Annals of Nuclear Medicine Vol. 17, No. 8, 633–640, 2003

Clinical usefulness of iodine-123-MIBG scintigraphy for patients with neuroblastoma detected by a mass screening survey

Tsuyoshi HASHIMOTO,* Kiyoshi KOIZUMI,* Takako NISHINA** and Kimihiko ABE***

*Department of Radiology, Hachioji Medical Center, Tokyo Medical University
**Department of Surgery, Tokyo Metropolitan Hachioji Children's Hospital
***Department of Radiology, Tokyo Medical University

The purpose of this study was to evaluate the usefulness in a clinical setting of iodine-123-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy, planar and single photon emission computed tomography (SPECT) images, in patients with neuroblastoma as detected by a mass screening survey. ***Methods:*** ^{123}I-MIBG planar whole body images, and regional SPECT images of patients with neuroblastoma in 51 studies were reviewed. They were all detected by a mass screening survey performed in the 6th month after birth using vanil mandelic acid (VMA), and homovanillic acid (HVA) and the neuroblastoma had been confirmed by surgery. Scintigraphy was performed 24 hours after injection of 111 MBq of ^{123}I-MIBG. We assessed the accuracy of the planar whole body images in order to demonstrate the extent of the lesion and the correlation between the degree and extent of the lesions of ^{123}I-MIBG accumulation and clinical staging with tumor markers, such as urinary VMA, urinary HVA, serum neuron specific enolase (NSE) and serum lactate dehydrogenase (LDH). Additionally, we evaluated SPECT how useful supplemental SPECT might be in a clinical setting as compared with planar whole body images. ***Results:*** ^{123}I-MIBG planar whole body images revealed all 33 (100%) primary lesions, 4 of the 5 cases (80%) with liver metastasis, 3 of the 13 (23%) with lymph nodes metastasis and 1 of 3 (33%) with bone marrow infiltration. The extent and degree of accumulation correlated with the values of urinary VMA, urinary HVA and serum NSE. SPECT images helped to understand the positional relation in all cases and provided useful additional information for clinical staging in 7 cases. ***Conclusion:*** ^{123}I-MIBG scintigraphy with planar and SPECT images is useful for evaluating patients with neuroblastoma, following detection by a mass screening survey.

Key words: iodine-123-MIBG, neuroblastoma, mass screening

INTRODUCTION

NEUROBLASTOMA, a tumor arising from the neural crest, is one of the main malignant tumors to affect young children. Its prognosis is rather poor but the recovery rate improves markedly if the tumor detected and treated early. In Japan, a number of mass screenings routinely take place, and when the urine of infants below the age of one year is positive for VMA and HVA (catecholamine metabolites), they are examined and treated earlier as per indications. This policy has produced satisfactory results.[1,2] Serum NSE and LDH are also used as tumor markers. Scintigraphy using ^{123}I-MIBG, which resembles noradrenaline in its chemical structure and metabolic pathway, has also proved effective.[3–9] In our hospitals, patients suspected of having neuroblastoma by the mass-screening are routinely examined using ^{123}I-MIBG scintigraphy combined with other imaging modalities. In this study, ^{123}I-MIBG planar and SPECT images were retrospectively evaluated for their diagnostic efficacy, and correlated with clinical stages and various tumor markers. There have been a few similar studies[3–5] but none of them

Received May 27, 2003, revision accepted August 12, 2003.
For reprint contact: Tsuyoshi Hashimoto, M.D., Department of Radiology, Hachioji Medical Center, Tokyo Medical University, 1163 Tate-machi, Hachioji, Tokyo 193–0998, JAPAN.
E-mail: tsuyoshi@tokyo-med.ac.jp

focused on patients where the neuroblastomas were only detected from mass screenings; furthermore, a large number of patients (33 infants) were included in this study.

MATERIALS AND METHODS

Patient population

A total of 33 patients (20 male and 13 female) were included in this study. They were suspected of having neuroblastoma by the mass screening of urinary VMA and HVA of urinary VMA and HVA in their 6th month after birth. They were then further examined using abdominal ultrasonography, abdominal CT and/or MRI, and ^{123}I-MIBG scintigraphy. Final confirmation of the diagnosis was made by surgery. Their ages ranged from 6 months and 12 days to 10 months and 3 days (mean 6 months and 27 days) at the time of their initial preoperative ^{123}I-MIBG scintigraphy. The primary foci of the tumors were the adrenal glands in 20 children (right in 8 and left in 12), the retroperitoneal space excluding the adrenal gland in 7, the pelvis in 1 and the mediastinum in 5. Liver metastases were confirmed in 5 patients using abdominal CT and/or MRI, and lymph node metastases in 13 patients by surgery. Bone marrow infiltration was confirmed in 3 patients using needle biopsy from the iliac bone. Clinical staging was based on the international neuroblastoma staging system (INSS); 16 patients in stage I, 1 in stage IIA, 4 in stage IIB, 4 in stage III, 6 in stage IV, and 2 in stage V. All the patients were under one year of age at the initiation of treatment. Treatment options included surgical procedure alone or in combination with chemotherapy. Some particular patients were excluded from positive treatment because of a prior agreement and followed up with the expectation that the tumor would spontaneously disappear. The exclusion criteria for these particular patients were when the primary focus of the tumor was the adrenal gland, less than 2 cm in size, without any distant metastasis or any increasing tendency in the urine VMA measured 3 times during 6 weeks of observation (Fig. 1).

