

One Hundred Two Patients With Pheochromocytoma Treated at a Single Institution Since the Introduction of Laparoscopic Adrenalectomy

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Hypothesis: Pheochromocytoma can be safely treated laparoscopically; “subclinical” pheochromocytoma is increasingly common.

Design: Retrospective review.

Setting: University hospital.

Patients: Patients undergoing adrenalectomy for pheochromocytoma at our institution in 1994 to 2009.

Interventions: Laparoscopic, hand-assisted, and open adrenalectomy.

Main Outcome Measures: Preoperative and postoperative clinical and biochemical data.

Results: One hundred two patients (52 women, 50 men) with pheochromocytoma underwent 108 operations. Ninety-seven operations were laparoscopic; 7, open; and

4, converted from laparoscopic to hand assisted or open. Six operations were bilateral; 3 were subtotal cortex-sparing resections. Thirty-four patients (33%) presented with adrenal incidentaloma and minimal symptoms, 28 within the past decade. Ten patients had paragangliomas, 7 of whom underwent laparoscopic resection. The mean (SD) tumor size was 5.3 (2.8) cm. Seven patients had recurrence requiring reoperation; the mean length of time between initial operation and recurrence was 6 years (range, 6 months to 17 years). There were no perioperative deaths.

Conclusions: Laparoscopic adrenalectomy can be safely performed for pheochromocytoma in more than 90% of cases. More than one-third of patients presented with subclinical pheochromocytoma. Patients should be followed up closely because recurrence may develop several years after adrenalectomy.

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PHEOCHROMOCYTOMAS ARE rare tumors, with an incidence of between 2 and 8 cases per million per year.¹ These tumors arise from the chromaffin cells of the neural crest and typically originate from the adrenal medulla, but extra-adrenal pheochromocytomas (paragangliomas) may also be found along the course of the sympathetic chain.

See Invited Critique at end of article

Pheochromocytomas secrete catecholamines and may cause life-threatening hypertensive crisis if left untreated. Approximately 10% of adrenal pheochromocytomas and 30% of paragangliomas are found to be malignant.² Between 70% and 80% of pheochromocytomas occur sporadically; the familial syndromes that may present with pheochromocytoma in-

clude multiple endocrine neoplasia type 2, von Hippel–Lindau syndrome, Osler-Weber-Rendu syndrome, and neurofibromatosis syndrome type 1.³ Recently, there has been increasing recognition of the prevalence of germline succinate dehydrogenase enzyme mutations (succinate dehydrogenase complex subunit B, succinate dehydrogenase complex subunit C, succinate dehydrogenase complex subunit D) causing familial paraganglioma-pheochromocytoma syndrome.⁴⁻⁶ Prior to the past 2 or 3 decades, pheochromocytomas were usually diagnosed in patients with severe paroxysmal hypertension and its associated symptoms (headache, anxiety, dizziness, palpitations), with some patients presenting in hypertensive crisis with subsequent cardiovascular collapse and death. Recent increases in the number and quality of abdominal imaging studies have resulted in heightened awareness of incidentally discovered adrenal tumors and a rise in the number of pheochromocyto-

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mas being diagnosed in minimally symptomatic or asymptomatic patients.^{7,8}

The only definitive treatment for pheochromocytoma is operative resection. Since the initial Gagner et al report⁹ in 1992, laparoscopic adrenalectomy has become the approach of choice for benign nonfunctioning adrenal tumors and tumors secreting aldosterone and glucocorticoids; surgeons have been less eager to perform laparoscopic resection of pheochromocytoma, however, because of perceived difficulties in the management of intraoperative hemodynamic fluctuations, tendency for these tumors to be bloody and adherent to adjacent structures, and uncertainty regarding the oncologic outcomes and the risk of malignancy and recurrence for laparoscopically resected tumors. Despite these reservations, numerous authors have reported on their experiences with laparoscopic resection of pheochromocytoma over the past decade.¹⁰⁻¹⁷ Most of these articles have been limited to relatively small numbers because of the rarity of these tumors, although some multi-institutional series have been published as well.

