Effects of Repeated ^{131}I-*Meta*-Iodobenzylguanidine Radiotherapy on Tumor Size and Tumor Metabolic Activity in Patients with Metastatic Neuroendocrine Tumors

Keiichiro Yoshinaga[†1], Takashige Abe[2], Shozo Okamoto[3,4], Yuko Uchiyama[3], Osamu Manabe[3], Yoichi M. Ito[5], Naomi Tamura[5], Natsue Ito[1], Naho Yoshioka[1], Komei Washino[1], Nobuo Shinohara[2], Nagara Tamaki[6], and Tohru Shiga[3]

[1]*Diagnostic and Therapeutic Nuclear Medicine, Quantum and Radiological Science and Technology, National Institute of Radiological Sciences, Chiba, Japan;* [2]*Department of Urological Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan;* [3]*Department of Diagnostic Radiology, Hokkaido University Graduate School of Medicine, Sapporo, Japan;* [4]*Department of Radiology, Obihiro Kosei Hospital, Obihiro, Japan;* [5]*Research Center for Medical and Health Data Science, Institute of Statistical Mathematics, Tokyo, Japan; and* [6]*Department of Radiology, Kyoto Prefectural Medical University, Kyoto, Japan*

^{131}I-*meta*-iodobenzylguanidine (^{131}I-MIBG) radiotherapy has shown some survival benefits in metastatic neuroendocrine tumors (NETs). European Association of Nuclear Medicine clinical guidelines for ^{131}I-MIBG radiotherapy suggest a repeated treatment protocol, although none currently exists. The existing single-high-dose ^{131}I-MIBG radiotherapy (444 MBq/kg) has been shown to have some benefits for patients with metastatic NETs. However, this protocol increases adverse effects and requires alternative therapeutic approaches. Therefore, the aim of this study was to evaluate the effects of repeated ^{131}I-MIBG therapy on tumor size and tumor metabolic response in patients with metastatic NETs. **Methods:** Eleven patients with metastatic NETs (aged 49.2 ± 16.3 y) prospectively received repeated 5,550-MBq doses of ^{131}I-MIBG therapy at 6-mo intervals. In total, 31 treatments were performed. The mean number of treatments was 2.8 ± 0.4, and the cumulative ^{131}I-MIBG dose was 15,640.9 ± 2,245.1 MBq (286.01 MBq/kg). Tumor response was observed by CT and ^{18}F-FDG PET or by ^{18}F-FDG PET/CT before and 3–6 mo after the final ^{131}I-MIBG treatment. **Results:** On the basis of the CT findings with RECIST, 3 patients showed a partial response and 6 patients showed stable disease. The remaining 2 patients showed progressive disease. Although there were 2 progressive-disease patients, analysis of all patients showed no increase in summed length diameter (median, 228.7 mm [interquartile range (IQR), 37.0–336.0 mm] to 171.0 mm [IQR, 38.0–270.0 mm]; $P = 0.563$). In tumor region–based analysis with partial-response and stable-disease patients ($n = 9$), ^{131}I-MIBG therapy significantly reduced tumor diameter (79 lesions; median, 16 mm [IQR, 12–22 mm] to 11 mm [IQR, 6–16 mm]; $P < 0.001$). Among 5 patients with hypertension, there was a strong trend toward systolic blood pressure reduction ($P = 0.058$), and diastolic blood pressure was significantly reduced ($P = 0.006$). **Conclusion:** Eighty-two percent of metastatic NET patients effectively achieved inhibition of disease progression, with reduced tumor size and reduced metabolic activity, through repeated ^{131}I-MIBG therapy. Therefore, this relatively short-term repeated ^{131}I-MIBG treatment may have potential as one option in the therapeutic protocol for metastatic NETs. Larger prospective studies with control groups are warranted.

Key Words: ^{131}I-MIBG; ^{18}F-FDG PET; metastasis; neuroendocrine tumor; radiotherapy; RECIST

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Beginning in 2017, the World Health Organization started defining pheochromocytoma and paraganglioma (PPGL) as a malignant disease, given that all those affected may develop metastatic lesions during their lifetime (*1*). The mean expected survival is 20.7 y for pheochromocytoma patients and 9.8 y for paraganglioma patients. These survivals are longer than those commonly associated with cancers of the lung, pancreas, and other malignancies but shorter than the life expectancy of the healthy population (*2*). In addition, metastatic pheochromocytoma has a 5-y survival rate of 50%–60% after diagnosis (*3*,*4*).

After the initial surgery, therapeutic options for metastatic PPGL include chemotherapy (cyclophosphamide, vincristine, and dacarbazine therapy), external radiotherapy, and radiotherapy (*1*,*4*,*5*). Cyclophosphamide, vincristine, and dacarbazine have been most widely applied in clinical practice (*1*). Although retrospective, the largest study looking at the effects of chemotherapy showed decreased tumor size and facilitated blood pressure (BP) control in about a third of patients (*6*). However, the median effective survival is 40 mo, and the survival benefits are not clear because of a lack of prospective comparative studies. ^{131}I-*meta*-iodobenzylguanidine (^{131}I-MIBG) is a substrate of the norepinephrine transporter system and has a structure similar to that of norepinephrine (*7*). Norepinephrine works as a neurotransmitter in the central and autonomic nervous systems. The concentrations of norepinephrine in the nervous systems are regulated by the norepinephrine transporter. ^{131}I-MIBG also accumulates in the nervous systems; however, unlike norepinephrine, ^{131}I-MIBG has little or no affinity for adrenergic receptors (*8*). ^{131}I-MIBG radiotherapy has been used to treat neuroendocrine tumors (NETs), including metastatic

