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SURGICAL ENDOSCOPY
and Other Interventional Techniques

Laparoscopic adrenalectomy

100 resections with clinical long-term follow-up

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Abstract
Background: The operative results of 100 laparoscopic adrenal resections in 94 patients and the subsequent impact on postoperative antihypertensive therapy are presented.
Methods: Clinical and follow-up data for resections performed between 1995 and 2003 were obtained from medical records, patient questionnaires, and telephone interviews.
Results: The diseases included Conn's syndrome (27 patients), Cushing's syndrome (30 patients), pheochromocytoma (11 patients), and Other tumors (26 patients). Antihypertensive therapy was eliminated or reduced for Conn's syndrome (75%), Cushing's syndrome (27%), pheochromocytoma (88%) and patients with Other tumors (54%). Clinical improvement was observed by 12 months for pheochromocytoma patients as compared with 35 to 45 months for the other groups ($p < 0.05$). Multivariate analysis showed that pheochromocytoma patients were more likely to experience improvement or cure than the Other tumor group (hazard ratio, 4.87; 95% confidence interval, 1.61–14.7).
Conclusions: Laparoscopic adrenalectomy continues to be safe and efficacious for benign adrenal diseases. Although patients with functional tumors can expect improvement or cure, the time until improvement may be longer than previously recognized.

Key words: Laparoscopy — Adrenalectomy — Antihypertensive agents

Advances in laparoscopic technique and instrumentation have enabled a growing array of complex surgical procedures to be performed using a minimal access approach. Traditional indications for adrenal resection include Conn's syndrome, Cushing's syndrome and Cushing's disease, pheochromocytoma, nonfunctioning adrenal masses, and malignant disease. Laparoscopic adrenal resection, first described by Gagner [6] in 1992, offers the benefits of minimal access surgery to patients with adrenal diseases. The technique for laparoscopic adrenalectomy has been refined and currently is considered standard for most patients with benign disease [10].

Few studies have examined the results of laparoscopic adrenalectomy from a long-term, medication use standpoint. Whereas the technique has been embraced readily for patients with a diagnosis of Conn's or Cushing's syndrome, acceptance of laparoscopic adrenalectomy for the resection of pheochromocytoma has been slow. Moreover, the application of proper analytical methods for variable follow-up time has been lacking. The primary purposes of this cohort analysis were to examine the operative and perioperative results for the transperitoneal laparoscopic technique of adrenalectomy in a relatively large clinical series, and to determine the long-term effectiveness of laparoscopic adrenalectomy in terms of improvement or cure in antihypertensive medication use. Specifically, postoperative improvement or cure in antihypertensive regimen was examined by disease entity, and long-term follow-up results were obtained by patient questionnaire.

Materials and Methods

Design overview

The main objective of this study was to evaluate the efficacy of laparoscopic adrenalectomy by examining the subsequent reduction or elimination of antihypertensive medication use after resection. In addition, the clinical indications and operative outcomes of laparoscopic adrenalectomy were reviewed. A cohort of laparoscopic adrenalectomy patients was identified and followed by means of computerized patient record or questionnaire. Informed consent was obtained from all the patients who responded to the follow-up questionnaire. Approval for this study was obtained from the Vanderbilt University Medical Center Institutional Review Board.

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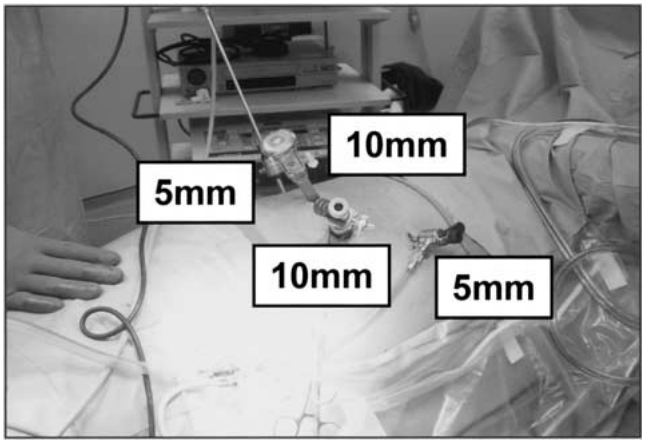

Fig. 1. Port placement for laparoscopic adrenalectomy. Right-sided procedure is shown. The cephalad direction is to the right, and the caudad to direction is to the left.

