Clinical outcome of 50 patients with malignant abdominal paragangliomas and malignant pheochromocytomas

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Abstract

Background: Tumors of the paraganglionic system represent a distinct, albeit uncommon, clinical entity characterized by catecholamine hypersecretion and hemodynamic instability; initial pathologic examination often cannot predict benign vs malignant behavior. An analysis of the clinical outcome of patients with known malignant tumors may serve to enhance the initial evaluation and therapeutic plan of all patients presenting with pheochromocytoma or paraganglioma.

Methods: At the University of Texas M D Anderson Cancer Center, 30 patients with malignant abdominal paraganglioma and 20 patients with malignant pheochromocytoma were diagnosed between 1971 and 1995. Their medical records were reviewed with particular attention to clinical characteristics and disease outcome.

Results: Among the 30 patients with paraganglioma, 73% were men, and 90% were younger than 50 years at the time of diagnosis. Sixteen patients have remained alive with persistent disease 0.2 to 25 years after initial diagnosis while eight patients died of their disease within 0.8 to 32 years. Regional recurrence and skeletal metastases were the most prominent events. Among the 20 patients with pheochromocytoma, 60% were men and 70% were younger than 50 years at the time of diagnosis. Ten patients have remained alive with persistent disease 0.8 to 20 years after initial diagnosis while five patients died of their disease within 1.5 to 39 years. Hypertension was a prominent presenting feature and regional recurrence was the most frequent pattern of treatment failure.

Conclusions: Important clinical differences distinguish adrenal pheochromocytomas from extra-adrenal, abdominal paragangliomas. Patients with paragangliomas are, as a group, younger men, more likely to have malignant lesions and a more aggressive clinical course. Patients with malignant pheochromocytomas usually present with hypertension, are somewhat older, and have less aggressive disease.
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Because metastases may not develop until more than 10 years have passed since the diagnosis, it is not possible to distinguish truly benign lesions without a very prolonged observation period for all reported cases. Lack of agreement exists as to the virulence and malignant potential of paragangliomas relative to pheochromocytomas (Lack et al. 1980, Scott & Halter 1984, Shapiro et al. 1984) and other distinguishing characteristics.

It has been our clinical impression that abdominal, extra-adrenal paragangliomas and adrenal pheochromocytomas are distinct clinical entities. Among these lesions, paragangliomas most often afflict young males and are more likely to be malignant and aggressive. Accordingly, we analyzed the clinical outcome of patients with paragangliomas and pheochromocytomas who were treated at the M.D. Anderson Cancer Center. Our aim was to distill individual characteristics of malignant, abdominal paraganglioma as distinct from malignant adrenal pheochromocytoma.

### Patients and methods

#### Patients

The patient population was identified through a search of the database maintained by the Department of Medical Informatics at M.D. Anderson Cancer Center. One hundred and eighty patients with a diagnosis of paraganglioma or pheochromocytoma registered at the cancer center between 1 January 1971 and 30 September 1995.

#### Clinical evaluation and treatment

Each patient had a complete medical evaluation, with history and physical examination. Serum or urinary catecholamines and their metabolites were measured preoperatively, depending on clinical suspicion. Surgical pathologic findings were reviewed and diagnosis established or confirmed at M.D. Anderson. Surgical resection or diagnostic biopsy was performed in all patients at the time of initial diagnosis. Clinical, biochemical, and radiologic surveillance was used to monitor patient outcome and to determine the development of regional recurrence or metastasis. Computerized tomography (CT) or magnetic resonance imaging (MRI) was used to monitor abdominal disease.

