood pressure to sudden death due to a hypertensive crisis, myocardial infarction, or cerebrovascular accident. The primary diagnosis of pheochromocytoma is based on the visualization of increased urinary excretion of free catecholamines and their metabolites [2, 6–8].

Both neuroblastoma and pheochromocytoma synthesize, store, and release catecholamines (adrenaline, noradrenalin) and their precursors. Metaiodobenzylguanidine (MIBG), an analog of guanethidine (noradrenalin precursor), is stored in cytoplasmic vesicles found in the cells of organs with rich adrenergic innervation, such as the heart, salivary glands, spleen, adrenal medulla, and tumors of medullary origin [2, 7]. It can therefore serve as a biomarker that, appropriately labeled, helps in the detection of such tumors and that is also used as a carrier for targeted radionuclide therapy [9, 10].

Iodine-labeled MIBG scintigraphy has good sensitivity for the diagnosis of neuroblastoma (93%) and of pheochromocytoma (87.5%) and high specificity close to 100% for both [2, 3, 5, 8]. The imperfect anatomic localization of MIBG scintigraphy is somewhat improved by SPECT. Among the other imaging techniques available for diagnosis and follow-up of neuroblastoma and pheochromocytoma (sonography, CT, MRI, and PET), the most commonly used today is CT with IV contrast material injection. Contrast-enhanced CT has high anatomic resolution, good sensitivity (87% for neuroblastoma, 92% for pheochromocytoma) but imperfect specificity (80% for both) [5, 8, 11]. Furthermore, contrast-enhanced CT interpretation can be impaired by anatomic distortion after surgery or irradiation. Another important contrast-enhanced CT limitation is the use of ionic IV contrast material in patients with pheochromocytoma, which could induce a sudden hypertensive crisis unless the patients were treated by α-blockers [6]. However, this does not seem relevant with the availability of nonionic contrast agents [12]. In any case, without IV contrast injection, the diagnostic confidence of CT decreases.

Last but not least, pathologic findings on MIBG scintigraphy (planar and SPECT) and on diagnostic CT are sometimes difficult to correlate anatomically. Integration of the highly specific metabolic imaging by nuclear medicine (MIBG scintigraphy) and the higher-resolution anatomic imaging (CT) can increase the accuracy of both methods. SPECT/CT technology inherently registers tomoscintigraphic (SPECT) with CT images and allows the studies to be superimposed, both studies being performed sequentially in the same session on a single-device hybrid scanner without the patient moving from the table between the two examinations [13].

The purpose of the present study was to evaluate the contribution of MIBG SPECT/CT to contrast-enhanced CT image analysis in the follow-up of patients with neuroblastoma and pheochromocytoma and to assess its impact on patient management.

Materials and Methods

Patients

We retrospectively analyzed 15 imaging studies of 11 patients followed up after treatment: eight children for neuroblastoma, four males and four females with a mean age of 28 months (age range, 6–72 months) and three adults for pheochromocytoma (ages, 40, 57, and 64 years). All patients had positive baseline MIBG scans. During the follow-up period of 2 to 36 months (mean, 17 months), they all underwent repeated MIBG scintigraphy (whole-body planar and MIBG SPECT/CT in the same session) and a separate contrast-enhanced CT within 30 days.

MIBG Scintigraphy and SPECT/CT

Whole-body planar images were acquired 4 and 24 hours after IV injection of 370 MBq (10 mCi) of ^{123}I-MIBG (peak energy, 159 keV; half-life, 13.3 hours) for adult patients or 7.4 MBq/kg (200 μCi/kg) for children using a large-field-of-view gamma camera equipped with a parallel-hole low-energy collimator and a 5/8-inch (1.6-cm) thick crystal. SPECT/CT scans of the anatomic region with a suspicious finding on planar whole-body imaging were acquired after this early planar imaging. A dual-headed variable-angle gamma camera and low-power X-ray transmission CT mounted on the same gantry (Millennium VG and Hawkeye, GE Healthcare) were used for combined SPECT/CT according to the follow protocol: CT acquisition: matrix, 256 × 256; SPECT acquisition: matrix, 128 × 128; 60 projections; 30 seconds per view. Image processing was performed on an eNTEGRA Workstation (GE Healthcare) using filtered back projection. Analysis of the images was done using a program displaying superimposed slices of the same MIBG SPECT and CT level (coregistered images).

