Pheochromocytomas detected by biochemical screening in predisposed subjects are associated with lower prevalence of clinical and biochemical manifestations and smaller tumors than pheochromocytomas detected by signs and symptoms

N van Duinen¹, D Steenvoorden¹, B A Bonsing², J Vuyk³, A H J T Vriends⁴, J C Jansen⁵, J A Romijn¹ and E P M Corssmit¹

¹Department of Endocrinology and Metabolic Diseases, ²Department of Surgery, ³Department of Anesthesiology, ⁴Center of Human and Clinical Genetics and ⁵Department of Otorhinolaryngology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands

(Correspondence should be addressed to N van Duinen; Email: n.van_duinen@lumc.nl)

Abstract

Context: Sporadic pheochromocytomas are detected by clinical signs and symptoms, whereas pheochromocytomas in patients with a known hereditary predisposition for these tumors are detected by repetitive screening for catecholamine excess.

Objective: To document the clinical, biochemical, and pathological differences between patients with sporadic pheochromocytomas, detected by signs and symptoms and patients with pheochromocytomas, detected by biochemical screening in established hereditary syndromes.

Design: Retrospective follow-up study.

Patients and methods: We included 60 consecutive patients diagnosed with pheochromocytoma (pheochromocytomas detected by signs and symptoms: n=28 and pheochromocytomas detected by screening: n=32) in our center.

Results: Patients with pheochromocytomas detected by screening presented with less complaints of diaphoresis (P<0.01), palpitations (P<0.01), paleness (P<0.01), nausea (P<0.01), and vomiting (P<0.01) compared with patients with symptomatic pheochromocytomas. Patients with pheochromocytomas detected by screening tended to be younger at the time of diagnosis (41 ± 2 vs 47 ± 3 years, P=0.07). In addition, patients with pheochromocytomas detected by screening had significantly lower rates of 24-h urinary catecholamine excretion, and considerably smaller tumors (3.7 ± 0.5 vs 7.3 ± 0.7 cm, P<0.01).

Conclusions: Pheochromocytomas detected by screening of patients with a hereditary predisposition have a much lower prevalence of signs and symptoms, lower catecholamine excess, and smaller tumors, compared with sporadic pheochromocytomas, detected by signs and symptoms. These data support the benefits of screening for pheochromocytomas in patients with hereditary syndromes predisposing for these tumors.

European Journal of Endocrinology 163 121–127

Introduction

Pheochromocytomas are rare neuroendocrine tumors derived from chromaffin tissue within the adrenal medulla (1). In 12–24% of cases of an apparently sporadic presentation, a pheochromocytoma is caused by germline mutations in the von Hippel–Lindau gene (VHL), the RET gene (leading to MEN2), the neurofibromatosis type I gene (NF1), or one of the SDH genes encoding for subunits B, D, and C of mitochondrial succinate dehydrogenase (2–8).

Sporadic pheochromocytomas are usually identified by signs and symptoms, including paroxysms of headache, sweating, palpitations, and hypertension resulting from the release of catecholamines from the tumor (9). However, a substantial proportion of patients with pheochromocytomas do not have signs and/or symptoms, which carries the risk of unexpected life-threatening catecholamine crises. Therefore, the advice is to screen patients with a known hereditary predisposition for the development of pheochromocytomas at regular intervals by the measurement of plasma levels and/or urinary catecholamine excretion rates (10). In case a pheochromocytoma is detected, adrenalectomy is indicated after appropriate preoperative care (11).

The benefits of screening may be intuitively reasonable, but these have not been formally tested. Therefore, we conducted a retrospective study comparing the data of patients with pheochromocytomas, detected by signs
and symptoms of patients with pheochromocytomas, detected by biochemical screening in hereditary syndromes. We compared signs and symptoms, biochemical parameters, (peri)operative outcome, and long-term results between these groups.