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For correspondence or reprints contact: Shozo Okamoto, Hokkaido University, Minami 10, Nishi 14, Obihiro, Sapporo, Hokkaido, 080-0024 Japan.
E-mail: shozo@med.hokudai.ac.jp
† Deceased.
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PPGL, medullary thyroid carcinoma, and carcinoid tumors that have the uptake-1 mechanism (*7*,*9*,*10*). ^{131}I-MIBG radiotherapy may be associated with survival improvement, although this possibility needs to be evaluated in a prospective randomized clinical trial. However, this type of trial could be difficult to develop, given the rarity of the disease. On the other hand, ^{131}I-MIBG radiotherapy is being investigated as a way to further increase the beneficial treatment effects with fewer side effects. Loh et al. reviewed 116 pheochromocytoma cases treated with ^{131}I-MIBG radiotherapy doses ranging from 3,552 to 85,914 MBq (*11*). In that analysis, 4 patients whose ^{131}I-MIBG dose ranged from 7,400 to 22,200 MBq showed complete tumor regression. High-dose ^{131}I-MIBG therapy combined with autologous bone marrow transplantation showed a high rate (83%) of complete remission (CR) or partial response (PR) (*12*). These data imply that controlling tumor progression or hormonal level may require a certain total accumulated dose of ^{131}I-MIBG.

In terms of side effects, Loh et al. also showed that radiation-induced toxicity such as bone marrow suppression was generally related to administered dose (*11*). Another analysis showed that 3 patients (9% of the study population) had ^{131}I-MIBG treatment–related death from acute myocardial infarctions (*13*). All these patients received 11,100 MBq of ^{131}I-MIBG as a single dose and may have had an acute catecholamine crisis resulting from tumor necrosis. In this regard, the ideal ^{131}I-MIBG treatment protocol should stipulate a certain total accumulated dose, with a single dose not exceeding 11,100 MBq to avoid inducing catecholamine acute toxicity. The total accumulated dose of ^{131}I-MIBG should be less than the dose that can induce severe bone marrow suppression.

To increase the total accumulated dose of ^{131}I-MIBG, we should also consider the treatment interval. A previous preliminary report on 2 cases showed the efficacy of a medium dose (7,400 MBq) of ^{131}I-MIBG repeated at intervals of 3 mo (*14*). These 2 cases showed a good therapeutic response, and the interval fell within the range of 3–6 mo recommended in European Association of Nuclear Medicine (EANM) guidelines for ^{131}I-MIBG radiotherapy (*15*). On the basis of this previous study and the EANM guidelines, we decided on an interval of 6 mo, which would be practical in a clinical setting.

The EANM guidelines suggest possible therapeutic protocols such as repeating 3,700–11,100 MBq of ^{131}I-MIBG at 3- to 6-mo intervals. However, no protocol has been established for ^{131}I-MIBG radiotherapy in metastatic NETs.

^{131}I-MIBG radiotherapy is effective in terms of reducing tumor size and producing a hormonal response (*11*) but still has limited therapeutic effects (*16*). Therefore, recent trials have evaluated the use of high-dose ^{131}I-MIBG radiotherapy and medium-dose ^{131}I-MIBG. A single high dose of ^{131}I-MIBG radiotherapy slightly improved outcomes in patients with metastatic PPGL. However, this approach also increased adverse effects, including fatal acute respiratory distress syndrome, bronchiolitis obliterans organizing pneumonia, and myelodysplastic syndrome (*17*). Another recent approach has been to apply high-specific-activity (HSA) ^{131}I-MIBG. Treatment involving a single high dose or 2 consecutive doses (in patients who recovered from bone marrow suppression) of HSA ^{131}I-MIBG radiotherapy resulted in PR in 23% of cases, and 49% of patients had an at least a 50% reduction in antihypertensive medication. Some patients developed a secondary cancer, resulting in death, that was possibly linked to high-dose radiotherapy (*18*). Since some NET patients displayed slower progression than that for other solid cancers, controlling adverse effects is also important for patient management.

A previous small study by Nakazawa et al. reported that ^{18}F-FDG PET SUV_{max} was reduced after ^{131}I-MIBG radiotherapy in patients considered to have responded (*19*). That study suggested the usefulness of ^{18}F-FDG PET imaging for treatment evaluation in patients with PPGL who had received ^{131}I-MIBG radiotherapy.

We aim to establish a suitable treatment protocol for ^{131}I-MIBG radiotherapy to achieve good treatment effects together with minimal side effects. In this regard, the purpose of this study was to evaluate the ability of repeated ^{131}I-MIBG therapy to inhibit progression of metastatic NETs with regard to symptoms, hormonal changes, tumor size, and tumor metabolic response as evaluated using CT and ^{18}F-FDG PET or using ^{18}F-FDG PET/CT.

MATERIALS AND METHODS

Patient Population

Patients were prospectively recruited through the Department of Nuclear Medicine at the Hokkaido University Hospital from August 2008 to December 2014. We enrolled patients diagnosed with metastatic PPGL and thyroid medullary cancer. Each patient was diagnosed with those diseases after assessment of histopathologic findings at surgery. The patients eligible for this study had the appearance of new metastatic lesions, multiple metastatic lesions, treatment resistance to other therapies, or elevated tumor markers, including catecholamine levels (*12*,*13*). The presence of multiple metastatic lesions was defined as more than 2 lesions. These patients were considered to have a progressive condition and to require specific treatment (Table 1). They met the criteria for the EANM guidelines after confirmation of avid ^{123}I-MIBG or ^{131}I-MIBG uptake in metastatic foci through diagnostic radioiodine ^{123}I-MIBG or ^{131}I-MIBG imaging (*10*,*15*). A ^{123}I-MIBG– or ^{131}I-MIBG–avid lesion was defined as having visible focal uptake greater than that in the surrounding normal tissue even if the patient had mixed tumors (*20*). Images were interpreted visually by at least 2 nuclear medicine physicians with more than 10 y of experience.