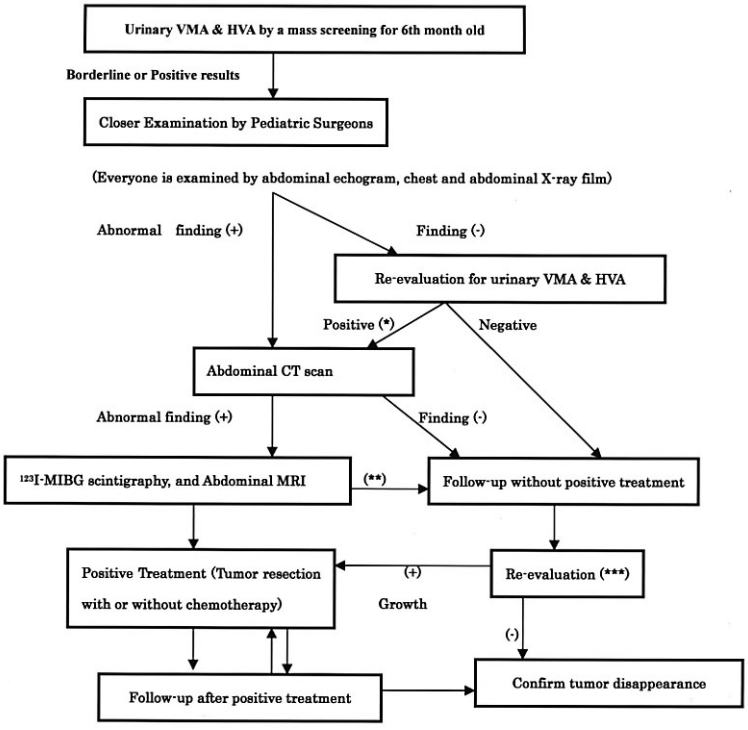


Fig. 1 Mass screening project of neuroblastoma for early detection and treatment. (*) If the value of urinary VMA and HVA, even which one, was 20 (μg/mg/Cre), and 35 (μg/mg/Cre) or more, we judged it as positive. (**) In this study, some particular patients were excluded from positive treatment because of a prior agreement and were followed up with the expectation that the tumor would naturally disappear by itself. The exclusion criteria for these particular patients were when the primary focus of the tumor was the adrenal gland, less than 2 cm in size, without any distant metastasis and showing no tendency to increasing urine VMA measured 3 times during 6 weeks of observation. (***) Those patients whose tumor markers were seen to have a tendency to rise during the follow up period were provided with all necessary additional examinations and re-evaluations, and the possible need of any further treatment was discussed.

Table 1

(A) Detectability for primary focus

Finding	Disease	
	Exist	Not exist
Positive	33	0
Negative	0	0
Total numbers	33	0

True positive rate ; 100%(33/33)
True negative rate ; No data available(0/0)
Accuracy ; 100%(33/33)

(B)Detectability for liver metastasis

Finding	Disease	
	Exist	Not exist
Positive	4	2
Negative	1	26
Total numbers	5	28

True positive rate ; 80%(4/5)
True negative rate ; 93%(26/28)
Accuracy ; 91%(30/33)

(C) Detectability for lymph-node metastasis

Finding	Disease	
	Exist	Not exist
Positive	3	0
Negative	10	20
Total numbers	13	20

True positive rate ; 23%(3/13)
True negative rate ; 100%(20/20)
Accuracy ; 70%(23/33)

(D) Detectability for bone marrow involvement

Finding	Disease	
	Exist	Not exist
Positive	1	0
Negative	2	30
Total numbers	3	30

True positive rate ; 33%(1/3)
True negative rate ; 100%(30/30)
Accuracy ; 91%(31/33)

Imaging procedure

A dose of 111 MBq of ^{123}I-MIBG (Daiichi Radioisotopes Lab., Tokyo, Japan) was intravenously injected after thyroid blockade with Lugol's solution. In our study, all the patients received the same dose of 111 MBq ^{123}I-MIBG without changing the dose according to the body size, because, it was considered necessary to obtain better SPECT images at 24 hours after administration for the more accurate evaluation of the extent and degree of the disease. Exposure doses for testis and ovary are estimated as 0.6 and 0.9 mGy respectively with this dose. Planar images were obtained routinely in all the studies of 33 patients, and supplementary SPECT images were obtained in 51 studies of the most recent 31 patients, 14 studies before surgery and 37 studies after surgery. Planar whole body images were acquired 24 hours after administration of the radionuclide with an acquisition time of 15 minutes using a gamma camera (SNC5100R and IRIX; Shimadzu, Kyoto, Japan) equipped with a low-energy, high-resolution collimator interfaced to a computer. A 15% window was centered over 159 keV. SPECT images were also acquired in addition to the planar images using a triple-head gamma camera (PRISM3000 and IRIX; Shimadzu, Kyoto, Japan) with a low-energy, high-resolution collimator in a 128 × 128 matrix, rotated through 120 degrees in 30 steps of 10–30 seconds. The SPECT was done over the chest-abdomen in 49 studies and abdomen or pelvis in 2 studies where disease was strongly suspected.

