Site-based performance of $^{131}$I-MIBG imaging and $^{99m}$Tc-HYNIC-TOC scintigraphy in the detection of nonmetastatic extra-adrenal paraganglioma

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**Objectives** This study aimed to evaluate the performance of $^{131}$I-metaiodobenzylguanidine (MIBG) imaging to detect nonmetastatic extra-adrenal paragangliomas at their respective sites (abdominal vs. thoracic vs. head and neck vs. urinary bladder), and compare it with that of $^{99m}$Tc-hydrazinonicotinyl-tyr3-octreotide (HYNIC-TOC) scintigraphy.

**Methods** We retrospectively analyzed 235 patients with nonmetastatic extra-adrenal paragangliomas who underwent preoperative $^{131}$I-MIBG imaging or $^{99m}$Tc-HYNIC-TOC scintigraphy. Of all 235 patients, 145 patients underwent both imaging procedures, 16 patients $^{131}$I-MIBG imaging only and 74 patients $^{99m}$Tc-HYNIC-TOC scintigraphy only.

**Results** The overall sensitivity of $^{131}$I-MIBG and $^{99m}$Tc-HYNIC-TOC imaging to detect extra-adrenal paragangliomas regardless of tumor sites was 75.8% (122/161) and 67.6% (148/219), respectively ($P=0.082$). However, when stratified by tumor sites, $^{131}$I-MIBG imaging showed a significant improvement in the detection of extra-adrenal abdominal paragangliomas with a sensitivity of 90.3% (103/114), which was significantly higher than that of $^{99m}$Tc-HYNIC-TOC scintigraphy (67.6% [96/142]; $P=0.000$). In addition, the intensity of tracer uptake in the extra-adrenal abdominal paragangliomas with $^{131}$I-MIBG imaging was evidently higher than with $^{99m}$Tc-HYNIC-TOC scintigraphy. The sensitivity of $^{131}$I-MIBG imaging and $^{99m}$Tc-HYNIC-TOC scintigraphy to detect urinary bladder, head and neck, and thoracic paragangliomas were 18.7 vs. 18.5% ($P=1.000$); 17.4% vs. 84.6% ($P=0.000$) and 60% vs. 94.4% ($P=0.030$), respectively.

**Conclusions** $^{131}$I-MIBG imaging could become the first-line investigation modality in patients with extra-adrenal abdominal paragangliomas. However, $^{99m}$Tc-HYNIC-TOC scintigraphy has high sensitivity and is superior to $^{131}$I-MIBG imaging for detecting head & neck and thoracic paraganglioma. Both $^{131}$I-MIBG imaging and $^{99m}$Tc-HYNIC-TOC scintigraphy have poor performance for detecting urinary bladder paragangliomas.

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**Introduction**

Pheochromocytoma and paraganglioma are neuroendocrine tumors derived from chromaffin cells and are located in the adrenal glands and at extra-adrenal locations, respectively [1,2]. For lesions detected by anatomical imaging, their preoperative identification as paraganglioma by functional imaging is critical. Extra-adrenal paragangliomas at different anatomical locations require different therapeutic strategies. Extra-adrenal abdominal paragangliomas generally arise from sympathetic paraganglia and produce catecholamines [3]. Therefore, a preoperative alpha-adrenoceptor blockade is necessary to avoid potential complications, including hypertensive and hypotensive episodes, myocardial infarction, cardiac arrhythmias and stroke, that may occur due to intraoperative release of catecholamines. Head and neck paragangliomas originate from the parasympathetic paraganglia and usually do not produce catecholamines [3]. It is necessary to establish an optimal functional imaging modality depending on the site of extra-adrenal paragangliomas.