To be included in the current study, patients had to be scheduled to receive ^{131}I-MIBG radiotherapy for the first time on clinical grounds. We excluded patients who had received ^{131}I-MIBG radiotherapy before enrollment.

Sample Size Based on Sample Size Calculation

The clinical benefit rate, including that in PR and stable disease (StaD) patients who received ^{131}I-MIBG radiotherapy, was 73% in a previous study (*21*). Neither the previous study nor the current study had a control group. However, if there had been a control group with a clinical benefit rate of 30% (whether for PR or StaD), detection of a 70% clinical benefit rate from ^{131}I-MIBG radiotherapy would have required 11 treated patients to obtain a power of at least 0.8 for a z test of 1-sample binomial proportion with a 2-sided significance level of 0.05.

This study was approved by the Hokkaido University Graduate School of Medicine Human Research Ethics Board and the Hokkaido University Hospital Institutional Review Board. All subjects gave written informed consent in accordance with the 2008 Declaration of Helsinki. This study is registered in the University Hospital Medical Information Network (registration 000007179).

Study Design

This was a prospective single-arm trial. Patients with metastatic PPGL and medullary thyroid cancer underwent clinical evaluations, blood work, urine measurements, and diagnostic imaging, including either whole-body CT and ^{18}F-FDG PET or ^{18}F-FDG PET/CT before and 3–6 mo after the final ^{131}I-MIBG radiotherapy (Supplemental Fig. 1; supplemental materials are available at http://jnm.snmjournals.org). In addition, the patients underwent ^{123}I-MIBG or ^{131}I-MIBG

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TABLE 1
Characteristics of 11 Metastatic NETs Treated with ^{131}I-MIBG Radiotherapy

				Treatment		^{131}I-MIBG dose (MBq)	
Patient no.	Age (y)	Sex	Type of disease	Reason	*n*	Total	Mean
1	64	F	Pheochromocytoma	New metastasis, multiple lesions, high CA	3	16,650	308.21
2	45	F	Paraganglioma	New metastasis, multiple lesions	3	16,650	326.34
3	45	M	Pheochromocytoma	New metastasis, multiple lesions	3	16,650	180.93
4	34	F	Pheochromocytoma	New metastasis, multiple lesions	2	11,100	182.41
5	62	F	Pheochromocytoma	New metastasis, multiple lesions, high CA	3	16,650	358.16
6	65	F	Paraganglioma	New metastasis, multiple lesions, high CA	3	16,650	323.38
7	67	F	Pheochromocytoma	New metastasis, multiple lesions, high CA	2	11,100	216.08
8	36	F	Pheochromocytoma	New metastasis, multiple lesions	3	16,650	391.83
9	49	M	Thyroid medullary cancer	New metastasis, multiple lesions	3	16,650	256.04
10	52	F	Pheochromocytoma	CVD resistance	3	16,650	263.07
11	22	F	Pheochromocytoma	New metastasis (recurrence), high CA	3	16,650	339.66
Mean ± SD	49 ± 15					15,640.9 ± 2,245.1	286.01 ± 71.33

CA = catecholamine; CVD = cyclophosphamide, vincristine, and dacarbazine; new metastasis = newly diagnosed metastasis.

scintigraphy before the first ^{131}I-MIBG radiotherapy (*10*,*15*). Patients also underwent whole-body ^{131}I-MIBG imaging after each ^{131}I-MIBG therapy to evaluate the uptake of therapeutic ^{131}I-MIBG (*15*). The therapeutic effects of ^{131}I-MIBG were estimated by CT. RECIST was considered the standard for treatment effects (*22*).

^{131}I-MIBG Radiotherapy Protocol

Each patient received a single dose of ^{131}I-MIBG (5,550 MBq [5.5 GBq]) (Izotop from August 2008 to March 2009 and POLATOM after April 2009) (*13*,*23*,*24*). The ^{131}I-MIBG dose was based on previous studies (*21*,*25*), EANM guidelines (*15*), our preliminary data related to the Japanese multicenter registry (*26*), and the Japanese Ministry of Health, Labor, and Welfare's approval of ^{131}I-labeled therapeutic radiopharmaceutical use in our facility. Patients with metastatic PPGL took thyroid protection measures (*15*). We repeated ^{131}I-MIBG therapy 2 or 3 times. Second and third ^{131}I-MIBG radiotherapies were given only after confirming recovery from any toxicity associated with the prior ^{131}I-MIBG radiotherapy. The interval between each ^{131}I-MIBG radiotherapy was between 3 and 6 mo as based on EANM guidelines (Supplemental Fig. 1) (*15*).

Posttherapy ^{131}I-MIBG scanning was performed to confirm ^{131}I-MIBG uptake in metastatic lesions (*23*).

Symptoms and Physical Findings

We evaluated symptoms and physical findings before and 3 mo after the radiotherapy. We evaluated catecholamine-related symptoms such as headache, palpitations, sweating, and pain due to bone metastasis, among others. Physical measurements included systolic and diastolic BP and heart rate.

A BP response after the repeated ^{131}I-MIBG radiotherapy was evaluated in patients with hypertension (*26*). With regard to hypertension, we used cutoffs for systolic BP subanalysis in normotensive (120–139 mm Hg) and hypertensive (>140 mm Hg) patients based on the seventh report of the U.S. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (*27*).

