Biodistribution and dosimetry of $^{18}$F-Meta Fluorobenzyl Guanidine (MFBG): A first-in-human PET-CT imaging study of patients with neuroendocrine malignancies

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ABSTRACT

Introduction: Iodine-123-meta-iodobenzylguanidine (123I-MIBG) imaging is currently a mainstay in the evaluation of many neuroendocrine tumors, especially neuroblastoma. 123I-MIBG imaging has several limitations that can be overcome by the use of a PET agent. 18F-MFBG is a positron emission tomography (PET) analog of MIBG that may allow for single-day, high-resolution quantitative imaging. We conducted a first-in-human study of 18F-MFBG PET imaging to evaluate the safety, feasibility, pharmacokinetics, and dosimetry of 18F-MFBG in neuroendocrine tumors (NETs).

Methods: Ten patients (five with neuroblastoma and five with paraganglioma/pheochromocytoma) received 148-444 MBq (4-12 mCi) of 18F-MFBG IV followed by serial whole-body imaging at 0.5-1 h, 1-2 h, and 3-4 h post-injection (p.i.). Serial blood samples (a total of 6) were also obtained starting at 5 min p.i. to as late as 4 h p.i. whole-body distribution and blood clearance data, lesion uptake, and normal tissue uptakes were determined; radiation-absorbed doses to normal organs were calculated using Organ Level INternal Dose Assessment (OLINDA).

Results: No side effects were seen in any patient after 18F-MFBG injection. Tracer distribution showed prominent activity in bloodpool, liver, and salivary glands that decreased with time. Mild uptake was seen in kidneys and spleen,
which also decreased with time. Urinary excretion was prominent, with an average of 45% of the administered activity in bladder by 1 h p.i. whole-body clearance was monoexponential with mean biologic half-life ($T_{1/2b}$) of 1.95 h, while blood clearance was bi-exponential with mean $T_{1/2b}$ of 0.3 h (58%) for the rapid $\alpha$ phase and 6.1 h (42%) for the slower $\beta$ phase. Urinary bladder received the highest radiation dose with a mean absorbed dose of 0.186 $\pm$ 0.195 mGy/MBq. Mean total body dose was 0.011 $\pm$ 0.011 mGy/MBq and the effective dose was 0.023 $\pm$ 0.012 mSv/Mbq. Both skeletal and soft tissue lesions were visualized with high contrast. The maximum standard uptake value ($SUV_{MAX}$) [mean $\pm$ standard deviation (SD)] of lesions at 1-2 h p.i. was 8.6 $\pm$ 9.6.

**Conclusion:** Preliminary data show that $^{18}$F-MFBG imaging is safe and has favorable biodistribution and kinetics with good targeting of lesions. PET imaging with $^{18}$F-MFBG allows for same-day imaging of NETs. $^{18}$F-MFBG appears highly promising for imaging of patients with NETs, especially children with neuroblastoma.
INTRODUCTION

Imaging plays a critical role in the diagnosis, staging, and follow-up of neuroendocrine tumors (NETs). Currently, $^{131}$I-MIBG and $^{123}$I-MIBG are widely used in NETs overexpressing the norepinephrine transporter and $^{123}$I-MIBG is routinely used for staging and follow-up of patients with neuroblastoma (1-8). $^{123}$I-MIBG imaging is also used for the evaluation of disease extent and suitability for $^{131}$I-MIBG therapy.

However, $^{123}$I-MIBG imaging has significant limitations, including: a) a two-day imaging schedule, with injection on the first day and imaging 24 hours later (3), and b) a need for thyroid protection with supersaturated potassium iodide prior to $^{123}$I-MIBG injection. Further, compared to PET, the images have poorer resolution and limited quantitative accuracy, which is typically associated with gamma camera imaging. These differences compromise sensitivity and the ability to evaluate tumor burden and tumor accumulation. Therefore, there is a clinical need for a PET imaging agent that would allow for same-day imaging with superior resolution and quantitation of the tracer uptake in lesions associated with PET imaging.