#### Table 1 Population characteristics of patients with paraganglioma or pheochromocytoma.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>M/F</th>
<th>Age (years)</th>
<th>Mean±S.E.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paragangliomas</td>
<td></td>
<td></td>
<td>Median (range)</td>
<td></td>
</tr>
<tr>
<td>Non-malignant</td>
<td>52</td>
<td>22/30</td>
<td>44 (13-78)</td>
<td>45±2.1</td>
</tr>
<tr>
<td>Malignant non-abdomen</td>
<td>19</td>
<td>7/12</td>
<td>52 (33-79)</td>
<td>53±2.9</td>
</tr>
<tr>
<td>Malignant abdomen</td>
<td>30</td>
<td>22/8</td>
<td>37 (11-73)</td>
<td>37±2.8*</td>
</tr>
<tr>
<td>All lesions</td>
<td>101</td>
<td>51/50</td>
<td>45 (13-79)</td>
<td>45±1.5</td>
</tr>
<tr>
<td>Pheochromocytomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-malignant, sporadic</td>
<td>27</td>
<td>15/12</td>
<td>51 (17-78)</td>
<td>49±3.0</td>
</tr>
<tr>
<td>Non-malignant MEN-2</td>
<td>16</td>
<td>9/7</td>
<td>34 (22-64)</td>
<td>36±2.9</td>
</tr>
<tr>
<td>Malignant lesions</td>
<td>20</td>
<td>12/8</td>
<td>50 (8-82)</td>
<td>50±3.7</td>
</tr>
<tr>
<td>All lesions</td>
<td>63</td>
<td>36/27</td>
<td>46 (8-82)</td>
<td>46±2.0</td>
</tr>
</tbody>
</table>

M/F, male/female; MEN-2, multiple endocrine neoplasia type 2; n, no. of patients.

* Patients with malignant abdominal paraganglioma were younger than those with malignant non-abdominal lesions (P<0.001), non-malignant abdominal lesions (P<0.05) and malignant pheochromocytoma (P=0.05).
Chest radiographs or CT were used for supra-diaphragmatic sites and bone scans for skeletal sites with MRI added for the evaluation of the spine in recent cases. Methyl-iodo-benzyl guanidine (MIBG) scans were performed in approximately half of the patients. Statistical calculations were done using the Mann-Whitney test and Student’s t-test, and survival tables were made using Kaplan-Meir plotting.

**Results**

**Patient population**

We identified 164 evaluable patients with the diagnosis of paraganglioma or pheochromocytoma; there were 84 men and 80 women with a median age of 45 years (range, 13 to 79 years).

Among 101 cases of paraganglioma (Table 1), there were 51 men and 50 women with a median age of 45 years. In 52 patients with nonmalignant tumors, women were affected more frequently than men but the patient age was not different from the age distribution of the overall group. The majority of nonmalignant lesions were carotid body tumors. Among the 30 patients with malignant, abdominal paraganglioma we noted a striking majority of male patients (73% of the malignant cases). In addition, they were, as a group, younger than patients with malignant nonabdominal paraganglioma (significant at 0.0003 by Mann-Whitney test).

Among 63 patients with pheochromocytoma, there were 36 men and 27 women. A small preponderance of men was seen in all the subgroups. In 27 patients with nonmalignant, sporadic tumors, patient age was not different from the overall group. The 16 patients with nonmalignant disease associated with multiple endocrine neoplasia (MEN)-2 syndrome tended to be younger, likely reflecting the impact of family screening patterns. Among the 20 patients with malignant pheochromocytoma, there were 12 men and 8 women; patient age (median and mean 50 years; range, 8 to 82 years) was not different from the overall group. However, patients with malignant pheochromocytoma were older than patients with malignant, abdominal paraganglioma (significant at 0.0089 by Mann-Whitney test).

