Phaeochromocytoma: a ten-year survey


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Summary

We retrospectively evaluated our experience with phaeochromocytoma from January 1986 to December 1995. There were 18 patients with surgically-proven phaeochromocytoma: three males, 15 females, aged 12–81 years (mean 42 years) at diagnosis. Sixteen were hypertensive; only 6/18 presented with two or more of the classical triad of headaches, palpitations and diaphoresis. One patient presented with hypertensive crisis. Duration of symptoms prior to diagnosis was 2 weeks to 6 years, mean 16.4 months. Sixteen patients had adrenal tumours and two had extra-adrenal tumours or paragangliomas. One had bilateral adrenal tumours and two had a combination of both adrenal and extra-adrenal tumours. There were four familial cases: two had multiple endocrine neoplasia type II A (MEN-II A), one had neurofibromatosis type I (NF-I) and one von Hippel-Lindau (VHL) disease. One patient had Cushing’s syndrome arising from ectopic production of adrenocorticotropic hormone (ACTH) by the phaeochromocytoma. Disease was recurrent in three patients. Pre-operative diagnosis was confirmed mainly by elevated urine vanillylmandelic acid (VMA) and/or catecholamine levels. Twelve patients had plasma catecholamine determinations: noradrenaline was elevated in all, adrenaline in six and dopamine in two. Pre-operative localization was by CT scan or MR imaging in all patients. At follow-up of 1–10 years (median 4.8 years), 15 patients were cured surgically while two were asymptomatic despite recurrence of disease. One patient with recurrent paragangliomas died post-operatively.

Introduction

Phaeochromocytoma is a rare but potentially devastating disorder, estimated to occur in 0.05–0.3% of hypertensive patients. Early diagnosis and cautious management is essential to avert the potentially lethal complications that may be precipitated by drugs, intravenous contrast agents, anaesthesia or surgery. As the tumour is noted for its protean manifestations, its detection requires a high degree of clinical alertness, while its diagnosis usually rests on laboratory demonstration of excess catecholamine secretion. This has been facilitated by recent advances in the accurate measurements of fractionated free catecholamines and/or metabolites in the urine and/or plasma. Localization of adrenal phaeochromocytomas can be readily made by computed tomographic (CT) scan or magnetic resonance (MR) imaging, while extra-adrenal tumors or paragangliomas may remain elusive, even with use of metaiodobenzylguanidine (MIBG) scintigraphy and vascular catheterization studies. Pre-operative preparation with pharmacological adrenergic blockade remains a cornerstone of management to reduce surgical morbidity. We evaluate our clinical experience with phaeochromocytoma over the past 10 years, followed by a review of the current management strategies.

Methods

The medical records of all patients with surgically proven phaeochromocytomas seen in our Endocrine Clinics from January 1986 to December 1995 were reviewed. Laboratory evaluation of excess catechola-
mine production included determinations of urinary VMA and free or unconjugated catecholamines by fluorometric methods in the earlier years. This was superseded by the determination of catecholamines in urine and/or plasma by high-performance liquid chromatographic fractionation and electrochemical detection (HPLC-ECD) in the recent years. Urine specimens were collected over a 24-h period on at least two occasions with concomitant creatinine estimations. The normal ranges for urinary free catecholamines are: noradrenaline <100 μg/day (<591 nmol/day), adrenaline <15 μg/day (<82 nmol/day), and dopamine 65–400 μg/day (424–2612 nmol/day). Blood was drawn for plasma catecholamines under carefully controlled conditions, with patients supine and cannulated 30 min beforehand. Plasma was stored at −70° C until assay. The normal ranges are: plasma noradrenaline 110–410 pg/ml (601–2239 pmol/l), adrenaline <50 pg/ml (<273 pmol/l), and dopamine <87 pg/ml (<475 pmol/l). Clonidine suppression test (300 μg orally at time 0, and plasma sampled at 0, 60, 120, and 180 min) was performed in selected patients; normal clonidine suppression should produce a fall in the basal values of noradrenaline and adrenaline to a level below 500 pg/ml 120 or 180 min after clonidine administration. No provocative tests were used in any patient. Tumour imaging was performed with unenhanced CT scan, while MR imaging was reserved for difficult cases. MIBG scintigraphy and/or selective venous sampling were performed when bilateral or extra-adrenal pheochromocytomas were suspected. All patients received alpha-adrenergic blockade prior to any interventional procedure or surgery; sufficiency of pharmacological blockade was assessed by attaining BP <135/85 mmHg and a postural drop of >25/15 mmHg.

