Clinical experience with $^{18}$F-FDG-PET and $^{123}$I-MIBG scintigraphy in pediatric neuroblastoma: complementary roles in follow-up of patients

Tae Young Gil, Do Kyung Lee, Jung Min Lee, Eun Sun Yoo, Kyung-Ha Ryu

Department of Pediatrics, Mokdong Hospital, Ewha Womans University School of Medicine, Seoul, Korea

Running title: $^{18}$F-FDG PET and $^{123}$I-MIBG scans in pediatric neuroblastoma

Correspondence to
Eun Sun Yoo, M.D., Ph.D.
Department of Pediatrics, Ewha Womans University MokDong Hospital, 911-1, Mokdong,
Yangcheon-gu, Seoul, 158-710, Korea
Tel: +82-2-2650-5586
Fax: +82-2-2653-3718
E-mail: eunyoo@ewha.ac.kr
ABSTRACT

Purpose: To evaluate the potential utility of $^{123}$I-metaiodobenzylguanine ($^{123}$I-MIBG) scintigraphy and $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) PET for the detection of primary and metastatic lesions in pediatric neuroblastoma (NBL) patients, and to decide whether $^{18}$F-FDG PET has as much benefits as $^{123}$I-MIBG imaging.

Methods: We selected 8 NBL patients who had significant residual mass after operation and who had available paired $^{123}$I-MIBG and $^{18}$F-FDG PET images obtained during follow-up. We retrospectively reviewed their clinical charts and findings of 45 paired scans.

Results: Both scans were relatively well correlated with disease status as determined by standard imaging modalities during follow-up; overall concordance rates were 32/45(71.1%) for primary tumor sites and 33/45(73.3%) for bone-bone marrow (BM) metastatic sites. In detecting primary tumor sites, $^{123}$I-MIBG might be superior to $^{18}$F-FDG PET. The sensitivity of $^{123}$I-MIBG and $^{18}$F-FDG PET were 96.7% and 70.9%, and their specificity values were 85.7% and 92.8%, respectively. $^{18}$F-FDG PET missed 9 true NBL lesions in 45 follow-up scans (29% false negative rate) with positive $^{123}$I-MIBG. Evaluation of bone-BM metastatic sites showed sensitivity values of $^{123}$I-MIBG and $^{18}$F-FDG PET of 72.7% and 81.8%, and specificity values of 79.1% and 100%, respectively. $^{123}$I-MIBG scans showed higher prevalence of false positivity (20.8%) than did $^{18}$F-FDG PET (0%).

Conclusion: $^{123}$I-MIBG is superior for delineating primary tumor sites, and $^{18}$F-FDG PET could aid in discriminating inconclusive findings on bony metastatic NBL. Both scans can be complementally used to clearly discriminate discrepancies or inconclusive findings on the primary or bone-BM metastatic NBL during follow-up.

Key Words: Neuroblastoma, $^{18}$F-FDG PET, $^{123}$ I-MIBG scans, Child, Follow-up
Introduction

Neuroblastoma (NBL) is the most common extracranial solid tumor in children\(^1\). It arises from embryonic neural crest cells derived from the peripheral sympathetic nervous system. Primary tumors can arise anywhere from the pelvis to the neck, and approximately 50% of patients present with distant metastasis to bone, bone marrow (BM), lymph node, and liver\(^2\). These clinical characteristics make assessment of the disease status dependent on a multitude of studies.