**Oncologic characteristics of malignant abdominal paragangliomas and malignant pheochromocytomas**

Abdominal paragangliomas were far more likely to be malignant lesions than were nonabdominal paragangliomas and pheochromocytomas. Among the 52 cases without evidence of malignant behavior, only 4 patients presented with abdominal tumors; the vast majority of nonmalignant cases were tumors of the carotid body. Conversely, among 34 cases with abdominal lesions, 30 patients had malignant disease. In contrast,
among 47 patients with sporadic, nonfamilial pheochromocytomas, 42% of cases had malignant disease, perhaps in part related to cancer center referral patterns. All paragangliomas were extra-adrenal tumors by definition; primary tumor locations were the retroperitoneum in 14 patients, para-aortic sites in 6 patients, and the bladder in 6 patients. We included one patient previously reported (Saad et al. 1983), with a primary lesion at the root of the aorta adhering to both atria because catecholamine hypersecretion was a preeminent characteristic feature of the case, unlike all the other non-abdominal lesions treated at the cancer center (see below). The largest diameter of the paragangliomas ranged between 2 cm and 20 cm (median, 6.0 cm; mean, 7.4 cm). All pheochromocytomas were adrenal tumors, by definition; their presenting size was also quite variable, ranging between 1.5 cm and 16 cm at the largest diameter (median, 6.0 cm; mean, 8.2 cm). There was no significant difference in size distinguishing malignant from non-malignant lesions at the time of diagnosis.

### Clinical characteristics of patients with malignant abdominal paraganglioma and malignant pheochromocytoma

Unlike many malignancies that become more frequent with increasing age, these two types of tumor afflict rather young men (Table 2). Among the 50 patients with malignant lesions, most were men, younger than 50 years of age. Among patients with paragangliomas, eight presented with abdominal pain, six with hypertension, and five with genitourinary symptoms. Two patients belonged to the same family. Patients with pheochromocytomas were more likely to present with hypertension (ten cases); three patients presented with painful bone metastases. Hypertension was present at the time of diagnosis in 65% of patients with pheochromocytoma but in only 43% of patients with paraganglioma. When catecholamine levels were assessed (most commonly norepinephrine and its metabolites), they were elevated in the majority of patients. When available, MIBG scanning was also positive in most patients. Surgical resection constituted the mainstay of therapy in all patients. During the course of their disease, approximately half of the patients with paraganglioma received palliative radiotherapy (typically to relieve pain in areas of skeletal metastases) and chemotherapy; the M D Anderson experience with chemotherapy has been published recently (Patel et al. 1995) and will not be discussed here. Radiotherapy was required in only three patients with malignant pheochromocytoma; conservative management with pharmacologic blockade of catecholamine secretion and action was used most frequently. Systemic chemotherapy (variable combinations of Adriamycin, cytoxan, ifosphamide, DTIC, vincristine, and cis-platinum) was used in five patients; no response could be discerned in three patients, and disease progressed in one case. In one patient, who presented with extensive distant metastases, catecholamine levels decreased transiently before radiologic progression occurred.

### Clinical outcome of patients with malignant abdominal paraganglioma and malignant pheochromocytoma

The majority of patients have either died of their disease or remain alive with persistent or recurrent disease (Table 3). Among those with paraganglioma, 16 of 18 patients who were alive at last evaluation had persistent disease for 0.2 to 25 years of available follow-up; of the 12 patients who died, 8 died of their disease within 0.8 to 32 years. Among patients with pheochromocytoma, 10 of 13 who were alive at last evaluation had persistent disease during 0.8 to 20 years of available follow-up; of the 7 patients...
who died, 5 died of disease within 1.5 to 30 years (median, 4.0 years; mean±S.E.M., 8.8±5.3 years). Overall survival time was significantly decreased in patients with para-gangliomas (Fig. 1).

Given the long delay between the time of diagnosis and the recognition of recurrent or metastatic disease in many patients with these tumors, we wished to define the length of available follow-up time for patients with nonmalignant lesions (Table 4). Indeed, patients with nonmalignant lesions were seen at the M D Anderson for shorter periods of time; this was especially true for four patients with cases of abdominal nonmalignant paragangliomas (not shown). The surveillance period was 5.9±0.3 years for patients with malignant abdominal paragangliomas vs 2.7±0.6 years for nonmalignant cases (P<0.05). For patients with pheochromocytomas, the surveillance period was 11.8±2.2 years for malignant tumors vs 5.5±1.6 years for nonmalignant sporadic cases and 7.0±1.6 years for patients with MEN-2 syndrome (6.9±1.1 years overall, for nonmalignant cases). These differences were also significant (P<0.05). Thus, it is possible that some cases that were originally considered nonmalignant may have to be reclassified with additional follow-up. However, the data reinforce the idea that survival time of patients with these malignancies is very variable but may be prolonged.