The PET imaging tracer $^{124}$I-MIBG has been studied previously (9), but the complex decay scheme, including the emission of high-energy cascade gamma
rays, leads to poorer image quality, less reliable quantification, and unfavorable dosimetry (10). Furthermore, $^{124}$I is not widely available for clinical use. $^{18}$F-fluorodopamine, a dopamine analogue, and $^{18}$F-fluorodopa PET have also been used to image noradrenaline and amino acid transporter expression, respectively, in neuroendocrine malignancies; however, the experience is limited, particularly in patients with neuroblastoma (11,12). $^{11}$C-hydroxyephedrine (HED), a catecholamine analogue (13), has also been shown to target tumors of the sympathetic nervous system. Current clinical data is again limited and use of short-lived isotope limits its use. These tracers are also currently limited in availability. There is a need for a NET imaging agent that allows for single-day imaging, and will enable faster evaluation of disease sites with high sensitivity within a more convenient imaging schedule. Given our extensive clinical experience with $^{123}$I-MIBG, a PET tracer such as an $^{18}$F-labeled analog of MIBG is appealing.

$^{18}$F-labeled meta-fluoro-benzylguanidine ($^{18}$F-MFBG) was synthesized to overcome these limitations and preclinical studies have shown a similarity to MIBG (14). In xenografts, $^{18}$F-MFBG showed similar lesion uptake, with significantly faster blood clearance as compared to $^{123}$I-MIBG, enabling high-contrast visualization of lesions as early as 1 h p.i. (15).
Based on these preclinical data, we initiated a first-in-human study (NCT 02348749) to evaluate the safety, pharmacokinetics, and radiation dosimetry of 18F-MFBG in patients with neuroblastoma and pheochromocytoma/paragangliomas. We report the results of the safety, biodistribution, pharmacokinetics, and organ dosimetry of 18F-MFBG in these patients.

**MATERIALS AND METHODS**

A prospective study of PET imaging with 18F-MFBG was performed. 18F-MFBG was administered under an Investigational New Drug application (IND# 125108) approved by the Food and Drug Administration. The protocol was approved by the Institutional Review Board and all patients or their legal guardians provided written informed consent.

**Patients**

Patients with confirmed neuroblastoma or paraganglioma/pheochromocytoma with evidence of evaluable disease/lesions on 123I-MIBG imaging were eligible. Additional eligibility criteria included a performance status of 60 or higher on the
Karnofsky or Lansky scale and adequate hepatic and renal function defined as no toxicity greater than grade 2 (CTC 4.0).

\textbf{\textsuperscript{18}}\textsuperscript{F}-MFBG \textbf{Preparation}

\textsuperscript{18}F-MFBG was manufactured at the MSK Radiochemistry and Molecular Imaging Probes Core Facility in compliance with the requirements specified in the Chemistry, Manufacturing, and Controls section of a Food and Drug Administration-approved IND. Clinical \textsuperscript{18}F-MFBG batches for the first four patients were prepared using the original manual method described previously (16). Subsequently, the method was changed to a less complex synthesis, utilizing the diaryliodonium salt (ALP)-MFBG precursor, supplied by Ground Fluor Pharmaceuticals, Inc. (Cambridge, MA). The revised synthesis, derived from the methods published in (17), involved nucleophilic incorporation of \textsuperscript{18}F-fluoride into the \textsuperscript{18}F-MFBG precursor, ALP-MFBG (7.5 mg dissolved in 1 mL of acetonitrile), at 120 °C for 20 min, followed by removal of protective groups by acid hydrolysis, reverse phase preparatory high-performance liquid chromatography (HPLC) purification, and terminal sterilization using a 0.22 μm sterilizing filter. The final \textsuperscript{18}F-MFBG drug product was formulated in 15 mL of ammonium acetate buffer and sterile water for injection, USP.
The final $^{18}$F-MFBG drug product batches underwent quality control (QC) testing, prior to batch release for patient administration. Radiochemical purity was more than 90%, as determined by reverse-phase HPLC; radiochemical identity was confirmed by comparison to a reference standard response on the HPLC; endotoxin content was less than 5 EU/mL, as measured by the portable test system supplied by Charles River Laboratories (Wilmington, Massachusetts, USA); sterilizing filter integrity pressure was more than 50 psi, as measured by the bubble point method; pH was 3.5-8.0, as measured by pH strips; residual acetonitrile concentration was less than 270 µg/mL, as measured by gas chromatography; appearance was a clear and particle-free solution, as determined by a visual inspection check; and radionuclide identity was verified, as measured by radioactive half-life determination. Sterility testing, using the direct media inoculation method, was performed post-release. Specific activity (MBq/µg) determinations were performed on the initial $^{18}$F-MFBG validation batches and calibrated to the end of synthesis time, and was calculated by dividing the total measured radioactivity at the end of synthesis time by the total mass of $^{18}$F-MFBG present in the final product, as measured by HPLC.

