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Comparison of diagnostic value of I-123 MIBG and high-dose I-131 MIBG scintigraphy including incremental value of SPECT/CT over planar image in patients with malignant pheochromocytoma/paraganglioma and neuroblastoma

Abbreviated title : **I-123 MIBG vs high-dose I-131 MIBG image**

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Abstract :

Purpose: To compare lesion detectability of I-123 MIBG scintigraphy with that of high-dose I-131 MIBG and to evaluate incremental benefit of SPECT/CT over planar image for the detection and localization of the lesions in patients with I-131 MIBG therapy for malignant pheochromocytoma/paraganglioma and neuroblastoma.

Materials and Methods : We retrospectively investigated 16 patients with malignant pheochromocytoma/paraganglioma and neuroblastoma, who were referred for I-131 MIBG therapy. We investigated the lesion detectability in 10 pairs of I-123 and high-dose I-131 MIBG studies of the same patient, obtained within 2 weeks. In 31 studies of I-123 MIBG scintigraphy in 16 patients and 17 studies of high-dose I-131 MIBG scintigraphy in 12 patients, we compared planar and SPECT/CT images for the lesion detectability and localization.

Results : The number of lesions detected by I-123 MIBG planer image and SPECT/CT, high-dose planer I-131 MIBG and SPECT/CT were 3.0 and 3.7, 7.3 and 7.7 per study, respectively. SPECT/CT images provided additional diagnostic information over planar images in 25 studies (81%) of 12 patients (75%) in I-123 MIBG scintigraphy and in 9 studies (53%) of 9 patients (75%) in high-dose I-131 MIBG scintigraphy.

Conclusion : Post-therapy high-dose I-131 MIBG scintigraphy is superior to I-123 MIBG scintigraphy in lesion detectability even in comparison with I-123 MIBG SPECT/CT images and high-dose I-131 MIBG planar images in patients with malignant neuroendocrine tumors. SPECT/CT images are helpful for accurate identification of anatomical localization compared to planar images.

Key Words : malignant neuroendocrine tumor; I-123-MIB; I-131 MIBG; SPECT/CT

Introduction

Metaiodobenzylguanidine (MIBG) is a guanetidine derivative resembling the neurotransmitter norepinephrine in chemical structure. Therefore, showing the similar performance as norepinephrine, MIBG is taken up by the norepinephrine transporter (uptake 1) or passive diffusion, and stored in chromaffin deposite granules or neurosecretory granules in tissues derived from sympathetic nervous system.^{1,2} In this mechanism, MIBG accumulates in tumors originated from neural crests.

Pheochromocytoma/paraganglioma and neuroblastoma are the representative neuroendocrine neoplasms showing intense MIBG accumulation. Pheochromocytoma/paraganglioma is a rare tumor which arises from chromaffin cells of the adrenal medulla/extra-adrenal sympathetic ganglia. It is reported that approximately 10% of pheochromocytoma and up to 40% of paraganglioma are malignant.^{3,4} Neuroblastoma is one of the most common tumor derived from the embryonal sympathetic nervous system in children. Approximately 30% of neuroblastoma originate from the adrenal medulla and the rest arise from anywhere extra-adrenal sympathetic nervous system.^{5,6} Malignant pheochromocytoma/paraganglioma and neuroblastoma usually matastasize to the bones, liver, lung and lymph nodes in early times.

Since I-131 labeled MIBG scintigraphy for pheochromocytoma was reported in 1981, I-131 and I-123 labeled MIBG scintigraphy has been widely used as an excellent functional imaging modality for detection of the lesions in patients with neuroendocrine tumors.⁷⁻⁹ MIBG scintigraphy is also useful for detection of the recurrent or metastatic lesions in patients with malignant pheochromocytoma/paraganglioma and neuroblastoma, although it is reported that the sensitivity in detecting extra-adrenal or malignant tumors is less than that in adrenal or benign

tumors.¹⁰⁻¹³ In the image quality and lesion detectability, I-123 MIBG image is superior to I-131 MIBG with diagnostic low radioactive dose,^{14,15} because the γ -ray energy of I-123 (159keV) is more suitable for scintigraphy compared to that of I-131 (364keV). In addition to low-dose I-123 MIBG imaging, high-dose I-131 MIBG imaging is possible in patients who underwent I-131 MIBG internal radiation therapy, which is a precious option of the systemic treatments especially in those patients who have irresectable or multiple metastatic lesions. A case report demonstrated that post-therapeutic high-dose I-131 MIBG scintigraphy detected more lesions than low-dose diagnostic I-123 MIBG scintigraphy in a patient underwent I-131 MIBG therapy.¹⁶