Diagnostic CT

CT was performed on a 16-MDCT scanner (Brilliance, Philips Medical Systems) with 5-mm-thick slices for adults and 3 mm for children (90–120 kV and 150–250 mA, according to body weight). All studies were performed after IV and oral contrast material administration, except for two cases of previously diagnosed pheochromocytoma. Because IV contrast was contraindicated in these cases, oral contrast only was used.

Image Interpretation

Contrast-enhanced CT and MIBG SPECT/CT were independently and blindly reviewed by two radiologists and by a team of two nuclear medicine physicians, respectively. A common compared reading of SPECT/CT and contrast-enhanced CT was then performed. Differences of opinion were resolved by consensus.

On MIBG SPECT/CT images, a focus of increased trace uptake was considered pathologic when above and distinct from the background and from MIBG normal biodistribution.

Data Analysis

Retrospective analysis of MIBG planar scintigraphy, MIBG SPECT/CT, and contrast-enhanced CT included assessment of the following: concordance or discordance between the MIBG SPECT and CT findings of SPECT/CT and between SPECT/CT and contrast-enhanced CT; correlation between the two series of data: SPECT/CT, contrast-enhanced CT, and all other available imaging or clinical information, among them clinical follow-up considered as the gold standard.

Results

The results of the contrast-enhanced CT, MIBG planar scintigraphy, and combined MIBG SPECT/CT read blindly for all cases are displayed in Table 1. The contrast-enhanced CT interpretation was considered equivocal in the following cases: residual mass, scar or tumor in six cases; distorted anatomy after surgery in four cases; suboptimal

TABLE 1: MIBG SPECT/CT, Diagnostic CT, and Correlative Findings

Examination No.	Age	Length of Follow-Up (mo)	Diagnosis	MIBG–SPECT/CT		Diagnostic CT	Correlative Findings
				SPECT	CT		
1[a]	9 mo		Neuroblastoma	–	Equivocal	Equivocal	–
2[a]	1.5 y	30	Neuroblastoma	–	Equivocal	Equivocal	–
3	3 y	2	Neuroblastoma	+	+	+	+
4	4 y	10	Neuroblastoma	+	Equivocal	Equivocal	+
5	1.8 y	36	Neuroblastoma	–	Equivocal	Equivocal	–
6[a]	1.5 y		Neuroblastoma	–	–	–	–
7[a]	1.8 y	12	Neuroblastoma	–	–	–	–
8[a]	5.6 y		Neuroblastoma	+	Equivocal	Equivocal	+
9[a]	5.8 y	2	Neuroblastoma	+	+	+	+
10	3 y	6	Neuroblastoma	+	Equivocal	Equivocal	+
11	7 mo	30	Neuroblastoma	–	Equivocal	Equivocal	–
12	40 y	24	Pheochromocytoma	+	Equivocal	–	–
13[a]	57 y		Pheochromocytoma	+	+	+	+
14[a]	58 y	33	Pheochromocytoma	+	+	+	+
15	64 y	3	Pheochromocytoma	+	Equivocal	–	+

Note—MIBG = metaiodobenzylguanidine, + indicates evidence of pathologic findings, – indicates no evidence of pathologic findings.
[a]Examinations 1 and 2, 6 and 7, 8 and 9, and 13 and 14 were paired studies of the same patients.

TABLE 2: Influence of MIBG SPECT/CT Findings on Diagnostic CT Reading

Examination No.	Diagnosis	^{123}I-MIBG–SPECT/CT	Diagnostic CT Read Blindly	Diagnostic CT Read with Knowledge of SPECT/CT	SPECT/CT Provided Additional Information
1	Neuroblastoma	–	Equivocal	–	+
2	Neuroblastoma	–	Equivocal	–	+
3	Neuroblastoma	+	+	+	–
4	Neuroblastoma	+	Equivocal	+	+ (Fig. 1)
5	Neuroblastoma	–	Equivocal	–	+
6	Neuroblastoma	–	–	–	–
7	Neuroblastoma	–	–	–	–
8	Neuroblastoma	+	Equivocal	+	+ (Fig. 2)
9	Neuroblastoma	+	+	+	–
10	Neuroblastoma	+	Equivocal	+	+ (Fig. 3)
11	Neuroblastoma	–	Equivocal	–	+
12	Pheochromocytoma	+	–	–	–
13	Pheochromocytoma	+	+	+	–
14	Pheochromocytoma	+	+	+	–
15	Pheochromocytoma	+	–	+	+

