Abstract. Background: Recommendations on the use of I-123 metaiodobenzylguanidine (MIBG) scintigraphy in localising phaeochromocytomas vary. The accuracy of I-123 MIBG scintigraphy was determined by evaluating our own I-123 MIBG scans and performing a meta-analysis. Materials and Methods: Between January 1992 and May 2002, the I-123 MIBG scans of consecutive patients suspected of a phaeochromocytoma were re-evaluated. For the meta-analysis, studies with more than 5 I-123 MIBG scans were selected. Results: Thirty patients were evaluated. The sensitivity in our own population was 92% and the specificity was 100%. Twelve articles were selected for our meta-analysis. The overall sensitivity and specificity were 96% and 100%, respectively. The sensitivity and specificity for tumours in the adrenal gland was 98% for both. For tumours located outside the adrenal gland, the sensitivity was 98% and the sensitivity for malignancies was 79%. Conclusion: I-123 MIBG scintigraphy has an excellent sensitivity and specificity in localising phaeochromocytomas, except for malignant tumours. I-123 MIBG scintigraphy is superior in localising tumours outside the adrenal gland.

Phaeochromocytomas are rare catecholamine-secreting neuroendocrine tumours arising from chromaffine tissue of the adrenal gland or extra-adrenal paraganglia (1). Phaeochromocytomas arising from the extra-adrenal paraganglia are also termed extra-adrenal phaeochromocytomas. About 80-85% of the phaeochromocytomas arise from the adrenal gland and about 15-20% arise from the extra-adrenal paraganglia, in the retroperitoneum, the mediastinum, the pelvic region and in the head and neck region (2, 3). The suspicion of a phaeochromocytoma is based on clinical signs and symptoms and includes a medical history of hypertension, episodic "spells" (i.e., headache, palpitation, sweating, pallor) or a family history of syndromes known to be associated with phaeochromocytomas (4-7). Laboratory investigations consist of the demonstration of biochemical excess of catecholamine and/or metabolites in blood and/or urine and should be performed for biochemical confirmation prior to the localisation of the tumour. Localisation of the tumour is necessary for surgical removal. This can be achieved by computed tomography (CT), magnetic resonance imaging (MRI) or metaiodobenzylguanidine (MIBG) scintigraphy. CT or MRI is mandatory for accurate anatomical information, especially since the introduction of laparoscopic techniques (8, 9).

The sensitivity for tumour localisation varies between 87%-100% for CT (10-13) and 91%-98% for MRI (13, 14). Studies comparing CT and MRI are in favour of MRI (13-15). The sensitivity is about 20% lower for phaeochromocytomas outside the adrenal gland, compared to phaeochromocytomas in the adrenal gland (14, 16). The specificity of MRI is reported to be higher compared to the specificity for CT for tumours of the adrenal gland, being between 88 and 100% for MRI (4, 14, 17-19).

Wieland et al. developed the use of whole body MIBG scintigraphy in 1980 (20). MIBG is a guanithidine analogue that is structurally similar to norepinephrine and is taken up by adrenergic storage vesicles in the adrenal gland and the paraganglia, thus visualising neuroendocrine tissue. MIBG can be labelled with I-131 or I-123. The sensitivity of I-131 MIBG scintigraphy is limited so I-123 MIBG scintigraphy was introduced to improve the image quality and to increase sensitivity (14). However, I-123 MIBG is not widely available and is more expensive. Recommendations on the use of MIBG scintigraphy in localising a phaeochromocytoma depend on the author. It is preferred as an initial diagnostic localising modality because whole body images can be obtained (14, 21-
25). It is recommended in addition to MRI or CT to rule out multiple lesions outside the adrenal gland and for confirmation of the lesion found on CT or MRI (15, 26-31). Other authors do not recommend routinely performing a MIGB scintigraphy (18, 32-34). These diverse recommendations have several drawbacks. Most recommendations are based on studies using I-131 as a label, since this was introduced before I-123 MIBG scintigraphy and because of the better availability of I-131 MIBG in the USA. Furthermore, studies using I-123 MIBG as a label are, because of the rarity of the disease, mostly retrospective and study populations are relatively small.