Accurate identification of anatomical localization of the lesions is important to perform I-131 MIBG therapy safely. However, it is difficult to identify accurate anatomical localization of the lesions in the conventional planar image. Comparing SPECT with CT or MRI image side-by-side or SPECT- CT or MRI fusion image by use of software has contributed to the precise definition of the localization to some degree.¹⁸⁻²⁰ Recently integrated SPECT/CT fusion system which acquires the dual modality in the same session provides more additional information for characterization and localization of the lesions in various neuroendocrine tumors.²¹⁻²⁶

The aim of this study was to compare lesion detectability of the I-123 MIBG scintigraphy with that of high-dose I-131 MIBG scintigraphy and to evaluate incremental benefit of I-123 MIBG and high-dose I-131 MIBG SPECT/CT over conventional planar image for the detection and localization of the lesions in patients underwent I-131 MIBG therapy for malignant pheochromocytoma/paraganglioma and neuroblastoma.

MATERIALS AND METHODS

Patients

We retrospectively investigated 16 patients with malignant pheochromocytoma/paraganglioma

and neuroblastoma, who were referred for I-131 MIBG therapy in our institute and underwent I-123 MIBG (111MBq (3 mCi)) and/or high-dose I-131 MIBG (3.7-14.8 GBq (100-400 mCi)) scintigraphy from June 2008 to August 2009 (5 males and 3 females of malignant pheochromocytoma/paraganglioma, mean age 54 years (range 36-69 years) ; 3 males and 5 females of neuroblastoma, mean age 8.8 years (range 7-13 years) (Table 1). 31 studies of I-123 MIBG scintigraphy were obtained in 16 patients and 17 studies of high-dose I-131 MIBG scintigraphy were acquired in 12 patients.

I-123 MIBG scintigraphy with diagnostic low-radioactive dose

I-123 MIBG scintigraphy was performed after intravenous injection of 111MBq (3mCi) of radiopharmaceutical for all patients, using a dual-head gamma camera equipped with a low-intermediate energy collimator and a 5/8 inch NaI crystal, which was combined to a low-dose spiral CT by the same gantry (Symbia, Siemens Medical Solutions). Whole-body planar images were acquired at 6 and 24 hours after I-123 MIBG injection at scanning speeds of 15cm/min. Following planar imaging after 6 hours of tracer injection, SPECT images were obtained to cover the areas suspected of abnormal tracer accumulations in whole-body planar images. SPECT data were acquired from 60 projections (20 seconds per view) with 128×128 matrix and reconstructed using a 3-dimensional iterative algorithm, ordered-subsets expectation maximization (OSEM). As soon as SPECT data acquisition was finished, CT transmission scans for tomography were performed. SPECT and CT data were analyzed and co-registered using an e-soft workstation.

I-131 MIBG therapy and scintigraphy with post-therapy high-radioactive dose

I-131 MIBG therapy was underwent to the patients who were considered to have beneficial

therapeutic effects by the findings of pre-therapy I-123 MIBG scintigraphy. 3.7-14.8GBq (100-400 mCi) of I-131 MIBG was injected intravenously through fixed peripheral venous lines for about an hour using lead-shielded infusion pump. Vital signs were monitored for more than 6 hours from the beginning of I-131 MIBG administration. I-131 MIBG planar and SPECT/CT images were acquired 3 days later in the same way as I-123 MIBG scintigraphy except for used collimator (high-energy).

Image interpretation

At first, I-123 or I-131 MIBG planar images were evaluated by two experienced nuclear medicine physicians, who were blinded to the findings of the other imaging modalities. They were asked to interpret all focal uptakes, except for physiological accumulation, as abnormal lesions and to define their anatomical locations. Diffuse accumulation at nasal cavity, salivary glands, thyroid, myocardium, liver and bladder was considered as physiological uptake. When their interpretations were discordant, consensus was obtained after conference. Then, SPECT/CT images were assessed by them independently with planar images and they were required to re-evaluate the lesional anatomical location of the lesions found in planar images and indicate new lesions. The findings suspected of metastasis in CT images alone were not included in new lesions if they did not accompany MIBG accumulation. Consensus was acquired in the same way as planar image if their interpretation was discordant.

Data analysis

In comparison of diagnostic value of I-123 MIBG and high-dose I-131 MIBG scintigraphy, we investigated the difference of the number of detected lesions in ten pairs of I-123 and high-dose I-131 MIBG studies of the same patient that were obtained within two weeks. In the evaluation

of incremental diagnostic value of SPECT/CT images over planar images with I-123 MIBG and high-dose I-131 MIBG, we performed comparative analysis between planar and SPECT/CT images in all patients.