Note—SPECT/CT provided additional information to diagnostic CT in eight of nine discordant studies: one pheochromocytoma and seven neuroblastomas (89%) and had an impact on the management of these patients. Diagnostic CT read blindly was equivocal in six studies and produced false-negative results in two studies (nos. 8 and 15). MIBG = metaiodobenzylguanidine, + indicates evidence of pathologic findings, – indicates no evidence of pathologic findings.

anatomic resolution because of lack of contrast material in one case.

Table 2 shows the influence of SPECT/CT on contrast-enhanced CT reading and the added diagnostic value contributed by MIBG SPECT/CT. There were nine of 15 cases of discordance between SPECT/CT and contrast-enhanced CT data. SPECT/CT provided additional information to contrast-enhanced CT or increased reading confidence of contrast-enhanced CT in eight of these nine cases (89%) and in eight of all 15 cases (53%).

In two of the nine discordant cases, MIBG SPECT/CT allowed for the localization of the pathologic site that was difficult to identify on the contrast-enhanced CT scan after surgical anatomic distortion. In one pheochromocytoma study with distorted anatomy after surgery, a focus of pathologic MIBG uptake on SPECT/CT overlapped the right adrenal gland, whereas on the previously performed contrast-enhanced CT, this finding had been misinterpreted as the inferior vena cava (IVC). In a study with neuroblastoma after multiple surgical procedures (Fig. 1), SPECT/CT allowed for precise localization of a focus of pathologic MIBG uptake medial to the IVC.

In two other discordant cases, SPECT/CT helped to elucidate the nature of the contrast-enhanced CT finding. In a study of neuroblastoma, the contrast-enhanced CT scan showed minimal soft-tissue thickening in the pre- and paravertebral area. MIBG pathologic uptake in the same area was observed on SPECT/CT and was suggestive of relapse (Fig. 2). Two months later, follow-up SPECT/CT clearly showed tumor growth (Fig. 2C) and confirmed tumor relapse. In a study of neuroblastoma, a soft-tissue mass was observed in the left iliac fossa on contrast-enhanced CT. Its nature was elucidated by MIBG uptake overlapping an involved lymph node on SPECT/CT, differentiating it from possible postsurgical changes and compatible with recurrent disease (Fig. 3).

In four additional discordant cases, the presence of a residual mass was equivocal on both CT of the SPECT/CT and on contrast-enhanced CT, with no corresponding finding on planar MIBG scintigraphy. MIBG SPECT/CT, focused on the area of the suspected CT-detected abnormality, confirmed the absence of MIBG planar scintigraphy findings, and thus increased the reading confidence and the diagnostic value of MIBG scintigraphy. These patients with high probability of remission only needed follow-up.