Hospital and operative procedure

All laparoscopic adrenalectomies were performed by a team of two surgeons (R.E.G. and M.D.H.). The details of the operative procedure have been reported previously [10]. In brief, each patient is placed in the lateral decubitus position with the operative table bent to 30° from horizontal. Initial access to the peritoneal cavity is obtained using a 10 mm Hasson cannula placed 2 to 3 cm inferiorly to the tip of the 10th rib. A second 10 mm port is placed in the anterior-axillary line. Two 5-mm ports are placed each in the posterior axillary line and the right (or left) upper quadrant (Fig. 1). A 30° laparoscope is used via the Hasson cannula.

For right adrenalectomy, the right lobe of the liver is fully mobilized by division of the triangular ligament. With the liver retracted cephalad and medially rotated, the peritoneum overlying the right adrenal gland is dissected using electrocautery, showing the right adrenal vein. This peritoneal dissection begins laterally and proceeds medially to the inferior vena cava. Next, the peritoneum is divided cephalad to caudad to the right renal vein along the lateral side of the vena cava. After the right adrenal vein is located, it is doubly clipped and cut. Occasionally, a vascular stapling device is used to control the adrenal vein. The remaining dissection is performed with electrocautery, freeing the gland from surrounding tissue. A laparoscopic retrieval bag is used to deliver the specimen through the Hasson cannula site.

For left-sided resection, the splenophrenic, splenocolic, and splenorenal ligaments are divided using electrocautery. The spleen and pancreatic tail are then rotated medially. The peritoneal dissection proceeds cephalad to caudad along the medial edge of the adrenal gland until the left renal vein is reached, exposing the adrenal gland and vasculature. The resection then proceeds as previously described for the right adrenal gland.

Cohort and data abstraction

All patients older than 18 years of age who had undergone laparoscopic adrenalectomy at Vanderbilt University Medical Center for nonmalignant indications were eligible for the study. Each patient's demographic information, age, preoperative medications, weight, comorbidities, presenting symptoms, imaging results, and laboratory workup were collected into a centralized database. Data were obtained from a computerized patient record system and from paper charts when appropriate.

Outcomes and follow-up evaluation

The primary outcome measure was postoperative improvement or cure of antihypertensive medication use. Brunt et al. [4] and Filipponi et al. [5] have successfully used the number of antihypertensive medications as a surrogate measure of functional outcome after adrenalectomy. Dual combination medications (i.e., thiazide diuretic plus angiotensin converting enzyme inhibitor) were counted as two medications.

Postoperative antihypertensive medication use, length of hospital stay, operative time, complications, pathologic diagnosis, blood pressure, and mortality status (via Social Security Death Index) were obtained for each patient. For our primary outcome measure, postoperative antihypertensive medication use, a questionnaire and informed consent document were mailed to all eligible patients in the cohort. Items in the questionnaire included a listing of current medications (with dose and frequency) and the reporting of any hospital admissions or interventions since laparoscopic adrenalectomy. To reduce selection bias in our primary outcome measure, family members or next of kin were invited to complete the questionnaire if the original patient was unable to do so. For questionnaire nonresponders, follow-up telephone calls were made inviting participation in the study. The questionnaire was then administered via telephone call after informed consent was obtained. If both computerized and questionnaire follow-up data were available, the most recent data were used.

Statistical analysis

Perioperative descriptive measures were obtained for each disease entity (Conn's syndrome, Cushing's syndrome, pheochromocytoma, and Other tumors). Continuous variables were expressed as mean ± standard deviation, and proportions as percentages. Because continuous measures were characterized by non-normality, comparison of means across more than two groups was performed with the Kruskal-Wallis test. For comparison of two means, the Mann-Whitney rank sum test was used with Bonferroni correction. Proportions were evaluated using Pearson's chi-square test.

Univariate analyses were performed using rate ratio calculations and the product-limit (Kaplan-Meier) method to account for variable follow-up times. All analyses involving the primary outcome measure (postoperative improvement or cure with antihypertensive medication use) were limited to patients receiving preoperative antihypertensive medications. Incidence rates for the primary outcome were calculated by dividing the number of primary outcome events (i.e., the number of patients with improvement or cure with postoperative antihypertensive medication use) by the cumulative follow-up (person-months) for each disease entity. These raw incidence rates were then normalized to rates per 1,000 person-months of follow-up evaluation. Incidence rate ratios and 95% confidence intervals were obtained by dividing the disease-specific incidence rate by the reference group rate (in this analysis, the Other tumor group served as the reference group). Hazard function curves were constructed for each disease entity and compared using the log-rank test. Cox proportional hazards regression was used to compare postoperative improvement or cure with antihypertensive medication use by disease entity. This was accomplished by calculating unadjusted hazard ratios with the primary outcome measure as the dependent variable and disease entity as the independent variable. To adjust for confounders in this analysis, a multivariate Cox proportional hazards regression model was constructed, controlling for race, sex, age, disease entity, maximum tumor dimension, and previous abdominal operations. All analyses were performed using STATA version 8.2 (STATA Corporation, College Station, TX, USA) with a p value less than 0.05 considered significant, or using the 95% confidence interval approach (with significant comparisons not crossing the value of 1).

