
Surgical Management of Hereditary Pheochromocytoma

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- BACKGROUND:** Surgical treatment of hereditary pheochromocytoma remains controversial because of the need for lifelong corticosteroid therapy and the risk of Addisonian crisis associated with bilateral total adrenalectomy. We examined our large series of patients with hereditary pheochromocytoma to evaluate postsurgical outcomes, particularly in those who underwent cortical-sparing adrenalectomy.
- STUDY DESIGN:** We retrospectively reviewed the outcomes of all patients with histopathologic diagnoses of hereditary pheochromocytoma treated at our institution from 1962 to 2003. Familial disease was initially determined by pedigree analysis, genetic testing, or both for multiple endocrine neoplasia (MEN) types 1, 2A, or 2B; von Hippel-Lindau disease (VHL); neurofibromatosis type 1 (NF-1); or familial paraganglioma syndrome (FP).
- RESULTS:** Adrenal pheochromocytomas were present in 56 of 59 patients (95%): MEN2A (39), MEN2B (7), VHL (6), MEN1 (2), NF-1 (2). Paragangliomas (extraadrenal pheochromocytomas) were present in the remaining 3 of 59 patients (5%): FP (2) and NF-1 (1). Thirty-eight of 56 patients with pheochromocytomas had cumulative operations resulting in total or subtotal bilateral adrenalectomy. Acute adrenal insufficiency (Addisonian crisis) occurred in 4 of these 38 patients (11%). Cortical-sparing adrenalectomy was performed in 26 patients who underwent bilateral adrenal resection; 17 (65%) were corticosteroid independent at a median followup of 71 months. Recurrent pheochromocytoma developed in an adrenal remnant in 3 of 30 patients (10%) who underwent unilateral or bilateral cortical-sparing procedures. Metastatic disease did not develop in any patient with pheochromocytoma, but has occurred in two of three patients with paragangliomas.
- CONCLUSIONS:** Our data suggest that a cortical-sparing adrenalectomy can successfully avoid the need for corticosteroid replacement in the majority of patients who undergo a bilateral adrenalectomy. Long-term followup should include monitoring of the remnant gland for recurrent pheochromocytoma with yearly biochemical screening studies. (J Am Coll Surg 2004;198:525–535. © 2004 by the American College of Surgeons)
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Up to 30% of pheochromocytomas occur as a component of hereditary syndromes, including multiple endocrine neoplasia types 1 and 2 (MEN1, MEN2), von

Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF-1), or as a result of mutations in the succinate dehydrogenase (*SDH*) genes resulting in familial paraganglioma syndrome (FP).^{1–3} These syndromes are associated with an autosomal dominant inheritance pattern and variable penetrance. Advances in our understanding of the genetic alterations causing hereditary forms of pheochromocytoma and the increasing sensitivity of biochemical assays now allow early identification of high-risk individuals and families.^{4–6} Appropriate surgical intervention continues to be the treatment of choice for affected patients.

Hereditary pheochromocytomas appear to have a

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Abbreviations and Acronyms

FP	=	familial paraganglioma syndrome
MEN	=	multiple endocrine neoplasia
MIBG	=	metaiodobenzylguanidine
MRI	=	magnetic resonance imaging
MTC	=	medullary thyroid carcinoma
NF-1	=	neurofibromatosis type 1
SDH	=	succinate dehydrogenase
VHL	=	von Hippel-Lindau disease

unique natural history and biologic behavior; they are believed to be frequently bilateral but rarely malignant.^{1,7} Total bilateral adrenalectomy to treat bilateral pheochromocytomas commits the patient to lifelong steroid dependence and incurs the risk of acute adrenal insufficiency (Addisonian crisis). Recent data suggest that total bilateral adrenalectomy may be associated with mortality and major morbidity from acute adrenal insufficiency.^{8,9} As a result, we and others have used a surgical strategy of subtotal or cortical-sparing adrenalectomy with the intent of leaving a portion of vascularized adrenal cortex in situ in patients with hereditary or sporadic bilateral pheochromocytoma.^{7,10-14} This strategy is based on the following assumptions: 1) metastatic pheochromocytoma rarely occurs in patients with MEN2, VHL, and other rare inherited pheochromocytoma-associated syndromes; 2) the remaining cortex left in situ may prevent the need for chronic corticosteroid replacement, minimizing the risk of adrenal insufficiency; and 3) the risk of recurrent pheochromocytoma in the remnant adrenal gland treated with a cortical-sparing technique is acceptably low. In an effort to verify these assumptions, we reviewed the outcomes for a large consecutive series of patients with hereditary pheochromocytoma.