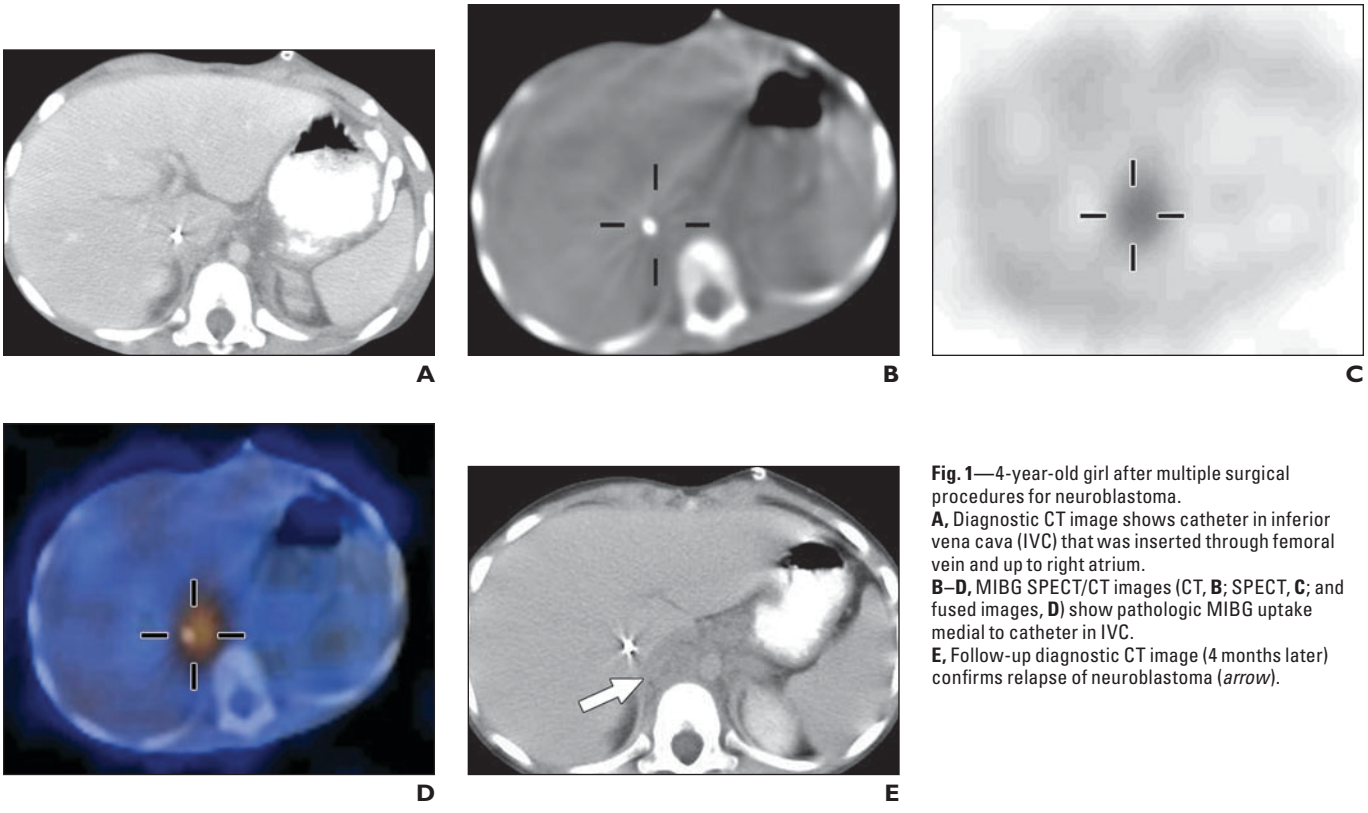

Fig. 1—4-year-old girl after multiple surgical procedures for neuroblastoma.
A, Diagnostic CT image shows catheter in inferior vena cava (IVC) that was inserted through femoral vein and up to right atrium.
B–D, MIBG SPECT/CT images (CT, **B**; SPECT, **C**; and fused images, **D**) show pathologic MIBG uptake medial to catheter in IVC.
E, Follow-up diagnostic CT image (4 months later) confirms relapse of neuroblastoma (*arrow*).