The aim of this study was to determine the diagnostic accuracy of I-123 MIBG scintigraphy in localising a phaeochromocytoma and to propose a diagnostic approach for localisation. Our I-123 MIBG scans were reviewed and a meta-analysis of previous studies, investigating the sensitivity and specificity of I-123 MIBG scintigraphy, was carried out.

### Materials and Methods

**Patient selection.** Between January 1992 and May 2002, all consecutive patients suspected of a phaeochromocytoma at the Department of Endocrinology, University Medical Center, Groningen, The Netherlands, were studied. Thirty-four patients were included. They had typical signs and symptoms combined with a consistent (≥2) increase in urinary excretion of the fractionated metanephrines (i.e., normetanephrine and metanephrine). Patients whose MIBG scintigraphy was not available for re-analysis (n=1) and patients without a final diagnosis (n=3) were excluded. The charts of the remaining 30 patients were retrospectively reviewed for data about age, gender, the presence of a familial syndrome, laboratory investigations, radiology examinations and therapy. For the gold standard the pathology reports were used, if patients underwent surgery. In those cases where histopathology was lacking, independent physicians were asked to review the case.

**Laboratory investigations.** The urinary excretion of fractionated normetanephrine and metanephrine was used for biochemical proof of increased catecholamine secretion. Fractionated total normetanephrine and metanephrine were determined using extractive derivatisation and stable isotope gas chromatography with mass fragmentographic detection (35). Values more than 1.5 times the upper limit (normal value metanephrine: 33-99 μmol/mol kreatinin, normal value normetanephrine: 64-260 μmol/mol kreatinin) were considered abnormal.

**I-123 MIBG scintigraphy.** All MIBG scans were made using I-123 as a label. The injected dose was 185 MBq. The scans were acquired after 24 h on a dedicated gammacamera (Siemens DIACAM or Multispect 2), in a 256 matrix, zoomfactor 1.23, using a 15% window centre around a I-123 photopeak of 159 keV. The original I-123 MIBG scans were re-evaluated by 2 experienced observers who were unaware of the clinical circumstances. Each independently rated the intensity of the lesions, on a range from 0 to grade 3. A score of 0 represented no uptake, grade 1 low uptake, lower than the liver, grade 2 moderate uptake, equal to the liver and grade 3 intense uptake, more than the liver. Grades 2 and 3 were defined as MIBG-positive. A consensus was reached if there was a discrepancy between the 2 observers.

**Gold standard.** The histopathological diagnosis was considered the gold standard. A distinction was made between a phaeochromocytoma and hyperplasia. Hyperplasia was defined as glands harbouring tumour nodules less than 1 cm. Normalisation of the urinary excretion of the catecholamines metabolites was considered proof of absence of disease. Three independent physicians reviewed the medical charts of patients with persistently elevated urinary excretion of the catecholamine metabolites, for whom no histopathological diagnosis had been obtained. They were unaware of the clinical outcome. Their consensus was considered the gold standard.

**Search strategy.** For the meta-analysis, the literature was searched and studies, on the value of I-123 MIBG scintigraphy were selected, including studies with more than 5 scans. The clinical database Medline (Pubmed) was consulted, using the following MESH headings and/or text words: MIBG, metaiodobenzylguanidine, MIBG scintigraphy, localisation, phaeochromocytoma, paraganglioma, sensitivity and specificity. We also used the references of the articles found. Only studies published in America or Europe were included. Studies were excluded if data from the same patients had been used in more than one publication, in which case the article that included the most patients was used.

**Statistical analysis.** Using the above-mentioned gold standard for the presence and absence of a phaeochromocytoma, the MIBG scintigraphy was classified as true-positive, true-negative, false-positive or false-negative on a patient level. For the meta-analysis, information about each I-123 MIBG scintigraphy given in the various studies was used. Because the number of studies overall showed no heterogeneity regarding the effect estimates (sensitivity and specificity), the results of the pooled analyses of sensitivity and specificity in the studies, using fixed-effect models with continuity correction, are shown. Fixed-effect analysis computes the summary estimates of the sensitivity and specificity.