Blood and Urine Biochemistry

We performed blood work before and 3 mo after the last radiotherapy. We estimated complete blood cell counts to evaluate the hematologic toxicity (*26*). Plasma concentrations of catecholamine and the urinary concentration of catecholamine, homovanillic acid, and vanillylmandelic acid were measured at baseline and 3–6 mo after the last radiotherapy. We measured thyroid function as well in metastatic PPGL (T4).

CT

The first 2 patients underwent an additional CT scan. Standard-dose CT with an automated 150-mAs tube current and 120-keV tube voltage was performed for all patients undergoing ^{18}F-FDG PET/CT. Section thickness was 5 mm from the neck to the pelvis. Since most patients had undergone heminephrectomy and had renal dysfunction, and contrast medium administration was relatively contraindicated (*28*), we acquired plain CT data for the current study.

^{123}I-MIBG and ^{131}I-MIBG Scintigraphy

As a diagnostic scan before ^{131}I-MIBG radiotherapy, 8 patients underwent ^{123}I-MIBG planar imaging and 3 patients underwent ^{131}I-MIBG planar imaging.

The ^{123}I-MIBG imaging occurred approximately 24 h after administration of 111 MBq of ^{123}I-MIBG (Fujifilm RI Pharma), and the ^{131}I-MIBG imaging occurred approximately 24 and 48 h after administration of 20 MBq of ^{131}I-MIBG (Fujifilm RI Pharma). Whole-body images were acquired using a dual-head γ-camera (Millennium; GE Healthcare) equipped with high-energy general-purpose collimators for ^{131}I-MIBG and medium-energy general-purpose collimators for ^{123}I-MIBG (*20*). Overlapping anterior and posterior images from the top of the head to the knee were acquired for 100,000 counts or 20 min, whichever came first.

^{18}F-FDG PET and ^{18}F-FDG PET/CT Imaging

The first patient underwent ^{18}F-FDG PET imaging before ^{131}I-MIBG radiotherapy. Subsequently, our institution installed a PET/CT scanner and all remaining ^{18}F-FDG studies and data acquisitions were performed using the PET/CT scanner.

The ^{18}F-FDG PET and ^{18}F-FDG PET/CT imaging were performed according to the standard approach (*29*). The serum glucose level was measured before intravenous ^{18}F-FDG administration (4 MBq/kg; total dose range, 185–400 MBq).

PET was performed using an ECAT EXACT 47 scanner (Siemens/CTI), and PET/CT was performed using a Biograph 64 TruePoint scanner with TrueV and multidetector CT (Siemens) (*30*).

Image Interpretations

Two nuclear physicians, one of whom was a certified radiologist, evaluated the diagnostic images without knowledge of other imaging findings or clinical information. Any discrepancies were discussed until a consensus could be reached.

Analysis of Response to Treatment Using CT

Images obtained 3 mo after the final ^{131}I-MIBG radiotherapy were compared with those obtained before the first radiotherapy. On whole-body CT images from the PET/CT scanner or the CT scanner, tumor response was measured according to the maximal tumor diameter of the predominant lesions and was defined on the basis of RECIST as CR (resolution of all tumors on imaging), PR (a reduction of ≥30% in the measured maximal tumor diameter), StaD, or progressive disease ([PD], an increase of ≥20% in a single lesion or development of new lesions) (*22*).

Evaluation of Biomarker Responses

The hormonal markers for patients with metastatic PPGL included catecholamines and their metabolites. All metastatic-PPGL patients with elevated catecholamine levels had norepinephrine-secreting tumors. Therefore, we focused on plasma norepinephrine and on urine norepinephrine and its metabolites, such as urine vanillylmandelic acid, in this analysis. A hormonal marker of overall response was defined as the best confirmed CR or PR for any of the biomarkers whose levels were at least over the upper limit of normal at baseline. Hormonal CR, PR, and PD (normalization of, 50% decrease in, and 25% increase in marker levels, respectively) were evaluated 3 mo after the final radiotherapy (*17*).

The hormonal markers for the patient with thyroid medullary carcinoma were carcinoembryonic antigen and calcitonin. In evaluating the therapeutic response, we applied the same criteria as for catecholamines and their metabolites (*18*).

Evaluation of Side Effects

The U.S. National Cancer Institute Common Toxicity Criteria, version 3.0, were used to evaluate side effects of ^{131}I-MIBG radiotherapy (*31*). We evaluated full blood count, symptoms, and hemodynamic changes during and after radiotherapy (*17*,*32*). Early side effects were defined as those that occurred from the time of ^{131}I-MIBG administration until the end of hospitalization, usually after 7 d. Late side effects were defined as those that occurred more than 6 wk after ^{131}I-MIBG administration (*15*). We recorded and addressed all side effects.

Statistical Analysis

Continuous variables are presented as medians with interquartile ranges (IQRs). Differences between groups were evaluated using the Wilcoxon rank sum test. The Fisher exact test was used to compare

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discrete data, as appropriate. A P value of less than 0.050 was considered to indicate a statistically significant difference. Statistical calculations were performed by JMP, version 13 (SAS Institute Inc.).

RESULTS

Patient Characteristics

This study included 11 patients with metastatic NETs: 8 with metastatic pheochromocytoma, 2 with metastatic paraganglioma, and 1 with thyroid medullary carcinoma (Table 1). Among the 11 patients, 10 had newly diagnosed metastatic lesions. The remaining patient had a cyclophosphamide, vincristine, and dacarbazine–resistant status. Therefore, these patients were referred to the Nuclear Medicine Department. Nine patients (81.8%) were women. Of the patients who had metastatic PPGL, none had thyroid dysfunction before ^{131}I-MIBG radiotherapy.