The primary adrenal surgeon (Q.-Y.D.) in our endocrine surgery group has been performing laparoscopic adrenalectomy for pheochromocytoma since 1994 and has built a robust adrenal surgery practice with a consistent referral base of patients with pheochromocytoma. We have recently reported on some of the issues surrounding the biochemical diagnosis of pheochromocytoma.^{3,8} For this study, we reviewed our overall experience with operative treatment of pheochromocytoma in the period since the introduction of laparoscopic adrenalectomy. We hypothesized that the majority of patients with pheochromocytoma who underwent operation during this period were safely and effectively treated with laparoscopic resection with minimal morbidity and mortality and acceptable oncologic outcomes. In addition, we have recently perceived that increasing numbers of patients with pheochromocytoma are presenting with a milder form of the disease, manifested by minimal or no symptoms and mild hypertension or normal blood pressure; we therefore hypothesized that patients within the past several years have been increasingly likely to come to medical attention with incidentally discovered adrenal tumors or as part of screening for familial syndromes rather than presenting with severe symptoms or hypertensive crisis.

METHODS

We reviewed the medical records of all patients undergoing laparoscopic or open adrenalectomy by one of the current endocrine surgeons (Q.-Y.D.) at our university medical center between January 1994 and June 2009. From this group of more than 500 patients, we identified all patients who had histopathologically confirmed pheochromocytomas resected. We included patients with paragangliomas and patients with both sporadic and familial disease; for the purposes of this article, we will use the term *pheochromocytoma* to refer to patients with both adrenal and extra-adrenal tumors and use the term *paraganglioma* when referring to the specific subset of patients with extra-adrenal tumors. We also included patients undergoing reoperation after prior resection of pheochromocytoma at another institution.

We analyzed this patient cohort with respect to patient demographics, clinical presentation, preoperative workup, operation performed, pathology results, postoperative hospital stay, postoperative complications, and recurrence. Clinical presentation was divided into 5 categories: clinically apparent hypertension or symptoms; hypertensive crisis; incidentally discovered adrenal tumor; prior operation for pheochromocytoma; and familial syndrome. For the purposes of this study, we defined an incidentally discovered adrenal tumor as an adrenal mass identified in a patient with minimal or no hypertension undergoing abdominal imaging for another indication. We defined complications as any adverse events occurring within 30 days of operation. Recurrence was defined as any clinically detectable tumor identified in the previous resection bed after at least 6 months following the initial operation.

RESULTS

Between January 1994 and January 2009, 102 patients underwent adrenalectomy for resection of pheochromocytoma by one of the current endocrine surgeons (Q.-Y.D.) at our institution. These 102 patients underwent a total of 108 operations. The 102 patients included 50 men and 52 women. The mean (SD) age was 46.7 (16.3) years. Sixteen patients (16%) had familial syndromes, including 8 with multiple endocrine neoplasia type 2A, 3 with von Hippel-Lindau syndrome, 2 with neurofibromatosis, 1 with a succinate dehydrogenase complex subunit B mutation and familial paraganglioma, 1 with multiple endocrine neoplasia type 2B, and 1 with Osler-Weber-Rendu syndrome.

We divided the clinical presentations of the 102 patients into 5 categories. Forty-two patients (41%) presented with hypertension and/or significant signs or symptoms of catecholamine excess (paroxysmal headache, dizziness, palpitations, anxiety); subsequent biochemical and radiologic workup confirmed the diagnosis of pheochromocytoma. In 34 patients (33%), pheochromocytoma was diagnosed during workup of an incidentally discovered adrenal tumor detected on abdominal imaging studies performed for a different clinical indication; 18 of these patients had mild or minimal hypertension or symptoms (that were not the reason for abdominal imaging), and 16 of these patients were asymptomatic and did not have hypertension. Twenty-eight of the 34 patients who presented with adrenal incidentalomas were diagnosed within the past decade. Fourteen patients (14%) presented in hypertensive crisis requiring hospitalization in the intensive care unit, aggressive intravenous antihypertensive therapy, and other supportive care; these included 7 patients who had been transferred directly from other institutions for further management and preoperative α -adrenergic blockade, and 4 who required placement of an intra-aortic balloon pump. Eight patients (7%) were diagnosed with pheochromocytoma because of screening performed for familial syndromes. Four patients (4%) presented to our institution with recurrent disease after having undergone prior adrenalectomy at a different institution.