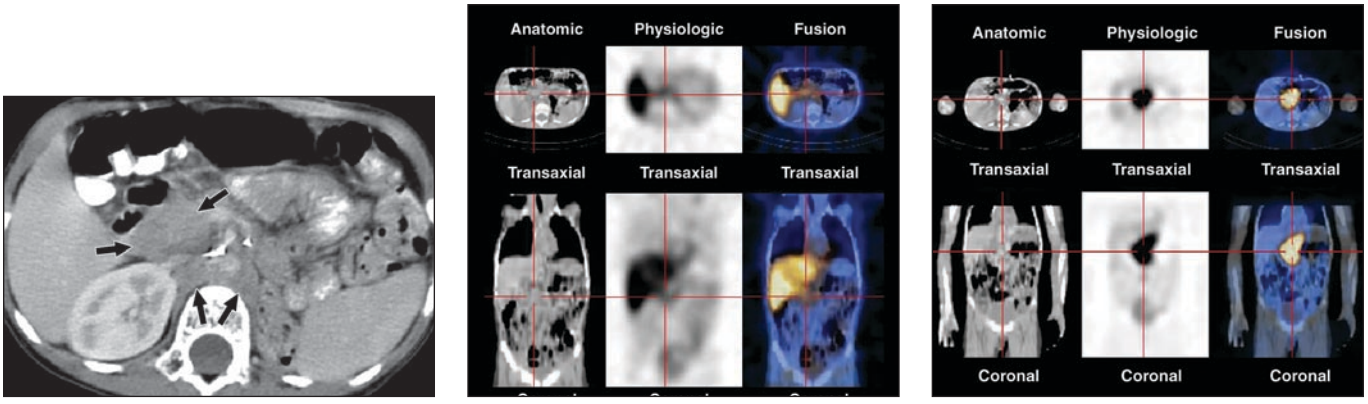

Fig. 2—5.6-year-old boy with neuroblastoma. Images show follow-up after treatment and disappearance of initial abdominal mass. There is pre- and paravertebral MIBG uptake that was overlooked on contrast-enhanced CT.
A, Contrast-enhanced CT image shows minimal pre- and right paravertebral soft-tissue thickening (*arrows*).
B, MIBG SPECT/CT images (CT, left column; SPECT, center column; and fused images, right column) show pathologic MIBG uptake in pre- and right paravertebral region.
C, MIBG SPECT/CT images (CT, left column; SPECT, center column; and fused images, right column) 3 months later confirm tumor growth. Note difference of liver uptake between **B** and **C**, most likely due to imbalance in tracer distribution caused by pathologically intense tumor uptake.

Overall, the reading of contrast-enhanced CT scans when the reader was blinded to the MIBG SPECT/CT findings was equivocal in seven cases and was changed to negative and positive in four and three cases, respectively, after comparison with the SPECT/CT data.

In a study of pheochromocytoma, MIBG scintigraphy showed a focus of increased uptake in the hepatic portal area. Contrast-enhanced CT was normal. There was no evidence of disease at 2 years' clinical and contrast-enhanced CT follow-up. The MIBG scintigraphy finding was therefore falsely interpreted as positive for relapse when, in fact, it represented physiologic uptake of MIBG in the liver or in the bowel.

In the six remaining studies of our series, findings on SPECT/CT and contrast-enhanced CT were concordant (6/15; 40% of all cases).

Discussion

In pheochromocytoma and neuroblastoma, early detection of relapse is understandably crucial and has a major impact on treatment

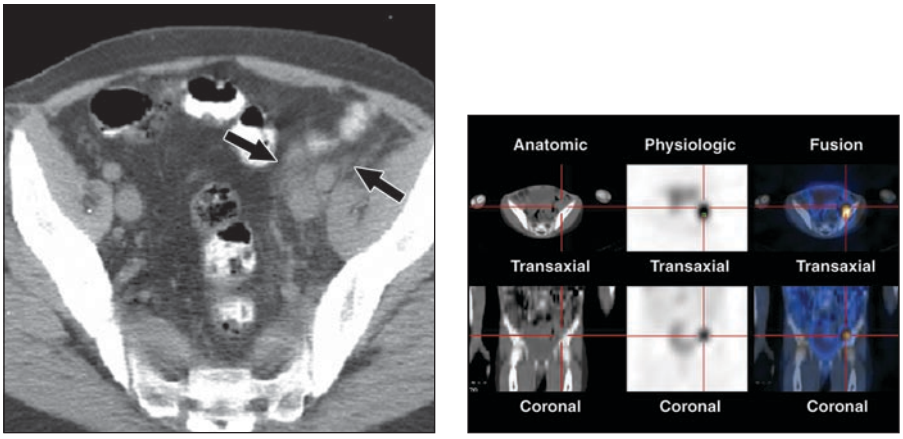

Fig. 3—3-year-old boy with neuroblastoma. Images show follow-up after treatment and soft-tissue changes in left iliac region.
A, Contrast-enhanced CT image shows nonspecific soft-tissue changes in iliac region (*arrows*).
B, MIBG SPECT/CT images (CT, left column; SPECT, center column; and fused images, right column) show pathologic MIBG uptake that was considered indicative of involved lymph node on CT of SPECT/CT.

and prognosis. CT and MRI have high anatomic resolution and good sensitivity but imperfect specificity. Furthermore, their interpretation may be impaired by anatomic distortion after surgery or irradiation, and in those cases, fused MIBG SPECT/CT images are helpful.

In our small series, in two postoperative cases, fused images enabled differentiation between tumor mass and surgically distorted anatomic structure (IVC) and accurate anatomic localization of pathologic MIBG uptake, whereas both contrast-enhanced CT and CT of SPECT/CT alone were equivocal. These cases exemplify the benefit of joint reading by nuclear medicine physicians and radiologists.