Patients

Of the eighteen patients identified, seventeen are currently alive, while one died postoperatively. The median duration of follow-up for the 17 patients was 4.8 years, with a range of 1–10 years.

Results

Clinical features at presentation

Table 1 summarizes the patient data in our series. There were three males and 15 females. Age at diagnosis was 12–81 years, with a mean of 42 years. All except one patient were screened based on suggestive clinical symptoms, while one elderly female (patient 8) had an incidental finding of left

adrenal tumour during imaging evaluation for pleural effusion and congestive cardiac failure. The three most frequent symptoms were headaches (67%, n = 12), palpitations (44%, n = 8) and chest discomfort (39%, n = 7), while flushing (n = 4), postural dizziness (n = 4), diaphoresis (n = 2), pallor (n = 1) and hypertensive crisis (n = 1) were uncommon features. Only two patients had the classical triad of headaches, palpitations and diaphoresis. Hypertension of persistent or episodic nature was found in 16 of the 18 patients (89%). Patient 7 was never hypertensive but instead had frequent episodes of postural hypotension and syncope. Patient 15 presented with progressive drowsiness and cranial CT scan showed obstructive hydrocephalus secondary to bilateral cerebellar infarctions with oedema. She had earlier manifested Cushing’s syndrome with biochemical findings consistent with ectopic ACTH production. This was later shown to arise from an adrenal phaeochromocytoma which showed strong immunostaining for ACTH. The duration of symptoms in all patients prior to diagnosis ranged from 2 weeks to 6 years, with a mean of 16.4 ± 19.7 months.

There were four familial patients (22%), consisting of two related patients with both personal and family history of medullary carcinoma of the thyroid (MEN-IIA, Patients 6 and 12), 1 with numerous ‘cafe-au-lait’ spots and neurofibromas (NF-I, patient11), and one with bilateral retinal haemangioblastomas, cerebral and spinal haemangiomas, and bilateral renal cystic disease (VHL disease, patient 17). Two patients gave a past history of paragangliomas that had been completely resected prior to their presentation to our centre; one patient (patient 4) had a past history of bilateral carotid body tumours resected 15 years earlier, while the other (patient 7) had a vesicular paraganglioma resected 12 years earlier at age 16.