Previous studies on the performance of metaiodobenzylguanidine (MIBG) imaging for the detection of extra-adrenal paragangliomas reported a relatively low sensitivity ranging from 52 to 75% [4–7]. Of note, these studies...
generally included heterogeneous groups of patients with respect to the paraganglioma site: abdominal vs. thoracic vs. head and neck vs. urinary bladder, benign vs. malignant paraganglioma and hereditary vs. sporadic paraganglioma. It is well recognized that MIBG imaging had a low sensitivity (18–50%) for detecting head and neck paragangliomas [8]. However, the efficacy of MIBG imaging to detect extra-adrenal paragangliomas at specific locations, including the abdomen, thorax and urinary bladder, is unknown and has been rarely investigated before. Therefore, it remains uncertain whether head and neck paragangliomas might contribute to the overall low sensitivity of MIBG imaging, and thus, lead to the underestimation of MIBG imaging in paragangliomas at other locations.

\[^{99m}\text{Te}}\)-hydrazinonicotinyl-tyr3-octreotide (HYNIC-TOC), an imaging agent for the localization of somatostatin receptor, is commonly used in the clinic for the detection of pheochromocytoma and paraganglioma. It was previously reported that \[^{99m}\text{Te}}\)-HYNIC-TOC showed higher overall sensitivity than \[^{131}\text{I}}\)-MIBG imaging to detect the extra-adrenal paragangliomas [7]. The purpose of this retrospective study was to evaluate the performance of \[^{131}\text{I}}\)-MIBG imaging for patients with non-metastatic extra-adrenal paragangliomas at their respective locations (abdominal vs. thoracic vs. head and neck vs. urinary bladder) and compare it with that of \[^{99m}\text{Te}}\)-HYNIC-TOC scintigraphy.

\begin{table}
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\begin{tabu}{llll}
\hline
\multicolumn{1}{c}{\textbf{Patients, \%}} & \multicolumn{1}{c}{\textbf{Patients, \%}} \\
\hline
\textbf{Age at presentation, years} & 47 (11–75) & \\
\textbf{Gender} & \\
\textbf{Man} & 108 & 45.9 & \\
\textbf{Woman} & 127 & 54.1 & \\
\textbf{Location of tumors (n=242)} & \\
\textbf{Abdomen} & 153 & 63.2 & \\
\textbf{Urinary bladder} & 29 & 11.9 & \\
\textbf{Head and Neck} & 42 & 17.3 & \\
\textbf{Thorax} & 18 & 7.4 & \\
\textbf{Patients, n} & \\
\textbf{42} & & & \\
\textbf{Patients, \%} & \\
\textbf{45.9} & & & \\
\textbf{54.1} & & & \\
\textbf{63.2} & & & \\
\textbf{11.9} & & & \\
\textbf{17.3} & & & \\
\textbf{7.4} & & & \\
\hline
\end{tabu}
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Patients and methods

Patients

We retrospectively reviewed preoperative \[^{131}\text{I}}\)-MIBG and \[^{99m}\text{Te}}\)-HYNIC-TOC images of 287 consecutive patients with pathologically proven extra-adrenal paragangliomas who underwent the imaging procedures from our hospital between 2010 and 2020. Patients who had malignant extra-adrenal paragangliomas with metastases at the time of imaging were excluded; these were defined as the presence of tumors at locations where the chromaffin tissue is normally absent (i.e. liver, lung, bone and lymph node). The study was approved by the institutional review board. However, because of the retrospective study design, the requirement for written informed consent was waived by the review board. Finally, a total of 235 patients with 242 paragangliomas were included in this study (108 men and 127 women; age range, 11–75 years; median age, 47 years) (Table 1). A total of 229 patients had a single lesion. Six patients had more than one lesion (two patients had both a head and neck paraganglioma and an extra-adrenal abdominal paraganglioma; one had two head and neck paragangliomas and a thoracic paraganglioma; two had both a thoracic paraganglioma and an extra-adrenal abdominal paraganglioma; one had two head and neck paragangliomas).