Two of the 11 patients had undergone ^{131}I-MIBG radiotherapy twice. Patient 4 was a young woman considering having a child after the treatment. She had only 1 visible metastatic lesion in the seventh thoracic vertebra. Therefore, we applied ^{131}I-MIBG radiotherapy twice and did not perform a third therapy. Another patient (patient 7) showed rapid progression and died after the second ^{131}I-MIBG radiotherapy. The remaining 9 patients had 3 ^{131}I-MIBG radiotherapies. The mean dose of ^{131}I-MIBG was 15,640.9 ± 2,245.1 MBq, and the mean dose per body weight was 286.01 MBq/kg.

Treatment Response Using Symptoms, BP, and Catecholamine-Related Hormones

Nine of the 11 patients had at least one symptom related to elevated catecholamine or bone metastasis (Table 2). Among these 9 patients, 3 with PR and 4 with StaD according to RECIST had a symptomatic response, and the symptoms of the 2 patients with PD by RECIST worsened after the ^{131}I-MIBG radiotherapy (Table 2).

Five of the 11 patients (45.5%) had elevated BP. Two of these had what the seventh report of the U.S. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure defines as "normal hypertension" (i.e., systolic BP of 121–139 mm Hg), and the other 3 had true hypertension (BP > 140/90 mm Hg) (*33*), before the first ^{131}I-MIBG radiotherapy. After the radiotherapy, 3 patients had normal hypertension and 2 had normal BP. In the hypertension group, there was no elevation of BP ($P = 0.215$) after the therapy. Among the 5 hypertension or normal-hypertension patients, systolic BP tended to be reduced ($P = 0.058$) and diastolic BP was significantly reduced ($P = 0.006$). None of the 11 patients showed a significant change in systolic BP ($P = 0.206$) or diastolic BP ($P = 0.375$) (Supplemental Table 1).

Biochemical Tumor Marker Response

Two of the 11 patients did not have elevated catecholamine levels before the first treatment. Of the remaining 9 patients, there was PR in 3 and StaD in 4 based on hormonal response criteria (Fig. 1) (*18*). Two patients showed PD (Table 2). In all patients, there was no significant change in plasma norepinephrine ($P = 0.577$) or urine vanillylmandelic acid ($n = 9$, $P = 0.203$) (Supplemental Table 1). In 9 PR or StaD patients, plasma norepinephrine tended to be reduced ($P = 0.109$) and urine vanillylmandelic acid was significantly reduced ($P = 0.031$) (Supplemental Table 2).

Treatment Response Evaluated Using CT

Patient-Based Analysis. On the basis of RECIST, 3 patients showed PR and 6 patients showed StaD. The remaining 2 patients were categorized as having PD (Table 2; Supplemental Table 3). Although there were 2 PD patients, none of the 11 patients showed a significant change in summed length diameter (median, 228.7 mm [IQR, 37.0–336.0 mm] to 171.0 mm [IQR, 38.0–270.0 mm]; $P = 0.563$) (Supplemental Table 1). The total numbers of metastatic lesions were similar before and after the ^{131}I-radiotherapy (median, 12 [IQR, 3–19] to 12 [IQR, 3–19]; $P = 0.625$). In 9 patients with PR or StaD, the total numbers of metastatic lesions were similar (median, 5 [IQR, 2–17] vs. 4 [IQR, 2–16]; $P = 0.500$), but summed length diameter was significantly reduced after the ^{131}I-MIGB radiotherapy (median, 81 mm [IQR, 27–278 mm] to 64 mm [IQR, 26–216 mm]; $P = 0.039$) (Supplemental Table 2).

Among the 6 StaD patients as defined by RECIST, 4 had improved symptoms, 1 had a hormonal response, and 1 with hypertension had reduced BP (Table 2).

Region-Based Analysis. On the basis of CT, there was no difference in metastatic lesion diameter before and after ^{131}I-MIBG radiotherapy ($n = 134$) (median, 15 mm [IQR, 10–22 mm] vs. 15 mm [IQR, 10–23 mm]; $P = 0.984$) (Supplemental Table 4). In the 9 PR or StaD patients, the mean diameter of metastatic lesions was significantly reduced ($n = 79$) (median, 16 mm [IQR, 12–22 mm] to 11 mm [IQR, 6–16 mm]; $P < 0.001$) after ^{131}I-MIBG radiotherapy (Fig. 2; Supplemental Table 4).

None of the patients showed a change in the mean SUV_{max} of metastatic lesions after ^{131}I-MIBG radiotherapy ($n = 134$) (median, 4.1 [IQR, 1.9–8.3] vs. 4.3 [IQR, 2.8–9.2]; $P = 0.24$). Patients with PR or StaD showed a significantly reduced mean regional SUV_{max} after the ^{131}I-MIBG radiotherapy ($n = 79$) (median, 4.0 [IQR, 2.6–5.4] to 3.2 [IQR, 1.0–4.3]; $P < 0.001$) (Fig. 2).

Side Effects of ^{131}I-MIBG Radiotherapy

Early Side Effects. All patients had at least one adverse effect. These included nausea (9/11, 81.8%), appetite loss (4/11, 36.4%), taste abnormality (1/11, 9.1%), elevated BP (1/11, 9.1%), orthostatic hypotension (3/11, 27.2%), bradycardia (1/11, 9.1%), and pleural effusion (1/11, 9.1%). These early side effects, except pleural effusion, were temporary. Other adverse effects included cholecystitis due to gallbladder stones and urinary tract stones.