Laboratory findings at diagnosis

Table 2 summarizes the results of urinary and plasma catecholamine and metabolite determinations. Urinary VMA was measured in all patients, with 16 of the 18 patients showing elevated levels in one or more specimens (sensitivity 89%). Fourteen patients had urinary total (unconjugated) catecholamines determined by fluorometric method, with all having one or more elevated values (sensitivity 100%). Four patients in whom individual urinary catecholamines were measured by the HPLC-ECD method showed positive results in all specimens obtained. Urinary total metanephrine was determined in six patients, with all showing positive results. Basal recumbent plasma catecholamines were measured in 12 patients: all showed elevated noradrenaline (100%), six had elevated adrenaline (46%) and two had
Table 1 Summary data for 18 patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/Age</th>
<th>Tumour location</th>
<th>Tumour size* (cm)</th>
<th>HPT**</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/30</td>
<td>(L) adrenal</td>
<td>5.5</td>
<td>Yes</td>
<td>Well at 10 yrs</td>
</tr>
<tr>
<td>2</td>
<td>F/49</td>
<td>(L) adrenal</td>
<td>7.5</td>
<td>Yes</td>
<td>Well at 9 yrs</td>
</tr>
<tr>
<td>3</td>
<td>F/33</td>
<td>(L) adrenal</td>
<td>7.0</td>
<td>Yes</td>
<td>Well at 9 yrs</td>
</tr>
<tr>
<td>4</td>
<td>F/65</td>
<td>Coeliac ganglion, (L) cervical chain</td>
<td>2.7</td>
<td>Yes</td>
<td>Past history of bilateral cervical paraganglioma</td>
</tr>
<tr>
<td>5</td>
<td>F/50</td>
<td>(L) adrenal</td>
<td>1.0</td>
<td>Yes</td>
<td>Died post operatively due to acute myocardial infarction</td>
</tr>
<tr>
<td>6</td>
<td>M/48</td>
<td>Bilateral adrenal</td>
<td>3.0 (R), 7.5 (L)</td>
<td>No</td>
<td>MEN-IIA syndrome; well at 6 yrs</td>
</tr>
<tr>
<td>7</td>
<td>M/28</td>
<td>(R) retrocaval</td>
<td>3.5</td>
<td>Yes</td>
<td>Past history of vesicular paraganglioma; recurrent disease at 4 yrs</td>
</tr>
<tr>
<td>8</td>
<td>F/81</td>
<td>(L) adrenal</td>
<td>4.5</td>
<td>Yes</td>
<td>Incidental finding on imaging; well at 5 yrs</td>
</tr>
<tr>
<td>9</td>
<td>F/48</td>
<td>(R) adrenal</td>
<td>3.0</td>
<td>Yes</td>
<td>Well at 4.5 yrs</td>
</tr>
<tr>
<td>10</td>
<td>F/58</td>
<td>(L) adrenal</td>
<td>3.5</td>
<td>Yes</td>
<td>Well at 4 yrs</td>
</tr>
<tr>
<td>11</td>
<td>F/24</td>
<td>(R) adrenal</td>
<td>4.5</td>
<td>Yes</td>
<td>Neurofibromatosis Type I; well at 4 yrs</td>
</tr>
<tr>
<td>12</td>
<td>F/32</td>
<td>(L) adrenal</td>
<td>5.5</td>
<td>Yes</td>
<td>MEN-IIA syndrome; well at 4 yrs</td>
</tr>
<tr>
<td>13</td>
<td>F/12</td>
<td>(L) adrenal</td>
<td>5.5</td>
<td>Yes</td>
<td>Recurrent disease at 3 yrs</td>
</tr>
<tr>
<td>14</td>
<td>F/65</td>
<td>(R) adrenal</td>
<td>1.5</td>
<td>Yes</td>
<td>Well at 3.5 yrs</td>
</tr>
<tr>
<td>15</td>
<td>F/25</td>
<td>(L) adrenal</td>
<td>4.0</td>
<td>Yes</td>
<td>Ectopic Cushing’s syndrome; well at 2 yrs</td>
</tr>
<tr>
<td>16</td>
<td>F/22</td>
<td>(L) adrenal</td>
<td>7.0</td>
<td>Yes</td>
<td>Well at 2 yrs</td>
</tr>
<tr>
<td>17</td>
<td>M/42</td>
<td>(R) adrenal</td>
<td>2.5</td>
<td>Yes</td>
<td>von Hippel Lindau disease; well at 1 yr</td>
</tr>
<tr>
<td>18</td>
<td>F/43</td>
<td>(L) adrenal</td>
<td>3.5</td>
<td>Yes</td>
<td>Well at 1 yr</td>
</tr>
</tbody>
</table>

* Largest dimension in cm; ** HPT, hypertension.

Elevated dopamine concentrations (15%). Clonidine suppression tests were positive in all six patients studied.