Functional imaging with the catecholamine analogue \(^{123}\)I-metaiodobenzylguanin (\(^{123}\)I-MIBG) has been widely used to assess tumors of the sympathetic nervous system since its development in the early 1980s\(^3\). \(^{123}\)I-MIBG scan was well proved its high diagnostic accuracy for NBL assessment in the diagnosis, staging, treatment response and recurrence\(^4\). \(^{123}\)I-MIBG scan showed high sensitivity and specificity in identifying metastatic involvement of the cortical bone, BM, and lymph nodes\(^5,6\). However, \(^{123}\)I-MIBG still has limitations in the interpretation of the normal distribution pattern in children\(^7\), and in the appearance of false-negative results\(^8\), which may lead to down-staging\(^9\).
\(^{18}\text{F}-\text{fluorodeoxyglucose positron emission tomography}\) \((^{18}\text{F-FDG PET})\) has recently emerged as a promising functional imaging modality for various types of adult cancers, and is most frequently investigated in lymphomas, brain tumors and sarcomas. However, no sufficient studies have investigated the use of \(^{18}\text{F-FDG PET}\) in \(\text{NBL}\). Although \(^{18}\text{F-FDG PET}\) showed tumor avidity for revealing \(\text{NBL}\) in both soft tissue and skeletons, providing a good correlation with the disease status\(^{10}\), questions still remain regarding when and in which patients \(^{18}\text{F-FDG PET}\) is most useful\(^{11-13}\).

The purpose of the present study was to evaluate the potential utility of \(^{123}\text{I-MIBG scintigraphy}\) and \(^{18}\text{F-FDG PET}\) for the detection of primary and metastatic lesions of \(\text{NBL}\), and to decide whether \(^{18}\text{F-FDG PET}\) was as beneficial as MIBG scintigraphy in \(\text{NBL}\) patients.

\textbf{Materials and methods}

1. Patients

We selected 8 patients \textit{with NBL diagnosed and treated} at Ewha Womans University Mokdong Hospital between November 2005 and January 2013,
who had residual mass due to incomplete tumor removal and who were able to simultaneously had both $^{123}$I-MIBG and $^{18}$F-FDG PET scans during follow-up. Their clinical charts and imaging findings were retrospectively reviewed with the approval from institutional review board.

All patients underwent staging evaluation in accordance with the International Neuroblastoma Staging Systems (INSS)\textsuperscript{[14]}, consisting of $^{123}$I-MIBG scans, $^{99m}$Tc- methylenediphosphonate (MDP) bone scans, computed tomography (CT) ad/or magnetic resonance imaging (MRI), urine vanillymandelic acid (VMA), urine homovanillic acid (HVA), neuron specific enolase (NSE) and BM examination.

The patients were treated with neo-adjuvant chemotherapy, surgery, 2 or 3 cycles of post-operative chemotherapy, high-dose chemotherapy and autologous stem cell transplantation according to our institutional protocol.

The paired $^{123}$I-MIBG and $^{18}$F-FDG PET scans were obtained during follow-up schedule at designated times, including at diagnosis, after 4 or 5 cycles of neoadjuvant chemotherapy, after surgery and after stem cell transplantation, to define accurate assessment of disease status according to treatment in the patients with residual mass during follow-up. The CT and/or MRI and
$^{99m}$Tc-MDP bone scan were also performed simultaneously. All imaging modalities were obtained within 14 days of each other after informed consent was obtained.

2. Scan acquisitions

$^{123}$I-MIBG scans were performed with the thyroid protection by ingestion of potassium iodide solution (10 mg/mL) (Lugol solution®) to block $^{123}$I-MIBG uptake in the thyroid glands. The dosages of $^{123}$I-MIBG were measured according to the body weight (0.2 mCi/kg). Multiple spot imagings of the entire body were acquired at 4 and 20 hours after the injection of $^{123}$I-MIBG.

$^{18}$F-FDG PET scans were preceded by a 6-hour period of fasting with water intake allowed. The dosage of $^{18}$F-FDG was 5.18-7.12 MBq/kg with a maximum dosage of 440 MBq (10 mCi). Whole-body scans were performed using a PET/CT scanner 60 minutes after the infusion of $^{18}$F-FDG. At first, CT scan was obtained, and transmission images were obtained after the emission scan. The images were reconstructed using filtered back-projection and iterative algorithm, and segmented attenuation and scatter correction was performed. A standardized uptake value (SUV), which is a quantitative
measurement of tumor uptake of the $^{18}$F-FDG adjusted for injected dose and body weight, was calculated for each lesion, and the maximum SUV (SUVmax) of each lesion was determined from the image.