Detectability of ^{123}I-MIBG scintigraphy

We evaluated the accuracy of the pre-operative ^{123}I-MIBG planar whole body images to demonstrate the primary and metastatic foci in the liver, lymph nodes and bone marrow, which were confirmed by surgery, biopsy, or other imaging modalities. Bone marrow infiltration was defined as positive if there were tumor cells in the specimen from the ilium and negative bone scintigraphy and bone X-ray pictures.

Correlation with tumor markers or clinical staging

We evaluated whether the degree and extent of the lesion of ^{123}I-MIBG accumulations correlate with the clinical staging and tumor markers, such as urinary VMA, urinary HVA, serum NSE, and serum LDH. The areas and extent of the major sites of abnormal radionuclide accumulation was determined from the pre-operative ^{123}I-MIBG planar whole body images (not necessarily coinciding with the primary foci). Among the 33 cases, the sites of abnormal accumulation in 31 cases appeared to coincide with the primary foci, but the accumulation in the liver metastasis was more pronounced as compared to that in the primary focus in 2 cases. These findings were visually categorized into 3 degrees and 2 levels based on its degree and extent. First, the degree of the major accumulation focus was compared to that of the myocardium in the whole body anterior image. This was labeled 2+, +, or –, signifying in excess of, equal to, or no accumulation, respectively. Secondly, the extent of accumulation was classified into 2 levels. If the accumulation of the lesion was solitary and was of a similar or smaller size compared to the myocardial accumulation, detected in the whole body anterior view, the accumulation was classified as a small area of accumulation (S). If the accumulation of the lesion was larger or multiple, the accumulation was classified as a large area of accumulation (L). The reason why we compared the tumor accumulation with the myocardial is that its accumulation was consistently observed near the abnormal accumulation in most of the patients. The statistical correlation between the categorized findings and the values of tumor markers (urinary VMA, urinary HVA, serum NSE and serum LDA levels) and clinical staging

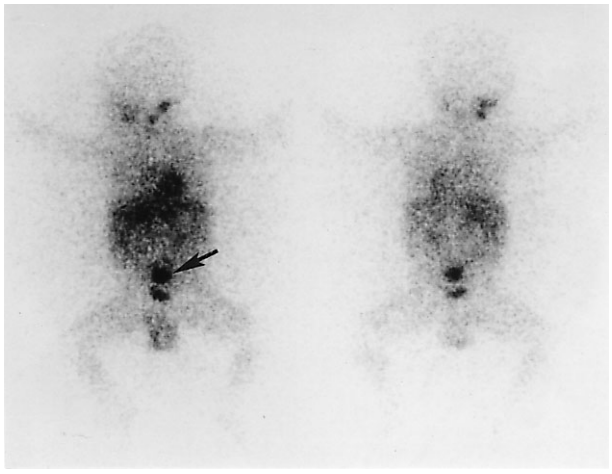


Fig. 2 Anterior and posterior planar whole body images of 8 month and 4 day old boy show ^{123}I-MIBG uptakes corresponding to the primary focus (*arrow*) just above the accumulation to the bladder. It was thought that the tumor of such a part could be overlooked by the usual inspection of abdominal ultrasonography, CT, and MRI. His ^{123}I-MIBG uptake was classified as (2+) and a small area of accumulation group (S).

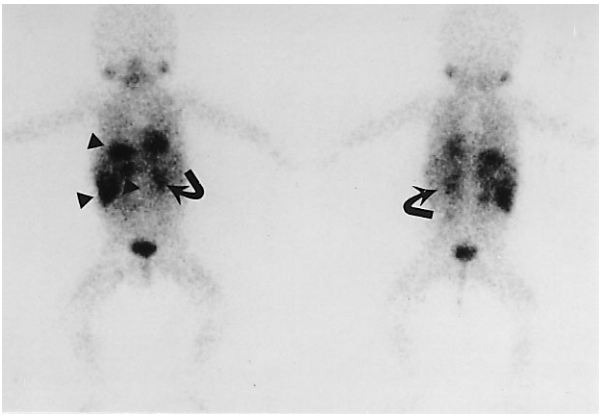


Fig. 3 Anterior and posterior planar whole body images of 7 month and 3 day old boy show increased ^{123}I-MIBG uptakes in the left adrenal grand corresponding to his primary focus (*curved arrow*). He had multiple liver metastases, and some abnormal uptakes were depicted on his liver (*arrowhead*). This picture showed stronger and wider accumulation for liver metastasis than in the primary site, so his ^{123}I-MIBG uptakes were classified as (2+) and a large area of accumulation group (L).