Late Side Effects. In terms of anemia from bone marrow suppression, 3 patients (27.3%) showed grade II toxicity and 1 patient (9.1%) showed grade III toxicity (Supplemental Fig. 2). In terms of leukopenia, 5 patients (45.5%) showed grade II toxicity and 1 patient (9.1%) showed grade III toxicity. In terms of thrombocytopenia, only 1 patient showed toxicity, and it was grade I. No patients required a blood transfusion during the observational period.

DISCUSSION

^{131}I-MIBG radiotherapy is performed as part of clinical practice in European countries (*15*), and HSA ^{131}I-MIBG was approved by the Food and Drug Administration in the United States in 2018 (*8*,*18*,*34*).

Metastatic PPGL normally accounts for 15%–17% of all PPGL cases (*35*). Most previous studies evaluating ^{131}I-MIBG treatment effects provided a retrospective analysis (*11*,*23*,*26*,*32*,*36*). There have been 3 prospective clinical trials; 2 looked at the effects of

TABLE 2
Major Symptoms Before ^{131}I-MIBG Therapy and Therapeutic Response

	Symptoms before ^{131}I-MIBG therapy							After ^{131}I-MIBG therapy				
Patient no.	A	B	C	D	E	F	G	Symptomatic response	Elevated BP	BP response	Hormonal response	Tumor size response (RECIST)
1	+	+	+	+	+	−	−	Improved	+	+	PR	PR
2	−	−	−	−	−	−	−	No change (none to none)	−	−	Not elevated	StaD
3	+	−	+	−	−	−	−	Improved	−	−	StaD	StaD
4	−	−	−	−	−	−	+	Improved	−	−	Not elevated	PR
5	+	+	+	−	−	−	−	Improved	+	+	PR	PR
6	+	−	−	−	−	−	+	Improved	+	+	PR	StaD
7	−	+	+	−	+	−	−	Deteriorated	+	+	PD	PD
8	−	−	−	−	−	−	+	Deteriorated	−	−	PD	PD
9	−	−	−	−	−	−	−	No change (none to none)	−	−	StaD*	StaD
10	−	+	+	−	−	−	+	Improved	+	−	StaD	StaD
11	+	+	+	+	−	+	−	Improved	−	−	StaD	StaD
n	5 (45.5%)	5 (45.5%)	6 (54.5%)	2 (18.2%)	2 (18.2%)	1 (9.0%)	4 (36.4%)					
PR (%)								7/9 (77.8%)	5/11 (45.5%)	4/5 (80.0%)	3/9 (33.3%)	3/11 (27.3%)

*Hormonal response was evaluated by plasma carcinoembryonic antigen and calcitonin.
A = headache; B = palpitations; C = sweating; D = irritation; E = insomnia; F = abdominal pain; G = pain; + = symptom observed; − = no symptom.
A–F are catecholamine-related symptoms; G is bone metastasis–related symptom.

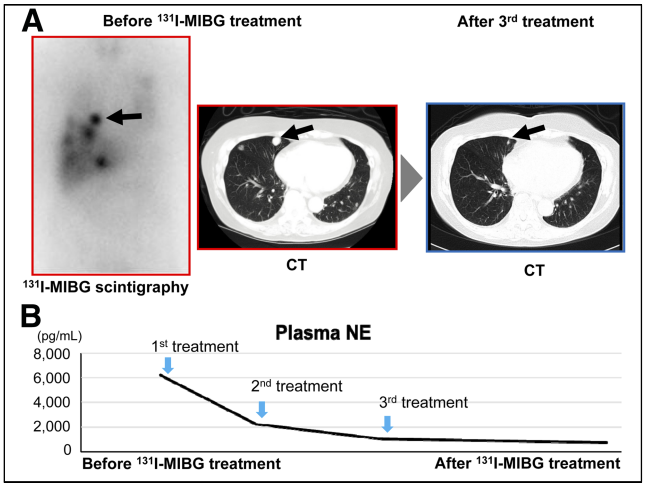

FIGURE 1. Representative case of 64-y-old woman with pheochromocytoma metastatic to lung, liver, and abdominal lymph nodes. (A) Initial ^{131}I-MIBG pretreatment scintigraphy shows uptake in multiple lung (arrow), skeletal, and hepatic metastatic lesions. CT shows marked reduction in lung metastasis after third treatment (arrows). (B) After 3 repeated ^{131}I-MIBG radiotherapies, her metastatic regions were reduced and she showed plasma norepinephrine reduction from 5,207 to 743 pg/mL. Total summed length diameter was reduced from 279 to 171 mm. NE = norepinephrine.

high-dose or relatively high-dose ^{131}I-MIBG radiotherapy (*17*,*18*). The remaining study looked at the safety aspects of ^{131}I-MIBG radiotherapy (*37*). To our knowledge, the current study was the first prospective study to evaluate ^{131}I-MIBG radiotherapy repeated within a relatively short time, using the dose suggested by the EANM guidelines for metastatic NETs. The approach using a single high dose of ^{131}I-MIBG radiotherapy slightly improved therapeutic effects. However, a study found that this approach had some fatal adverse effects, such as acute respiratory distress syndrome, bronchiolitis obliterans organizing pneumonia, and myelodysplastic syndrome (*17*). Another study, of other treatments involving a relatively high single dose or 2 consecutive doses of HSA ^{131}I-MIBG, also found adverse events—an association with pulmonary embolism, myelodysplastic syndrome, and increased risk of secondary cancer resulting in death (*18*). These 2 studies imply that high-dose ^{131}I-MIBG therapy can improve treatment effects but at the same time may increase the risk of fatal adverse effects related to higher radiation exposure at one time. Therefore, an alternative therapeutic approach involving a higher total accumulated dose of ^{131}I-MIBG with fewer fatal adverse effects than those associated with a single high-dose therapy may be required.