$^{18}$F-MFBG Administration
A dose of 148-444 MBq (4-12 mCi) of $^{18}$F-MFBG was administered as a slow IV bolus over one minute, followed by a saline flush. Patients were not required to fast. No premedications were administered, and no patients were taking any medications known to interfere with MIBG uptake (3). Patients were monitored for at least three hours p.i. with vitals and for any reactions or adverse events and later at 24 hours follow-up. Side effects and reactions were graded according to Common Terminology Criteria for Adverse Events, version 4.0.

$^{18}$F-MFBG Scans

Scanning included dynamic imaging for the first 30 min with images acquired in list mode, 128x128 matrix (6 frames for 5 sec each, followed by 3 frames for 10 sec each, 4 frames for 1 min each, 2 frames for 2.5 min each, 2 frames for 5 min each, and 1 frame for 10 min) over the chest (including cardiac bloodpool, lung, and liver) followed by whole-body (vertex to feet) imaging within the first hour p.i., a second whole-body scan at 1-2 h, and a third whole-body scan at 3-4 h p.i. A single low-dose CT scan, at 80 mA for adults and a weight-based scaled mA for children, was performed. The two remaining PET/CT scans were performed with an ultra-low-dose CT at 10 mA for attenuation. All scans were performed on the same scanner (GE Discovery 710) in 3D mode with a three-minute acquisition time per field of view for the torso (vertex to pelvis) and one to two-minute field
of view for the lower limb. Images were reconstructed using a manufacturer-
provided iterative reconstruction algorithm and attenuation and scatter corrections
similar to FDG imaging.

**Blood Clearance Measurements**

Multiple venous blood samples were obtained, including a baseline sample prior
to injection of $^{18}$F- MFBG, at 5 ± 2 min, 15 ± 5 min, 30 ± 5 min, 60 ± 5 min, 90 ±
10 min, 120 ± 10 min, and 180 ± 10 min p.i. Activity in blood (aliquots of about
500 µl) was measured in duplicate using a NaI (Tl) gamma counter (Wallac
Wizard 1480 automatic gamma counter, Perkin Elmer) together with appropriate
standards. The measured activity concentrations were converted to percent
injected activity/liter (% IA/L). Metabolite analysis of activity in plasma was
performed by reverse-phase HPLC with in-line radiation detection on samples
obtained up to at least 120 min p.i. in all patients.

**Whole-Body and Blood Parameters**

Activity in the whole body was determined based on whole-body scans; the first
scan was obtained prior to voiding. A mono-exponential function was fitted to the
whole-body activity data and a bi-exponential function to the blood activity
concentration data ($I_8$). Values of cumulated activity per unit administered
activity (residence time) for whole body (in h) and blood (in h/L), \( \tau \), were calculated according to the formula \( \tau = \frac{\bar{A}}{A_0} \) where \( \bar{A} \), the cumulated activity, was estimated by integration of the activity-time curve and \( A_0 \) was the administered activity. Effective and biological clearance rates and corresponding half-times were derived from the fitted curves.

**Normal-organ Uptake and Dosimetry**

Regions of interest were drawn on the PET images over normal organs, including lacrimal gland, salivary gland, thyroid gland, lung, right atrium, ventricular myocardium, liver, renal parenchyma, pancreas, spleen, adrenal gland, and bladder. Multiple regions of interest were used to generate volumes of interest (VOIs) of a representative site in organs that were copied to all scans (Hermes Medical Solutions, Chicago, IL). Activity concentration per unit mass (kBq/g) was generated for organs and area under the activity concentration-time curves were integrated. Whole organ areas under the curve were estimated by multiplying the activity concentration area under the curve by the respective organ masses, as given in the OLINDA/EXM dosimetry program, which was then used to derive the organ residence times (19).