The location of the tumours is shown in Table 1. CT scan localized the tumour to one adrenal gland in 14 patients (78%). Bilateral adrenal lesions were noted in two patients (patients 5 and 6), one of whom (patient 5) proved to have a non-functioning adrenal cortical tumour on the contralateral side. Two patients (patients 6 and 13) had evidence of paracaval masses in close proximity to the adrenal lesions, which were later found at surgery to be paragangliomas of the sympathetic chain. Two other patients (patients 4 and 7) had normal adrenal glands, but extra-adrenal lesions, localized around the coeliac axis in one and in the right obturator fossa in the other. Initial MIBG scans were positive in all the patients with extra-adrenal lesions, whereas repeat scans were negative in two patients (patient 7 and 13) with suspected recurrent disease.

Treatment

All except patient 8 received preoperative alpha-adrenergic blockade with either phenoxybenzamine or prazosin. Phenoxybenzamine was used in 12 patients (20–80 mg daily) while prazosin was used in 5 patients (3–24 mg daily). Two patients were poorly controlled on prazosin therapy and required additional medication. Beta-1 selective adrenergic blockers were added in six patients for control of tachyarrhythmias. Patient 8 had been treated with
Table 2 Results of biochemical tests in 18 patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Urine VMA</th>
<th>Urine catecholamines*</th>
<th>Urine metanephrines**</th>
<th>Plasma (supine) catecholamines***</th>
<th>Clonidine suppression test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n–2 x</td>
<td>n–2.5 x</td>
<td>–</td>
<td>N: 2.5 x; A/D: n</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>3 x</td>
<td>2–3 x</td>
<td>–</td>
<td>N: 7 x; A: 2 x; D: n</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>2 x</td>
<td>3 x</td>
<td>2.5–3.5 x</td>
<td>N: 2 x; A: 1.5 x; D: 6 x</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>n</td>
<td>2 x</td>
<td>2.5 x</td>
<td>N: 7 x; A/D: n</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>n–2 x</td>
<td>2 x</td>
<td>–</td>
<td>N: 1.5–2.5 x; A/D: n</td>
<td>Positive</td>
</tr>
<tr>
<td>6</td>
<td>2 x</td>
<td>2.5–3.5 x</td>
<td>–</td>
<td>N: 1.5 x; A: 4.5 x; D: n</td>
<td>Positive</td>
</tr>
<tr>
<td>7</td>
<td>2 x</td>
<td>6.5–8 x</td>
<td>2–3 x</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>n–1.5 x</td>
<td>n–2 x</td>
<td>1.5–2 x</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>1.5 x</td>
<td>16–20 x</td>
<td>–</td>
<td>N: 1.5 x; A/D: n</td>
<td>Positive</td>
</tr>
<tr>
<td>10</td>
<td>3–3.5 x</td>
<td>20–25 x</td>
<td>–</td>
<td>N: 30–35 x; A/D: n</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>2.5–3 x</td>
<td>6–7.5 x</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>n–1.5 x</td>
<td>1.5–3 x</td>
<td>8 x</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>4 x</td>
<td>31 x</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>n</td>
<td>2–4.5 x</td>
<td>–</td>
<td>N: 4.5 x; A: 5.5 x; D: n</td>
<td>–</td>
</tr>
<tr>
<td>15</td>
<td>n–1.5 x</td>
<td>N: 3.5 x; A/D: n</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>16</td>
<td>3.5–6.5 x</td>
<td>N: 3–6 x; A: 3.5 x</td>
<td>4–7 x</td>
<td>N: 18 x; A: 1.5 x; D: n</td>
<td>–</td>
</tr>
<tr>
<td>17</td>
<td>1.5 x</td>
<td>N: 2.5–3.5 x; A/D: n</td>
<td>–</td>
<td>N: 1.5–3 x; A/D: n</td>
<td>Positive</td>
</tr>
<tr>
<td>18</td>
<td>1.5–3 x</td>
<td>N: 4.5 x; A/D: n</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Results are expressed as number of times (x) elevated above the upper limit of normal range: n, normal; N, noradrenaline; A, adrenaline; D, dopamine. Normal ranges: urine VMA, 2–7 mg/day (10–35 μmol/day); urine catecholamines: total <100 μg/day (<546 nmol/day); urine metanephrines: total <1.2 mg/day (<6.5 μmol/day); plasma (supine) catecholamines: N 110–410 pg/ml (601–2239 pmol/l); A <50 pg/ml (<273 pmol/l); D <87 pg/ml (<475 pmol/l); clonidine suppression test: abnormal or positive test defined as total catecholamines (N+A) >500 pg/ml at 2 or 3 h post clonidine.