Considering this balance between treatment effects and adverse effects, we used a relatively short-term repeated ^{131}I-MIBG radiotherapy with a standard single dose as suggested by EANM ^{131}I-MIBG radiotherapy guidelines (*15*). The EANM guidelines suggested that the single dose could be 3,700–11,100 MBq. We therefore used a single dose of 5,550 MBq. In the current study, 3 patients (27.3%) showed PR and 6 patients (54.5%) showed StaD after the treatment, based on RECIST. A systematic review looking at 17 previous studies revealed CR in 3%, PR in 27%, StaD in 52%, and PD in 18% (*38*). This implies that in 82% of cases, ^{131}I-MIBG therapy may have clinical benefits. The treatment effects of the current study agree with data from the systematic review. Data in the systematic review were from retrospective studies. The current study was a prospective study and therefore adds new insights to those found in the systematic review.

The interval between ^{131}I-MIBG treatments in the current study was 3–6 mo, based on EANM guidelines, and achieved disease control in 81.8% of the study population, including 3 with PR. Therefore, the interval between ^{131}I-MIBG treatments in the current study appears to be appropriate. With regard to dose and interval, the current study protocol may be suitable for clinical practice, and further study within a greater population may be beneficial. In this study, PR and StaD patients showed a significant reduction in regions of SUV_{max} after treatment. This result may indicate that this repeated treatment protocol effectively suppressed tumor growth potential in the PR and StaD groups.

A recent study using HSA ^{131}I-MIBG with a high dose (3,774–40,552 MBq) showed therapeutic effects from a single administration: CR, 0%; PR, 0%; StaD, 71%; and PD, 14% (*18*). A 2-administration protocol showed the therapeutic effects as CR, 0%; PR, 30%; StaD, 68%; and PD 2% (*18*). Even with HSA ^{131}I-MIBG, ^{131}I-MIBG therapy can achieve a limited CR. Although the sample size of the current study was small, the treatment effects of the current study may be comparable to those for HSA ^{131}I-MIBG treatment. These data also may imply that a higher total dose can improve treatment effects. In addition, Noto el al. reported a single maximum tolerated specific ^{131}I-MIBG dose of 296 MBq/kg (*39*). In the subgroup of Noto's study using a specific ^{131}I-MIBG dose of less than 18,500 MBq, the therapeutic responses were CR, 0%; PR, 0%; StaD, 85.7%; PD, 0%; and none-valuable results, 14.3%. The current study used a similar dose of ^{131}I-MIBG and may show a slightly better (but not significant) therapeutic response than that in the study of Noto et al. Although both studies had a small sample size, this slightly better therapeutic response may imply that a repeated ^{131}I-MIBG treatment protocol may be more useful in clinical practice than is a single treatment.

In light of the hormonal response, one of the major aims of ^{131}I-MIBG radiotherapy is hormonal reduction. A previous systematic review reported a hormonal response to ^{131}I-MIBG radiotherapy of CR in 11% of patients, PR in 40%, StaD in 41%, and PD in 27% (*38*). The current study showed a trend toward a reduction in plasma norepinephrine and a significant reduction in urine vanillylmandelic acid in PR or StaD patients. The current data also showed a hormonal reduction similar to that in previous studies.

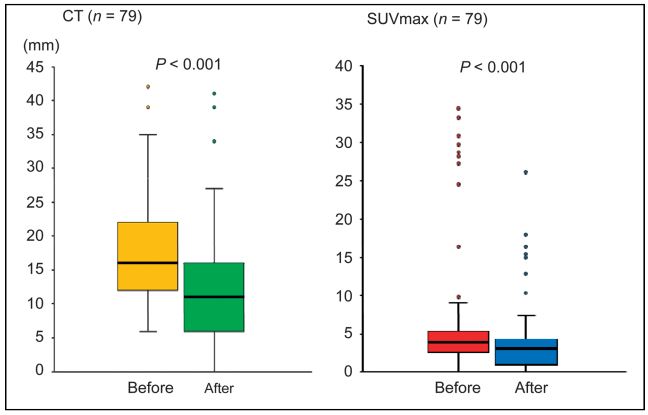

FIGURE 2. Tumor size on CT and tumor metabolic activity before and after ^{131}I-MIBG radiotherapy in 9 patients with either PR or StaD using region-based analysis. Tumor size and SUV_{max} were significantly reduced after ^{131}I-MIBG radiotherapy.

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This reduction may have been associated with improvement in symptoms and with BP reduction. Patients with PR by RECIST also showed a hormonal response. Among 3 PR patients, 2 also showed a hormonal reduction according to RECIST. This finding may imply that tumor size reduction was associated with hormonal reduction.

The major cause of mortality in patients with metastatic PPGL includes catecholamine-related issues such as hypertension and catecholamine-induced heart failure, so-called Takotsubo syndrome (*40*). Therefore, phase 3 of the study, using HSA ^{131}I-MIBG, defined reducing hypertension medication as a major endpoint (*18*). BP reduction is also considered an important goal for metastatic PPGL management. Although the current study had a limited number of hypertension patients, the reported ^{131}I-MIBG radiotherapy significantly reduced diastolic BP and moved patients in the hypertension category into the normal-BP-range category after the treatment.