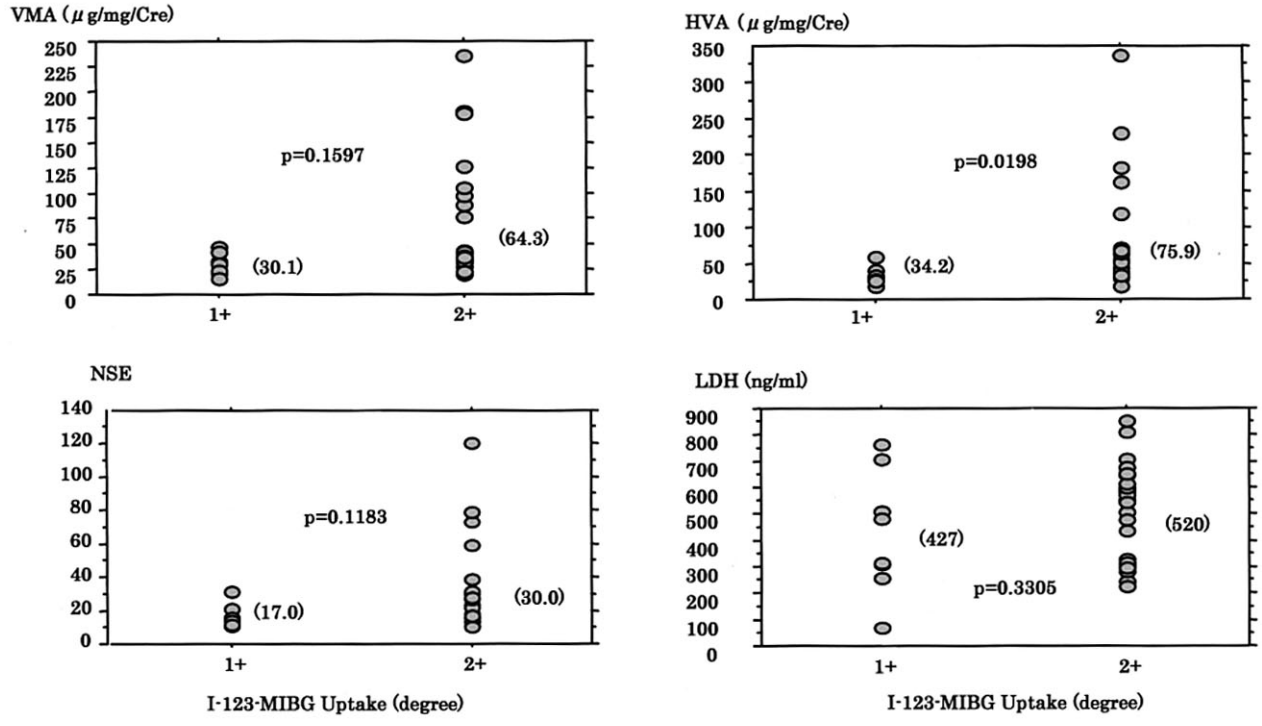


Fig. 4 Correlation between ^{123}I-MIBG accumulation (degree) and tumor markers was shown. Inside parentheses are the mean values for each tumor marker. There were tendencies that the mean value of accumulation degree (2+) group all showed higher values than those of (1+) group for each value. And when urinary VMA, HVA and serum NSE levels exceeded certain levels, more than 50 (μg/mg/Cre), 60 (μg/mg/Cre), 35 (ng/m*l*) respectively, the scintigram exhibited a high accumulation degree (2+) in all cases.