METHODS

In accordance with the Institutional Review Board and a waiver of informed consent, the endocrine surgery database and medical records were used to identify and retrospectively review all patients who underwent surgical resection of hereditary pheochromocytoma or extraadrenal pheochromocytoma (paraganglioma) at The University of Texas MD Anderson Cancer Center between March 1962 and October 2003. Paragangliomas were defined as catecholamine-producing tumors arising in the autonomic ganglia outside of the adrenal medulla.

Patients with carotid body paragangliomas and those without histopathologic evidence of pheochromocytoma or paraganglioma were excluded from analysis. Demographic and disease characteristics and outcomes were determined by reviewing original laboratory results (either plasma, 24-hour urinary fractionated catecholamines, or metanephrines, or all three), radiographic imaging studies (CT, MRI, or metaiodobenzylguanidine [MIBG] scintigraphy), and operative and pathology reports.

Hereditary disease was initially determined by family history and clinical diagnostic criteria for MEN1, MEN2, VHL, NF-1, or FP. Pedigrees documenting family history were prepared using information collected from medical records and patient interviews. Clinical diagnosis of MEN1 in patients with pheochromocytomas required either tumor involvement of two of three designated endocrine glands (parathyroid, pancreas, or pituitary) or tumor involvement of a single designated endocrine gland plus a blood relative affected with MEN1.¹⁵ The clinical diagnosis of MEN2A was made in patients with pheochromocytoma who had a personal or family history of medullary thyroid carcinoma (MTC) with or without hyperparathyroidism.¹⁵

The clinical diagnosis of MEN2B was made in patients with pheochromocytoma who had a personal history of MTC and characteristic physical stigmata (eg, mucosal ganglioneuromas, marfanoid habitus).¹⁵ The clinical diagnosis of VHL in a patient with pheochromocytoma required either a positive family history of VHL or the presence of at least one retinal or central nervous system hemangioblastoma.¹⁶ The clinical diagnosis of NF-1 required two or more of the following: six or more café-au-lait spots, two or more neurofibromas (or one plexiform neurofibroma), two or more Lisch nodules (benign iris hamartomas), axillary or inguinal freckling, optic glioma, a distinctive bony lesion, or a first-degree relative with NF-1.¹⁷ Patients with paragangliomas who had a family history of paragangliomas and an absence of other endocrine neoplasms were diagnosed with FP.¹⁸ For confirmation of the clinical diagnosis, genetic testing was done when possible for the *RET* proto-oncogene (MEN2A, MEN2B), the *VHL* gene, and the *MEN1* gene. None of the patients in this series underwent mutation analysis of the *SDH* or *NF-1* genes.

Pheochromocytomas were diagnosed by annual screening of at-risk individuals in affected families or

when clinical signs and symptoms of catecholamine excess developed. Adrenalectomy was performed laparoscopically or by laparotomy. Laparoscopic adrenalectomy was performed with the patient in the full lateral position using the transperitoneal approach. Laparotomies were performed using a transverse or midline incision. Access to the right adrenal gland was achieved by fully mobilizing the right lobe of the liver to expose the intraabdominal inferior vena cava from the right hepatic vein to the right renal vein. Exposure of the left adrenal gland involved complete mobilization of the spleen and distal pancreas out of the left upper quadrant to expose the underlying adrenal neoplasm, left crus of the diaphragm, and left renal vein. Cortical-sparing adrenalectomy usually involved ligation and division of the adrenal vein. To preserve its blood supply, the portion of adrenal cortex to be preserved in situ was not mobilized out of the retroperitoneum.

Patients who had a cortical-sparing adrenalectomy as part of a bilateral adrenal procedure (performed separately or concurrently) were evaluated postoperatively for adrenal cortical reserve by measurement of baseline cortisol and ACTH and response to cosyntropin stimulation testing. A patient was defined as being corticosteroid independent if daily corticosteroid supplementation was not required. For cosyntropin stimulation testing, baseline cortisol and ACTH levels were obtained before the intravenous administration of 0.25 mg cosyntropin; cortisol levels were then drawn at 30, 45, or 60 minutes, or all, after cosyntropin injection.¹² Patients were considered to have adequate cortical reserve if the plasma cortisol rose to 18 mg/dL or higher or rose 7 mg/dL or more over baseline within 60 minutes after cosyntropin injection.

Patients were monitored after operations by history, physical examination, laboratory studies, and radiographic imaging to assess for signs and symptoms of adrenal insufficiency and recurrent disease in the ipsilateral (remnant) or contralateral adrenal gland. Addisonian crisis was defined by symptoms of acute life-threatening adrenal insufficiency (eg, hypotension, weakness, nausea, vomiting, or mental status changes) developing spontaneously or in response to infection or dehydration, with improvement of symptoms after administration of corticosteroids.¹⁹ Diagnosis of recurrent pheochromocytoma within 6 months of the initial tumor diagnosis was considered a synchronous presenta-

tion; recurrent pheochromocytoma occurring more than 6 months after initial adrenal surgery was considered metachronous.