Patients and methods

We included 60 consecutive patients treated at our center between 1975 and 2008 by adrenalectomy for pheochromocytomas. The Leiden University Medical Center is a tertiary referral center for patients with pheochromocytomas. Of these 60 patients, 28 patients had sporadic pheochromocytoma, detected by signs and symptoms of catecholamine excess, whereas 32 patients had a pheochromocytoma detected by screening in subjects with a hereditary predisposition. Hereditary predisposition, which indicated the need for biochemical screening, was defined by a positive family history with phenotypic evidence of a syndrome, predisposing for pheochromocytomas, and/or the presence of germline mutations of the RET, VHL, NF1, or SDH genes respectively. Patients who presented with signs and symptoms, which resulted in the diagnosis and treatment of pheochromocytoma, were defined as having sporadic pheochromocytomas. In patients with hereditary pheochromocytomas, clinical follow-up and screening for catecholamine excess were performed at least every 2 years. In case of excessive catecholamine excretion, abdominal magnetic resonance imaging (MRI) and/or computed tomography (CT) scanning was performed.

One patient was incidentally diagnosed with a pheochromocytoma after CT scanning because of a rectal adenoma. The patient had no catecholamine-related sign or symptom, an increased urinary excretion rate of catecholamines, and a 5.2-cm tumor in the right adrenal. Because the aim of the study was to compare the clinical features of patients with pheochromocytomas who present with tumor and/or catecholamine-related signs or symptoms versus patients who are screened for pheochromocytoma, we could not classify this patient into one of these categories. Therefore, the patient was excluded from the study.

All patients were investigated at the outpatient clinic according to the structured clinical protocols, which were standard care. These included questions focused on tumor- and catecholamine-related signs and symptoms, measurement of blood pressure in the supine position, and after 5 min in upright position, in order to screen for orthostatic hypotension.

The diagnosis of pheochromocytoma was established by increased urinary excretion rates of catecholamines and/or their metabolites, and confirmed by pathological examination. Radiological examination was performed by (a combination of) ultrasonography, CT, MRI, and metaiodobenzylguanidine (MIBG) scanning. Clinical, endocrinological, radiological, and (peri)operative data were available for all patients.

Prior to surgery, the patients were treated with \(\alpha\)-receptor blocking drugs (doxazosin or phenoxybenzamine) titrated on orthostatic hypotension followed by \(\beta\)-blockade (propanolol) if necessary (pulse rate > 70 bpm during \(\alpha\)-blockade), and i.v. hydration with isotonic saline the day preceding the operation. Hemodynamic instability during surgery was defined as an episode of systolic arterial pressure above 160 mmHg and/or a mean arterial pressure < 60 mmHg. All episodes were counted, and the total duration of hyper/hypotension was recorded. Complications occurring in the pre-, peri-, and postoperative periods were recorded. A diagnosis of malignancy was made in case of distant metastases and/or local recurrence. Recurrence was defined as the reappearance of the disease after eradication of the tumor had been confirmed by negative biochemical and imaging tests. The diameter of the tumor was determined on postoperative histopathology.

The study was an evaluation of routine patient care. According to the requirements of Dutch law, it was not necessary to obtain permission from the institutional ethical commission. Prior to germline mutation testing, informed consent was obtained from each patient.

The screening group comprised 32 patients, 17 with familial paraganglioma syndrome (16 with an SDHD mutation and 1 unknown), 12 with MEN2, 2 with NF, and 1 with VHL disease. In patients with familial paraganglioma syndrome, 14 patients presented with head and neck paragangliomas were screened for pheochromocytoma. 3 patients were referred for screening because an SDH mutation was found in a family member. In the MEN2 patient group, 11 patients were known with the disease and were screened for pheochromocytoma, and 1 patient was screened for pheochromocytoma after his son was diagnosed with MEN2 syndrome and was found to have a tumor. Both patients with NF were diagnosed with pheochromocytoma after they were screened for pheochromocytoma. One patient with a hemangioblastoma of the retina was referred to the department of endocrinology because of suspected VHL disease. During clinical assessment, he was found having a pheochromocytoma.