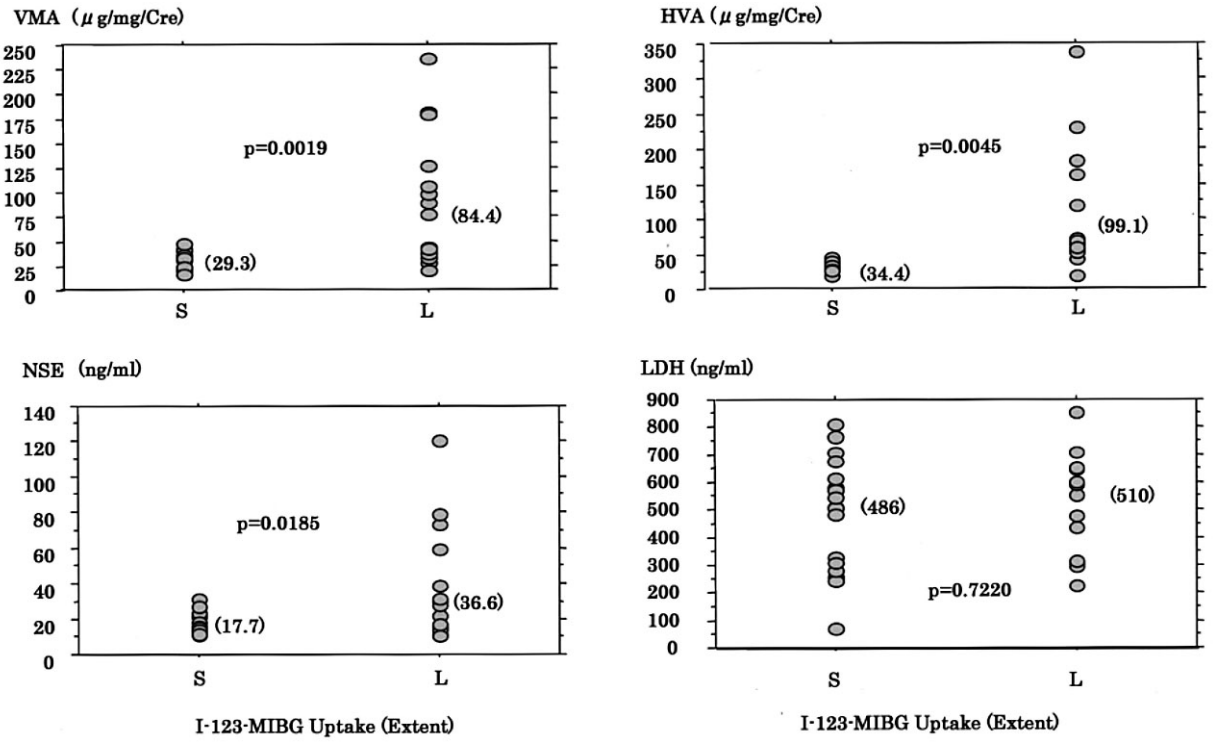


Fig. 5 Correlation between ^{123}I-MIBG accumulation (extent) and tumor markers was shown. Inside parentheses are the mean values for each tumor marker. There were tendencies that the mean value of accumulation degree (L) group all showed higher value than that of (S) group in each tumor marker. And when urinary VMA, HVA and serum NSE levels exceeded certain levels; more than 50 (μg/mg/Cre), 60 (μg/mg/Cre), 35 (ng/m*l*) respectively, the scintigram exhibited a high accumulation extent (L) in all cases.

were evaluated using two sided Mann-Whitney U test ($p < 0.05$).

Evaluation of SPECT

The usefulness of supplemental SPECT was evaluated in 51 studies. The primary and metastatic foci were first evaluated by planar images only, and then re-evaluated with additional SPECT images. If the supplemental SPECT images provided no additional information that influenced clinical staging or tumor recurrence, compared with planar whole body images its usefulness was considered as not changed (category NC). When the result provided some additional and accurate information, it was considered as an advantage (category A) and if wrong, it was considered as a disadvantage (category D). Two radiologists familiar with these nuclear medicine procedures judged independently and conferred as to the final decision.

RESULTS

Table 1 (A–D) show the true positive rate, true negative rate, and accuracy of ^{123}I-MIBG planar whole body images for primary focus, liver metastasis, lymph-node metastasis, and bone marrow infiltration, respectively. The primary focus was depicted from the planar whole body images in all 33 patients (true positive rate 100%). Representative planar images that were useful in the detection of the primary focus of the pelvic space are illustrated in Figure 2. Metastatic foci in the liver were detected in 4 of 5 patients (true positive rate; 80%, true negative rate; 26/28: 93%). Representative planar images that clearly depict multiple liver metastases are illustrated in Figure 3. Metastases to lymph nodes were detected in 3 of 13 patients (true positive rate, 23%, true negative rate; 20/20: 100%). Bone marrow infiltration by tumor cells was detected in one of the 3 patients (true positive rate 33%, true negative rate; 30/30: 100%).

The degree of accumulation was "2+" in 25, "1+" in 8, and "–" in 0. The extent of accumulation was "S" in 17 and "L" in 16. The mean values of VMA (μg/mg/Cre), HVA (μg/mg/Cre), NSE (ng/m*l*) and LDA (ng/m*l*) were 30.1, 34.2, 17.0, 427 respectively in the accumulation degree "1+" group, and 64.3, 75.9, 30.0, 520 respectively in "2+" group. Similarly, those values were 29.3, 34.4, 17.7, 486 respectively in the accumulation extent "S" group and 84.4, 99.1, 36.6, 510 respectively in "L" group. Regarding the correlation between ^{123}I-MIBG accumulation and the tumor markers, the mean urinary VMA, HVA and serum NSE were generally higher in the groups with wider and