RESULTS

We identified 59 patients (34 women and 25 men) from 40 kindreds who underwent surgical resection of hereditary pheochromocytoma or paraganglioma. Thirteen of 59 patients were included in our previously reported study examining the longterm effects of cortical-sparing adrenalectomy on corticosteroid dependence and Addisonian crisis.¹² Thirty-nine patients were diagnosed with MEN2A, seven with MEN2B, six with VHL, three with NF-1, and two each with MEN1 and FP. Patient and disease characteristics are shown in Table 1. Genetic testing was performed in 40 (68%) of the patients, and a mutation was identified in the *RET*, *VHL*, or *MEN1* gene in all cases (Table 2). Thirty-seven of the 40 patients had MEN2A or MEN2B and underwent *RET* mutation analysis: mutations were found in codon 634 in 30 (81%), codon 918 in 5 (14%), and codon 618 in 1 (3%). Pedigree analysis revealed that 14 patients had no obvious family history of hereditary pheochromocytoma or paraganglioma, whereas the remaining 45 patients were members of well-defined kindreds.

Pheochromocytoma or paraganglioma was the initial manifestation of an inherited syndrome in 9 of 59 patients (15%), including 6 of the 39 patients with MEN2A (15%), 1 of the 6 patients with VHL (17%), and both patients with FP. An additional 16 patients (27%) were diagnosed with pheochromocytoma synchronously (ie, within 6 months), with other initial manifestations of their inherited syndromes.

The median age at the time of initial adrenal surgery (initial tumor diagnosis) was 36 years (range 13 to 73 years). Pheochromocytomas were present in 56 of 59 patients (95%). At the first adrenal operation, pheochromocytomas were pathologically confirmed to be bilateral in 27 of 56 patients (48%) and unilateral in 29 patients (52%). Malignant pheochromocytoma was not present in any of the 56 patients from 38 kindreds with pheochromocytoma. Detailed pedigree analysis of the 39 kindreds with MEN2A, MEN2B, VHL, or MEN1 revealed a history suggesting malignant pheochromocytoma in a single patient from a kindred with MEN2A based on an isolated entry in the medical record, but histopathologic confirmation was not available.

Table 1. Demographic and Disease Characteristics of 59 Patients with Hereditary Pheochromocytoma or Paraganglioma

Characteristic	No. of patients by hereditary syndrome						Total
	MEN2A	MEN2B	VHL	NF-1	FP	MEN1	
Total no. of patients	39	7	6	3	2	2	59
No. of kindreds	21	7	6	3	1	2	40
Patient characteristics							
Men	15	3	3	1	2	1	25
Women	24	4	3	2	0	1	34
Syndrome confirmed by genetic testing	32	5	1	0	0	2	40
Tumor characteristics							
Median age, y (range) at diagnosis	36 (19–60)	26 (19–34)	44 (13–73)	50 (50–63)	34 (20–47)	34 (30–38)	36 (13–73)
Adrenal: initial manifestation	6	0	1	0	2	0	9
Adrenal: concomitant with initial manifestation*	9	1	3	2	0	1	16
Synchronous bilateral pheo [†]	20	4	3	0	0	0	27
Unilateral pheo	19	3	3	2	0	2	29
Malignant pheo	0	0	0	0	NA	0	0
Extraadrenal pheo (paraganglioma)	0	0	0	1	2	0	3
Malignant paraganglioma	NA	NA	NA	0	2	NA	2
Recurrent disease							
None	32	7	5	3	0	2	49
Ipsilateral (remnant)	1	0	0	0	0	0	1
Contralateral (metachronous)	4	0	1	0	0	0	5
Ipsilateral + contralateral	2	0	0	0	0	0	2
Extraadrenal distant metastases	0	0	0	0	2	0	2
Vital status							
Alive	34	4	5	3	2	1	49
Dead	5	3	1	0	0	1	10
Median age at death, y (range)	52 (34–71)	37 (27–37)	41	NA	NA	45	43 (27–71)
Cause of death							
HTN crisis (pheo)	0	0	0	NA	NA	0	0
Metastatic MTC	3	1	0	NA	NA	0	4
Metastatic PET	0	0	0	NA	NA	1	1
Cardiac arrest/CAD	1	0	1	NA	NA	0	2
Unknown	1	2	0	NA	NA	0	3

*Pheochromocytomas were diagnosed within 6 months of the initial syndrome manifestation.

[†]Bilateral pheochromocytomas were considered synchronous if they were diagnosed within a 6-month time frame.

CAD, coronary artery disease; FP, familial paraganglioma; HTN, hypertension; MEN, multiple endocrine neoplasia; MTC, medullary thyroid carcinoma; NA, not applicable; NF-1, neurofibromatosis type 1; PET, pancreatic neuroendocrine tumor; pheo, pheochromocytoma; VHL, von Hippel-Lindau disease.