During the course of diagnostic workup, 6 patients in this series underwent fine-needle aspiration biopsy as ordered by the referring primary care physician, endocrinologist, oncologist, or radiologist. None of these biop-

sies was ordered by the surgical team. None of these patients had immediate or long-standing complications as a result of the biopsy.

The operations performed included 97 laparoscopic adrenalectomies (91%), 7 open resections (6%), and 4 operations (3%) that were converted from laparoscopic to either the open (3 cases) or hand-assisted (1 case) technique. The reasons for conversion from the laparoscopic approach included 3 patients with tumors that were either too large or adherent to surrounding structures for safe laparoscopic resection and 1 patient who sustained a splenic capsular tear requiring conversion to open operation for visualization and control of the bleeding. Six operations (6%) were bilateral adrenalectomies for familial disease (5 laparoscopic, 1 open). Three patients underwent subtotal cortex-sparing adrenalectomy. Ten patients had paragangliomas; of these patients, 7 had laparoscopic resections and 3 underwent open resections.

The mean (SD) operating time was 3.1 (1.5) hours (range, 1.25-9 hours). Thirteen patients (9%) required postoperative intravenous pressors to maintain normal blood pressure. Five patients (5%) received blood transfusions. The mean (SD) hospital stay was 2.5 (3.0) days (range, 1-21 days). The mean (SD) tumor size of the resected specimens was 5.3 (2.8) cm (range, 1-15 cm).

There were no intraoperative or perioperative deaths. Morbidity from the operation was divided into several categories. Seven patients (6%) developed postoperative pulmonary emboli requiring anticoagulation and supportive respiratory care; all 7 of these patients who developed pulmonary emboli had presented in hypertensive crisis prior to undergoing operation. Three patients (3%) had postoperative cardiac events, including 2 who had myocardial infarctions and 1 who had significant electrocardiogram changes. Two patients had postoperative pneumonia requiring antibiotic therapy and prolonged hospital stay. One patient had a significant radial nerve palsy (that eventually resolved), and 1 had a wound infection requiring incision and drainage. There were no perioperative deaths as a result of these complications.

Seven patients who underwent initial operation at our institution developed recurrent disease requiring further operation or other intervention. The mean time between prior operation and development of recurrence was 6 years (range, 6 months to 17 years). Three patients with recurrences died of their disease; the mean time from last operation until death was 3.5 years (range, 1-7 years).

COMMENT

This case series of 102 patients undergoing 108 operations for pheochromocytoma since 1994 represents one of the largest single-institution reports of laparoscopic resection of pheochromocytoma. Walz and colleagues¹⁷ from Essen, Germany, have previously reported their experience with 126 patients undergoing 130 laparoscopic and retroperitoneoscopic operations for pheochromocytoma, but to our knowledge, ours is the largest series reported from a single institution in the United States. We reviewed our experience with operative treatment of pheochromocytoma to demonstrate the safety

and efficacy of the laparoscopic approach and also to better understand the changing clinical profiles of patients in this era of widespread abdominal imaging with resultant identification of increasing numbers of adrenal incidentalomas. While many of the results of this review confirmed our existing suspicions and perceptions, we were surprised by some of the data that emerged.