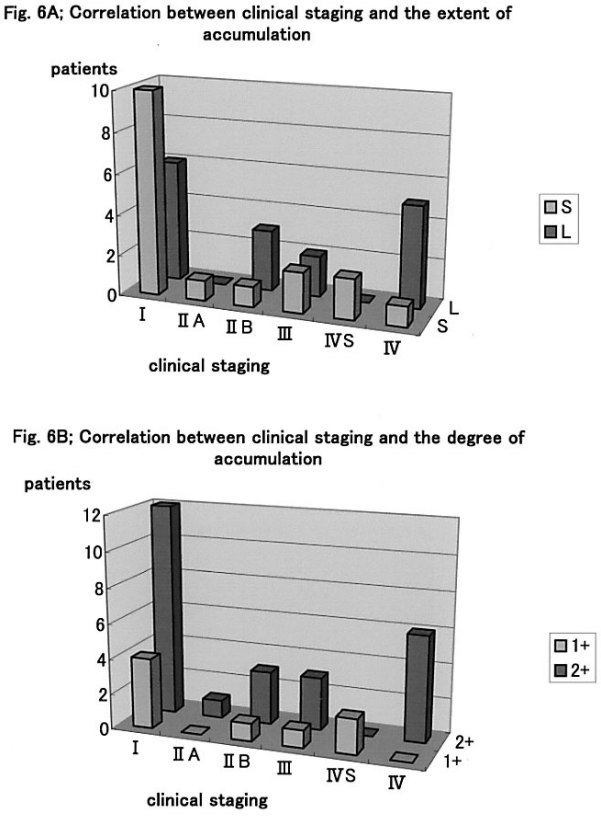
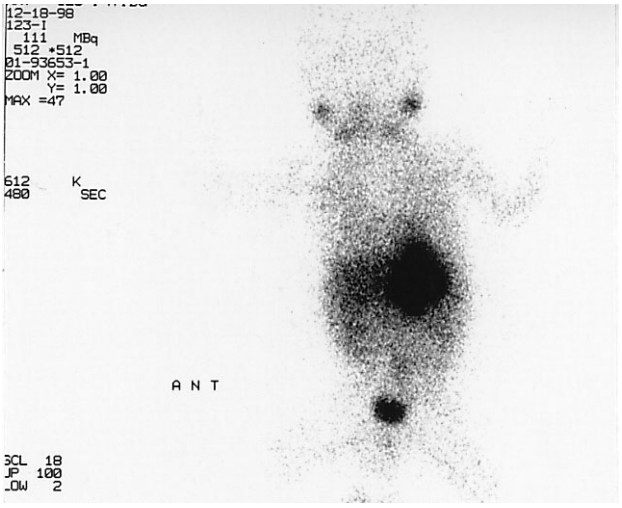
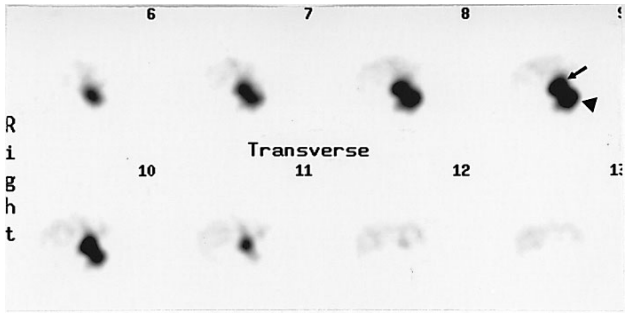


Fig. 6 Correlation between the accumulation and clinical staging was shown. These relations were considered to be poor in this study.



A



B

Fig. 7 An anterior planar whole body image (A) and SPECT images (B) of 7 month and 6 day old boy. In planar image, N1 lymph-node metastasis (*arrow*) and primary site (*arrowhead*) were overlapping, but they were depicted separately in SPECT images. In this case, SPECT images gave us an additional information that influenced clinical staging compared with planar whole body image, so this case was considered to had some advantage compared with planar image, and classified (category A).

more accentuated ^{123}I-MIBG accumulation. All the groups showing elevated urinary VMA and HVA levels and blood NSE levels, exhibited wider and higher concentrations of ^{123}I-MIBG accumulation. However, the groups showing low urinary VMA, HVA and blood NSE failed to show any specific patterns in the areas relating to extent of accumulation. The extent and degree of accumulation did not correlate with LDH or clinical staging (Figs. 4, 5, 6).

Supplemental SPECT images clarified more detailed three-dimensional anatomical locations and obviously increased the diagnostic certainty in all cases. Compared with the planar images alone, there were 7 studies in which the SPECT images provided some correct information that influenced clinical staging or detection of tumor recurrence and were classified as category A. Only 3 studies were classified as category D, and the remaining 41 studies were as category NC. In the 7 studies considered as "A", there were four true positives and three true negatives. Only SPECT studies could depict lymph node metastasis on the side ipsilateral to the primary foci in 2 cases (Fig. 7), liver metastasis in 1 case, and the extent beyond the midline of the primary focus in 1 case, though the respective planar images failed to show these findings. In 3 cases, abnormal uptakes were initially suspected as lymph node metastasis or tumor recurrence in planar images; however, they turned out to be normal uptake to adrenal gland or gastrointestinal tract with SPECT images. In the 3 studies considered as "D", abnormal accumulations were suspected using the supplemental SPECT images, but they were not detected in planar whole body images in any case and were revealed as negative by surgery. A part of the liver deformity in one case and accumulations to gastrointestinal tracts in two cases were considered as abnormal accumulations by SPECT images.

DISCUSSION

In 1974, a mass-screening program by a qualitative VMA spot test for early detection of this tumor in infants under the age of one year was started in Kyoto, Japan. In 1985, mass screening commenced as a nationwide program

throughout Japan and in 1988, screening by quantitative measurement of VMA, HVA, and creatinine was recommended by the Ministry of Health and Welfare.[1] Sawada reported that the survival rate in 357 cases detected by mass screening in Kyoto up to December of 1988 was 97%.[1] This indicates a very favorable prognosis in cases detected at an early stage by screening. Similar attempts are being carried out in some other countries as well.[10–13]

The patient detected by these tumor markers is then examined by a series of imaging modalities for accurate clinical staging of the disease. As the primary foci of this tumor are often found in the adrenal glands or in the retroperitoneal space, and this tumor often gives metastases to the neighboring lymph nodes and the liver, abdominal ultrasonography and CT are frequently employed. As the occasion demands, abdominal MRI is also added. However, these examinations are associated with a risk of overlooking tumors originating in the mediastinum, in the pelvic cavity and their distant metastases. ^{131}I-MIBG has been widely used as one of the imaging methods for detecting neuroblastoma, and some authors have already reported its high sensitivity and usefulness. With it, one can examine the whole body and areas easily, which considerably decreases the risk of missing anything.