Of all 235 patients, 145 patients underwent both imaging procedures, 16 patients \[^{131}\text{I}}\)-MIBG imaging only and 74 patients \[^{99m}\text{Te}}\)-HYNIC-TOC scintigraphy only. In patients who underwent both imaging procedures, \[^{131}\text{I}}\)-MIBG and \[^{99m}\text{Te}}\)-HYNIC-TOC scans were performed with a 2-week interval.

\[^{131}\text{I}}\)-metaiodobenzylguanidine imaging

Each patient received a potassium iodide preparation for thyroid blockade, starting 3 days before the intravenous administration of \[^{131}\text{I}}\)-MIBG and continuing 2 days after the imaging. After injection of \[^{131}\text{I}}\)-MIBG (1.48 MBq per kg of body weight), whole-body planar images were acquired at 1 and 2 days after injection using a dual-head gamma camera. Single-photon emission computed tomography/computed tomography (SPECT/CT) images were also acquired in some patients when necessary (i.e. those with urinary bladder paraganglioma).

\[^{99m}\text{Te}}\)-hydrazinonicotinyl-tyr3-octreotide scintigraphy

\[^{99m}\text{Te}}\)-HYNIC-TOC was synthesized and labeled as previously described [9]. After intravenous administration of the tracer, whole-body planar images were acquired using a double-head gamma camera at 1 and 4 h after injection. Some patients also underwent SPECT/CT imaging when necessary (i.e. those with urinary bladder paraganglioma).

Image interpretation

All scans were visually analyzed by two experienced nuclear medicine physicians. For head and neck paragangliomas, and extra-adrenal paragangliomas in the thorax and abdomen, we only assessed and compared the whole-body planar images acquired by the two modalities. For urinary bladder paraganglioma cases, in addition to the whole-body planar images, we also evaluated and compared the SPECT/CT images acquired with both radiotracers. The intensity of tumor uptake with \[^{131}\text{I}}\)-MIBG imaging and \[^{99m}\text{Te}}\)-HYNIC-TOC scintigraphy were graded on a scale from 0 to 3 by comparing them with the tracer uptake intensity of the normal liver (0: background activity, negative scan; 1: mild uptake, abnormal uptake higher than the background but less than that in the normal liver; 2: moderate uptake, abnormal uptake equal to that in the normal liver and 3: intense uptake, abnormal uptake greater than that in the normal liver). Tumors with a score of 1, 2 or 3 were considered positive.
Statistical analysis
The overall sensitivity of the two imaging modalities regardless of tumor sites was calculated on a per-patient basis as most of the patients included in this study had a single lesion. The sensitivity stratified by tumor locations was calculated on a per-lesion basis. All calculations were performed using SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, New York, USA). The chi-square test was used to statistically compare the difference between the different study groups. In patients who have undergone both imaging modalities, the comparison was performed using McNemar test. P values <0.05 were considered statistically significant.

Results

Overall sensitivity of extra-adrenal paragangliomas by $^{131}$I-MIBG imaging and $^{99m}$Tc-HYNIC-TOC scintigraphy

$^{131}$I-MIBG imaging positively identified extra-adrenal paraganglioma regardless of tumor sites in 122/161 patients, whereas $^{99m}$Tc-HYNIC-TOC scintigraphy was positive in 148/219 patients (overall sensitivity, 75.8 vs. 67.6%, respectively; \(P = 0.082\)). In the 145 patients who underwent both imaging modalities, the overall sensitivity of $^{131}$I-MIBG and $^{99m}$Tc-HYNIC-TOC imaging was 73.1% (106/145) and 68.3% (99/145), respectively (\(P = 0.367\)). Seventy-nine of these 145 patients showed positive findings with both imaging modalities. Twenty patients had positive findings on $^{99m}$Tc-HYNIC-TOC, but were $^{131}$I-MIBG negative. Twenty-seven patients were positive with $^{131}$I-MIBG, but negative with $^{99m}$Tc-HYNIC-TOC. Nineteen patients had negative findings on both $^{131}$I-MIBG and $^{99m}$Tc-HYNIC-TOC images.