RESULTS

In I-123 MIBG scintigraphy, a total of 145 and 155 abnormal uptakes were pointed out in planar and SPECT/CT images, respectively, in 31 studies of 16 patients. In high-dose I-131 MIBG scintigraphy, a total of 136 and 140 abnormal uptakes were pointed out in planar and SPECT/CT images, respectively, in 17 studies of 12 patients.

In comparison of all ten pairs of I-123 and high-dose I-131 MIBG studies in the same patient that were obtained within two weeks, the lesions detected by I-123 MIBG scintigraphy were 3.0/study in planar image, 3.7/study in SPECT/CT image and the lesions detected by high-dose I-131 MIBG scintigraphy were 7.3/study in planar image, 7.7 /study in SPECT/CT images. The number of detected lesions is summarized in Table 2.

In all I-123 MIBG SPECT/CT images, 18 new lesions, which had not been pointed out in planar images, were detected in 14 studies (45.2 %) of 11 patients (68.8 %), but 8 lesions that had been recognized in planar images became undetectable in 4 studies (12.9 %) of 2 patients (12.5 %). Anatomical locations of 21 lesions in planar image were modified after analysis of SPECT/CT images in 14 studies (45.2 %) of 10 patients (62.5 %). As a whole, SPECT/CT images provided additional diagnostic information over planar images in 25 studies (80.6 %) of 12 patients (75.0 %). Number of the lesions detected in I-123 MIBG planar and SPECT/CT imaging is summarized in Table 3.

In high-dose I-131 MIBG SPECT/CT images, 6 new lesions were detected in 4 studies (23.5 %) of 4 patients (33.3 %), but 2 lesions that had been recognized in planar images became obscure

in 2 studies (11.8 %) of 2 patients (16.7 %). Anatomical locations of 17 lesions were altered after the evaluation of SPECT/CT images in 8 studies (47.1 %) of 8 patients (66.7 %). As a whole, SPECT/CT images provided additional diagnostic information in 9 studies (52.9 %) of 9 patients (75.0 %) over planar images. Number of the lesions in high-dose I-131 MIBG planar and SPECT/CT imaging is summarized in Table 4.

Most of the new lesions detected in SPECT/CT were located near the physiological uptake or overlapping the physiological accumulation. In I-123 MIBG SPECT/CT images, 10 of 18 newly detected lesions by SPECT/CT were overlapped with the physiological accumulation and one new lesion was detected as a lymph node, 4 were in bones and 3 were in lungs. In high-dose I-131 MIBG SPECT/CT images, 4 of 6 newly detected lesions were overlapped with the physiological accumulation and other one lesion was detected as a lymph node and another one was in a bone. All of the lesions turned to be negative in SPECT/CT were suspected to be located in bones in planar images.

The representative comparative planar images with I-123 MIBG and high-dose I-131 MIBG of a 10-year-old male patient with neuroblastoma are shown in Figure 1. A representative case with beneficial I-123 MIBG SPECT/CT over planar image for the detection of the lesion is shown in Figure 2. A case with beneficial SPECT/CT over planar image for the localization of the abnormal uptake is shown in Figure 3.

DISCUSSION

I-131 MIBG internal radiation therapy has become popular as a systemic therapy for patients with malignant neuroendocrine tumors such as malignant pheochromocytoma, malignant paraganglioma, and neuroblastoma with metastatic lesions²⁷⁻³⁰ in addition to chemotherapy represented by combined regimen of cyclophosphamide, vincristine and dacarbazine (CVD).³¹

For the indication of I-131 MIBG therapy, it is essential to confirm MIBG accumulation to the metastatic lesions and to rule out MIBG accumulation to high risk sites such as the lesion compressing spinal cord. In our institute, indication of I-131 MIBG therapy is usually determined based on the results of I-123 MIBG scintigraphy including SPECT/CT in order to identify accurate anatomical localization of the lesions, because image quality of I-123 MIBG scintigraphy is generally superior to diagnostic low-dose I-131 MIBG scintigraphy^{14,15}. After I-131 MIBG therapy, I-131 MIBG imaging might be recommended in order to confirm the lesions with MIBG accumulation. In this study, more than 2 times lesions were detected in high-dose I-131 MIBG scintigraphy than in diagnostic I-123 MIBG scintigraphy. Even an I-123 MIBG SPECT/CT was inferior to planar high-dose I-131 MIBG image in lesion detectability (3.7 vs 7.3 lesions/study, respectively). Since high-dose I-131 MIBG scintigraphy have great diagnostic value in the detection of the lesions, it is believed that I-131 MIBG scintigraphy after I-131 MIBG therapy is essential for the management of patients.