Absorbed radiation doses to the whole body and various organs and the effective dose were calculated using the image-derived cumulated activities/residence time
and the OLINDA/EXM program (19). The anatomic model in OLINDA whose whole-body mass most closely matched that of the patient was used, with the organ masses in OLINDA then scaled in proportion to the patient-to-anatomic model whole-body mass ratio.

RESULTS

Patients and \(^{18}\text{F}\)-MFBG Administration

Ten patients including five with neuroblastoma (age 5-23; 3 males and 2 females) and five with paraganglioma/pheochromocytoma (age 16-68; 2 males and 3 females) were imaged. All patients with neuroblastoma had recurrent disease. The patients with paraganglioma/pheochromocytoma had measurable and progressive disease as noted on standard imaging (CT/MRI/MIBG scan), performed as standard of care. All patients had prior \(^{123}\text{I}\)-MIBG scans performed within four weeks before the \(^{18}\text{F}\)-MFBG PET scan that included whole-body planar imaging and single-photon emission computed tomography/computed tomography (SPECT/CT) of chest, abdomen, and pelvis. The injections were tolerated well with no reactions or adverse events seen in any patients. The injected activity ranged from 162-436 MBq (4.37-11.8 mCi). The mean specific activity was 610.5 MBq/\(\mu\)g (16.5 mCi/\(\mu\)g) [range: 573.5 - >1061.9 MBq/\(\mu\)g or 15.5 - >28.7 mCi/\(\mu\)g]
for $^{18}$F-MFBG produced via the initial radiosynthesis method, and 138.1 MBq/µg (3.73 mCi/µg) [range: 16.7-442.2 MBq/µg or 0.45-11.95 mCi/µg] for the ALP-MFBG-based radiosynthesis method. Radiochemical purity was greater than 95% in all batches.

Metabolite analysis showed that MFBG (mean ± SD), eluted with a retention time of 12.5 min, accounted for 90.0 ± 6.7% and 92.4 ± 4.6 of the plasma-borne activity in the blood samples obtained at 60 and 120 min p.i., respectively. The $^{18}$F-MFBG thus indicated excellent stability in vivo.

**Whole-Body and Blood Kinetics**

Blood clearance was bi-exponential, characterized by an initial rapid phase followed by a mean (± SD) half-time of biological clearance of 0.31 ± 0.20 h (range 0.12-0.35 h) for the fast component, α phase (57.6 %), and 6.09 ± 3.8 h (range 2.2-15.0 h) for the slow component, β phase (42.4 %) (Fig. 1A). For patients with paraganglioma/pheochromocytoma, the mean (± SD) half-time of clearance was 0.26 ± 0.12 h for the α phase (57.3 %) and 4.8 h ± 2.7 h (42.7%) for the β phase, while corresponding values for patients with neuroblastoma were 0.36 ± 0.26 h for the α phase (57.6 %) and 7.3 ± 4.6 h for the β phase (42.4%).
Whole-body biological clearance was mono-exponential with a mean half-life (± SD) of 1.95 ± 1.22 h (range 1.2-5.2 h) (Fig. 1B).

**Biodistribution and Normal-Organ Uptake**

$^{18}$F-MFBG biodistribution (Fig. 2A) was characterized by a rapid drop in the cardiac bloodpool activity (Fig. 2, A and C). Activity in the urinary bladder was seen early with significant excretion—an average of 45% within the first hour and 61-95% excretion noted by 3-4 h p.i. Liver showed prominent activity that decreased with time; diffuse uptake in the left lobe of the liver (mean SUVmax 6.0, range 2.3-11.8) was greater than that in the right lobe (3.9, range 1.1-7.1) (Fig. 2F). The mean biologic liver clearance $T_{1/2}$ was 80 min. Uptake in the ventricular myocardium (mean SUVmax 3.9, range 0.63-7.8 at 1 h p.i.) showed an initial prominent decrease followed by minimal decrease at later times (Fig. 2G). Renal activity was mainly in the pelvicalyceal system with minimal activity seen in the cortex. Diffuse mild splenic activity was seen (mean SUVmax 1.5, range 0.72-2.7 at 1 h p.i.). Salivary gland uptake was prominently seen at all scanning time points with a decrease in later scans (mean SUVmax 8.6, range 3.8-12.4 at 1 h p.i.). Lacrimal gland activity was seen, also decreasing in later images (mean SUVmax 3.1, range 0.68-3.8 at 1 h p.i.). Prostate gland uptake was seen in males (mean SUVmax 8.6, range 4.6-10.8 at 1 h p.i.). Physiologic uptake was seen in
adrenal glands and pancreas with an average SUVmax of 6.3 (range 3.9-9.2) and 3.6 (range 1.23-5.8), respectively. Diffuse physiologic thyroid uptake was also seen (mean SUVmax 3.5, range 0.7-6.8 at 1 h p.i.). Organ uptake curves are shown in Figure 3.