Extra-adrenal abdominal paraganglioma

A total of 153 extra-adrenal abdominal paragangliomas were detected in 153 patients, all of which were located in the retroperitoneum. $^{131}$I-MIBG imaging was performed in 114 patients, whereas $^{99m}$Tc-HYNIC-TOC scintigraphy was performed in 142 patients. The sensitivity of $^{131}$I-MIBG imaging and $^{99m}$Tc-HYNIC-TOC scintigraphy to detect extra-adrenal abdominal paraganglioma was 90.3% (103/114) and 67.6% (96/142), respectively (\(P = 0.000\)) (Table 2; Fig. 1).

With $^{131}$I-MIBG imaging, 9.6% (11/114) of the patients had tumor uptake with a score of 0 according to the visual assessment criteria, 2.6% (3/114) had a score of 1, 10.5% (12/114) had a score of 2 and 77.2% (88/114) had a score of 3. While with $^{99m}$Tc-HYNIC-TOC scintigraphy, 32.4% (46/142) of the patients had tumor uptake with a score of 0, 35.9% (51/142) had a score of 1, 14.8% (21/142) had a score of 2 and 16.9% (24/142) had a score of 3. The proportion of patients who had tumor uptake with a score of 3 on $^{131}$I-MIBG imaging was significantly higher than those with the same score on $^{99m}$Tc-HYNIC-TOC scintigraphy (77.2 vs. 16.9%; \(P = 0.000\)) (Table 3; Fig. 2).

One-hundred-and-three of the 153 patients with extra-adrenal abdominal paragangliomas underwent both $^{131}$I-MIBG imaging and $^{99m}$Tc-HYNIC-TOC scintigraphy. In this subgroup, the sensitivity for $^{131}$I-MIBG imaging and $^{99m}$Tc-HYNIC-TOC scintigraphy to detect the paraganglioma was 90.3% (93/103) and 69.9% (72/103), respectively (\(P = 0.000\)). Sixty-seven of these 103 patients had positive findings on both imaging modalities. On comparing $^{131}$I-MIBG imaging findings with those of $^{99m}$Tc-HYNIC-TOC scintigraphy in these 67 patients, 43 patients had visually obvious higher intra-tumor uptake of the tracer on $^{131}$I-MIBG imaging than on $^{99m}$Tc-HYNIC-TOC scintigraphy (Fig. 3); 22 patients had visually comparable intra-tumor tracer uptake on both $^{131}$I-MIBG imaging and $^{99m}$Tc-HYNIC-TOC scintigraphy; and only in 2 patients, the intensity of intra-tumor tracer uptake was higher with $^{99m}$Tc-HYNIC-TOC scintigraphy than with $^{131}$I-MIBG imaging. 26/103 patients were $^{99m}$Tc-HYNIC-TOC-negative but were $^{131}$I-MIBG-positive (Fig. 4). Only 5/103 patients with paraganglioma were negative of $^{131}$I-MIBG uptake, but they were positive on $^{99m}$Tc-HYNIC-TOC images. In the remaining 5/103 patients, both $^{131}$I-MIBG imaging and $^{99m}$Tc-HYNIC-TOC scintigraphy were negative.

Urinary bladder paraganglioma

Twenty-nine urinary bladder paragangliomas were found in 29 patients. $^{131}$I-MIBG imaging and $^{99m}$Tc-HYNIC-TOC scintigraphy were performed in 16 and 27 patients, respectively, with a sensitivity of 18.7% (3/16) and 18.5% (5/27), respectively (\(P = 1.000\)). Fourteen patients underwent both $^{131}$I-MIBG and $^{99m}$Tc-HYNIC-TOC imaging with a sensitivity of 14.3% (2/14) and 14.3% (2/14), respectively (\(P = 1.000\)). In addition, $^{131}$I-MIBG SPECT/CT and $^{99m}$Tc-HYNIC-TOC SPECT/CT was performed in 7 and 12 patients, respectively, yielding a sensitivity of 71.4% (5/7) and 33.3% (4/12), respectively (\(P = 0.170\)) (Fig. 5).