Recently many studies investigated the incremental value of SPECT/CT over planar image in various tumors. Even-Sapir et al. reported that SPECT/CT improved image interpretation by providing a better anatomical localization of SPECT-detected lesions in 41% of the patients with known or suspected endocrine tumor and detected unsuspected bone involvement in 15% of the patients.²¹ Rozovsky et al. investigated added value of SPECT/CT over the correlation of I-123 MIBG scintigraphy and diagnostic CT in neuroblastoma and pheochromocytoma and reported that SPECT/CT provided additional information in 53% of all cases.²⁶ In various type of tumor scans, Roach et al. reported that SPECT/CT modified the interpretation with planar/SPECT alone in 56% of the cases.³² Chen et. al. reported that, in patients with differentiated thyroid carcinoma, precise localization and characterization of I-131-avid foci were achieved through I-131 SPECT/CT over planar image in 69 (85.2%) and 67 (82.7%) of the 81 foci, respectively and

uncommon metastatic lesions were found in 9 (13.6%) of 66 patients with regard to SPECT/CT fusion images.³³ In our study, unknown lesions in planar images were detected by SPECT/CT images in 45.2% of studies and 68.8% of patients and anatomical locations of the lesions were modified after analysis of SPECT/CT in 45.2% of studies and 62.5% of patients in I-123 MIBG scintigraphy. In high-dose I-131 MIBG scintigraphy, unknown lesions in planar images were detected by SPECT/CT in 23.5% of studies and 33.3% of patients and anatomical locations of the lesions were altered after analysis of SPECT/CT in 47.1% of studies and 66.7% of patients. As a whole, SPECT/CT images provided additional diagnostic information in 80.6% of studies, 75.0% of patients and 52.9% of studies, 75.0% of patients over planar images in I-123 MIBG scintigraphy and high-dose I-131 MIBG scintigraphy, respectively. The detection rate of the new lesions by SPECT/CT was higher in I-123 MIBG scintigraphy than in high-dose I-131 MIBG scintigraphy. It is thought that signal to noise ratio is high enough to be identified in planar image when high dose is administered. There were no apparent differences in the rate of alteration of anatomical location of the lesions between diagnostic I-123 MIBG and high dose I-131 MIBG images.

A few lesions found in planar images became undetectable in SPECT/CT images in both I-123 MIBG and I-131 MIBG. Since all lesions showed weak uptake, low lesion's counts of each projection image might not permit to develop tomographic image.

CONCLUSION

Post-therapy high-dose I-131 MIBG scintigraphy is superior to diagnostic I-123 MIBG scintigraphy for lesion detectability even in comparison with I-123 MIBG SPECT/CT images and high-dose I-131 MIBG planar images in patients with malignant neuroendocrine tumor. SPECT/CT images are helpful for the detection of the new lesions and accurate identification of

anatomical localization compared to planar images. SPECT/CT imaging is especially useful for the detection of the lesions near or overlapping physiological accumulation compared to planar images.

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FIGURE.1

A 10-year-old male with neuroblastoma underwent 14.8 GBq (400mCi) of I-131 MIBG therapy. In the planar image with diagnostic I-123 MIBG, only 3 abnormal uptakes were detected in the upper mediastinum, left lower abdomen and left thigh. In the planar image with therapeutic high-dose I-131 MIBG, total of 13 abnormal uptakes were detected in the left shoulder, mediastinum, vertebrae, upper and lower abdomen, and in the left thigh.

FIGURE.2

A 54-year-old female with malignant paraganglioma underwent diagnostic I-123 MIBG scintigraphy. In the planar image, it is easy to point out the abnormal accumulation in the lower abdomen (narrow arrow), however, it is difficult to detect the abnormal uptake beside the bladder

(wide arrow) because of physiological accumulation to the bladder. In the SPECT/CT, it is easy to detect the abnormal MIBG accumulation corresponding to the nodular lesion in the left side of the bladder

FIGURE.3

A 47-year-old female with malignant pheochromocytoma underwent diagnostic low-dose I-123 MIBG scintigraphy. In the planar image, it is difficult to determine whether the abnormal uptake in the right upper abdomen exists in the right rib or in the liver. In the SPECT/CT, it is proved that the abnormal accumulation exists in the liver.