* Total urinary catecholamines (N+A) measured by fluorometry for patients 1 to 14 and fractionated urinary free catecholamines (N, A, D) measured by HPLC-ECD method for patients 15 to 18.

** Total urinary metanephrines (normetanephrine and metanephrine) measured by fluorometry.

*** Fractionated plasma free catecholamines (N, A, D) measured by HPLC-ECD method.

Labetalol for hypertension, which was continued unchanged prior to surgery. All patients were rendered normovolaemic and normotensive prior to surgery, and adequacy of pharmacologic blockade was ensured by demonstrating modest postural hypotension (postural drop of >25/15 mmHg).

Fourteen patients had unilateral adrenalectomy (10 left and 4 right), two had bilateral adrenalectomy, and two had excision of extra-adrenal tumours. Extra-adrenal lesions were also resected in one patient (patient 13) who underwent unilateral adrenalectomy and another (patient 6) with bilateral adrenalectomy. There were no significant intraoperative haemodynamic disturbances that necessitated acute intervention. One early postoperative mortality was recorded (patient 4).

Course

Fifteen patients remained well postoperatively with normal catecholamine levels determined at the last follow-up. Patient 15, who developed hypertensive crisis and obstructive hydrocephalus from posterior fossa oedema, made an uneventful recovery after acute neurosurgical intervention and subsequent resection of the adrenal tumour. All but two (patients 4 and 8) of the hypertensive patients were rendered normotensive postoperatively. Patient 8, the oldest patient, had a long standing history of hypertension, most probably of essential aetiology. Recurrent disease was noted in three patients as described below (patient 4, 7 and 13).

Patient 4 had a past history of bilateral cervical paragangliomas which had been excised 15 years previously. She was suspected to have recurrent disease based on elevated plasma catecholamines in the left jugular vein obtained from selective venous sampling, as well as a new lesion in the abdomen detected by CT scan and MIBG study. She had an initial uneventful resection of intra-abdominal paraganglioma, while her blood pressure and catecholamine levels remained elevated postoperatively. The patient was put back on phenoxybenzamine 60 mg daily with good control, and she underwent an excision of the recurrent cervical paraganglioma a month later. Unfortunately, she succumbed to an acute myocardial infarction on the fourth postoperative day.
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Patient 7 had a past history of a vesicular paraganglioma resected at age 16. He presented 12 years later with frequent postural syncope and catecholamine oversecretion. He had complete symptomatic and biochemical regression after removal of a paraganglioma in the right obturator fossa which was discovered by MR imaging. He has remained well clinically but showed a two-fold elevation of urinary noradrenaline levels 4 years later. A recent MIBG scan, as well as MR imaging of the abdomen and pelvis, was negative. He is currently being followed carefully.

Patient 13, the youngest patient, underwent initial surgery to remove a left adrenal phaeochromocytoma and a right paracaval paraganglioma (Figure 1) with clinical and biochemical remission. She had biochemical evidence of recurrence 3 years later, with a three-fold elevation of both plasma and urinary noradrenaline levels. An inconclusive result was obtained on repeat CT scanning (Figure 2a,b) while new lesions were detected in the right paracaval and the left para-aortic regions on MR imaging (Figure 3a,b). Her repeat MIBG scan, however, did not reveal any abnormal uptake. She is currently awaiting repeat surgery.