Paragangliomas were found in 3 of 59 patients (5%) (two patients from a single FP kindred and one patient with NF-1). Two patients had solitary paragangliomas in the paraaortic region, and one patient had a tumor in the bladder. Malignant paraganglioma was documented in two of the three patients, both with FP; one presented with synchronous bone metastases, and the other patient developed metachronous lung metastases.

The adrenal operations performed in the 56 patients with pheochromocytoma are illustrated in Figure 1. Bi-

lateral adrenal procedures were performed at a single operation in 31 of 56 patients (55%) and consisted of total bilateral adrenalectomy in 11, total adrenalectomy and a contralateral cortical-sparing adrenalectomy in 14, and bilateral cortical-sparing adrenalectomy in 6. Based on histopathologic evaluation of the adrenalectomy specimens, 4 of the 31 patients (13%) had only unilateral pheochromocytoma. Two patients subsequently underwent completion total adrenalectomy; recurrent pheochromocytoma was histopathologically confirmed in one patient. The second patient, operated on outside

Table 2. Results of Genetic Testing in 40 Patients with Hereditary Pheochromocytoma

Gene, mutation	No. of patients
<i>RET</i>	37
codon 618	1
codon 634	30
codon 918	5
Not reported*	1
<i>MEN1</i>	2
1216_1217insA	1
210_211delC	1
<i>VHL</i>	1
Not reported*	1

*Genetic test was noted to be positive but specific mutation was not documented in the medical record.

of our institution, was found to have cortical hyperplasia with no evidence of recurrent pheochromocytoma.

Unilateral adrenalectomy was performed in 25 of 56 patients (45%): a total adrenalectomy in 19 and a cortical-sparing adrenalectomy in 6. Seven of these 25 patients (28%) developed recurrent pheochromocytoma in the contralateral adrenal gland; it was treated with total adrenalectomy in 2 patients and a cortical-sparing adrenalectomy in 5. Two of these seven patients required a third operation for recurrent pheochromocytoma in a previously operated gland (recurrence in the remnant gland after cortical-sparing surgery).

Thirty-eight patients were at risk for adrenal insufficiency as a result of having undergone bilateral adrenal procedures either concurrently for synchronous disease (31) or separately after development of recurrent contralateral pheochromocytoma (7). Total adrenalectomy was performed in 12 of the 38 patients, and the remaining 26 underwent unilateral or bilateral cortical-sparing adrenalectomy. Four of 26 patients treated with the cortical-sparing technique subsequently underwent completion total adrenalectomy. At the time of last followup, 22 patients were evaluable, having undergone bilateral cortical-sparing adrenalectomies or unilateral cortical-sparing adrenalectomy with a contralateral total adrenalectomy. Signs and symptoms of acute adrenal insufficiency (Addisonian crisis) occurred in 4 of 38 patients (11%) after their last adrenal operation: 3 of 16 patients after total bilateral adrenalectomy, and 1 of 22 patients after subtotal adrenalectomy. Of the 22 patients who had a cortical-sparing procedure as part of a bilateral adrenalectomy, 13 (59%) were corticosteroid independent at last followup, 6 (27%) were receiving daily steroid supplements, and 3 (14%) were awaiting early postoperative evaluation or had incomplete followup data. Fifteen of the 22 patients had documentation of postoperative cosyntropin stimulation testing. A normal response to cosyntropin occurred in 4 of 15 patients.