TABLE.1. Clinical Characteristics of Patients

Patient no.	Age	Sex	Diagnosis	Number of I-131 MIBG therapy	Cumulative dose of I-131MIBG (mCi)	Number of I-123MIBG scintigraphy	Number of high-dose I-131MIBG scintigraphy
1	69	M	pheo	2	400	3	2
2	37	F	pheo	2	400	3	2
3	60	F	pheo	2	400	3	2
4	63	M	para	1	200	3	1
5	66	M	pheo	3	600	2	0
6	54	F	para	1	200	3	1
7	47	M	pheo	4	1360	2	1
8	36	M	para	0	0	1	0
9	7	F	neuro	1	100	1	1
10	8	M	neuro	0	0	1	0
11	13	F	neuro	3	600	3	3
12	7	M	neuro	1	300	1	1
13	11	F	neuro	1	400	1	1
14	7	F	neuro	1	300	1	1
15	8	F	neuro	1	100	2	0
16	10	M	neuro	1	400	1	1

pheo, malignant pheochromocytoma

para, malignant paraganglioma

neuro, neuroblastoma

TABLE 2. the number of detected lesions in ten pairs of I-123 and high-dose I-131 MIBG scinitographies performed within 2 weeks in the same patient

Patient no.	I-123 MIBG planar image	I-123 MIBG SPECT/CT	I-131MIBG planar image	I-131 MIBG SPECT/CT
1	0	1	1	1
2	6	6	6	6
3	1	2	4	6
4	1	1	1	1
5	1	3	15	15
6	1	2	8	9
7	2	2	7	7
8	0	0	3	2
9	15	15	15	17
10	3	5	13	13
total	30	37	73	77

TABLE 3. Number of lesions in I-123 MIBG imaging

study No.	Diagnosis	Number of lesions in planar image	Number of lesions in SPECT/CT	Number of new lesions in SPECT/CT	Number of lesions turned to be negative in SPECT/CT	Number of lesions modified anatomical localization by SPECT/CT
1	neuro	0	0	0	0	0
2	para	1	2	1	0	1
3	pheo	2	3	1	0	0
4	neuro	2	3	1	0	1
5	pheo	1	1	0	0	0
6	pheo	6	6	0	0	2
7	pheo	3	4	1	0	0
8	pheo	0	1	1	0	0
9	neuro	1	1	0	0	0
10	para	2	3	1	0	1
11	para	25	25	0	0	2
12	neuro	3	5	2	0	0
13	neuro	0	0	0	0	0
14	neuro	23	18	0	5	3
15	neuro	1	2	1	0	1
16	neuro	1	3	2	0	0
17	para	1	2	1	0	1

18	pheo	2	2	0	0	1
19	neuro	1	1	0	0	0
20	pheo	2	2	0	0	0
21	pheo	1	3	2	0	0
22	pheo	3	3	0	0	0
23	pheo	1	1	0	0	1
24	para	16	16	0	0	2
25	neuro	2	2	1	1	0
26	pheo	3	4	1	0	0
27	pheo	1	1	0	0	0
28	pheo	3	3	0	0	1
29	pheo	1	1	1	1	0
30	para	22	22	0	0	3
31	neuro	15	15	1	1	1
total		145	155	18	8	21

pheo, malignant pheochromocytoma

para, malignant paraganglioma

neuro, neuroblastoma

TABLE 4. Number of lesions in high-dose I-131 MIBG imaging

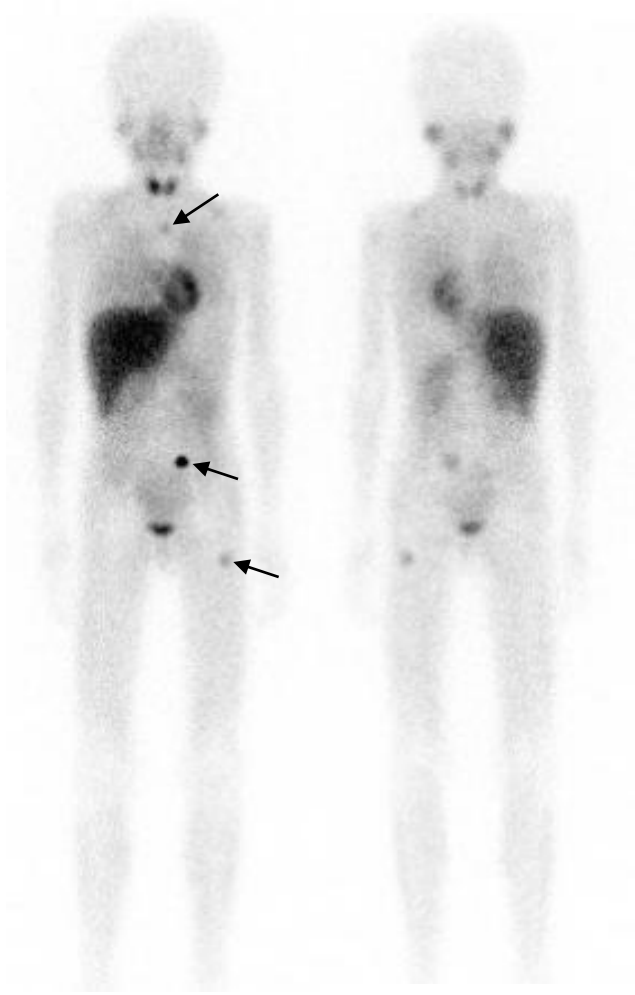
study No.	Diagnosis	Number of lesions in planar image	Number of lesions in SPECT/CT	Number of newly detected lesions in SPECT/CT	Number of lesions turned to be negative in SPECT/CT	Number of lesions modified anatomical localization by SPECT/CT
1	pheo	2	2	0	0	0
2	pheo	1	1	0	0	0
3	pheo	6	6	0	0	0
4	pheo	5	6	1	0	0
5	para	4	6	2	0	3
6	para	35	35	0	0	3
7	pheo	2	2	0	0	0
8	pheo	3	3	0	0	0
9	pheo	7	7	0	0	1
10	neuro	1	1	0	0	0
11	neuro	15	15	0	0	1
12	neuro	9	8	0	1	0
13	neuro	8	9	1	0	2
14	neuro	7	7	0	0	0
15	neuro	3	2	0	1	1
16	neuro	15	17	2	0	5
17	neuro	13	13	0	0	1