**Radiation Doses to Normal Organs**

The average absorbed dose estimates are summarized in Table 1. The urinary bladder wall received the highest radiation dose with a mean absorbed dose (± SD) of 0.186 ± 0.195 mGy/MBq (0.689 ± 0.720 cGy/mCi). Mean absorbed dose to salivary glands was 0.058 ± 0.069 mGy/MBq (0.213 ± 0.253 cGy/mCi), liver was 0.046 ± 0.026 mGy/MBq (0.171 ± 0.097 cGy/mCi), and 0.028 ± 0.025 mGy/MBq (0.105 ± 0.092 cGy/mCi) to kidney. Myocardial/heart wall absorbed dose was 0.031 ± 0.016 mGy/MBq (0.115 ± 0.057 cGy/mCi). Mean total body dose was 0.011 ± 0.011 mGy/MBq (0.042 ± 0.041 cGy/mCi) and the mean effective dose was 0.023 ± 0.012 mSv/MBq (0.085 ± 0.043 cSv (rem)/mCi).

**Preliminary Assessment of Lesion Targeting and Uptake**

Targeting of lesions was seen in all patients. Both skeletal and soft tissue lesions were visualized with high contrast, even in the initial scans acquired 30-60 min p.i., with most lesions seen at 3-4 h p.i. The mean ± SD lesion SUVmax - body
weight \((SUV_{bw_{MAX}})\) was 8.6 ± 9.6 (range 1.3-67.6) at 1-2 h p.i. and 9.2 ± 11.4 (1.1-80.7) at 3-4 h p.i. The tumor-to-background \((T/BG)\) ratios obtained by comparison of bone with adjacent normal bone and muscle for soft tissue ranged from 1.35-36.2 at 1-2 h p.i. and 1.22-28.5 at 3-4 h p.i. for bone lesions and 1.2-35.2 at 1-2 h p.i. and 1.4-31.4 at 3-4 h p.i. for soft tissue lesions. The lung lesions were visualized at lower uptakes due to no uptake in lungs with SUV range 1.3-4.7 at 1-2 h p.i and 0.8-5.0 at 3-4 h p.i.

Assessment of lesions detected at various imaging times indicated that 103 lesions were seen at 30-60 min imaging, and 117 lesions were detected at 1-2 h imaging as compared to 122 lesions at 3-4 h imaging. The five additional lesions seen at the last time-point of imaging were seen in the liver of two patients (Fig. 4). All lesions seen on \(^{123}\text{I}\)-MIBG imaging were seen on \(^{18}\text{F}\)-MFBG scans. There were no lesions seen on MIBG that were not targeted by MFBG. However, MFBG showed additional lesions in all patients, with an overall 122 lesions seen vs. 63 by MIBG (Table 2). An additional 59 sites seen on MFBG included bones \((n = 29)\) and 30 soft tissue lesions, including lung \((n = 6)\), liver \((n = 8)\), nodes \((n = 10)\), and other soft tissue lesions \((n = 6)\).

**DISCUSSION**
Given the current limitations of imaging with $^{123}$I-MIBG, and in an effort to develop a better imaging biomarker for NETs, we performed first-in-human imaging with $^{18}$F-MFBG in 10 patients with metastatic neuroblastoma and paraganglioma/pheochromocytoma. The purpose of this study was to determine the safety, pharmacokinetics, normal tissue distribution, and organ dosimetry of $^{18}$F-MFBG. In addition, an initial evaluation of tumor-targeting properties and detection of lesions at various time-points of imaging p.i. was performed.