^{123}I-labeled MIBG has been developed recently. It has superior imaging characteristics, better image quality and safer radionuclide with a shorter half-life and no β-ray discharge, compared with ^{131}I-MIBG and is gradually replacing it in the diagnosis of neuroblastoma. Ishii et al. reported high sensitivity and specificity of ^{123}I-MIBG scintigraphy for visualization and localization of tumors of sympathetic and adrenomedullary origin.[6,7] There have been several reports in the literature regarding the diagnostic capability of ^{123}I-MIBG in detecting the primary and metastatic foci of a neuroblastoma and determining the correlation between the extent of ^{123}I-MIBG accumulation and tumor markers. However, from our literature search, we did not find any reports where the subjects (as many as 33 in number) were limited to newborn infants below the age of one year, detected by urinary VMA and HVA mass screening.

Considering the detectability of the primary foci and metastatic foci in the liver, lymph nodes or bone marrow before the surgery, the results of the current study demonstrate that the planar whole body images show a very high sensitivity. This result was better than the result reported by Rufini et al. (86.7%),[9] and as good as the result reported by Ishii et al. (100%).[7] Scintigraphy was inferior with regard to space resolution in comparison with other imaging modalities. However, it can depict the functioning lesions very clearly even when small. This was considered the reason for the high sensitivity of the primary foci. The planar whole body images also showed a high detection rate for liver metastases. The reason may be that this disease tends to easily make a large metastatic focus with accelerated function. This result indicates that during a single examination, ^{123}I-MIBG scintigraphy planar image can evaluate the existence of liver metastasis and primary focus with quite a high sensitivity. The poor detectability of lymph node metastasis may be due to a limitation of planar imaging for small metastatic lymph nodes. The sensitivity of bone marrow infiltration also showed a low value. However, this part of metastasis was also difficult to detect using other imaging methods, and ^{123}I-MIBG is considered to be an important method for detecting it. Okuyama et al. reported that scintigrams 24 hours later are better than 6 hours later for detecting primary or metastatic lesion of neuroblastoma, apart from bone and bone marrow infiltration. In our study, there were only 3 cases that showed bone marrow infiltration, and fortunately these cases were all detected by bone marrow aspiration. We could detect several primary lesions in the mediastinum or pelvis that were overlooked during routine abdominal ultrasonography, CT, or MRI. And there were also some cases where ^{123}I-MIBG scintigraphy added a cumulative reliability of diagnosis to the other imaging modalities. On the other hand, ^{123}I-MIBG scintigraphy is considered to be inferior to the other modalities for detecting small metastatic lesions in the lymph nodes or the liver without accelerated function in relation to spatial resolution.

We did not find any significant correlation between the value of any tumor marker and the degree and extent of a major site of abnormal radionuclide accumulation. However, several tendencies towards correlation were found between the degree and extent of the lesion of ^{123}I-MIBG accumulations with some tumor markers and clinical staging. First, the mean values of each tumor marker were higher, including urinary VMA, urinary HVA, serum NSE, or serum LDH, and accumulation degree 2+ group compared to the 1+ group, and extent L group compared to the S group. Second, when urinary VMA, HVA and serum NSE levels exceeded certain levels, namely, more than 50 (μg/mg/Cre), 60 (μg/mg/Cre), 35 (ng/m*l*) respectively, the scintigram exhibited a high degree and extensive area of abnormal radionuclide accumulation in all cases. These findings suggest that by examining these tumor marker levels while interpreting the ^{123}I-MIBG scintigram, an abnormal accumulation might be anticipated to a certain extent. However, when the urinary or serum levels of these tumor markers decreased below a certain level, there were no specific patterns in the extent or area of abnormal accumulation.

Regarding the usefulness of supplemental SPECT images in the diagnosis of tumors, a more detailed three-dimensional anatomical location was obtained in all cases and therefore reading scintigrams in combination with planar whole body images obviously increased the certainty of the evaluation of abnormal uptake. Supplemental SPECT images were also useful in some cases for evaluating the local extent of the primary tumor and metastases to the lymph nodes and liver. On the other

hand, it was initially expected that supplemental SPECT would allow detection of more metastases to the lymph nodes and liver, but additional lesions were detected in only a few cases. The accumulation to the lymph node metastasis was minimal or absent in many cases, and so it was considered difficult to distinguish it completely from that of normal accumulation to the gastrointestinal tract. There was a risk of increase in false positive results while trying to raise its detectability. Concerning accumulation in liver metastasis, radionuclide accumulation becomes more pronounced near the liver surface because attenuation begins to occur at these depths, resulting in an irregular appearance. Therefore, also when evaluating liver metastasis, small lesions, or those that occur on the surface of the liver were impossible or difficult to detect. There was one case of a false positive MIBG for hepatic metastasis. When viewing the SPECT image, the heterogeneous accumulation in the liver was mistaken for a metastasis. On the other hand, when a SPECT image detects an abnormal accumulation of radionuclide in the deep section of the liver, it is almost certain that the tumor has metastasized to the liver.