Head and neck paraganglioma

Forty-two head and neck paragangliomas occurred in 40 patients. Twenty-one patients with 23 head and neck paragangliomas underwent $^{131}$I-MIBG imaging, and 37 patients with 39 head and neck paragangliomas underwent $^{99m}$Tc-HYNIC-TOC scintigraphy. $^{131}$I-MIBG imaging findings were positive in 4/23 (17.4%) lesions, whereas $^{99m}$Tc-HYNIC-TOC scintigraphy findings were positive in 33/39 (84.6%) lesions (Fig. 6). The sensitivity of $^{99m}$Tc-HYNIC-TOC scintigraphy for head and neck paraganglioma was significantly higher than that of $^{131}$I-MIBG imaging (84.6 vs. 17.4%; \(P = 0.000\)). Eighteen patients with 20 head and neck paragangliomas underwent both $^{131}$I-MIBG and $^{99m}$Tc-HYNIC-TOC imaging, with a sensitivity of 15% (3/20) and 90% (18/20), respectively (\(P = 0.000\)). Three of the 20 head and neck paragangliomas were positively identified with both imaging
modalities. Two head and neck paragangliomas were negative on both $^{131}$I-MIBG and $^{99m}$Tc-HYNIC-TOC imaging. The remaining 15 cases with head and neck paraganglioma were positive with $^{99m}$Tc-HYNIC-TOC uptake, but negative on $^{131}$I-MIBG images.

**Thoracic paraganglioma**

Eighteen thoracic paragangliomas were identified in 18 patients. The tumors were all located in the mediastinal region. Sixteen were cardiac paragangliomas, and the remaining two were in the posterior mediastinum. $^{131}$I-MIBG imaging and $^{99m}$Tc-HYNIC-TOC scintigraphy were performed in 15 and 18 patients, respectively. The sensitivity of $^{99m}$Tc-HYNIC-TOC scintigraphy and $^{131}$I-MIBG imaging for the localization of thoracic paragangliomas was 94.4% (17/18) and 60% (9/15), respectively ($P = 0.030$) (Fig. 7). Fifteen patients underwent both $^{131}$I-MIBG and $^{99m}$Tc-HYNIC-TOC imaging, with a sensitivity of 60% (9/15) and 93.3% (14/15), respectively ($P = 0.063$). Nine of the 15 patients showed positive findings with both imaging modalities. Five of the 15 patients had positive findings on $^{99m}$Tc-HYNIC-TOC, but were $^{131}$I-MIBG-negative. One of the 15 patients had negative findings on both $^{131}$I-MIBG and $^{99m}$Tc-HYNIC-TOC imaging.