Although the majority of patients in this series presented either with clinically significant signs and symptoms related to paroxysmal hypertension or in hypertensive crisis, more than a third of patients were diagnosed with pheochromocytoma during the workup of an incidentally discovered adrenal mass and had minimal or no symptoms and either mild hypertension or normal blood pressure (in allusion to the well-recognized syndrome of "subclinical Cushing," we have taken to referring to these patients as having "subclinical pheochromocytoma"). An additional 7% of patients were diagnosed during the course of genetic screening for familial diseases such as multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome, and neurofibromatosis syndrome type 1; these patients were all minimally symptomatic or asymptomatic. When we reviewed the period during which the patients from this series were diagnosed, we found that the majority (28 of 34) of patients with subclinical pheochromocytoma were diagnosed within the past decade. This finding corroborates data published by other authors, such as Kopetschke et al⁷ of Berlin, Germany, who recently reported a 30% rate of incidentally discovered pheochromocytomas in their cohort of patients with the disease, compared with a 10% rate in prior decades. We believe that this rise in the number of patients with subclinical pheochromocytoma is the result of increasing numbers of abdominal imaging studies being ordered and heightened awareness of the proper biochemical workup for the adrenal masses that are incidentally discovered on these imaging studies (especially following the publication of the 2002 National Institutes of Health consensus guidelines for management of adrenal incidentaloma¹⁸). While there have been recent reports of increased malignancy rates as a result of injudicious use of abdominal computed tomographic scans,¹⁹ we expect that there will continue to be significant numbers of patients being diagnosed with subclinical pheochromocytoma in the coming decades and that these patients may at some point outnumber the population of patients who present with the "classic" signs and symptoms of clinically significant hypertension from catecholamine excess. Patients with subclinical pheochromocytoma should undergo the same preoperative preparation with α -adrenergic-blocking agents (oral phenoxybenzamine hydrochloride, starting at 10 mg twice daily and titrated to blood pressure and symptoms) as patients with classic symptomatic pheochromocytoma because they may still manifest intraoperative and postoperative hemodynamic derangements even with minimal hormonal secretion.

Laparoscopic adrenalectomy has become the gold standard operation for almost all benign adrenal tumors as well as an increasing number of isolated malignant adrenal tumors; while pheochromocytomas were once considered by some authors to be a contraindication to laparoscopic resection, most experienced endocrine surgeons

now routinely resect these tumors laparoscopically unless significant barriers to safe laparoscopic operation are present (prior abdominal operation, imaging features worrisome for malignancy, tumor size greater than 10-15 cm). Greater than 90% of operations in this series were performed laparoscopically, including several bilateral adrenalectomies, resections of paragangliomas and large tumors (up to 16 cm), reoperations for recurrent disease,²⁰ and a few cortex-sparing operations. Of the 4 operations that were converted from laparoscopic to open or hand assisted, 3 were because of technical factors such as tumor size and adherence to surrounding structures, and the other was converted because of steady bleeding from a splenic capsular tear that impaired visibility. While 9% of patients required pressors in the postoperative period and 5% received transfusions, none of the patients undergoing laparoscopic resection had significant intraoperative hemodynamic compromise, and there were no perioperative deaths.

We were somewhat surprised to learn that 7% of patients undergoing operation for pheochromocytoma developed clinically significant pulmonary emboli. All of these patients had initially presented in hypertensive crisis; most had been transferred from other facilities and had been hospitalized for at least several days prior to adrenalectomy. This finding has prompted us to review our protocols for perioperative venous thromboembolism prevention in our patients undergoing adrenalectomy, especially those who have been hospitalized prior to operation.

One of the major concerns regarding laparoscopic resection of pheochromocytoma has been the risk of tumor seeding and recurrence; Li and colleagues²¹ have previously reported on the phenomenon of "iatrogenic pheochromocytomatosis" in patients undergoing laparoscopic adrenalectomy. We identified 7 patients (6%) who developed recurrent disease requiring further operation; all of these were isolated recurrences in the resection bed and none had significant tumor spillage or seeding. We take measures in all laparoscopic adrenalectomies to prevent disruption of the tumor capsule; when this cannot be avoided, we will then convert to the open or hand-assisted approach.²² The length of time from prior operation to recurrence varied widely, from 6 months to 17 years. All patients undergoing resection of pheochromocytoma should be counseled that the disease may recur years after treatment and should be carefully followed up after operation.

While numerous organizations, including the 2002 National Institutes of Health consensus panel on the management of adrenal incidentaloma, have strongly discouraged the use of fine-needle aspiration biopsy for the workup of adrenal masses, we identified 6 patients with pheochromocytoma in our series who had undergone fine-needle aspiration biopsy, some at our own institution. Fortunately, none of these patients had adverse outcomes as a result of biopsy. However, there have been reports of hypertensive crises, patient deaths, and intra-abdominal tumor spillage as a result of fine-needle aspiration biopsy of an unsuspected pheochromocytoma.²³ The diagnosis of pheochromocytoma is made based on biochemical testing; fine-needle aspiration biopsy plays little role in the

workup of any adrenal mass and, if performed, should not be done until the patient has conclusive biochemical proof that he or she does not have a pheochromocytoma or other type of functioning tumor.