CONCLUSION

^{123}I-MIBG scintigraphy can easily visualize the extent of the neuroblastoma, detected by a mass screening survey of urinary VMA and HVA, especially for primary focus and liver metastasis. The area and degree of accumulation correlated with elevated levels of urinary VMA, HVA, and NSE. Supplemental SPECT images helped to understand the positional relation in all cases and provided additional useful information concerning tumor staging or recurrence in some cases, although care must be taken to avoid overdiagnosis.

REFERENCES

1. Sawada T. Past and future of neuroblastoma screening in Japan. *American Journal of Pediatric Hematology-Oncology* 1992; 14: 320–326.
2. Sawada T. Outcome of 25 neuroblastomas revealed by screening in Japan. *Lancet* 1986; 1: 377.
3. Okuyama C, Ushijima Y, Sugihara H, Okitsu S, Maeda T. ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy for the staging of neuroblastoma. *KAKU IGAKU (Jpn J Nucl Med)* 1998; 35: 835–842.
4. Gelfand MJ, Elgazzar AH, Kriss VM, Masters PR, Golsch GJ. Iodine-123-MIBG SPECT versus planar imaging in children with neural crest tumors. *J Nucl Med* 1994; 35: 1753–1757.
5. Rufini V, Fisher GA, Shulkin BL, Sisson JC, Shapiro B. Iodine-123-MIBG imaging of neuroblastoma: utility of SPECT and delayed imaging. *J Nucl Med* 1996; 37: 1464–1468.
6. Ikekubo K, Hino M, Ootsuka H, Ito H, Yamaguchi H, Dan Y. Detection of neural crest tumors by iodine-123-MIBG scintigraphy. *KAKU IGAKU (Jpn J Nucl Med)* 1994; 31: 1357–1364.
7. Ishii K, Kubo A, Kusakabe K, Murata H, Masaki H, Horiike S, et al. Evaluation of clinical utility of ^{123}I-MIBG scintigraphy in localization of tumors of sympathetic and adrenomedullary origin—A report of multicenter phase III clinical trials. *KAKU IGAKU (Jpn J Nucl Med)* 2000; 37: 43–59.
8. Okuyama C, Ushijima Y, Watanabe K, Sugihara H, Nishimura T. Iodine-123-MIBG scintigraphy in neuroblastoma: relationship between the intensity of uptake and tumor characteristics. *KAKU IGAKU (Jpn J Nucl Med)* 1999; 36: 827–834.
9. Rufini V, Giordano A, Di Giuda D, Petrone A, Deb G, De Sio L, et al. ^{123}I-MIBG scintigraphy in neuroblastoma: a comparison between planar and SPECT imaging. *Quarterly J Nucl Med* 1995; 39: 25–28.
10. Kawakami T, Monobe Y, Monforte H, Woods WG, Tuchman M, Lemieux B, et al. Pathology review of screening negative neuroblastomas: a report from the Quebec neuroblastoma screening project. *Cancer* 1998; 83: 575–581.
11. Nesbit ME Jr. Advances and management of solid tumors in children. *Cancer* 1990; 65: 696–702.
12. Ater JL, Gardner KL, Foxhall LE, Therrell BL Jr, Bleyer WA. Neuroblastoma screening in the United States: results of the Texas outreach program for neuroblastoma screening. *Cancer* 1998; 82: 1593–1602.
13. Bozkowa K, Cabalska B, Radomyska B, Oltarzewski M, Lenartowska I. Evaluation of the usefulness for neonatal mass screening in light of 35 years personal experience. *Medycyna Wieku Rozwojowego* 1999; 3: 529–559.
14. Wieland DM, Swanson DP, Brown LE, Beierwaltes WH. Imaging the adrenal medulla with an iodine-131-labeled antiadrenergic agent. *J Nucl Med* 1979; 20: 155–158.
15. Edeling CJ, Frederiksen PB, Kamper J, Jeppesen P. Diagnosis and treatment of neuroblastoma using metaiodobenzylguanidine. *Clin Nucl Med* 1987; 12: 632–637.
16. Iwahita S, Nakajo M, Nakabeppu Y, Tanoue T, Yonekura R, Taguchi M, et al. Clinical evaluation of I-131-metaiodobenzylguanidine (MIBG) imaging in suspected neuroblastoma. *KAKU IGAKU (Jpn J Nucl Med)* 1989; 26: 1135–1147.
17. Murashima S, Takeda K, Okuda Y, Nakagawa T, Sakurai M. Assessment of biological activity of recurrent tumor of neuroblastoma with iodine-131-metaiodobenzylguanidine (MIBG) scintigraphy. *KAKU IGAKU (Jpn J Nucl Med)* 1990; 27: 1393–1400.
18. Odano I, Takeda M, Kimura M, Sakai K. Clinical significance of iodine-131-metaiodobenzylguanidine scintigraphy in neuroblastoma. *Nippon Act Radiol* 1988; 48: 623–632.
19. Mark E, Nesbit ME Jr. Advances and management of solid tumors in children. *Cancer* 1990; 65: 696–702.