**Discussion**

This study mainly investigated the performance of $^{131}$I-MIBG imaging and $^{99m}$Tc-HYNIC-TOC scintigraphy to detect extra-adrenal paragangliomas with regard to their respective tumor locations (abdominal vs. thoracic vs. head and neck vs. urinary bladder). The
Present study results showed that the overall sensitivity of $^{131}$I-MIBG imaging for the detection of extra-adrenal paragangliomas was 75.8%. However, when the sensitivity was calculated separately based on the paraganglioma sites, $^{131}$I-MIBG scintigraphy had a poor performance for detecting head and neck, thoracic and urinary bladder paragangliomas with a sensitivity of 17.4, 60 and 18.7%, respectively. Interestingly, for extra-adrenal paragangliomas located in the abdomen, $^{131}$I-MIBG imaging showed a significant improvement in the detection ability with a sensitivity of 90.3%, which was also the highest among all other extra-adrenal paragangliomas. These findings indicated that the sensitivity of $^{131}$I-MIBG scintigraphy for extra-adrenal paragangliomas varied greatly with tumor locations. The overall sensitivity of 75.8% for $^{131}$I-MIBG scintigraphy is not representative of its detection ability to accurately identify extra-adrenal paragangliomas at specific anatomic locations. In other words, the overall sensitivity might overestimate the performance of $^{131}$I-MIBG to detect head and neck, thoracic and urinary bladder paragangliomas, but underestimate its performance to detect extra-adrenal abdominal paragangliomas. Based on these findings, we suspected that the previously reported sensitivity of 52–75% for $^{131}$I-MIBG imaging to detect extra-adrenal paragangliomas might also have underestimated the value of $^{131}$I-MIBG imaging for detecting extra-adrenal abdominal paragangliomas as these studies generally enrolled heterogeneous patient groups [4,7,8]. In a study by Chen et al., [7] $^{131}$I-MIBG imaging was positive in 10/14 of patients with benign extra-adrenal paragangliomas, offering a sensitivity of 71.4%. However, these 14 patients consisted of those with thoracic paraganglioma and those with abdominal paraganglioma [7]. As indicated by our results, $^{131}$I-MIBG imaging had a relatively low sensitivity of 60% for detecting thoracic paragangliomas, which might decrease the

| Score | $^{131}$I-MIBG, $n=114$, No, (%) | $^{99m}$Tc-HYNIC-TOC, $n=142$, No, (%) | $P$ value |
|-------|-----------------------------------|---------------------------------------|-----------|
| 3     | 88 (77.2)                         | 24 (16.9)                             | 0.000     |
| 2     | 12 (10.8)                          | 21 (14.8)                             | 0.312     |
| 1     | 3 (2.6)                            | 51 (35.8)                             | 0.000     |
| 0     | 11 (9.7)                           | 46 (32.4)                             | 0.000     |

HYNIC-TOC, hydrazinonicotinyl-tyr3-octreotide; MIBG, metaiodobenzylguanidine.

MIBG and $^{99m}$Tc-HYNIC-TOC scores were as follows: 3 (or intense uptake) meant tracer uptake of the tumor was higher than that of the liver; 2 (or moderate uptake) meant tracer uptake was similar to that of the liver; 1 (or mild uptake) meant tracer uptake was lower than that of the liver but higher than background; and 0 (or negative uptake) meant tracer uptake similar to background.

The proportion of patients with a tumor uptake score of 3, 2, 1 and 0 for extra-adrenal abdominal paragangliomas on $^{131}$I-metaiodobenzylguanidine (MIBG) imaging and $^{99m}$Tc-hydrazinonicotinyl-tyr3-octreotide (HYNIC-TOC) scintigraphy. The scores of tumor uptake were as follows: 3 (or intense uptake) meant tracer uptake of tumor was higher than that of the liver; 2 (or moderate uptake) meant tracer uptake was similar to that of the liver; 1 (or mild uptake) meant tracer uptake was lower than that of the liver but higher than background; and 0 (or negative uptake) meant tracer uptake similar to background.
Performance of 131I-MIBG imaging and 99mTc-HYNIC-TOC scintigraphy

Overall sensitivity. A prospective multicenter trial by Wiseman et al., [4] found that 123I-MIBG imaging had a 67% sensitivity to detect paragangliomas in a subgroup of 22 patients with extra-adrenal paragangliomas; however, the information concerning the tumor sites was not provided in this study [4]. A recent prospective study by Arora et al., [10] reported a relatively low sensitivity of 71% (23/32) of 131I-MIBG planar imaging to detect extra-adrenal abdominal paragangliomas. Of note, 7 of the 32 patients had malignant paragangliomas at the time of presentation [10]. In the present study, only patients with benign extra-adrenal paragangliomas were included. MIBG uptake is lower in malignant pheochromocytomas or paragangliomas as compared to their benign counterparts [11]. Malignant pheochromocytomas or paragangliomas may undergo a process of tumor de-differentiation with loss of specific neurotransmitter transporters, which resulted in an inability for tumor cells to accumulate tracer [12].