total	136	140	6	2	17
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pheo, malignant pheochromocytoma
para, malignant paraganglioma
neuro, neuroblastoma

Figure
Figure 1

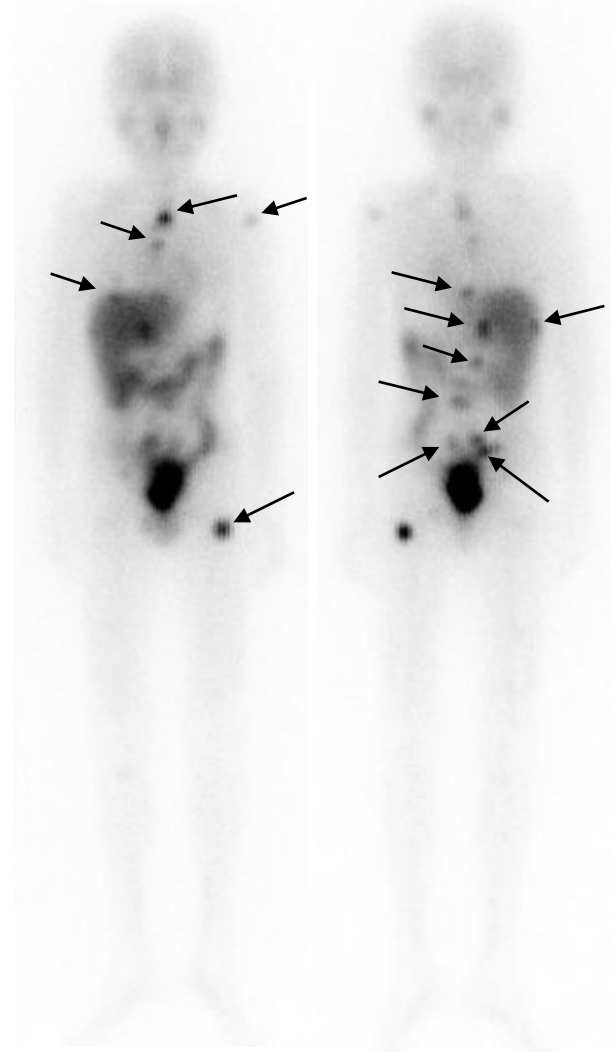