Assays

Excretion rates of epinephrine, norepinephrine, and dopamine in 24-h urine collections were quantified by reverse HPLC using electrochemical detector. Inter- and intra-assay coefficients of variations (CV) for epinephrine were 4.3–9.0% ranging from high to low levels. For norepinephrine, CV were 2.7–3.6%, and for dopamine, CV were 3.1–4.8%. Vanillylic mandelic acid (VMA) in urine was measured using HPLC with fluorometric detection with inter- and
intra-assay CV of 2.4–9.1%. Reference ranges (expressed as μmol/24 h) obtained in healthy subjects was 0.06–0.47 for norepinephrine, <0.16 for epinephrine, 0.46–3.40 for dopamine and <30 for VMA (12). In order to ascertain adequacy of collection, the urinary creatinine content was assessed as well. Urine samples were considered to be positive if 24-h urinary excretion of catecholamines exceeded the reference limit.

**Statistical analysis**

SPSS for windows version 16.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Patients were divided into sporadic and hereditary groups. Results are expressed as means ± S.E.M., unless otherwise specified. Independent sample t-tests and χ² tests were used to compare the data obtained in patients screened for hereditary pheochromocytomas and those in patients with sporadic pheochromocytomas. A P value <0.05 was considered to represent a significant difference.

**Results**

**Clinical characteristics**

Patients with pheochromocytomas detected by biochemical screening, presented with significantly less complaints of diaphoresis, palpitations, paleness, nausea, vomiting, and a significantly lower prevalence of type 2 diabetes mellitus, significantly lower systolic blood pressure, and significantly lower mean arterial pressure compared with patients with pheochromocytomas detected by signs and symptoms (Table 1). The classical triad of diaphoresis, palpitations, and headache were reported by only 5 of the 32 patients with pheochromocytomas detected by screening (16%) and by 11 of 28 patients (39%) with sporadic pheochromocytomas (P=0.04 between both groups). Ten patients in the screening group (31%) had no tumor or catecholamine-related signs or symptoms. In addition, patients with pheochromocytomas detected by screening tended to be younger at the time of diagnosis. The mean age of the hereditary paraganglioma patients was 46 ± 3 years (range 25–65 years), 36 ± 4 years (range 19–61 years) for the MEN2 patients, 27 ± 11 years (16–38 years) for the NF patients, and 37 years for the patient with VHL disease.

Time between presentation and surgery was 123 ± 21 days (mean ± S.E.M.) in the sporadic group. Time between diagnosis of pheochromocytoma and surgery was 420 ± 162 days (mean ± S.E.M.) in the screening group. Patients in the screening group had been observed for an average duration of 8.4 ± 1.5 years (mean ± S.E.M.). In the sporadic group, two patients were diagnosed with a hereditary syndrome after surgery.

**Biochemical results**

All patients had increased 24-h urinary excretion rates of catecholamines and/or their O-methylated metabolites ((nor)epinephrine, dopamine, and/or VMA; Table 2). Patients with pheochromocytomas detected by biochemical screening had lower rates of urinary excretion of (nor)epinephrine, dopamine, and VMA than patients with sporadic pheochromocytomas.

**MIBG scintigraphy**

In 40 patients with 44 pheochromocytomas, additional 123I-MIBG scanning was performed. Overall, 35 of 44 (80%) adrenal tumors showed increased uptake. Patient-based sensitivity of MIBG scanning was 77% in the screening group and 86% in the sporadic group. MIBG uptake was increased in 7/7 of MEN2, 12/16 PGL patients, and 1/2 of NF patients. No increased uptake was shown in the patient with VHL disease. Tumors of patients with a positive MIBG scan tended to be larger than in the patients with a negative scan (3.4 ± 0.6 vs 2.5 ± 0.7 cm; P=0.08).