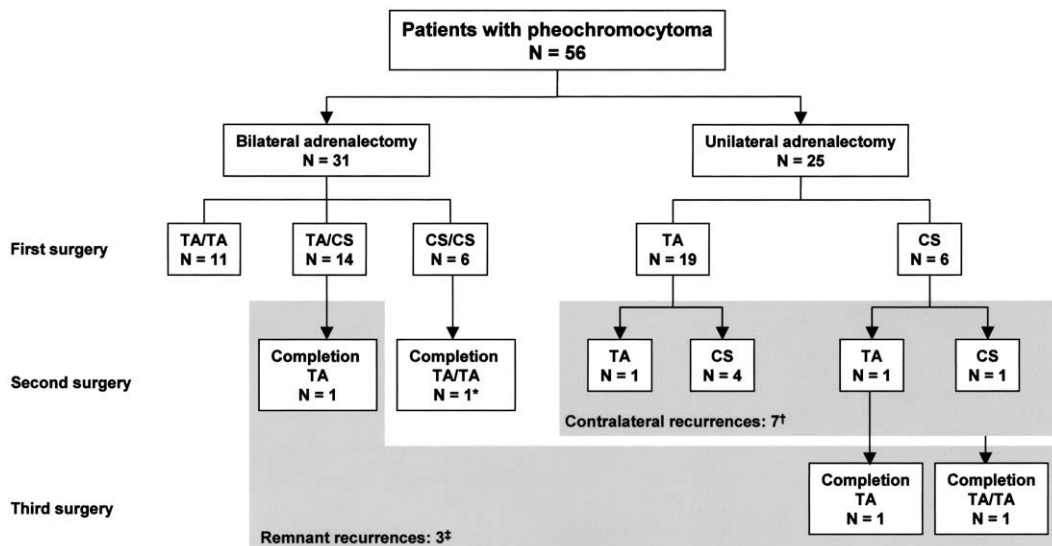


Figure 1. Adrenal operations performed in 56 patients with hereditary pheochromocytoma. *Bilateral completion adrenalectomy was performed for presumed recurrent pheochromocytoma, but histopathology showed bilateral cortical hyperplasia with no evidence of recurrent pheochromocytoma. †Recurrent pheochromocytoma in contralateral nonoperated gland. ‡Recurrent pheochromocytoma in ipsilateral operated gland. CS, cortical-sparing adrenalectomy; TA, total adrenalectomy.

Test results in the remaining 11 were abnormal, but only 6 of them required daily corticosteroid replacement at last followup. Additionally, all four patients who underwent reoperative completion total adrenalectomy after a bilateral adrenalectomy with a cortical-sparing procedure had cosyntropin stimulation testing before their completion total adrenalectomy. A normal response to cosyntropin was documented in three of the four patients; none of these patients required daily corticosteroid replacement before completion total adrenalectomy. In total, 17 of 26 patients (65%) who underwent cortical-sparing adrenalectomy were corticosteroid independent either at last followup (13) or before completion total adrenalectomy (4).

Recurrent pheochromocytoma developed in 8 (14%; 7 with MEN2A and 1 with VHL) of 56 patients in a total of 10 adrenal glands. Recurrences occurred in the contralateral gland in five patients, the remnant after a cortical-sparing procedure in one patient, and in both the ipsilateral remnant and the contralateral gland in two patients. So metachronous pheochromocytomas developed in the contralateral adrenal gland after unilateral adrenalectomy in a total of 7 of 25 at-risk patients (28%) at a median of 55 months (range 22 to 244 months) after initial adrenalectomy. Of the remaining 18 patients who had a unilateral adrenalectomy but have not had recurrences, 11 (61%) have followup of less than 55 months.

Among 56 patients with pheochromocytomas, 30 patients had one or more cortical-sparing adrenalectomies performed on a total of 37 adrenal glands (7 bilateral, 23 unilateral). Recurrent pheochromocytoma in a remnant adrenal gland after cortical-sparing adrenalectomy was diagnosed in 3 glands from 3 patients (all with MEN2A) at 12, 19, and 27 years after cortical-sparing adrenalectomy. Of the remaining 27 patients who have not had a recurrence in an adrenal gland treated with cortical-sparing surgery, 22 (81%) have followup of less than 10 years.

Forty-one of the 59 patients evaluated for hereditary pheochromocytomas or paragangliomas underwent operations for primary or recurrent disease at our institution; the remaining 18 underwent operation outside of our institution. Twenty-one of the 41 patients (51%) were symptomatic at the time of diagnosis, and 20 (49%) were asymptomatic. Preoperative radiologic studies confirmed an adrenal or extraadrenal neoplasm in 34 of 34 patients (100%) who had CT scan, 17 of 18 (94%)

who had MRI, and 6 of 9 (67%) who had an MIBG scan. Alpha blockade with phenoxybenzamine was used for preoperative biochemical preparation in all patients; beta blockade was used selectively. The index surgical procedures at our institution included 3 bilateral total adrenalectomies (7%) performed before cortical-sparing adrenalectomy or because large tumor size prohibited consideration of cortical-sparing adrenalectomy, 11 unilateral total adrenalectomies combined with a contralateral cortical-sparing adrenalectomy (27%), 6 bilateral cortical-sparing adrenalectomies (15%, 1 laparoscopically), 11 unilateral total adrenalectomies (27%, 6 laparoscopically), and 9 unilateral cortical-sparing adrenalectomies (22%, 1 laparoscopically). A paraganglioma resection was performed in one patient with FP. There were no perioperative complications related to catecholamine excess such as hypertensive crisis, myocardial infarction, or stroke. All laparoscopic adrenalectomies were successfully completed without the need to convert to laparotomy, and no patient required reoperation.