I-123 MIBG



Anterior

Posterior

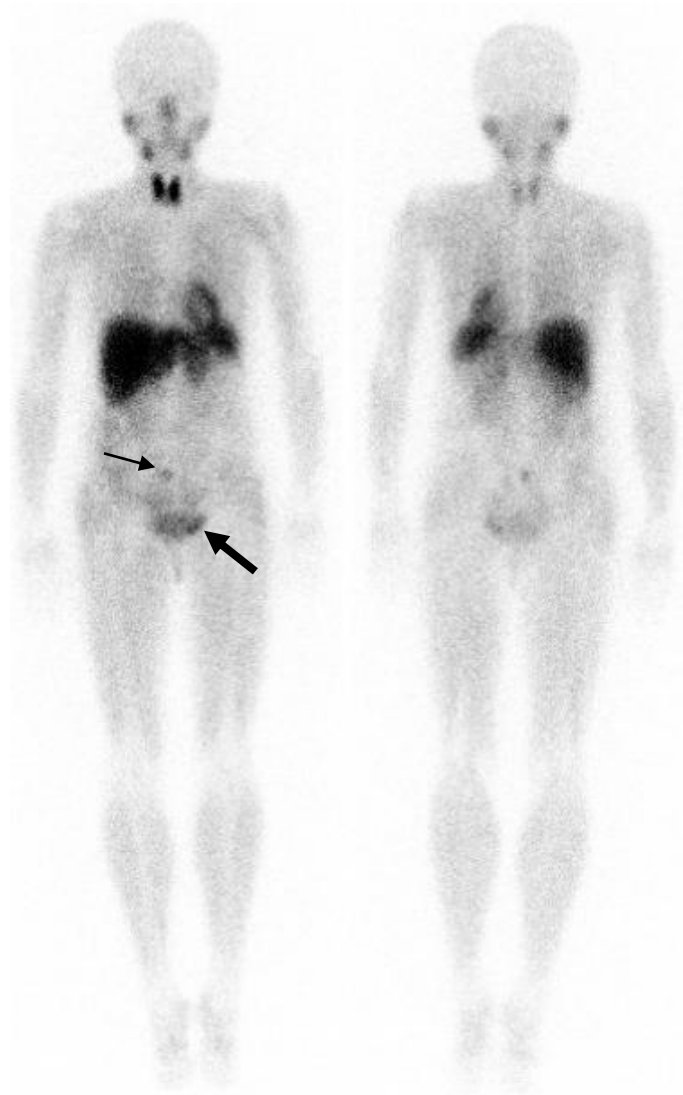
I-131 MIBG



Anterior

Posterior

Figure 2



Anterior

Posterior

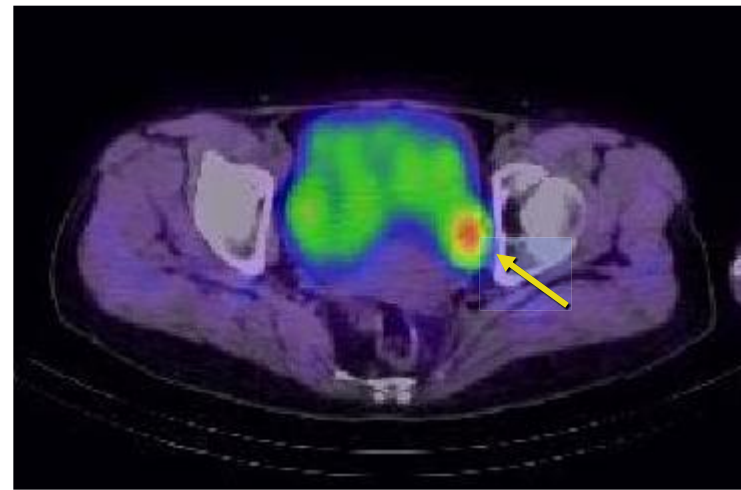
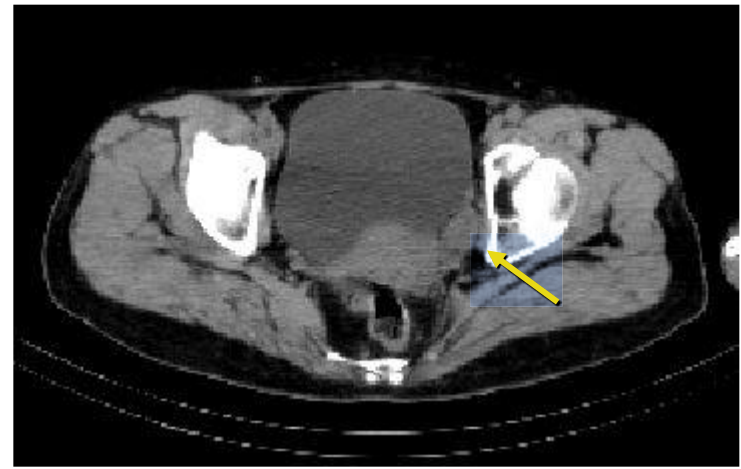