### Extent of disease in patients with malignant abdominal paraganglioma and malignant pheochromocytoma

Among the 30 patients with malignant abdominal paragangliomas (Table 5), 11 had distant metastases at the time of initial diagnosis while 7 had evidence of regional extension (lymphadenopathy or invasive tumor); the other

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**Figure 1** Overall survival time (in months) of patients with pheochromocytoma or paraganglioma.

**Table 4** Duration of follow-up in patients with the diagnosis of paraganglioma and pheochromocytoma.

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>n</th>
<th>Median (range)</th>
<th>Mean±S.E.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-malignant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pheo sporadic</td>
<td>27</td>
<td>4.0 (0.5-20.0)</td>
<td>5.5±1.6</td>
</tr>
<tr>
<td>Pheo MEN-2</td>
<td>16</td>
<td>5.5 (0.2-30.0)</td>
<td>7.0±1.6</td>
</tr>
<tr>
<td>Para</td>
<td>52</td>
<td>1.0 (0.5-20.0)</td>
<td>2.7±0.6</td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Para non-abdominal</td>
<td>19</td>
<td>8.0 (0.5-29.0)</td>
<td>10.7±2.1</td>
</tr>
<tr>
<td>Para abdomen</td>
<td>30</td>
<td>3.5 (0.2-32.0)</td>
<td>5.9±1.3</td>
</tr>
<tr>
<td>Pheo</td>
<td>20</td>
<td>10.2 (0.8-39.0)</td>
<td>11.8±2.2</td>
</tr>
</tbody>
</table>

MEN-2, multiple endocrine neoplasia type 2; Para, paraganglioma; Pheo, pheochromocytoma.
12 patients developed recurrent disease within the subsequent 0.2 to 24 years. Recurrent disease was limited to the tumor bed region in 6 patients, while regional plus distant sites became involved in half of the patients. Distant metastases affected multiple skeletal sites most frequently (19 of 30 cases); lung metastases and liver metastases were seen in 5 patients each. Of note, there are 2 patients with no evidence of disease at their most recent evaluation (1.7 and 3.7 years after diagnosis). But, because recurrence may occur much later in this disease, caution should be expressed about their eventual outcome.

Among the 20 patients with malignant pheochromocytomas, 5 had distant metastases at the time of initial diagnosis; extra-capsular extension of the primary tumor was described in some of these cases. The other 15 patients developed recurrent disease within the subsequent 1.6 to 36 years. Recurrent disease was limited to the tumor bed region in six patients, while regional plus distant sites became involved in half the cases. Distant metastases affected skeletal sites in seven patients; while multiple areas were involved in many patients, the overall skeletal burden appeared less extensive than the pattern observed in paragangliomas. Liver metastases were seen in seven patients, lung metastases in four patients, and adrenal, heart, mediastinal, or bladder in one patient each. Of note, there are three patients with no evidence of disease 14 to 30 years after initial diagnosis; because recurrence is most frequent during the first decade of follow-up these cases may well represent cured patients.

### Clinical characteristics and outcome of patients with malignant nonabdominal paragangliomas

During the course of our case review for this report we had the opportunity to examine the records of all the patients with malignant paraganglioma, including nonabdominal cases. Given the rarity of this disease, we considered that a summary of our experience with this subgroup would be of interest. Among 19 patients, sufficient information was available for 18 only; their population characteristics and duration of follow-up have already been outlined in Tables 1 and 4 respectively. Most patients presented with a neck mass and were classified as having tumor of the carotid body. In six patients, unresectable disease or distant metastases were recognized at the time of initial diagnosis. In nine patients, recurrent disease developed within 2.0 to 29 years while three patients did not experience recurrence during the available observation period.

Overall, disease was confined to the region of the initial tumor in 11 of 18 patients. Distant metastases affected the other seven patients. Among those seven patients, bone lesions were present in six, lung metastases in three, and brain metastases in one. At the conclusion of the observation period, three patients were alive with no evidence of disease 2 to 7 years after diagnosis and eight patients remained alive with persistent disease 0.2 to 29 years after diagnosis, while five patients died of their disease within 3 to 18 years. The cause of death was unclear in two cases. Catecholamine hypersecretion was not seen in any of the patients.