At last followup, 49 of 59 patients (83%) were alive at a median of 71 months (range 0 to 412 months) after initial adrenalectomy. Causes of death in the other 10 patients included metastatic MTC in 4 patients (ages 34, 37, 47, and 52 years), metastatic pancreatic neuroendocrine carcinoma in 1 patient (age 45 years), and causes unrelated to the genetic syndrome in 2 patients (ages 41 and 66 years). The causes of death were unknown in the remaining 3 patients (ages 27, 37, and 71 years).

DISCUSSION

Our data support all three assumptions that are used to justify the surgical strategy of cortical-sparing adrenalectomy in patients with hereditary pheochromocytoma. First, metastatic pheochromocytoma rarely occurs in patients with inherited pheochromocytoma (0 of 56 patients in this study), in contrast to patients with sporadic pheochromocytoma and especially those with paraganglioma (two of three malignant in this study). Second, in contrast to total bilateral adrenalectomy, cortical-sparing adrenalectomy prevented the need for chronic corticosteroid replacement in the majority (65%) of patients, and acute adrenal insufficiency occurred in only one patient. Finally, the risk of recurrent pheochromocytoma in the remnant adrenal gland treated with the cortical-sparing technique was low (10%).

Genetically inherited susceptibility genes including *RET* (associated with MEN2), *VHL*, the *SDH* genes (*SDHB*, *SDHC*, and *SDHD*, associated with FP), *NF-1*, and *MEN1* are responsible for up to 30% of patients with pheochromocytoma or paraganglioma, with or without known familial syndromes.^{1,2,20} In a patient with apparently sporadic pheochromocytoma, a hereditary cause is often best predicted by the presence of bilateral tumors, multifocal tumors, extraadrenal location (paraganglioma), tumor onset at a young age, or a positive family history of related manifestations of a genetic syndrome.²

Pheochromocytomas in MEN2 patients are associated with germline mutations in *RET* in all MEN2-associated codons except 768 and a valine to methionine substitution at codon 804, and are most frequently associated with mutations in codons 634 and 918.²¹ In this article, mutations were found in codon 634 in 81% of MEN2 patients, codon 918 in 14%, and codon 618 in 3%. The incidence of pheochromocytoma is quite high in MEN2 and *VHL* (50% and 10% to 20%, respectively) compared with the frequencies reported in *MEN1* and *NF-1* (1% and less than 1% to 6%, respectively).^{2,3,15,22,23} But *MEN2*, *VHL*, *MEN1*, and *NF-1* have been estimated to account for only half of all cases of hereditary pheochromocytoma; a significant proportion of isolated pheochromocytoma and paraganglioma are likely related to mutations in the *SDH* gene family.^{1,2,20,24}

Pheochromocytomas in patients with MEN2 appear to be biologically distinct from sporadic tumors in that they are rarely extraadrenal or malignant and are diagnosed at a younger age. Pheochromocytomas in patients with MEN2A are most often diagnosed before the age of 40 years, are frequently found at the time of MTC diagnosis, and are occasionally the first manifestation of MEN2A.¹ In this article, the median age of pheochromocytoma diagnosis in MEN2A patients was 36 years (range 19 to 60 years), pheochromocytoma was the initial manifestation of MEN 2A in six patients (15%), and an additional nine patients (23%) had pheochromocytomas diagnosed concomitantly with MTC. The timing of pheochromocytoma diagnosis is dependent on the age routine screening is initiated rather than the age at presentation of symptoms, so it is not surprising that 18 of 39 patients (46%) with MEN2A in this series were asymptomatic at the time of initial pheochromocytoma diagnosis.

Bilateral adrenal involvement, although common in patients with familial pheochromocytoma, was histologically confirmed in only 34 of 56 patients (61%) in this series. Importantly, of 25 patients who underwent a unilateral adrenalectomy, only 7 (28%) developed a metachronous contralateral recurrence at a median of slightly more than 4 years after initial adrenalectomy. We expect the incidence of contralateral recurrence to increase with the duration of followup, but it is impossible at this time to predict the long-term recurrence rate from this data set.

The concept of subtotal adrenal resection (cortical-sparing adrenalectomy) in patients with inherited pheochromocytoma, particularly those with MEN2 and *VHL*, evolved from the realization that malignancy is uncommon in this subset of pheochromocytoma patients and that death from metastatic pheochromocytoma may be less common than the morbidity and mortality of adrenal insufficiency. A 1996 review of the literature from our institution reported an overall rate of malignant pheochromocytoma of 3.9% in patients with MEN2 and 3.3% in patients with *VHL*.¹² More recently published articles about cortical-sparing adrenalectomy have failed to report any additional MEN2 or *VHL* patients with malignant pheochromocytoma.^{7,10,11,13,14} In the present article about 56 patients with pathologically confirmed intraadrenal pheochromocytoma, no patient developed metastatic pheochromocytoma. Detailed analysis of all kindreds represented in this article revealed a historic reference to one patient with possible metastatic pheochromocytoma. But it may be difficult or impossible to retrospectively determine the origin of metastatic neuroendocrine carcinoma in a patient with MEN2 in the setting of both MTC and pheochromocytoma. It is reasonable to assume that the reported frequency of metastatic pheochromocytoma in patients with MEN2 (3% to 4%) may represent an overestimation in the absence of careful pathologic analysis to exclude metastatic MTC. In contrast, the risk of Addisonian crisis may be as high as 23% to 32% in patients who undergo bilateral total adrenalectomy.^{8,9} In addition to significant patient morbidity associated with such episodes of adrenal insufficiency (usually requiring hospital admission), deaths from adrenal insufficiency have been reported.¹² One would assume that the risk of Addisonian crisis would be minimized by improving patient education and having patients carry an emergency card or medical identification bracelet. Patients with im-