**Discussion**

Adrenomedullary catecholamine-secreting tumours are called phaeochromocytomas; those arising in extra-adrenal chromaffin tissues, paragangliomas. They may also produce a number of other biologically active neuropeptides that cause vascular and visceral disturbances, contributing to the protean clinical manifestations. Hypertension, of sustained or paroxysmal nature, is the most consistent manifestation of this disorder, as found in 89% of our patients. The failure to document any blood pressure elevation, even of paroxysmal nature, despite marked catecholamine excess, as noted in patient 7, constitutes an extremely unusual finding in phaeochromocytoma. Although the classic triad is not a universal feature (noted in only 11% of our series), its presence improves the positive predictive value of biochemical screening. Headaches, palpitations, and chest discomfort were the three most frequent symptoms noted in our series. In a subject without coronary atherosclerotic disease, chest pain could arise from either myocarditis or coronary spasm, leading rarely to myocardial infarction. Patients with tumours that secrete predominantly adrenaline, dopamine or other vasodilatory compounds may have hypotension, as in patient 7, who had a paraganglioma. Orthostatic hypotension is not a common finding in our study, as also reported in other series. Another possible complication is stroke associated with cerebral infarction, intracranial haemorrhage or embolism. This was noted in one of our young patients (patient 15) who had acute bilateral cerebellar infarcts, most likely secondary to embolism.

![Figure 1. CT scan of the abdomen for patient 13 showing a left adrenal phaeochromocytoma (arrowhead). The extra-adrenal phaeochromocytoma located at the right paracaval region is not well demonstrated in this tomogram.](https://academic.oup.com/qjmed/article-abstract/90/1/51/1549472)
Dilated cardiomyopathy with mural thrombus is a common source of cerebral emboli, although not proven in this patient who also manifested Cushing's syndrome arising from ectopic ACTH secretion. Conversely, in a large number of patients, the phaeochromocytoma may be clinically silent (non-secretory) or present with relatively minor signs and symptoms. In an autopsy series from the Mayo Clinic, 76% of phaeochromocytomas were clinically unsuspected during life. This is especially likely to occur in the elderly, as exemplified by the oldest patient in our series. The elderly may exhibit decreased...
catecholamine responsiveness, or concomitant diseases that mask the diagnosis of phaeochromocytoma.

Phaeochromocytoma is familial in 10% of cases, often in association with autosomal dominantly inherited disorders: MEN-II syndrome (50% of cases), VHL disease (15% of cases), and NF-I (1% of cases). Familial phaeochromocytomas, like childhood cases, tend to be multifocal and to recur. All these associations were found in our series, and hence the
The importance of family screening and of lifelong surveillance of affected individuals for recurrence or the development of associated neoplasms.

The diagnosis of phaeochromocytoma is established by the presence of elevated levels of plasma and urinary catecholamines or metabolites, either individually or in combination. Noradrenaline is generally the major hormone secreted; but approximately 15% of tumours, especially in familial cases, secrete predominantly adrenaline.

Paragangliomas, apart from those arising from the organ of Zuckerkandl, do not secrete adrenaline, because they lack the enzyme phenylethanolamine-N-methyltransferase (PNMT). Malignant phaeochromocytomas also have increased quantities of dopa and dopamine, representing less efficient catecholamine synthesis from the precursors. VMA is the major urinary metabolite in normal catecholamine metabolism which is mediated initially by neuronal monoamine oxidase (MAO) and subsequently by catechol-O-methyltransferase (COMT) in the circulation. In patients with phaeochromocytoma, catecholamines are metabolized primarily by COMT which results in a proportionally greater increase in metanephrine and free catecholamine concentrations than in VMA levels. The size of the tumour may also be an important determinant of the relative amounts of catecholamine excretory products. Small tumours usually have rapid catecholamine turnover, with large increases in circulating catecholamine levels and relatively small increases in urinary catecholamine metabolites. Conversely, large tumours have slow turnover rates which release mainly metabolized catecholamines into the circulation.