### Discussion

Our study demonstrates that important clinical differences exist between the clinical presentation and outcome of patients with malignant abdominal paragangliomas and those of patients with malignant pheochromocytomas. Patients with paragangliomas are, as a group, younger. Most of them are men. This tumor follows a more aggressive clinical course characterized by prominent
regional recurrence, skeletal metastases, and decreased survival time. On the other hand, patients with malignant pheochromocytomas are somewhat older. More equal numbers of men and woman are affected. Patients with these tumors have less prominent distant metastases and longer survival times. In both groups, however, recurrence may not be seen for many years after initial diagnosis; both lesions appear to be ultimately lethal, but affected patients may live with recurring or persistent disease for many years.

Despite their rarity, tumors of chromaffin tissues continue to capture interest and generate controversy regarding their clinical outcome and optimal classification. Both lesions develop from neural crest derivatives (pheochromocytes) that migrate to populate the paraganglia during embryologic development. The paraganglionic system (Table 6) gives rise to both benign and malignant tumors, which may be classified according to their anatomic and functional distribution (Melicow 1977, Mayer 1980, DeLellis 1989). The adrenal medulla and the sympathetic ganglia are homologous; however, the medulla is unique in its ability to secrete epinephrine (rather than norepinephrine) in an endocrine fashion (rather than via postganglionic afferent fibers). The paraganglia of the neck and upper chest area (e.g. carotid or aortic bodies) are distinct from paravertebral or sympathetic outflow paraganglia; they are autonomic system chemoreceptors rather than neuroendocrine cells, and they do not secrete catecholamines (Lack et al. 1979, Bishop et al. 1992).

For the most part, tumors of the adrenal medulla are called pheochromocytomas while tumors of all other paraganglia are called paragangliomas; an anatomic modifier is often added for clarity. In clinical practice, the diagnostic and therapeutic issues raised with paragangliomas of the neck area (also referred to as ‘chemodectomas’ by some authors) (Lack et al. 1979, Merino & Livolsi 1981, Parry et al. 1982, Bishop et al. 1992) are quite different from those with tumors capable of catecholamine hypersecretion. Accordingly, intra-abdominal, sympathetic system lesions are usually discussed separately; both adrenal and extra-adrenal tumors are often combined in such reviews, perhaps to allow examination of larger samples of this rare disease. In the present report, we chose to compare and contrast the features of adrenal vs extra-adrenal abdominal tumors to highlight several important differences in their clinical profile and biology.

Pheochromocytomas are rare tumors affecting less than 1% of the hypertensive population (Bravo et al. 1993) with reported incidence rates of less than five cases per million people (Stenstrom & Svarsdudd 1986). Patients with the MEN-2 syndrome have bilateral, almost always nonmalignant pheochromocytomas and tend to be younger, most likely due to prospective surveillance and early detection (Webb et al. 1980, Caty et al. 1990). Our patient population was also younger and consisted of approximately equal numbers of men and women in agreement with published reports; their clinical outcome (not shown) was influenced by the course of their

Table 6 The paraganglionic system and related tumors.

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Neurohumoral transmission</th>
<th>Related tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branchiomeric</td>
<td>Nonchromaffin</td>
<td>Carotid body</td>
</tr>
<tr>
<td>intravagal</td>
<td>Presso/chemoreceptor</td>
<td>Glomus jugulare (paranglioma)</td>
</tr>
<tr>
<td></td>
<td>Parasympathetic</td>
<td>(chemodectoma)</td>
</tr>
<tr>
<td>Paravertebral</td>
<td>Chromaffin</td>
<td>Para-aortic</td>
</tr>
<tr>
<td></td>
<td>Neuroendocrine</td>
<td>Zuckerkand (paranglioma)</td>
</tr>
<tr>
<td></td>
<td>Sympathetic</td>
<td>(extra-adrenal pheochromocytoma)</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine</td>
<td></td>
</tr>
<tr>
<td>Adrenal medulla</td>
<td>Chromaffin</td>
<td>Pheochromocytoma (adrenal paraganglioma)</td>
</tr>
<tr>
<td></td>
<td>Neuroendocrine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sympathetic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epinephrine</td>
<td></td>
</tr>
<tr>
<td>Sacral outflow</td>
<td>Chromaffin</td>
<td>Bladder</td>
</tr>
<tr>
<td></td>
<td>Visceraautonomic</td>
<td>Spermatic cord (paranglioma)</td>
</tr>
<tr>
<td></td>
<td>Sympathetic</td>
<td>(extra-adrenal pheochromocytoma)</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine</td>
<td></td>
</tr>
</tbody>
</table>