As demonstrated in our study, 131I-MIBG imaging had significantly higher sensitivity than 99mTc-HYNIC-TOC scintigraphy to detect extra-adrenal abdominal paragangliomas. In addition, when visually comparing 131I-MIBG images with 99mTc-HYNIC-TOC scintigraphy images, we observed that the intensity of tumor uptake with 131I-MIBG imaging was almost always higher than with 99mTc-HYNIC-TOC scintigraphy. These observations suggested that 131I-MIBG imaging is superior to 99mTc-HYNIC-TOC scintigraphy to detect extra-adrenal abdominal paragangliomas in terms of both sensitivity and intensity of intra-tumor tracer uptake. Extra-adrenal abdominal paragangliomas are tumors that arise from the sympathetic paraganglia with functional catecholamine production. 131I-MIBG tracer acts as a norepinephrine analog, thus facilitates its uptake by functional paragangliomas [13]. This might be attributed to its relatively high uptake in extra-adrenal abdominal paragangliomas on 131I-MIBG imaging. In contrast, the relatively low uptake of 99mTc-HYNIC-TOC in tumors might indicate the low expression level of somatostatin receptor in extra-adrenal abdominal paragangliomas.

According to the European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of pheochromocytoma and paraganglioma, 131I-MIBG imaging was recommended as the third-line imaging investigation for extra-adrenal paragangliomas only when 68Ga-labelled somatostatin analogues (SSAs) and 18F-fluorodihydroxyphenylalanine (FDOPA) are unavailable [8]. In a recent study, 68Ga-DOTA-NOC showed a high sensitivity of 96.8% in
a subgroup of patients with extra-adrenal abdominal paragangliomas and proved to be valuable for imaging such cases [10]. As for 18F-FDOPA, most studies, to date, have only focused on a selected group of patients with recurrent or metastatic paragangliomas, paragangliomas associated with genetic disorders, or head and neck paragangliomas [14–21]. On literature review, we made some unexpected discoveries. A study that compared 18F-FDOPA and 123I-MIBG in 25 patients with either adrenal pheochromocytomas or extra-adrenal paragangliomas reported an overall sensitivity of 98 and 53% with the two imaging modalities, respectively. Of the 25 patients examined, 4 had extra-adrenal abdominal paragangliomas. We noticed that MIBG imaging was positive in all these 4 (100%) patients, whereas 18F-FDOPA was only positive in 3 patients (75%) [22]. Timmers et al., [5] conducted a prospective study and compared the performance of different functional imaging in 52 patients, including 20 nonmetastatic paraganglioma cases (11 adrenal) and 28 metastatic paraganglioma cases (13 adrenal). Five patients with nonmetastatic paragangliomas had primary extra-adrenal abdominal paragangliomas; MIBG showed positive findings in 4 (80%) patients, while 18F-FDOPA showed positive findings in only 2 (40%) patients [5]. Similarly, Charrier et al., [23] evaluated the performance of 18F-FDOPA in patients with nonmetastatic extra-adrenal paragangliomas (head and neck paragangliomas, 29; thoracic paraganglioma, 1 and extra-adrenal abdominal paragangliomas, 12) and reported 18F-FDOPA-positive finding in 7 of the 12 cases of (58.3%) extra-adrenal abdominal paragangliomas [23]. Although these studies had limited number of patients with extra-adrenal abdominal paragangliomas, the combined findings tended to suggest that 18F-FDOPA had a relatively poor performance for detecting extra-adrenal abdominal paraganglioma, and showed a lower sensitivity than MIBG on reevaluation of the reported data. In contrast to the situation with MIBG, the excellent performance of 18F-FDOPA in head and neck paragangliomas, recurrent or metastatic extra-adrenal paragangliomas or genetic-associated paragangliomas may lead to the overestimation of its efficacy in extra-adrenal abdominal paragangliomas. Therefore, studies that compare 18F-FDOPA and MIBG in the same group of patients with extra-adrenal abdominal paragangliomas are warranted to achieve conclusive results. Our results illustrated that 131I-MIBG imaging is a highly valuable modality for detecting extra-adrenal abdominal paragangliomas and should be given more priority than before when recommending functional imaging modality for preoperative identification of suspected extra-adrenal abdominal paragangliomas. The value of 131I-MIBG imaging in this setting must not be underestimated despite its poor performance in the detection of extra-adrenal paraganglioma at other sites.