Table 1  Clinical characteristics at the time of diagnosis of patients with sporadic pheochromocytomas versus patients with pheochromocytomas detected by screening. Data are shown as mean (±S.E.M.), unless otherwise mentioned.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sporadic</th>
<th>Screening</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>28</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Gender (n (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>14 (50%)</td>
<td>21 (66%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.5 ± 0.7</td>
<td>25.3 ± 0.7</td>
<td>0.44</td>
</tr>
<tr>
<td>Age (at diagnosis (years))</td>
<td>47 ± 3</td>
<td>41 ± 2</td>
<td>0.07</td>
</tr>
<tr>
<td>Symptoms (n (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>21 (75%)</td>
<td>11 (34%)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Palpitations</td>
<td>18 (64%)</td>
<td>9 (28%)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Headache</td>
<td>16 (57%)</td>
<td>12 (38%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Diap. + palp. + head.</td>
<td>11 (39%)</td>
<td>5 (16%)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (32%)</td>
<td>9 (28%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Pallor</td>
<td>12 (43%)</td>
<td>4 (13%)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (43%)</td>
<td>1 (3%)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (21%)</td>
<td>0</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Flushed</td>
<td>2 (7%)</td>
<td>5 (16%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (54%)</td>
<td>11 (34%)</td>
<td>0.13</td>
</tr>
<tr>
<td>(&gt;140/90 mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes mellitus (n (%))</td>
<td>5 (18%)</td>
<td>1 (3%)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>156.4 ± 4.7</td>
<td>143.1 ± 2.8</td>
<td>0.02*</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>116.0 ± 3.5</td>
<td>106.8 ± 2.0</td>
<td>0.03*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>95.7 ± 0.4</td>
<td>88.6 ± 1.9</td>
<td>0.07</td>
</tr>
<tr>
<td>Antihypertensive medication (n (%))</td>
<td>13 (46%)</td>
<td>4 (13%)</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

Diap., diaphoresis; Palp., palpitations; head, headache; *Statistically significant.
Table 2  Biochemical characteristics of patients with sporadic pheochromocytomas versus patients with pheochromocytomas detected by screening. Data are shown as mean (s.E.M.), unless otherwise mentioned.

<table>
<thead>
<tr>
<th>Catecholamines</th>
<th>Sporadic N tested pos</th>
<th>Screening N tested pos</th>
<th>Sporadic Mean ± S.E.M.</th>
<th>Screening Mean ± S.E.M.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mmol/24 h)</td>
<td>12.8 ± 1.1</td>
<td>13.8 ± 0.8</td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>Epinephrine (μmol/24 h)</td>
<td>17/22</td>
<td>8/29</td>
<td>1.9 ± 0.5</td>
<td>0.3 ± 0.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Norepinephrine (μmol/24 h)</td>
<td>18/23</td>
<td>22/30</td>
<td>5.5 ± 1.6</td>
<td>1.4 ± 0.3</td>
<td>0.02*</td>
</tr>
<tr>
<td>Dopamine (μmol/24 h)</td>
<td>9/21</td>
<td>9/29</td>
<td>7.5 ± 2.4</td>
<td>3.1 ± 0.3</td>
<td>0.09</td>
</tr>
<tr>
<td>VMA (μmol/24 h)</td>
<td>21/23</td>
<td>20/30</td>
<td>127.2 ± 23.1</td>
<td>42.1 ± 4.2</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Positive urine sample</td>
<td>28/28</td>
<td>32/32</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VMA, vanillylmandelic acid; *Statistically significant.

**Intra- and postoperative events**

Laparoscopic surgery was performed in 18% of patients in the sporadic group versus 59% of patients in the screening group. Open surgery was performed in 82% of patients in the sporadic group versus 41% of patients in the screening group. There was no difference in the number of complications between the patients treated with laparoscopic surgery versus open surgery ($P = 1.00$). There were no differences in the duration of surgery, blood loss, and hemodynamic instability between the two groups (Table 3). Adverse intraoperative events or complications occurred in nine patients in the group detected by screening and in 11 patients in the sporadic group (NS). There were no perioperative deaths or cardiovascular events.