In addition to the increasing numbers of patients with subclinical pheochromocytoma who are being diagnosed during the workup of adrenal incidentaloma, we believe that we will encounter increasing numbers of patients who are diagnosed because of testing performed during the workup of familial syndromes. Pheochromocytoma is a component of several familial syndromes, including multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome, Osler-Weber-Rendu syndrome, and neurofibromatosis syndrome type 1. Increasing awareness of the prevalence of succinate dehydrogenase mutations in patients with paragangliomas and adrenal pheochromocytomas has led to recommendations for more aggressive genetic screening and biochemical testing for pheochromocytoma in family members of patients with the germline succinate dehydrogenase complex subunits B, C, or D mutation.⁴⁻⁶ Many of these affected family members will be minimally symptomatic or asymptomatic if detected early. We have revised our own protocols and are now recommending testing for succinate dehydrogenase mutations in all patients with paragangliomas and are establishing criteria for testing patients with adrenal pheochromocytomas. We refer these patients for genetic counseling and testing of family members if they are found to carry the mutation.

In conclusion, this review of our experience with 102 patients undergoing 108 operations for pheochromocytoma since the introduction of laparoscopic adrenalectomy demonstrates that the laparoscopic approach is safe and effective for greater than 90% of patients; in addition, the clinical profiles of patients undergoing operation for pheochromocytoma has changed in the past decade, with increasing numbers of patients with minimal or no symptoms coming to attention because of an incidentally discovered adrenal mass or screening for genetic syndromes.

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Author Contributions: Dr Shen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Shen, Clark, and Duh. *Acquisition of data:* Shen, Grogan, and Duh. *Analysis and interpretation of data:* Shen, Grogan, Vriens, and Duh. *Drafting of the manuscript:* Shen and Duh. *Critical revision of the manuscript for important intellectual content:* Grogan, Vriens, Clark, and Duh. *Statistical analysis:* Grogan and Duh. *Administrative, technical, and material support:* Vriens. *Study supervision:* Clark and Duh.

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INVITED CRITIQUE

The Changing Face of Pheochromocytoma

Varied Presentations, Better Outcomes

The report by Shen and associates from University of California, San Francisco is one of the largest single-institution experiences in pheochromocytoma ever published. They describe a great diversity in the initial clinical manifestations encountered, with only a minority of patients presenting electively with classic signs and symptoms. The growing fraction of patients identified through incidental radiographic findings and known familial syndromes reflects the changing face of this disease and our increasing understanding of genotype-phenotype correlations. The fact that 14 patients presented in overt hemodynamic crisis likely reflects selective referral of high-risk patients to this established center of expertise. The 4 patients who required intra-aortic balloon counterpulsation are a reminder that pheochromocytoma can present with refractory cardiogenic shock. Despite these challenges, Shen and associates achieved a zero mortality rate in their series. Their work adds to the existing literature demonstrating that laparoscopic adrenalectomy is the procedure of choice for the treatment of pheochromocytoma.

In 2007, the University of California, San Francisco group initially described the "subclinical" pheochromocytoma and recommended routine preoperative α -adrenergic blockade in patients with suspicious plasma or urine catecholamine levels in the setting of an incidentally discovered adrenal mass.¹ However, only one-third of these patients turned out to have pheochromocytomas on final pathologic examination. A potential concern here is perioperative hypotension in the majority of these patients who received α -adrenergic blockade while having normal catecholamine levels.

Shen and associates do not comment on the utility of functional (nuclear medicine) imaging in the characterization of cases with borderline catecholamine elevations. Iodine 131-meta-iodobenzylguanidine scanning, with a sensitivity in the 85% range, is likely insufficiently sensitive to exclude pheochromocytoma. At our institution, we have found fluorodopa positron emission tomography/computed tomography scanning to be highly sensitive and helpful in clarifying ambiguous cases.²