To date, only a few case reports have described functional imaging findings for urinary bladder paragangliomas [24–30]. In the present study, both planar 131I-MIBG imaging and 99mTc-HYNIC-TOC scintigraphy had poor
Performance of 131I-MIBG imaging and 99mTc-HYNIC-TOC scintigraphy

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The inclusion of SPECT/CT might help to differentiate intra-tumor tracer uptake from radioactive urine. Our results suggested that, in combination with SPECT/CT, 131I-MIBG seemed to perform better than 99mTc-HYNIC-TOC for detecting urinary bladder paragangliomas, although the difference was not statistically significant, possibly due to the small number of patients who underwent SPECT/CT. Previously published case reports also presented similar tracer uptake pattern in which urinary bladder paraganglioma was negative on somatostatin receptor imaging but positive on MIBG scan [26,28]. These findings led to the speculation that there may be a variety or lack of somatostatin receptor expression on urinary bladder paragangliomas.

In the head and neck paragangliomas group, the sensitivity of 131I-MIBG imaging was as low as 17.4%. This result was consistent with the previous findings that MIBG imaging offered a sensitivity of 18–50% for head and neck paragangliomas [8,22,31,32]. 99mTc-HYNIC-TOC scintigraphy was superior to 131I-MIBG imaging owing to its significantly higher sensitivity, which was also consistent with previous results [31,33]. For paragangliomas of the thorax, 99mTc-HYNIC-TOC scintigraphy also performed better than 131I-MIBG scintigraphy. One reason for this might be that 131I-MIBG has a varying degree of physiologic cardiac uptake, while 99mTc-HYNIC-TOC does not [34,35]. Therefore, it might be easier for 99mTc-HYNIC-TOC to recognize paragangliomas in the mediastinal region. Additionally, for head and neck, and thoracic paragangliomas, no MIBG-positive/99mTc-HYNIC-TOC-negative patients in our cohort were present. Therefore, we consider that 131I-MIBG should not be recommended in these two conditions when 99mTc-HYNIC-TOC is available.

The present study has several limitations. First, this was a retrospective study, which made it difficult to avoid the unintended bias in patient selection. Second, the number of patients with thoracic and urinary bladder paragangliomas was relatively small compared to those with extra-adrenal head and neck, and abdominal paragangliomas. Third, the comparison between 131I-MIBG imaging and 99mTc-HYNIC-TOC scintigraphy may be hampered as not all patients included in this study underwent both imaging modalities.

**Conclusion**

We conclude that 131I-MIBG imaging should be considered as a front-line investigation modality in patients...
with extra-adrenal abdominal paraganglioma. $^{131}$I-MIBG imaging should be given more priority when recommending functional imaging for the preoperative identification of suspected extra-adrenal abdominal paraganglioma. 99mTc-HYNIC-TOC scintigraphy has high sensitivity and was superior to $^{131}$I-MIBG imaging for head and neck paraganglioma and thoracic paraganglioma. Both $^{131}$I-MIBG and 99mTc-HYNIC-TOC imaging have poor performance for detecting urinary bladder paragangliomas, which was probably due to the interference of radioactive urine, whereas the inclusion of SPECT/CT may aid in the detection of tumors.

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Conflicts of interest
There are no conflicts of interest.

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