**Pathology**

In the patients with pheochromocytomas detected by screening, 8 patients (25%) had a pheochromocytoma in the right adrenal gland, 18 patients (56%) had a pheochromocytoma in the left adrenal gland, and 6 patients (19%) had bilateral pheochromocytomas. In the sporadic group, 16 of the 28 patients had a pheochromocytoma located in the right adrenal gland (57%), and 10 patients had a pheochromocytoma located in the left adrenal gland (36%), whereas there was a bilateral pheochromocytoma in two patients (7%). Pheochromocytomas in the sporadic group were significantly larger compared with the hereditary group ($7.3 ± 0.7$ vs $3.7 ± 0.5$ cm, $P < 0.01$). One patient in the sporadic group had a malignant tumor, reflected by metastatic disease.

**Long-term follow-up**

Mean follow-up time was $7.5 ± 1.4$ years in the patients with pheochromocytomas detected by screening and $7.8 ± 1.4$ years in the patients with sporadic pheochromocytomas. In the patients with pheochromocytomas detected by screening, six patients (five with MEN 2A and one with hereditary paragangliomas) developed a pheochromocytoma in the opposite adrenal gland, but none developed metastatic or locally recurrent disease. In the patients with sporadic pheochromocytomas, one patient developed a second pheochromocytoma, one patient developed metastatic disease, and one patient developed local recurrence and metastases. In the sporadic group, two patients died of nontumor-related conditions, whereas the cause of death was unknown in one other patient.

**Discussion**

We compared the differences between patients with pheochromocytomas detected by biochemical screening in hereditary syndromes predisposing for pheochromocytomas and patients with sporadic pheochromocytomas (patients with incidentalomas were excluded). Our study clearly shows that patients screened for pheochromocytoma because of a hereditary predisposition presented with less signs and symptoms, lower urinary excretion rates of catecholamines, and smaller tumors than patients presenting with symptomatic pheochromocytomas.

The patients with pheochromocytomas detected by screening had significantly less pheochromocytoma-related complaints. This can be explained by the fact...
that these pheochromocytomas were found at an earlier stage when the tumor is smaller and produces less catecholamines. Our data is in line with those of Pomares et al., (13) who compared patients with sporadic pheochromocytomas and patients with pheochromocytomas caused by the MEN 2A syndrome. They reported similar differences in age at presentation, clinical signs and symptoms, radiological findings, and unilateral pheochromocytomas versus bilateral pheochromocytomas (13). We included patients with pheochromocytomas detected by screening for several hereditary syndromes predisposing to pheochromocytomas (MEN 2A syndrome, NF1, VHL disease, and familial paraganglioma syndrome) and patients presenting with sporadic pheochromocytomas. In the patients with pheochromocytomas detected by screening, the age at presentation was 6 years younger than in the sporadic group, which might reflect a benefit of screening and/or earlier development of pheochromocytoma in patients with hereditary disease. The ages of the patients with SDHD-related pheochromocytoma found in our study are higher compared with the mean ages reported in the literature. This difference can be explained by the fact that the other studies included children in their studies (2, 4, 14). The mean ages of the patients with MEN2, VHL, and NF included in our study are comparable with those reported in the literature (4, 6, 13, 15, 16). The higher age range of our hereditary paraganglioma patients increases the mean age of the hereditary patient group in total.

All our patients had increased urinary catecholamine excretion. In the patients with pheochromocytomas detected by screening, the mean excretion rates of (nor)epinephrine were significantly lower compared with patients with sporadic pheochromocytomas. In accordance with the study of Eisenhofer et al., (15) who documented a positive relation between the size of the pheochromocytoma and urinary catecholamine excretion, the patients with the sporadic pheochromocytomas had larger pheochromocytomas and higher urinary excretion rates of catecholamines.