coexisting medullary thyroid cancer rather than the pheochromocytomas.

How frequently sporadic pheochromocytomas behave in a malignant fashion remains subject to discussion; that fewer than 10% do so is the accepted community observation (Bravo et al. 1993). However, much higher rates are being reported, especially from tertiary referral centers and when extra-adrenal lesions are included in the reviews (Mornex et al. 1992, Proye et al. 1992, Schlumberger et al. 1992). This emerging apparent increase of malignant lesions may be attributed to several nononcologic factors. It is quite possible that unsuspected residual or recurrent lesions are being detected with the aid of powerful diagnostic techniques (Samaan et al. 1988, Sheps et al. 1990, Peplinski & Norton 1994), especially MIBG scanning, which has become available for both the diagnosis and treatment of these tumors (Sisson et al. 1984, Geatti et al. 1989, Khafagi et al. 1991, Krempf et al. 1991). Because disease recurrence may take place many years after initial diagnosis (Sparagana 1986, Stenstrom et al. 1988, Vassilopoulou-Sellin et al. 1993), prolonged surveillance is being instituted more systematically in many centers, leading to increased recognition of the malignant potential for the disease. In our review, we found evidence of malignancy in 42% of sporadic adrenal pheochromocytomas; we consider this figure to represent a likely overestimate of community prevalence resulting from cancer center referral patterns. Our results are certainly in agreement with prior reports confirming both the potential latency of recurrence and the prolonged survival time of affected patients. Our limited experience with radiotherapy and chemotherapy for these tumors was not very encouraging, similar to that reported by other investigators (Averbuch et al. 1988, Siddiqui et al. 1988). Surgical resection, when feasible, along with pharmacologic blockade of catecholamine hypersecretion or action remain the most important modalities for long-term management of malignant adrenal pheochromocytomas.

The clinical course and malignant potential of extra-adrenal paragangliomas has been the focus of several recent careful analyses. Pommier et al. (1993) were unable to demonstrate any differences between extra-adrenal and adrenal lesions with respect to malignancy; while survival time was reduced in patients with extra-adrenal malignancies, the differences were not significant. Proye et al. (1992), however, noted that chromaffin tumors located extra-adrenally were more likely to be malignant. Among analyses that focus on extra-adrenal retroperitoneal paragangliomas, the risk of malignancy has varied widely from 9% to 50% (Hall et al. 1980, Lack et al. 1980, Krzyger-Baggesen 1985, Mikhail et al. 1986, Goldfarb et al. 1989, Hayes et al. 1990, Sclafani et al. 1990). Among our cases, malignant biology was the rule for patients with extra-adrenal, abdominal paragangliomas. Young age and a male preponderance has also been suggested by other investigators (Lack et al. 1980, Mikhail et al. 1986, Goldfarb et al. 1989, Hayes et al. 1990) and was certainly a characteristic feature in our patients.

Regional recurrence and distant (primarily skeletal) metastases characterized treatment failure in both groups of patients. The disease appeared more aggressive in patients with paragangliomas; however, many such patients lived for years despite widespread, persistent disease. We suggest that young men with extra-adrenal, abdominal paragangliomas are at very high risk for the development of malignant disease. These patients should be carefully evaluated and observed for well over 10 years after diagnosis and initial surgical therapy.

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