Determination of fractionated catecholamines and their metabolites by the HPLC-ECD method represents a significant improvement in diagnostic accuracy over the traditional fluorometric assays. However, urinary free catecholamine or metanephrine measurements by fluorometry, spectrophotometry or radioenzymatic assays remain useful alternatives if HPLC is not available. It is essential to avoid certain drugs or social habits to ensure reliable results: labetalol interferes with HPLC-ECD estimation of adrenaline in both urine and plasma; while adrenergic-blockers, calcium-blockers, amphetamines, nicotine and caffeine may increase plasma catecholamine levels up to two-fold. The stress of acute trauma or illnesses such as myocardial infarction or stroke may produce even more significant elevations in plasma catecholamines and urinary metabolites.

Much controversy surrounds the choice of the ‘gold standard’ biochemical screening test for phaeochromocytoma, which is likely to remain a difficult issue. It may not be pertinent to consider any one biochemical test to be absolutely better than another, as this depends very much on the local expertise and facilities available. Measurement of 24-h urinary fractionated free catecholamines by HPLC-ECD on two or more occasions is reported to give a diagnostic sensitivity and specificity close to 100% and 95%, respectively. Conversely, Lenders and coworkers from NIH reported that tests for plasma metanephrines supersede that of plasma catecholamines or urinary metanephrines, whereas the measurement of urinary metanephrines is considered superior by other investigators. However, the conclusion made by Lender et al. was based on comparing tests performed by HPLC technique with that of colorimetric assays. Urinary VMA measurement is generally of inferior sensitivity and specificity, although this remains available in some local settings as it is inexpensive and easy to perform by colorimetry. Concomitant urinary creatinine estimation is essential to ensure consistency of collections rather than to determine excretion of catecholamines or metabolites relative to creatinine, as individuals with low muscle mass often show falsely elevated values.

Except in a situation of crisis, plasma catecholamine determination is less useful than urinary assessment, as it measures a single time-point. Its role in routine screening is not advocated, as this may either generate more pharmacological testing because of equivocal results or provide little value in patients with unequivocally high urinary catecholamine levels. Measurement of free plasma dopamine may fail to reveal excessive dopamine secretion, as 99% of plasma dopamine is conjugated. Pharmacological testing is seldom indicated, as biochemical tests using current methods can establish the diagnosis in more than 95% of cases. The clonidine suppression test is useful in cases with equivocal elevations in plasma catecholamines. Provocative testing, such as the glucagon stimulation test, is potentially dangerous and rarely necessary. A review of our series showed that the results of the plasma catecholamine measured in 12 patients as well as the clonidine suppression test performed in six patients did not add further information to the interpretation of their urinary catecholamine results.

Anatomical localization should be done only after biochemical confirmation of the diagnosis. CT scan of the adrenals should be the initial imaging modality, as it can demonstrate adrenal lesions in virtually all patients and 90% of these tumours are intra-adrenal, as exemplified by our series. If the adrenal glands are normal, imaging of the entire abdomen and pelvis is appropriate because 85% of all extra-adrenal tumours occur below the diaphragm. The use of oral or intravenous contrasts are usually not required but can be helpful in some patients; prior adrenergic blockade is recommended in such instances. MR imaging is considerably more
expensive and offers no improvement in spatial resolution. However, it is helpful in certain instances, such as in the differential diagnosis of a known adrenal mass or in the localization of extra-adrenal lesions.\textsuperscript{5,14} Phaeochromocytomas tend to demonstrate characteristic high signal intensities on T2-dependent spin-echo images, as illustrated by patient 13 (Figure 3a,b).