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**Table I. Results of re-evaluation of I-123 MIBG scintigraphy.**

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>MIBG +</th>
<th>MIBG -</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phaeochromocytoma (total)</td>
<td>24</td>
<td>2</td>
<td>26</td>
</tr>
<tr>
<td>In adrenal gland</td>
<td>19</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>MEN 2a</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>unilateral</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>bilateral</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Recklinghausen</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Sporadic</td>
<td>11</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Outside adrenal gland</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Malignant</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Other diagnosis, no phaeochromocytoma

| MIBG=metaiodobenzylguanidine. MEN2a=multiple endocrine neoplasia type 2a. |
with its confidence interval of the individual studies, and Woolf’s test for heterogeneity. The method presented here gives standard meta-analysis estimates and the 95% confidence interval with continuity correction for each study is provided as well. The sensitivity has, by definition, been truncated at 1.0. The sensitivity of I-123 MIBG scintigraphy for phaeochromocytoma inside the adrenal gland, outside the adrenal gland and for malignant disease has been computed. Meta-analyses were performed using the Rmeta package of the R Project for Statistical Computing (Build 1.8.1).

Results

Patients. Thirty patients were included. The median age was 44 years (range 23-78) and 12 were men (40%). Ten patients (33%) were evaluated because of a familial syndrome, 8 because of multiple endocrine neoplasia (MEN) type 2a and 2 because of M. Recklinghausen. The final diagnosis was phaeochromocytoma in 26 patients (87%). In 24 out of the 26 patients, there was histopathological proof, while in 2 patients the judgement of the reviewers served as the gold standard. Both of these patients had recurrent disease, 1 patient was not operated on because of malignant disease and in the other patient imaging showed no tumour, although he had a rise in the urinary excretion of normetanephrines 15 years after the resection of a phaeochromocytoma outside the adrenal gland. The tumour was located in the adrenal gland in 20 out of 26 patients (77%), in 4 patients (15%) it was located outside the adrenal gland and 2 patients (8%) had malignant disease.

Four patients (13%) were classified with another diagnosis; 3 patients had a spontaneous normalisation of the urinary excretion of catecholamine metabolites and remained free of symptoms after a median follow-up of 3 years; the remaining patient was analysed because of abdominal pain, dizzy spells and marginally raised urinary excretions of metanephrines. She underwent surgery because of a suspected phaeochromocytoma outside the adrenal gland. During the operation no phaeochromocytoma could be detected and post-operatively the urinary excretion of metanephrines normalised spontaneously.

Sensitivity and specificity of I-123 MIBG scintigraphy in our own population (Table I). The I-123 MIBG scintigraphy was false-negative in 2 patients. One I-123 MIBG scan did not localise a phaeochromocytoma in the right adrenal gland in a patient with MEN 2a syndrome and bilateral phaeochromocytoma. The tumour in the right adrenal gland had a diameter of 2.4 cm. Another false-negative scan concerned the patient with the recurrent phaeochromocytoma 15 years after the resection of a phaeochromocytoma outside the adrenal gland. The sensitivity of the I-123 MIBG in the localisation of phaeochromocytoma was 92%. There were no false-positive results, thus the specificity was 100%. The patient operated on because of a suspected phaeochromocytoma originally had had a positive scintigraphy, however the revised scintigraphy was negative.

An additional SPECT view was available in 15 patients, which was of additional value in 2 patients, whereby a tumour in the adrenal gland that was not visualised with the planar view was visualised.

Meta-analysis. Using the above-mentioned search strategy, 21 articles investigating the sensitivity and/or specificity of the I-123 MIBG scintigraphy were identified. Twelve articles were included in the meta-analysis (12, 18, 23, 27, 33, 34, 36-41) and 9 articles were excluded. Three articles from de Graaf et al. included similar patients, and the study including the most patients was included in our meta-analysis (11, 32, 37). Two studies did not provide information about the final diagnosis (42, 43) and 3 studies could not be included because no distinction was made between I-131 MIBG and I-123 MIBG scans (10, 44, 45). Two additional studies were excluded because phaeochromocytomas as well as non-functioning paragangliomas were included (38, 46), leaving 12 articles for meta-analysis. The results are provided in Table II. The overall sensitivity and specificity were 96% and 100%, respectively. For phaeochromocytomas in the adrenal gland, the sensitivity and specificity both were 98%. The sensitivity for tumours located outside the adrenal gland was 98% and that for malignant disease was 79%.

Table II. Pooled sensitivity and specificity of I-123 MIBG scintigraphy.