3. Image analysis

All $^{123}$I-MIBG and $^{18}$F-FDG PET scan images were reviewed by well experienced nuclear medicine physician blinded to the clinical data of the patients. Images for both $^{123}$I-MIBG and $^{18}$F-FDG PET scans were analyzed by direct comparison on a patient basis as positive or negative, and recorded separately for the primary mass and bone/BM compartment instead of semiquantitative scoring systems for NBL.$^{15}$ On the $^{18}$F-FDG PET scan, lesion was interpreted as positive lesion if lesion have focally increased $^{18}$F-FDG uptake exceeding normal background uptake.

During the routine follow-up, patients were followed by diagnostic CT or MRI of the abdomen or thorax every 6–12 months, and these morphological imaging were compared with the functional imaging for verification of the lesions. For the bone-BM lesion, BM examination by bilateral aspiration and biopsy in each case at diagnosis and follow-up examinations $^{99m}$Tc- MDP
bone scans were performed. For the verification of lesions, histopathological finding, follow-up evaluation, and clinical response were used because histopathological verification of all metastases is impossible. A lesion was classified as either ‘false-positive’ or ‘true-negative’ if it disappeared without any therapy during the follow-up period, or if lesion did not have viable tumor by histological verification. A lesion was classified as either “true-positive” or “false-negative” if it persisted or progressed during follow-up, or showed objective regression with therapy\textsuperscript{13}. 
Results

The clinical characteristics of the 8 patients are described in Table 1. There were 3 males and 5 females and their median age at diagnosis was 3 years 6 months (range, 2 years 9 months – 5 years 6 months) and their INSS stages were; stage III in one and stage IV in seven cases. The primary tumor sites were; adrenal gland (n=5), posterior mediastinum (n=2), and organ of zuckerkandi (n=1). The patients had variable sizes of residual mass on the primary site after operation with range from about 1 cm to 6 cm in maximum diameter.

To define clinical significance of the residual tumor at the primary site and metastatic sites, a total of 45 combined $^{123}$I-MIBG and F$^{18}$-FDG PET scans were obtained from eight patients during the follow-up. The frequency of paired scan per patient were; six in patient 1, six in patient 2, seven in patient 3, four in patient 4, six in patient 5, four in patient 6, six in patient 7 and six in patient 8.

1. Detection of post-therapeutic residual tumor at the primary site
The patients had evidence of a residual primary tumor in the post-operative CT scans showing about an 1-6 cm range. All residual lesions were examined by CT, $^{18}$F-FDG PET, $^{123}$I-MIBG scans and $^{99m}$Tc-MDP bone scans to assess their viability.

A total 30 out of 45 studies were positive on $^{123}$I-MIBG images, whereas 37 out of 45 scans were positive on $^{18}$F-FDG PET images. The sensitivity of both modalities for NBL detection was 96.7% in $^{123}$I-MIBG scan and 70.9% in $^{18}$F-FDG PET scan.

On the primary tumor sites, $^{18}$F-FDG PET and $^{123}$I-MIBG scans were concordant for the positive or negative avidity in 32 of 45 scans (71.1%) at diagnosis and during follow-up (Table 2). The concordance between the both scans was observed 5 of 8 patients (62.5%).

The $^{18}$F-FDG PET scans missed 9 studies out of 31 images (29%), and the $^{123}$I-MIBG scan missed 1 study out of 31 images (3.2%) for detection of NBL in primary tumor sites (Table 2). The Patient 3, who had a large residual abdominal mass (lesion diameter 4.5x5.5 cm) was observed with positive uptake for $^{123}$I-MIBG but a negative result in the $^{18}$F-FDG PET scan (Fig. 1). These false-negative findings were repeatedly observed in 2 out of 7 follow-
up scans. Finally, the negative avidity on the $^{18}$F-FDG scan was false negative finding, which was confirmed as viable tumor by biopsy.