$^{18}$F-MFBG injections were well tolerated with no toxicity or reactions seen in any patients. The overall distribution of $^{18}$F-MFBG appeared similar to that of $^{123}$I-MIBG. The $^{18}$F-MFBG distribution showed rapid clearance from the bloodpool with a mean biological T1/2 of 18 min for early phase and 6 h for slower phase. While prominent uptake was seen in normal liver, the activity decreased with time and lesions were detectable at 1 h p.i. with high contrast, though later images showed more contrast and a higher number of lesions in some patients. The differential uptake in the right vs. left lobe was noted, as with $^{123}$I-MIBG scans. While the exact mechanism is for this difference is unknown, it is postulated to be secondary to differential blood supply and not due to direct uptake mechanism (20). The kidneys were the primary route of excretion and the bladder was the critical organ, similar to $^{123}$I-MIBG. Since excreted activity accumulates in the
bladder by one hour; voiding prior to imaging will reduce bladder exposure. With respect to $^{123}$I-MIBG biodistribution, similar $^{18}$F-MFBG myocardial uptake was seen, and while prominent in the initial scans, the activity decreased with time. Gastrointestinal uptake was seen, but was not very prominent and did not affect the detection of small lesions in the abdomen and pelvis. Additionally, because of the superior resolution of PET compared to SPECT, it is possible to visualize uptake in lesions in the abdomen and pelvis that would otherwise be obscured by excreted activity in the bowel, ureters, and bladder.

The clearance of $^{18}$F-MFBG from the bloodpool and organs is more rapid than $^{123}$I-MIBG when compared to published data (21, 22). As with $^{123}$I-MIBG, the blood clearance of $^{18}$F-MFBG was biexponential with a shorter biological T1/2 (second component) for $^{18}$F-MFBG (ranging between 2-15 h) compared to $^{123}$I-MIBG (ranging between 9-130 h) (22). In addition, there is faster and increased excretion into the urine of $^{18}$F-MFBG (61-95%) compared to $^{123}$I-MIBG (11-26%) (22) by 3 h p.i. The whole-body biological half-life was monoexponential for $^{18}$F-MFBG up to 3-4 h imaging and is much shorter (1.2-5.2 h) in comparison to the biexponential $^{123}$I/$^{131}$I-MIBG clearance with second-phase T1/2 of 19-45 h (27). This allows for earlier imaging and detection of lesions as a result of high contrast and T/BG ratios noted as early as 1 h p.i., compared to the recommended 24 h p.i.
imaging for $^{123}$I-MIBG. The radiation exposure (overall effective dose) for $^{18}$F-MFBG (0.023 mSv/MBq) is comparable to that of $^{123}$I-MIBG (0.014 mSv/MBq for adults and 0.026 mSv/MBq for 10 years old (3,21-23). The relative organ doses from $^{18}$F-MFBG are also comparable to $^{123}$I-MIBG—lower for liver and spleen and slightly higher for heart with $^{18}$F-MFBG. The fact that the effective doses are similar despite faster blood and whole-body clearance is likely secondary to the higher energy associated with the $^{18}$F emissions.

The PET images provided high-contrast visualization of lesions due to rapid blood and whole-body background clearance of $^{18}$F-MFBG, resulting in high T/BG ratios. $^{18}$F-MFBG showed good targeting of both bone and soft tissue lesions and high T/BG ratios were noted for both (Fig. 5). Despite modest uptake in liver, lesions were detectable with relatively high contrast at the 3-4 h p.i. imaging times (Figs. 2 and 4). We found that both bone and soft tissue lesions showed high uptake and were prominently visualized at both 1-2 h and 3-4 h p.i. imaging times, with no statistically significant difference between uptake in lesions at 1-2 h p.i. vs. 3-4 h p.i. ($P = 0.31$ for bone and $p = 0.23$ for soft tissue). Given the high contrast of $^{18}$F-MFBG images, it is possible to image patients with lower activities, which can further reduce radiation exposure (e.g., Figs. 4C and 4D were obtained with a 162 MBq dose of $^{18}$F-MFBG).
While tracer uptake in lesions continued to increase up to the last imaging time-point (3-4 h p.i.), a decrease in the T/BG ratios was noted at 3-4 h p.i. Although the overall number of lesions detected was highest for the last time-point of imaging, no statistical significant difference was evident in the number of lesions detected between 1-2 h p.i. vs. 3-4 h p.i. (P = 0.24). A total of 5 additional lesions were detected at 3-4 h p.i. imaging vs. 1-2 h imaging and were liver lesions seen in 2 patients. However, other liver lesions present in these 2 patients were detected at both 1-2 h and 3-4 h imaging. Given that imaging at 1-2 h p.i. showed the highest T/BG ratios for both soft tissue and bone lesions, this would be the optimal time-point for imaging to provide adequate high-contrast images and good lesion detection (Fig. 3).