The reported sensitivity and specificity of MIBG scanning in patients with (suspected) pheochromocytoma range from 80 to 100% (17–22). MIBG uptake correlates with the production of catecholamines (18). The detection rate of MIBG scanning in the screening group was lower because of the smaller tumors and the lower biochemical activity.

Despite these differences in biochemical activity and the sizes of the pheochromocytomas, there were no differences between both groups in perioperative complications. There were no perioperative deaths, or cardiovascular events. This was probably related to careful pre- and (peri)operative care with careful titration of α- and β-blocker drugs. Patients in the screening group were treated more often with laparoscopic surgery. The differences in the method of operation resulted from differences in tumor diameter (larger in the sporadic group) and because of the innovation with regard to operation technique during the decades. Despite the differences in operation technique, the number of complications were not different between the patients treated with laparoscopic surgery versus open surgery.

Long-term follow-up revealed additional manifestations of disease in both groups of patients. In the patients with a documented hereditary predisposition, several patients developed an additional pheochromocytoma in the contralateral adrenal gland, especially in the case of MEN 2A syndrome (5). In the sporadic group, there were several patients with malignant pheochromocytomas. Therefore, long-term follow-up seems to be warranted in all pheochromocytoma patients, irrespective of initial presentation.

The sporadic group also contained patients with germline mutations predisposing to the development of pheochromocytomas, which were detected by signs and symptoms because they had not been identified previously by prior knowledge of the predisposing hereditary syndrome. However, this does not invalidate our conclusions, because we report the benefits of screening, once this genetic predisposition has been documented.

Because the aim of the study was to compare the clinical features of patients with pheochromocytoma who present with tumor and/or catecholamine-related signs or symptoms versus patients who are screened for pheochromocytoma, we excluded patients who presented with an incidentaloma. Studies comparing the clinical features of patients with incidentalomas versus patients who presented with adrenergic symptoms reported less catecholamine-related signs and symptoms, lower plasma catecholamines concentrations, similar tumor size, and an older age at presentation in the patient group with incidentalomas (23–25). Because patients with incidentalomas were excluded from the sporadic group in our study, the reported signs and symptoms, the mean urinary catecholamine excretion rate, and the mean age at presentation found in our study might be different compared with studies that included patients with incidentalomas.

Patients at risk for developing a pheochromocytoma should be regularly screened. The diagnostic test of choice is the measurement of fractionated plasma and/or urinary metanephrines (26). Patients with a SDHx mutation, MEN2 disease, or VHL disease are advised to be screened for pheochromocytoma annually. In case of increased plasma/urinary catecholamines or their metabolites, additional radiological investigation should be performed to identify the culprit lesion (2, 6, 13, 27). The prevalence of pheochromocytoma is quite low in patients with NF, and therefore, screening is not recommended in all patients, but it may be justified in those patients with NF with hypertension, or in those patients who will undergo provocative interventions.
such as surgery or pregnancy (7). Children who are predisposed to the development of a pheochromocytoma should be screened annually. The age of initial screening should be determined by the specific gene mutation (28).

In conclusion, screening for pheochromocytomas in patients with a hereditary predisposition for these tumors was associated with a much lower prevalence of signs and symptoms, lower values of catecholamine excess, and smaller tumors, compared with sporadic pheochromocytomas, detected by signs and symptoms. This observational study supports the usefulness of a screening program for pheochromocytomas in subjects with hereditary predispositions. In addition, we recommend lifelong follow-up of all patients with pheochromocytomas, irrespective of the initial manifestation, because of the risk of developing a new tumor, recurrent or metastatic disease.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

References

22 Wiseman GA, Pacak K, O'Dorisio MS, Neumann DR, Waxman AD, Mankoff DA, Heiba SI, Serafini AN, Tumeh SS, Khutoryansky N & Jacobson AF. Usefulness of 123I-MIBG scintigraphy in the evaluation of patients with known or suspected primary or metastatic pheochromocytoma or paraganglioma: results from a prospective multicenter trial. *Journal of Nuclear Medicine* 2009 50 1448–1454.