Single or consecutive high-dose ^{131}I-MIBG radiotherapy had some fatal adverse effects caused by radiation exposure as previously described (*17*,*18*). Although the prognosis for metastatic PPGL patients is worse than that for patients without metastasis (*41*), the 5-y survival rate is 50%–60%, which is better than that for patients with other solid cancers (*2*,*35*,*42*). Given the survival rate for metastatic PPGL, treatment options without life-threatening adverse effects would be preferable. Most early adverse effects of ^{131}I-MIBG radiotherapy were related to radiation exposure. All early side effects within the current study were common and not serious. The only late adverse effect was myelosuppression. There were no extrahematopoietic adverse effects. Noto et al. reported the early and late side effects of HSA ^{131}I-MIBG (*39*). They also reported that a specific ^{131}I-MIBG activity of less than 18,500 MBq did not have fatal adverse effects. ^{131}I-MIBG of less than 18,500 MBq either in a single therapy or in repeated therapies may not have fatal side effects. However, the study of Noto et al. and our study had a small sample size, and therefore, this possibility should be examined in greater depth in the future.

Myelosuppression was the main adverse effect of the repeated ^{131}I-MIBG radiotherapy. However, the myelosuppression involved mainly grade 1 and grade 2 myelotoxicity. No patients showed grade 4 myelotoxicity. These patients did not have a blood transfusion. The single-high-dose ^{131}I-MIBG radiotherapy may cause acute respiratory distress syndrome, bronchiolitis obliterans organizing pneumonia, or myelodysplastic syndrome and may require autologous bone marrow transplantation. The therapy may also cause acute hypertension or severe bone marrow insufficiency (*17*). These side effects present significant hurdles to using this therapy in routine clinical practice. However, in this study, no patient developed these severe side effects. The current protocol would be more suitable for clinical practice.

In the current study, all patients had early temporary myelosuppression just after ^{131}I-MIBG administration. However, these patients recovered from myelosuppression 3–6 mo after the first and second ^{131}I-MIBG therapies. In terms of complete blood cell counts, these patients did not have a contraindication to a second or third therapy based on EANM procedure guidelines (*15*). In contrast, with high-dose ^{131}I-MIBG therapy, 26.5% of patients did not recover from myelosuppression and did not receive a second therapy (*18*). This finding may imply that lower-dose ^{131}I-MIBG radiotherapy may be an option for subsequent treatment strategies. Myelosuppression limits treatment options such as additional radionuclide therapy or chemotherapy. Not causing sustained myelosuppression may be one of the advantages of this treatment protocol.

This study had several limitations. PPGL is considered to be rare, with limited patient numbers (*1*). The present study had an open-label single-arm design and did not have a control. However, a phase III HSA ^{131}I-MIBG trial had an open-label single-arm design (*18*). Therefore, the present study design meets the current standard clinical study protocol.

The incidence of PPGL is 0.6 cases per 100,000 persons per year (*43*). Regarding cases of metastatic PPGL, approximately 10% of pheochromocytomas and 15%–35% of paragangliomas involve metastasis (*44*). Therefore, few patients are eligible for ^{131}I-MIBG radiotherapy. Loh et al. reviewed 21 previously published articles looking at the effects of ^{131}I-MIBG radiotherapy (*11*) and found that the study populations ranged from 1 to 20 patients, with a mean of 5.7 patients. Despite its limited study population, the present study added several insights over those from previous studies. Although the number of patients in the current study was small, we performed a total of 31 ^{131}I-MIBG treatments and showed therapeutic effects with limited adverse effects. We recognize that we will need a study with a larger sample size and that this should be the next step.

We did not measure SDHB mutation in paraganglioma. SDHB-positive patients may have a poor treatment response and may have had an impact on the current study. We included 2 paraganglioma patients, and they showed StaD after the ^{131}I-MIBG radiotherapies; the impact of possible SDHB-positive patients may therefore have been minimal. It has been reported that multiple primary tumors often occur in patients with germline mutations in RET, VHL, SDHD, or MAX (*45*). Mutation of the SDHB gene may also have an impact on the treatment response. Not having evaluated this gene mutation was another limitation of the current study.

We did not have long-term outcome data and did not evaluate the survival benefits of this treatment protocol. These issues should also be evaluated in the future as a next step.

Among the 11 patients, 1 patient had undergone cyclophosphamide, vincristine, and dacarbazine therapy but had not received any heavy chemotherapy. This patient showed late hematologic adverse effects: leukocytopenia grade 2, anemia grade 1, and normal platelet number. Thus, the impact of prior chemotherapy on hematologic side effects should be minimal.

CONCLUSION

Repeated ^{131}I-MIBG therapy reduced tumor size and tumor metabolic activity according to lesion-based analysis in about one third of patients and stabilized a majority. This treatment approach also showed hormonal improvement with minimal side effects in PR and StaD patients. A protocol involving repeated ^{131}I-MIBG treatments may have potential for metastatic NETs. However, larger prospective studies with control groups should be performed to further test this hypothesis.

DISCLOSURE

This work was supported in part by the Mitsui Life Social Welfare Foundation (Tokyo, Japan). No other potential conflict of interest relevant to this article was reported.

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KEY POINTS

QUESTION: Can repeated ^{131}I-MIBG radiotherapy for metastatic NETs be an option that provides a good balance between therapeutic effects and adverse effects?

PERTINENT FINDINGS: NET patients who underwent our ^{131}I-MIBG radiotherapy protocol achieved a clinical benefit rate of 82%, according to RECIST, without fatal adverse effects. Patients with either PR or StaD showed a reduction in tumor diameter and tumor metabolic activity as evaluated by ^{18}F-FDG PET/CT.

IMPLICATIONS FOR PATIENT CARE: The treatment protocol established here can be widely applied in clinical settings, may improve symptoms related to catecholamine, and may prolong survival with fewer adverse effects in patients with NETs.

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