\(^{123}\)I-MIBG is Food and Drug Administration-approved for imaging neuroendocrine malignancies and is extensively used in the clinical assessment of neuroblastoma (24). The biodistribution of \(^{18}\)F-MFBG is very similar to that of \(^{123}\)I-MIBG, with the added advantage of clearing more rapidly from the body, and higher resolution and improved assessment of lesion uptake (SUV) by PET imaging. Another advantage of \(^{18}\)F-MFBG, particularly in pediatric patients, is the ability to image with PET-MR, which would reduce radiation exposure by
eliminating the CT component of imaging. $^{18}$F-MFBG PET/CT imaging also overcomes several limitations of $^{123}$I-MIBG SPECT/CT imaging, such as offering single-day imaging at 1-2 h p.i. vs. a two-day imaging procedure, and reducing the lag time for scanning p.i., thereby providing a more convenient option for patients.

**CONCLUSION**

Imaging with $^{18}$F-MFBG is feasible and safe. It is well tolerated by adults and pediatric patients. $^{18}$F-MFBG has favorable biodistribution and acceptable organ dosimetry and targets both bone and soft tissue lesions with high contrast, enabling early imaging at 1-2 h p.i. $^{18}$F-MFBG is highly promising for imaging patients with NETs, especially children with neuroblastoma.
DISCLOSURE

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23. Adreview.
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FIGURE LEGENDS

A

FIGURE 1. Whole-body (A) and blood (B) clearance time-activity curves. Whole-body activity showed monoexponential clearance and blood activity showed biexponential clearance.
FIGURE 2. Patient with metastatic pheochromocytoma. Whole-body MIP scans of $^{18}$F-MFBG performed 30-60 min p.i. (A), 1-2 h p.i. (B), and 3-4 h p.i. (C) as against a uniform SUV scale (right bar). Lesions are distinctly seen in the liver at 1-2 h and 3-4 h p.i. (B, C; arrows). Fused images show lesions more distinctly in liver (D, E; arrows). Lesion in MIP image is localized to left iliac bone (F; short arrow).
FIGURE 3. Uptake in normal organs at various scan times post-injection. Uptake decreases from scan 1 (0.5-1 h p.i.) to scan 2 (1-2 h p.i.) and scan 3 (3-4 h p.i.) (A). Prominent activity is seen in liver, which decreases over time (B). Focal uptake posteromedially is uptake along the adrenal (SUV 5.6). Cardiac activity is most prominent in early images, decreasing with time; distribution is seen along the ventricular myocardium (C). Diffuse uptake is seen along pancreas (SUV 3.5) (D; arrow). Posteromedial uptake is along adrenal gland; uptake is seen in prostate (SUV 5.6) (E).
FIGURE 4. Patient with NB for follow-up evaluation and possible therapy with $^{131}$I-MIBG. $^{123}$I-MIBG images (A-anterior, B-posterior) show foci of suspicious activity in skull, lumbar vertebra, right and left acetabula, and right femur (black arrows). Patient underwent imaging with 162 MBq $^{18}$F-MFBG a week later. Whole-body maximum-intensity projection (MIP) scans with $^{18}$F-MFBG (C, D) show all lesions seen on $^{123}$I-MIBG scan but with greater contrast and clarity (black arrows). In addition, several lesions are seen on MFBG scan only (red arrows) that are not visible on $^{123}$I-MIBG images. For example, fused PET/CT transaxial $^{18}$F-MFBG image (F) shows intense uptake in left acetabulum (red arrow), suspicious for disease, that is not seen on the $^{123}$I-MIBG SPECT/CT fused transaxial image (E). Also, left iliac bone lesions are clearly avid on $^{18}$F-MFBG (H) vs. $^{123}$I-MIBG imaging (G).
FIGURE 5. Tumor-to-normal bone and soft tissue uptake ratios at different scan times post-injection of \(^{18}\text{F}-\text{MFBG}\) (scan 1 at 30-60 min, scan 2 at 60-120 min, and scan 3 at 180-240 min). Uptake ratios were based on mean SUVs in the respective tissues of 10 patients. Numbers = number of observations (i.e., lesions); error bars = standard error of mean.
**TABLE 1.** Average absorbed dose estimates.