paired comprehension of such education are also those likely to be at greater risk for hypertensive crisis because of untreated pheochromocytoma; their management clearly must be individualized and combined with contemporary genetic counseling and aggressive multimodality followup.²⁵

Cortical-sparing adrenalectomy represents a logical treatment alternative for patients with hereditary pheochromocytoma. The ability to preserve a small portion of adrenal cortex in situ is dependent on the arterial supply to the adrenal gland that includes small tributaries from the abdominal aorta, renal artery, and, most important, the inferior phrenic artery. In our experience, the cephalad aspect of the adrenal gland, based on the phrenic circulation, is most suitable for subtotal adrenal preservation in situ. It is rare that the adrenal vein can be preserved regardless of whether one is operating on the right or left adrenal gland. Importantly, large tumor size makes cortical preservation unlikely, so most candidates for cortical-sparing procedures will have small tumors diagnosed by routine screening in the setting with inherited endocrinopathy syndromes. From a technical perspective, a successful cortical-sparing procedure involves the following key elements. First, accurate preoperative imaging, which at our institution includes multislice or multidetector CT, is necessary to identify the portion of cortex most likely to be spared. Second, at the time of operation, exposure of the adrenal gland in a bloodless field is critically important. For access to the right adrenal gland, full mobilization of the liver is performed to expose the intraabdominal inferior vena cava and allow full visualization of the right adrenal gland. Exposure of the left adrenal gland requires complete mobilization of the spleen and distal pancreas; the left renal vein at its junction with the adrenal vein is then easily visualized. Preoperative imaging, intraoperative visual inspection and palpation, and, if necessary, intraoperative ultrasonography, are all used to determine which portion of the gland is to be left in situ. Third, it is critically important that the portion of adrenal gland to be preserved in situ not be mobilized out of the retroperitoneum. This is especially important when ligation of the adrenal vein is necessary. For this reason, we prefer open laparotomy when performing cortical-sparing adrenalectomy. Although previous authors have reported successful laparoscopic cortical-sparing procedures,^{10,13} a laparoscopic adrenalectomy involves mobilization of the adrenal gland before the gland is divided. This may result in

devascularization of the portion of adrenal cortex to be preserved in situ. Open laparotomy allows transection of the adrenal gland without full mobilization. Bleeding from the adrenal cortex left in situ is controlled very gently with cautery, Surgicel (Johnson & Johnson Medical, Inc), Avitene (Davol, Inc), or other topical hemostatic agents. In general, laparoscopic adrenalectomy is preferred when a total adrenalectomy is planned.

Knowledge of normal adrenal anatomy suggests that it is virtually impossible to leave a vascularized portion of adrenal cortex adequate to prevent corticosteroid dependence without leaving some amount of adrenal medulla. So performing a cortical-sparing adrenalectomy clearly puts the patient at risk for recurrent pheochromocytoma in the adrenal remnant. The risk of recurrent pheochromocytoma is dependent on the age at which adrenalectomy is performed (younger patients will have a much longer period of time during which recurrence can develop), the duration of followup, and the technical aspects of the procedure (the amount of medulla left in situ). To date, experience with cortical-sparing adrenalectomy is largely anecdotal, so accurate data on the frequency of recurrent pheochromocytoma in adrenal glands treated with subtotal resection are not yet available. Our current experience is no exception; although recurrent pheochromocytoma has developed in only 3 of 30 patients, longer-term followup is needed.

For patients undergoing subtotal adrenalectomy, the risk of recurrent pheochromocytoma, no matter how small, is unacceptable unless cortical preservation results in a reasonable likelihood of corticosteroid independence. Our experience, combined with reports from the literature, suggests that the majority of patients (65% in this series) do not require chronic daily hormone replacement.^{7,10-14} Assuming that their baseline cortisol levels are within the normal range, even those who have a subnormal response to cosyntropin may not require the chronic administration of corticosteroids in the absence of a systemic stress. In the first few months after operation, patients require monitoring of ACTH levels and intermittent cosyntropin stimulation testing as the dose of hydrocortisone is decreased. Currently we obtain a serum ACTH and a cosyntropin stimulation test at 2-month intervals for the first 6 postoperative months. Patients are instructed to discontinue hydrocortisone for 24 hours before these studies.