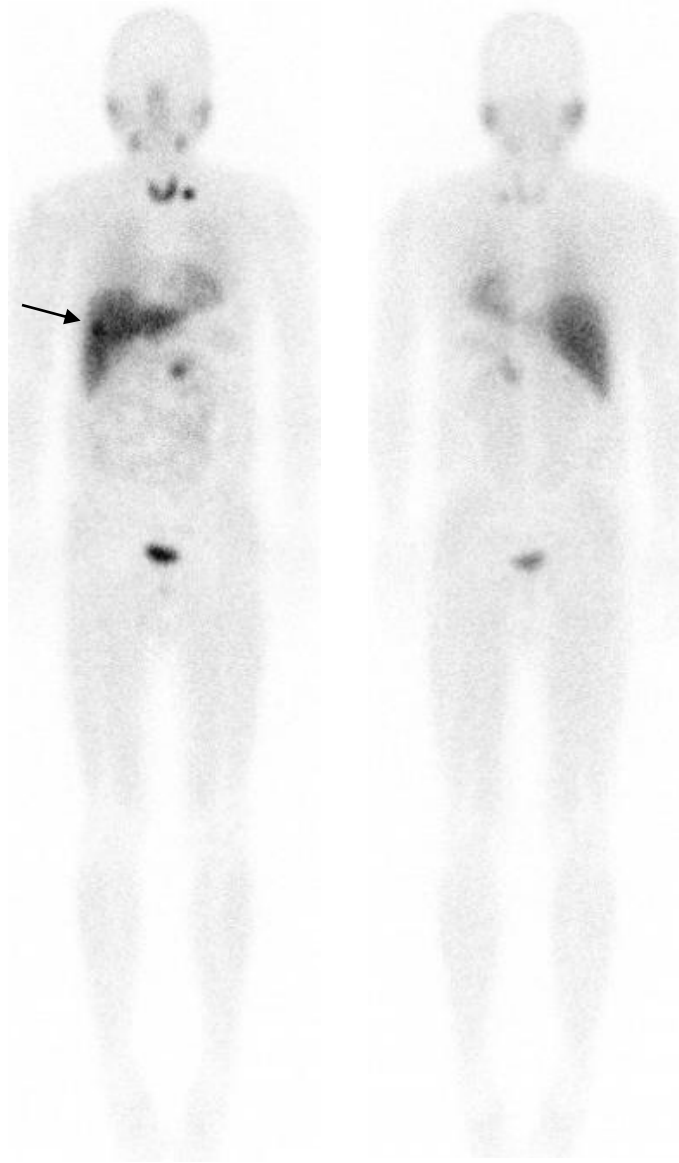
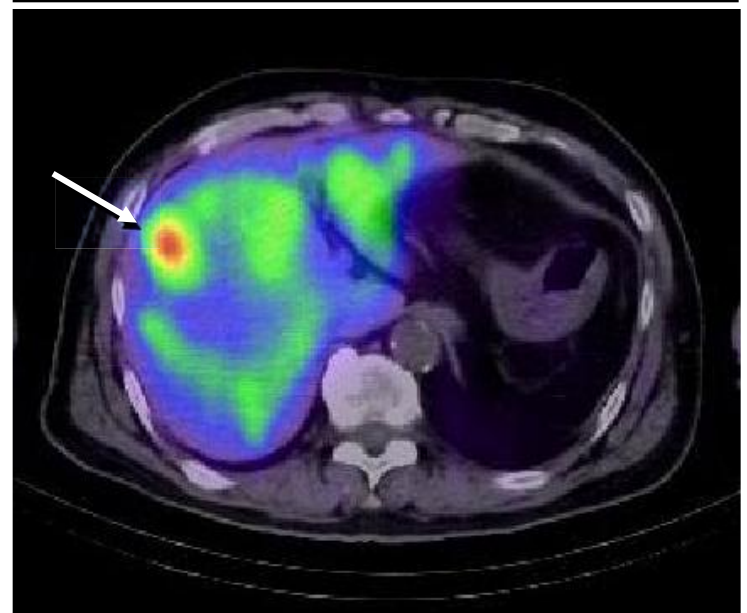
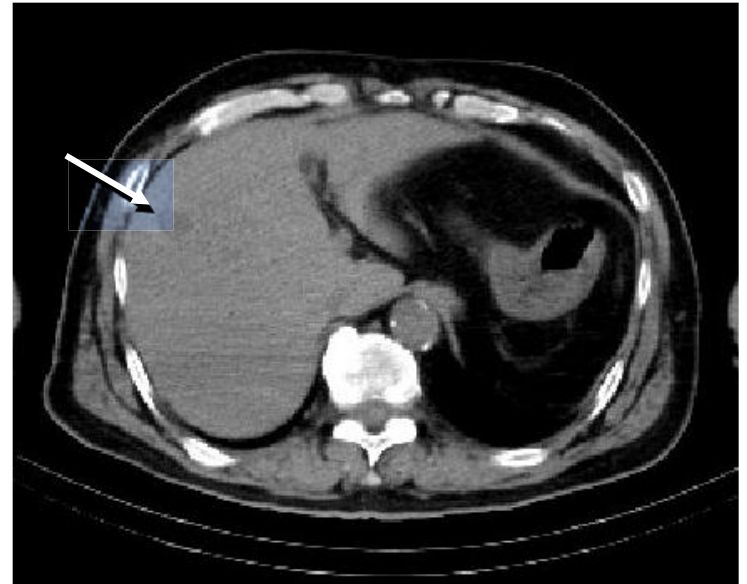


Figure 3



Anterior

Posterior



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