<table>
<thead>
<tr>
<th>(Studies used, reference, including own results)</th>
<th>% (95% CI)</th>
<th>Total no. observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (12, 18, 23, 27, 33, 34, 36-41)</td>
<td>96% (94-99%)</td>
<td>303</td>
</tr>
<tr>
<td>Specificity (12, 18, 23, 27, 36, 39, 40)</td>
<td>100% (99-100%)</td>
<td>207</td>
</tr>
<tr>
<td>Sensitivity in adrenal gland (12, 18, 27, 34, 40, 41)</td>
<td>98% (95-100%)</td>
<td>133</td>
</tr>
<tr>
<td>Specificity in adrenal gland (23, 33)</td>
<td>98% (95-100%)</td>
<td>357*</td>
</tr>
<tr>
<td>Sensitivity outside adrenal gland (12, 18, 23, 27, 41)</td>
<td>98% (91-100%)</td>
<td>22</td>
</tr>
<tr>
<td>Sensitivity malignancy (33)</td>
<td>79% (37-100%)</td>
<td>16</td>
</tr>
</tbody>
</table>

*Based on no. of adrenal glands.
**Discussion**

This is the first meta-analysis concerning the accuracy of I-123 MIBG scintigraphy, confirming it as an excellent diagnostic tool in localising phaeochromocytomas, with an overall sensitivity and specificity of 96% and 100%, respectively.

The accuracy of I-123 MIBG scintigraphy appears to be superior in the visualisation of phaeochromocytomas located outside the adrenal gland compared to the reported sensitivity of I-131 MIBG scintigraphy, CT and MRI. In our meta-analysis, the sensitivity was 98% for phaeochromocytomas located outside the adrenal gland, compared to a sensitivity of 80% for CT and MRI and 64% for I-131 MIBG scintigraphy (14, 16, 18). Although other studies have also reported this high sensitivity for tumours outside the adrenal gland, they were based on very few patients. Our meta-analysis included 22 observations. We were not informed about possible interfering medication in the separate studies, so the sensitivity of I-123 MIBG scintigraphy could even be higher. Therefore, for patients suspected of phaeochromocytoma with no tumour localisation on MRI and/or CT, an I-123 MIBG scintigraphy should be performed to rule out tumours outside the adrenal gland (Figure 1). A complementary MRI or CT after the localisation with I-123 MIBG scintigraphy is helpful for anatomical information (Figure 1).

Our meta-analysis, however, had a few drawbacks. We found a high specificity for phaeochromocytomas in the adrenal gland. This high specificity of I-123 MIBG scintigraphy was probably overestimated in patients with MEN type 2a. We excluded the de Graaf study that included patients with MEN type 2a. I-123 MIBG scintigraphy was false-positive in 5 out of 6 adrenal glands, 4 of them being classified as hyperplastic glands (32). Although hyperplasia is probably a precursor of a phaeochromocytoma, there is no evidence that a hyperplastic gland should be operated on (47, 48). Therefore, for patients with MEN type 2a, because of the
risk of visualising a contralateral normal or hyperplastic gland, I-123 MIBG scintigraphy should probably not be performed (32, 33, 42, 43) (Figure 1).

In patients without MEN type 2a, we suggest that an I-123 MIBG scintigraphy be performed for confirmation of the tumour detected by MRI or CT. This can exclude the possibility of an incidentaloma and the possibility that the pheochromocytoma is located outside the adrenal gland. These incidentalomas were found in 1.5% of CT scans in a large survey (49).

Although, in our population, I-123 MIBG scintigraphy showed 1 malignant lesion not visualised with MRI, the diagnostic value of I-123 MIBG scintigraphy for malignant tumours is disappointing. A sensitivity of 79%, however was based on only 16 patients. The affinity towards I-123 MIBG appears to be low for malignant tumours because dedifferentiated tumours can lose their ability to accumulate MIBG. In these patients, whole-body MRI or 6-[18F]-fluorodopamine positron emission tomography is an alternative (50).

We conclude that the diagnostic value of I-123 MIBG scintigraphy is excellent. It should always be performed when MRI or CT fails to localise a tumour, which is more likely to occur when the tumour is located outside the adrenal gland. When MRI or CT localises a tumour in the adrenal gland in patients with MEN type 2, I-123 MIBG scintigraphy should not be performed. The role of I-123 MIBG scintigraphy in malignant disease is disappointing and remains unclear.

References