The false positive findings were comparable between $^{123}$I-MIBG and $^{18}$F-FDG PET images, which were shown in 2 out of 14 scans (14.3%) on $^{123}$I-MIBG and in 1 out of 14 scans (7.1%) at the primary tumor sites at diagnosis and during follow-up (Table 2, Fig. 2). These results implicated $^{18}$F-FDG PET scan was worse in depicting disease in the soft-tissue compartment, and the $^{123}$I-MIBG scan might be superior to $^{18}$F-FDG PET for detecting a region of the primary tumor.

The $^{123}$I-MIBG scintigraphy, showed a false negative finding in 1 of 31 scans (3.2%), and false positive findings in 2 of 14 scans (14.3%) at the primary tumor sites at diagnosis and during follow-up (Table 2). The patient 7, had a residual mass (adrenal gland, diameter less than 1 cm) after operation. The residual mass twice showed negative findings on $^{123}$I-MIBG scans, but positive on $^{18}$F-FDG PET scans. $^{18}$F-FDG PET scan can be useful identify an active viable tumor in an $^{123}$I-MIBG negative lesion (Fig. 3). The patient 2 who had a residual mass (adrenal gland, diameter 3x4 cm) had been monitored regularly, and showed positive uptake in an $^{123}$I-MIBG scan.
but negative in $^{18}$F-FDG PET at 10 months after treatment completion. Both scans repeated nine months afterwards, and the positive avidity on the $^{123}$I-MIBG scan was converted to negative imaging without any treatment with good clinical status.

These results indicated that the $^{123}$I-MIBG scan might be superior to $^{18}$F-FDG PET for detecting a region of the primary tumor.

2. Detection of bone-BM involvement

A total 21 $^{123}$I-MIBG images were positive in 45 scans, whereas $^{18}$F-FDG PET images were positive in 18 of 45 scans. The sensitivity of both modalities for NBL detection was 72.7% in $^{123}$I-MIBG scan and 81.8% in $^{18}$F-FDG PET scan.

In the evaluation of bone-BM metastatic sites, $^{18}$F-FDG PET and $^{123}$I-MIBG scans were concordant for the positive or negative avidity in 33 of 45 scans (73.3%) at the diagnosis and during the follow-ups (Table 2). The concordance between the both scans was observed 6 of 8 patients (73.3%). Nevertheless, both $^{18}$F-FDG PET and $^{123}$I-MIBG scans missed metastatic bone-
BM lesions in 3 studies although the $^{99m}$Tc-MDP bone scan showed disseminated involvement of multiple skeletal uptake (Fig. 4).

Both modalities showed overall equivalence in detecting bone or BM metastasis; $^{18}$F-FDG PET scans missed 4 studies (8.9%) of 2 patients (Fig. 4) and $^{123}$I-MIBG scans missed 6 studies (13.3%) of 3 patients. However, $^{123}$I-MIBG scan showed higher presentation of false positive findings than $^{18}$F-FDG PET scan. There were false positive findings in 5 out of 45 scans (11.1%) by $^{123}$I-MIBG scan, but there were no false positive findings in $^{18}$F-FDG PET scan in bone-BM sites during the follow-ups of NBL patients.

These results implicated that $^{18}$F-FDG PET might be better for detecting bone or BM metastasis than $^{123}$I-MIBG scan. The bone scan did not precisely detect bone lesions, and it missed active bony lesion in 4 studies (8.8%) of Patient 5. Data in all patients are summarized on Table 3.

**Discussion**

In this retrospective study, we investigated whether $^{18}$F-FDG PET was useful as much as $^{123}$I-MIBG scintigraphy in detecting the primary and metastatic lesions during the follow-up of high-risk NBL patients. In our 8 patients with
high risk NBL, 45 studies were performed. And they showed that both modalities are relatively well-correlated with the disease status as determined by standard imaging modalities during follow-ups; overall concordance rates were 32/45(71.1%) on primary tumor sites and 33/45(73.3%) at bone-BM metastatic sites.