Our analysis of 56 patients from 38 kindreds with hereditary intraadrenal pheochromocytoma (excluding

the 3 patients from 2 kindreds with paraganglioma) confirms the clinical impression that malignant pheochromocytoma in this setting is very rare. In fact, we did not have a single patient with documented malignant pheochromocytoma, and analysis of all involved kindreds failed to disclose a histopathologically confirmed case of malignant pheochromocytoma. In contrast, Addisonian crisis occurred in 4 of 38 at-risk patients (11%). This was despite close medical supervision of these patients. Cortical-sparing adrenalectomy, as part of a bilateral adrenal resection, was performed in 26 patients, and 17 (65%) were corticosteroid independent. So we have adopted the following surgical strategy for familial pheochromocytoma. In patients with a unilateral pheochromocytoma and a normal contralateral gland, our preferred procedure is a laparoscopic total adrenalectomy. In patients who present with bilateral pheochromocytoma, we use a midline incision to perform a unilateral cortical-sparing procedure, with removal of the entire contralateral gland. In general, we prefer to preserve cortex on only one side rather than assume double the risk of recurrent pheochromocytoma by preserving cortex on both sides. Finally, in patients who present with a metachronous contralateral pheochromocytoma after a previous unilateral total adrenalectomy, we prefer an open cortical-sparing procedure. Short-term followup includes reinforcement of preoperative patient education about adrenal insufficiency and regularly scheduled testing of adrenal reserve. In all patients, long-term followup should include monitoring of the remaining adrenal gland or portion of adrenal gland for recurrent pheochromocytoma, with yearly plasma or urinary screening studies.

Author Contributions

Study conception and design: Yip, Lee, Evans

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Analysis and interpretation of data: Yip, Shapiro, Lee, Evans

Drafting of manuscript: Yip, Shapiro, Evans

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Statistical expertise: Yip, Shapiro, Evans

Supervision: Lee, Evans

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MD Anderson Cancer Center as a referral center for the surgical management of inherited endocrinopathy syndromes, particularly pheochromocytoma.

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Invited Commentary

Gerard M Doherty, MD, FACS
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This nicely presented article evaluates a strategy designed to limit the end-organ effects of genetic defects that predispose to pheochromocytoma. With genetic cancer syndromes, the only current curative option is complete ablation of adrenal medullary tissue, but this creates a separate set of complications associated with loss of adrenocortical function. So a strategy must be devised that limits patient morbidity from either pheochromocytoma or Addisonian crisis for as long as possible. The options for this include resection of both adrenal glands at the time of initial tumor development, resection of one gland, and careful surveillance for development of tumor in the other gland, and attempts to do cortical-sparing operations as detailed here. I have two questions for the authors regarding their arguments and experience for this latter as a sensible strategy:

First, did any patients whose pheochromocytoma recurred, present with life-threatening symptoms of their recurrence?

Second, were laparoscopic approaches ever used for the partial adrenalectomy, or for resection of the recurrent pheochromocytoma, and if not, why not?

Reply

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Thank you, Dr Doherty, for reviewing our article and for your thoughtful comments. Recurrent pheochromocytoma developed in 10 adrenal glands of 8 patients. Five patients experienced metachronous recurrence in the contralateral (nonoperated) adrenal gland, two patients had recurrent pheochromocytoma in both the contralateral nonoperated adrenal gland and in the previously operated ipsilateral gland after a cortical-sparing procedure, and one patient suffered recurrence isolated to the previously operated adrenal gland, also after a cortical-sparing procedure. So, a total of three patients experienced a recurrence in the remnant adrenal gland after a cortical-sparing adrenalectomy. Interestingly, recurrent pheochromocytoma in a remnant gland appeared to take a long time to develop, occurring 12, 19, and 27 years after the initial cortical-sparing procedure.

Eight of 10 recurrences were diagnosed by one or more signs and symptoms consistent with pheochromocytoma (eg, hypertension, headache, diaphoresis, palpitation, flushing, anxiety, etc), which prompted further biochemical and radiographic investigation. None of these patients presented with life-threatening symptoms. The remaining two recurrences were identified in asymptomatic patients by routine followup biochemical screening studies.

In response to your second question, we prefer the laparoscopic approach when performing a total unilateral adrenalectomy. We have attempted a cortical-sparing procedure laparoscopically in only two patients. When performing a cortical-sparing adrenalectomy, it is critically important that the portion of adrenal gland to be preserved in situ not be mobilized out of the retroperitoneum (and thereby risk disruption of its blood