Because it was commonly accepted that IV injection of contrast material could induce a hypertensive crisis in pheochromocytoma patients, CT in case 15 was performed without IV contrast material. However, a recently published article [12] indicates that there is no increase in the risk of adverse events in patients with pheochromocytoma or paraganglioma if nonionic contrast injection is used.

In two other follow-up studies, differentiation between small residual mass and scar was difficult on contrast-enhanced CT alone, and the fused anatomometabolic images enabled characterization of these findings as tumor masses.

Discrepancy between negative MIBG scintigraphy findings, corroborated by correlative data, and equivocal CT findings (both CT of SPECT/CT and contrast-enhanced CT) was observed in four studies. The fact that these cases (and all the others) had positive baseline MIBG scintigraphy and negative follow-up strengthens the accuracy of MIBG scintigraphy as the first line follow-up detection tool. A negative baseline MIBG scintigraphy usually precludes its use in the follow-up.

There was only one false-positive MIBG scintigraphy finding, attributed in retrospect to physiologic MIBG uptake in the liver or the intestine. Because of its low resolution, CT of SPECT/CT was not helpful in accurately localizing MIBG uptake in this case.

MIBG scintigraphy is indeed considered today as the best diagnostic technique for evaluation of disease activity, both at presentation and at follow-up. In 5–7% of cases, however, MIBG scintigraphy is negative at presentation (there is no MIBG uptake by tumor cells) [6, 7, 14]. In such cases, PET using ^{18}F-FDG, ^{18}F-DOPA (dihydroxyphenylalanine), or ^{68}Ga-DOTATOC (DOTA-D-Phe[1]-Tyr[3]-octreotide) might be indicated [15–17].

The two limitations of this study are its retrospective nature and the small, heterogeneous sample of patients. We were therefore not able to base the conclusions of our observations on a solid statistically significant ground. Notwithstanding, in our study MIBG SPECT/CT greatly contributed to the diagnostic accuracy in 53% of all cases and 89% of discordant cases. These results are consistent with other recently published studies [18–21]. In a prospective study including 31 adult patients with pheochromocytoma, Ozer et al. [18] found that fused images of MIBG SPECT/CT assisted in clarifying physiologic MIBG uptake in 81% of the patients and in identifying MIBG as pathologic in the remaining 19%. Schillaci et al. [19] showed in a heterogeneous group of 81 patients that SPECT/CT had a significant impact on the interpretation of findings in 33 of 81 patients (40.7%). In another study of 27 patients with various endocrine tumors, SPECT/CT improved image interpretation by providing a better anatomic localization in 41% [20]. In a prospective study including a heterogeneous group of 50 patients with various endocrine tumors, consensus reading of fused images (SPECT/CT) changed the image interpretation in 51%.

Thus, SPECT/CT appears to be a useful adjunct, bridging between MIBG scintigraphy and contrast-enhanced CT, and might even reduce the role of contrast-enhanced CT in posttherapy follow-up studies. This assumption should become valid with a better CT scanner than the one used in our hybrid system and if IV contrast material is used because it is a growing trend in PET/CT. However, it is relevant to note that in only two of our 15 studies, interpretation of the CT of the SPECT/CT and of the contrast-enhanced CT was different. In both cases, there was MIBG uptake (one true positive and one false positive). However, when MIBG SPECT/CT is negative at follow-up, it seems that additional contrast-enhanced CT is unnecessary, sparing additional radiation exposure, which is especially important in children.

In conclusion, in cases of equivocal diagnostic CT (mainly distorted anatomy) or of suboptimal localization of MIBG-avid foci, SPECT/CT bridges the gap between MIBG scintigraphy and CT, helping to define the anatomic location of these foci and to characterize the benign or malignant significance of uncertain CT findings.

Low-resolution CT of SPECT/CT does not always allow an optimal interpretation of the CT images and should be supplemented—at least at presentation—by diagnostic contrast-enhanced CT, providing superior anatomic resolution. New-generation SPECT/CT machines with improved CT spatial resolution will enable the avoidance of an additional, separate CT study. When SPECT/IV contrast-enhanced CT becomes routine practice, MIBG SPECT/CT will become a diagnostic one-stop shop for diagnosis and monitoring of neuroblastoma and pheochromocytoma.

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