Many authors have been investigating to assess the potential utility of $^{18}$F-FDG PET and $^{123}$I-MIBG scans in children with NBL. So far, there are no conclusive reports to support which modality is more useful for monitoring the primary and metastatic lesions during follow-up. $^{123}$I-MIBG scintigraphy has been widely used in clinical settings for the past 25 years in pediatric oncology providing high sensitivity and specificity in NBL. Nevertheless, it still has limitations in interpretation of unusual appearance of normal physiologic uptake such as upper thoracic and gastric region in children, and leading to false-negative results. Moreover, there are some difficulties in detecting lesions during the follow-ups of NBL, because $^{123}$I-MIBG positivity on initial diagnosis may reverse negative avidity when the disease relapses. Although $^{18}$F-FDG PET is increasingly used to overcome these limitations, $^{18}$F-FDG uptake into non-tumor sites can cause potential false-
positive or false-negative results. Also, there is no evidence to support the use of $^{18}$F-FDG PET in the initial diagnosis.

In our study, we separately assessed avidity between primary and metastatic bony lesions. In detecting the primary tumor sites, $^{123}$I-MIBG scans might be superior to $^{18}$F-FDG PET, and the sensitivity values of $^{123}$I-MIBG and $^{18}$F-FDG PET were 96.7% and 70.9%, respectively, and their specificity values were 85.7% and 92.8%, respectively. Although $^{18}$F-FDG PET was able to reveal the metabolic states of the primary or residual NBL as much as $^{123}$I-MIBG, $^{18}$F-FDG PET missed 9 true NBL lesions in 45 follow-up scans (29% false positive negative rate) with a positive $^{123}$I-MIBG, in which histopathologically viable tumor activity was proven (patient 3). $^{18}$F-FDG PET did not show any advantage over $^{123}$I-MIBG. Our results accord with the several of the recent studies\textsuperscript{11,17}. Shulkin et al\textsuperscript{11} reported that $^{123}$I-MIBG scan was superior to $^{18}$F-FDG PET, which showed lower tumor-to-nontumor uptake ratio and physiological $^{18}$F-FDG accumulation, for NBL tumor delineation. Sharp et al\textsuperscript{17} reported that $^{123}$I-MIBG scan was superior to $^{18}$F-FDG PET in 40 patients with stage IV NBL. $^{123}$I-MIBG was more sensitive for bone lesions than $^{18}$F-FDG PET in patients of the New Approaches to Neuroblastoma Therapy (NANT)
18F-FDG PET might be better in detection for bone or BM metastases during follow-up than 123I-MIBG scan. The sensitivity values of 123I-MIBG and 18F-FDG PET were 72.7% and 81.8%, respectively, and their specificity values were 79.1% and 100%, respectively. 123I-MIBG scans showed a higher prevalence of false positivity (20.8%) than 18F-FDG PET (0%). 18F-FDG PET provided important information for the patient with false positive lesions on 123I-MIBG at the major decision points during follow-up (patient 2). Therefore, 18F-FDG PET may be useful to clearly discriminate discrepancies, or inconclusive findings on the bone/BM metastatic NBL during follow-up.

The role of 18F-FDG PET for detecting bone or BM metastases is controversial. Kushner et al12) reviewed 92 18F-FDG PET scans obtained from 51 patients with NBL, and reported that 18F-FDG PET is better than 123I-MIBG for detection of both soft tissue and extracranial osteomedullary lesions12). Colavolpe et al16) reported that 18F-FDG PET scans are helpful in detecting the multiple hypermetabolic osteo-medullary metastasis in the patients with negative 123I-MIBG scintigraphy. In contrast, several studies reported 123I-MIBG scan is superior to 18F-FDG PET in the assessment of disease extent in
high-risk NBL\textsuperscript{18,19}. \textsuperscript{123}I-MIBG was more sensitive for bone lesions than \textsuperscript{18}F-FDG PET in patients of the NANT trial\textsuperscript{18}. Consequently, it still remains difficult to predict the clinical roles and accuracy of \textsuperscript{18}F-FDG PET scans in NBL.