Multiple tumours tend to occur in familial cases, children, and individuals with extra-adrenal tumours, as illustrated by our series. It is important to perform MIBG scanning to determine bilateral or extra-adrenal involvement in such instances before planning surgery.\textsuperscript{14,15} The MIBG scan is helpful only if there is a relative increase in uptake and sequestration of the radiolabelled guanethidine analogue by the chromaffin cells within the tumour, an energy-dependent mechanism which occurs mainly in tumours with abundant neurosecretory granules.\textsuperscript{39} This functional radioscintigraphy may identify small, active tumours that are not detected on anatomical imaging. However, it may not detect large tumours with low uptake activity, as illustrated by the discordant findings in MR imaging and MIBG studies in patient 13 when evaluated for recurrence. Various drugs can also interfere with neuronal MIBG uptake, including tricyclic antidepressants, neuroleptics, reserpine, sympathomimetics, adrenergic blockers, and labetalol. However, neuronal uptake of this radionuclide is not blocked by phenoxybenzamine, while calcium-channel blockers may actually prolong its half-life in targeted tissues.\textsuperscript{33,34} For this reason, calcium-channel blockers are preferred for individuals requiring ongoing treatment of hypertension during investigation.\textsuperscript{6,15} The MIBG scan offers a sensitivity of 80% and specificity of 95%.\textsuperscript{35} Venous sampling procedures are rarely required apart from instances where negative or discordant findings arise on anatomical and functional characterization studies.

Surgery provides the definitive treatment for phaeochromocytoma. There is a risk of hypertensive crisis because of the excessive release of catecholamines during induction of anesthesia or surgical manipulation of the tumour, or severe hypotension due to a sudden decrease in catecholamine levels upon tumour removal.\textsuperscript{6-8} Preoperative preparation with alpha-adrenergic-blocking drugs has substantially decreased the high surgical morbidity noted previously, although some authorities believe that adequate intravascular volume repletion preoperatively along with careful monitoring intra-operatively may preclude the need for routine preoperative adrenergic blockade except in high-risk patients.\textsuperscript{5,6,36} We prefer the conservative approach, as pharmacological blockade has been proved to be safe and efficacious, whereas the unfortunate death of patient 4 was unlikely to have been due to inadequate pre-operative preparation. We have found phenoxybenzamine to be better than alpha-1-selective antagonists, despite the theoretical advantage of the latter as proposed by Bravo.\textsuperscript{6} Cardioselective beta-adrenergic blockers may be added for control of tachycardia after adequate alpha-blockade.

Successful tumour excision results in complete cure in 75%-90% of cases, as defined by normalization of catecholamine and metabolite concentrations on follow-up.\textsuperscript{6,9} Asymptomatic individuals should have at least annual estimation of urinary free catecholamines for 5 years.\textsuperscript{6-9} Recurrent disease outside the adrenal gland is diagnosed by the presence of tumour within or near the sympathetic ganglia at locations corresponding to the anatomical distribution of extra-adrenal chromaffin tissue. Lifelong follow-up and surveillance is necessary in patients with an increased propensity for recurrence, such as familial, childhood, or extra-adrenal tumours.

Of our three patients with recurrent disease, all had extra-adrenal lesions at presentation and two presented in childhood. No recurrence has been noted in our four familial cases, with a follow-up period ranging from 1 to 6 years. Malignant phaeochromocytoma is diagnosed by the presence of invasive or metastatic disease; this has been reported in 10% of cases but was not found in our series.

Phaeochromocytoma remains a fascinating and challenging endocrine neoplasm for the physician. Although conclusions are not meant to be drawn from this small clinical series, we encountered a wide spectrum of presentations and manifestations, as well as the association with genetically inherited diseases. The discussion focuses on the biochemical evaluation of catecholamine excess, anatomical and functional localization of suspected phaeochromocytomas, and appropriate pre-operative management to improve surgical outcome. The management of recurrent disease, especially the extra-adrenal paragangliomas, however, remains elusive and difficult.

References