Table 1. $^{18}$F-MFBG: Normal-Organ Absorbed Doses and Effective Doses in Patients

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mGy/MBq</td>
<td>mGy/MBq</td>
<td>cGy/mCi</td>
<td>cGy/mCi</td>
</tr>
<tr>
<td>Salivary Gland</td>
<td>0.058</td>
<td>0.069</td>
<td>0.213</td>
<td>0.253</td>
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<tr>
<td>Adrenals</td>
<td>0.023</td>
<td>0.024</td>
<td>0.085</td>
<td>0.089</td>
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<tr>
<td>Brain</td>
<td>0.004</td>
<td>0.002</td>
<td>0.014</td>
<td>0.008</td>
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<tr>
<td>Breasts</td>
<td>0.005</td>
<td>0.002</td>
<td>0.017</td>
<td>0.008</td>
</tr>
<tr>
<td>Gall Bladder Wall</td>
<td>0.012</td>
<td>0.005</td>
<td>0.046</td>
<td>0.020</td>
</tr>
<tr>
<td>Lower Large Intestine Wall</td>
<td>0.011</td>
<td>0.005</td>
<td>0.041</td>
<td>0.020</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>0.009</td>
<td>0.004</td>
<td>0.033</td>
<td>0.015</td>
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<tr>
<td>Stomach Wall</td>
<td>0.007</td>
<td>0.003</td>
<td>0.027</td>
<td>0.012</td>
</tr>
<tr>
<td>Upper Large Intestine Wall</td>
<td>0.009</td>
<td>0.004</td>
<td>0.032</td>
<td>0.014</td>
</tr>
<tr>
<td>Heart Wall</td>
<td>0.031</td>
<td>0.016</td>
<td>0.115</td>
<td>0.057</td>
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<tr>
<td>Kidneys</td>
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<td>0.025</td>
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<td>0.092</td>
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<tr>
<td>Liver</td>
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<td>0.026</td>
<td>0.171</td>
<td>0.097</td>
</tr>
<tr>
<td>Lungs</td>
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<td>0.035</td>
<td>0.017</td>
</tr>
<tr>
<td>Muscle</td>
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<td>0.003</td>
<td>0.024</td>
<td>0.010</td>
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<tr>
<td>Ovaries</td>
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<td>0.005</td>
<td>0.041</td>
<td>0.019</td>
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<tr>
<td>Pancreas</td>
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<td>0.021</td>
<td>0.119</td>
<td>0.078</td>
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<tr>
<td>Red Marrow</td>
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<tr>
<td>Osteogenic Cells</td>
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<tr>
<td>Spleen</td>
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<tr>
<td>Thymus</td>
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<td>0.010</td>
</tr>
<tr>
<td>Thyroid</td>
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<td>0.028</td>
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<td>0.103</td>
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<tr>
<td>Urinary Bladder Wall</td>
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<td>0.195</td>
<td>0.689</td>
<td>0.720</td>
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<tr>
<td>Total Body</td>
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<td>0.011</td>
<td>0.042</td>
<td>0.041</td>
</tr>
<tr>
<td>Effective dose (mSv/MBq)/*(cSv or rem/mCi)</td>
<td>0.023</td>
<td>0.012</td>
<td>0.085*</td>
<td>0.043*</td>
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**TABLE 2.** Lesion detection per patient with $^{18}$F-MFBG and $^{123}$I-MIBG.

<table>
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<tr>
<th>Neuroblastoma Pt #</th>
<th>$^{123}$I-MIBG + Lesion #</th>
<th>$^{18}$F-MFBG + Lesion #</th>
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<tr>
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<td>5</td>
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</table>

<table>
<thead>
<tr>
<th>Pheo/PGL Pt #</th>
<th>$^{123}$I-MIBG + Lesion #</th>
<th>$^{18}$F-MFBG + Lesion #</th>
</tr>
</thead>
<tbody>
<tr>
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