\textsuperscript{123}I-MIBG is known to be highly sensitive and specific for identifying metastatic involvement of cortical bone and BM, and \textsuperscript{18}F-FDG PET was better for identifying soft tissue lesions. However, our study showed conflicting results for identifying individual lesion in NBL. The discrepancy between the two modalities for detecting individual tumor lesions may be due to small sample size, preselected high-risk study populations, and variability of tumor tracer uptake in different radiopharmaceutical. Actually, mechanism of tracer uptake is different between \textsuperscript{123}I-MIBG and \textsuperscript{18}F-FDG. MIBG is an analog of the adrenergic norepinephrine neurotransmitter, which is taken by the adrenergic origin of NBL and pheochromocytoma using the type 1 catecholamine uptake mechanism for transport into tumor cells\textsuperscript{17}. Uptake of \textsuperscript{123}I-MIBG was highly variable in vivo, and probably influenced by multiple factors such as degree of differentiation in neuroendocrine tumor, interfering medication, and change in the metabolism of the malignant cells due to
altered biology\textsuperscript{13,20}. \(^{18}\)F-FDG, similar to glucose, is transported to within the cells via the GULT (glucose transporters) and intracellular phosphorylated by hexokinase into glucose-6-phosphate and \(^{18}\)F-FDG-6-phosphate. \(^{18}\)F-FDG-6-phosphate entrapped, and steadily accumulates in metabolically active cells with different uptake mechanism with \(^{123}\)I-MIBG\textsuperscript{21}). Although most NBL and associated metastases have been shown to have good avidity for FDG, \(^{18}\)F-FDG PET have shown variable results during/after treatment due to its lower tumor-to-nontumor uptake ratio and FDG uptake in nontumor sites\textsuperscript{4,22).} \(^{18}\)F-FDG PET also show false positive results in osteo-medullary assessment due to diffuse BM uptake after treatment (hyperactivity) with growth factors or radio-chemotherapy (rebound after treatment).

Another possibility for discrepant result is spontaneous regression or cellular differentiation of NBL tumor cells leading to false negative activity in \(^{123}\)I-MIBG scan due to modification in the uptake mechanism, but we did not analyzed as a contributory factor in this study.

Our study showed both \(^{123}\)I-MIBG and \(^{18}\)F-FDG PET scans complement each other which is comparable to the recent study by Melzer et al\textsuperscript{13).} In their study, they showed the sensitivity values of \(^{123}\)I-MIBG scintigraphy and
$^{18}$F-FDG PET to be 50% and 78%, respectively, and their specificity values to be 85.7% and 92%, respectively. They recommended $^{18}$F-FDG PET as an additional modality when the results were discrepant or inconclusive with $^{123}$I-MIBG, $^{18}$F-FDG PET, and morphological imaging during the follow-up.

The limitations of this study is the small number of cases, which could have an influence in determining concordance or discordance rate, and the sensitivity or specificity. We recalculated the sensitivity and specificity from each patient to evaluate their effect. We finally confirmed that there was very little difference in values. Our study population to selective patients in the high risk NBL, who had residual tumors, and who were available for paired scans. The sensitivity and specificity of $^{123}$I-MIBG scintigraphy is not applicable to the general population of NBL patients. This makes it difficult to compare our study results with the studies already published in the literature.

In conclusion, the functional studies, such as $^{123}$I-MIBG and $^{18}$F-FDG PET scans, surely are valuable in distinguishing the residual active disease from residual operative scars. However, $^{18}$F-FDG PET cannot replace $^{123}$I-MIBG or bone scans in the evaluation for primary or metastatic NBL disease during
the follow-up, because they show relatively higher false-negative results. Both scans have complementary roles to clearly discriminate discrepancies, or inconclusive findings on the primary or bone-BM metastatic NBL during the follow-up. Further studies in larger sample size will be needed.

Conflict of interest

No potential conflict of interest relevant to this article is reported.
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Table 1. Clinical data in 8 high-risk neuroblastoma patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age at diagnosis</th>
<th>Gender</th>
<th>Primary tumor</th>
<th>Metastasis</th>
<th>INSS stage</th>
<th>Status of 1° tumor after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4yr</td>
<td>M</td>
<td>Rt. Posterior mediastinum</td>
<td>Bone, BM</td>
<td>IV</td>
<td>&lt;1 cm</td>
</tr>
<tr>
<td>2</td>
<td>3yr 6mo</td>
<td>F</td>
<td>Adrenal gland</td>
<td>Bone, BM</td>
<td>IV</td>
<td>3x4 cm</td>
</tr>
<tr>
<td>3</td>
<td>3yr 2mo</td>
<td>F</td>
<td>Adrenal gland, Liver</td>
<td>Bone, BM</td>
<td>IV</td>
<td>4.5x5.5 cm</td>
</tr>
<tr>
<td>4</td>
<td>5yr 6mo</td>
<td>F</td>
<td>Adrenal gland region</td>
<td>Paravertebral Bone, BM</td>
<td>III</td>
<td>1x2 cm</td>
</tr>
<tr>
<td>5</td>
<td>2yr 9mo</td>
<td>M</td>
<td>Adrenal gland</td>
<td>Bone, BM</td>
<td>IV</td>
<td>&lt;1 cm</td>
</tr>
<tr>
<td>6</td>
<td>3yr 2mo</td>
<td>F</td>
<td>Posterior mediastinum</td>
<td>Bone, BM</td>
<td>IV</td>
<td>3x4 cm</td>
</tr>
<tr>
<td>7</td>
<td>3yr 9mo</td>
<td>M</td>
<td>Adrenal gland</td>
<td>Bone, BM</td>
<td>IV</td>
<td>&lt;1 cm</td>
</tr>
<tr>
<td>8</td>
<td>3yr 9mo</td>
<td>F</td>
<td>Organ of zuckerkandl</td>
<td>Bone, skull, Rt.acetabulum, Rt. SI joint, sternum, BM</td>
<td>IV</td>
<td>4x5 cm</td>
</tr>
</tbody>
</table>

Abbreviations: INSS, international NBL staging system; M, male; F, female; BM, bone marrow.
Table 2. Imaging findings at the site of primary tumor and metastatic bone/bone marrow 45 paired $^{123}$I-MIBG scintigraphy and $^{18}$F-FDG PET in 8 patients

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Findings</th>
<th>$^{123}$I-MIBG No (%)</th>
<th>$^{18}$F-FDG PET No (%)</th>
<th>Concordance* No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary mass</td>
<td>True positive</td>
<td>30/31 (96.7)</td>
<td>22/31 (70.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>True negative</td>
<td>12/14 (85.7)</td>
<td>13/14 (92.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>False positive</td>
<td>2/14 (14.3)</td>
<td>1/14 (7.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>False negative</td>
<td>1/31 (3.2)</td>
<td>9/31 (29)</td>
<td></td>
</tr>
<tr>
<td>Bone/Bone marrow</td>
<td>True positive</td>
<td>16/22 (72.7)</td>
<td>18/22 (81.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>True negative</td>
<td>19/24 (79.1)</td>
<td>24/24 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>False positive</td>
<td>5/24 (20.8)</td>
<td>0/24 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>False negative</td>
<td>6/22 (27.2)</td>
<td>4/22 (18.1)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Percentage in $^{123}$I-MIBG and $^{18}$F-FDG PET denotes sensitivity, specificity, and false rate.

* Rate of concordance reflects accuracy between $^{123}$I-MIBG and $^{18}$F-FDG PET in each primary mass or bone/bone marrow metastasis.
Table 3. Summarized results of both $^{123}$I-MIBG and $^{18}$F-FDG PET findings in 8 patients

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Patient No.</th>
<th>Residual tumor by CT after operation</th>
<th>$^{123}$I-MIBG</th>
<th>$^{18}$F-FDG PET</th>
<th>B. scan</th>
<th>Interpretation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary mass</td>
<td>1</td>
<td>&lt;1 cm</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>M=P; (+)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3-4 cm</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>M&lt;P; (-)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4.5-5.5 cm</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>M&gt;P; (+)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2-3 cm</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>M=P; (-)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>&lt;1 cm</td>
<td>+++</td>
<td>-/+</td>
<td>+</td>
<td>M=P; (+)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>3-4 cm</td>
<td>-</td>
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<td>-</td>
<td>M&gt;P; (-)</td>
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<tr>
<td></td>
<td>7</td>
<td>&lt;1 cm</td>
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<td>++</td>
<td>++</td>
<td>M&lt;P; (+)</td>
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<tr>
<td></td>
<td>8</td>
<td>4-5 cm</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>M=P; (+)</td>
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<tr>
<td>Bone/BM</td>
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<td>-</td>
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<td>++</td>
<td>-</td>
<td>M=P&lt; B scan</td>
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<td>M&lt;P</td>
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<td>3</td>
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<td>+</td>
<td>M&gt;P</td>
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<td>4</td>
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<td>M=P</td>
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<td>8</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>M=P</td>
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Abbreviations: M, $^{123}$I-MIBG; P, $^{18}$F-FDG PET

*Interpretation: Write as M>P if $^{123}$I-MIBG is better than $^{18}$F-FDG PET in detecting regions of the primary or metastatic tumor (M<P if $^{18}$F-FDG PET is better than $^{123}$I-MIBG, M=P if both scans are similar). Avidity to both $^{123}$I-MIBG and $^{18}$F-FDG expressed by -, -/+ , +, +++ according to intensity.
Fig. 1. A 6-year-old female patient with neuroblastoma in the adrenal gland and the false-negative finding on $^{18}$F-FDG PET scan. (A) She had a large residual abdominal mass (lesion diameter about 4.5-5.5 cm) on CT after autologous stem cell transplantation. After 7 months, $^{123}$I-MIBG scintigraphy images show a lesion in the right adrenal region (B). $^{18}$F-FDG PET images do not show any positive uptake (C, D).

Fig. 2. A 3-year-old female patient with stage IV neuroblastoma in the posterior mediastinum and the false-positive finding on $^{18}$F-FDG PET scan. She had a residual primary mass in the posterior mediastinum of about 3-4 cm in size after operation (A). During follow-up, we found suspicious metastatic nodules in both the upper and right middle lung on CT (B). These nodules showed positive result in $^{18}$F-FDG PET (C) but were negative in $^{123}$I-MIBG scans (D). Finally, nodules nearly disappeared without any recurrence during the follow-up.

Fig. 3. A 5-year-old male patient with stage 4 neuroblastoma in the adrenal gland and the false-negative finding on $^{123}$I-MIBG scans. He had a residual mass in the adrenal gland, with diameter less than 1 cm. The residual mass showed negative finding on $^{123}$I-MIBG scintigraphy, but positive on $^{18}$F-FDG PET scan.

Fig. 4. A 5-year-old female patient with stage IV neuroblastoma in the right posterior mediastinum. (A) $^{18}$F-FDG PET and $^{123}$I-MIBG scans showed similar results, in which the neck and posterior mediastinal primary mass are well-delineated with $^{18}$F-FDG PET and $^{123}$I-MIBG scans at diagnosis. They are falsely negative of bone involvement. (B) At 10 months after high-dose chemotherapy and autologous stem cell transplantation, $^{18}$F-FDG PET and $^{123}$I-MIBG scans showed similar negative results in the previous neck and posterior mediastinal primary mass.