Results

Cohort characteristics

Between 1995 and 2003, 94 patients underwent laparoscopic adrenalectomy at Vanderbilt University Medical Center. Six bilateral procedures were performed, totaling 100 resections. Disease entities were categorized as Conn's syndrome (n = 27), Cushing's syndrome (n = 30), pheochromocytoma (n = 12), or Other tu-

Table 1. Characteristics of patients with laparoscopic adrenalectomy by disease entity

	Conn's syndrome (n = 27)	Cushing's syndrome (n = 30)	Pheochromo cytoma (n = 12)	Other tumors (n = 26)	p Value
Age (years)[a]	40 ± 12	49 ± 13	51 ± 13	53 ± 15	0.49[b]
Female (%)	41	83	46	69	0.005[c]
Whites (%)	81	97	100	92	0.58[c]
Weight (kg)	91 ± 24	94 ± 122	81 ± 15	91 ± 63	0.51[b]
ASA class	2.6 ± 0.5	2.7 ± 0.5	3.1 ± 0.6	2.5 ± 0.5	0.06[b]
Preoperative antihypertensive medication use (%)	100	59	91	74	0.002[c]
Mean follow-up time (months)	33 ± 2	17 ± 15	17 ± 12	23 ± 24	0.04[b]
Median follow-up time (months)	33	13	15	15	
Previous abdominal operations (%)	44	79	55	65	0.054[c]

ASA, American Society of Anesthesiology
[a] Continuous measures are presented as mean ± standard deviation
[b] Kruskal-Wallis test (p value tests mean differences between all groups)
[c] Pearson's chi-square test (p value tests proportion differences between all groups)

mors (n = 26). The Other tumor category consisted of nonfunctional adenoma (n = 15), adrenal pseudocyst (n = 12), ganglioneuroma (n = 2), metastatic lung cancer (n = 2), hematoma (n = 4), scar tissue (n = 1), virilizing adenoma (n = 1), myelolipoma (n = 1), and adrenal cyst (n = 1) on the basis of histologic findings and biochemical function.

Table 1 summarizes characteristics of the cohort by disease type. Mean age for the cohort (63% women and 91% white) was 51 ± 13 years. The mean preoperative weight was 91 ± 22 kg, and the mean American Society of Anesthesiologists (ASA) score 2.7 ± 0.5 [1]. Of all patients undergoing laparoscopic resection, 62% had previous abdominal operations, and 78% were receiving antihypertensive therapy preoperatively. The mean follow-up time was 23 ± 20 months (range, 1–75 months). Postoperative blood pressure data were available for 76% of the patients, showing that 72% had normal blood pressure at a mean of 8 ± 14 months. No significant differences in postoperative blood pressure were observed between disease groups. The questionnaire response rate was 75%, and follow-up data was available for 90% of the cohort.

Diagnostic errors

Errors in diagnosis were observed in nine patients (10%), including seven false positive evaluations and two false negatives. Seven patients who proved to have nonfunctional tumors postoperatively were preoperatively diagnosed with pheochromocytoma (6 patients) and Conn's syndrome (1 patient). Two functional tumors, pheochromocytoma (1 patient) and Conn's syndrome (1 patient), were preoperatively diagnosed as nonfunctional. In these analyses, final diagnoses were used to categorize patients by disease entity.

Operative results, mortality, and complications

In this series, 53% of the patients underwent left-sided laparoscopic adrenalectomy and six (7%) had bilateral procedures performed for refractory Cushing's disease. For the first 20 unilateral resections, the operative time was 3.3 ± 2.1 h, as compared with 2.3 ± 0.2 h for the remaining procedures ($p < 0.05$, Mann-Whitney rank sum test). The mean tumor size was 2.7 ± 1.5 cm (range. 0.5–7.5 cm), and the maximum tumor dimension was 10 cm, with 21% of the tumors having at least one dimension 5 cm or larger. One resection required the use of a laparoscopic hand-assist port. The mean length of stay was 2.6 ± 1.5 days. One patient with pheochromocytoma had persistent hypertension after initial resection. Metaiodobenzylguanidine scan showed an extraadrenal pheochromocytoma, which was resected without difficulty. One conversion to an open procedure was required in the Cushing's syndrome group for a 33 year old woman undergoing bilateral adrenalectomy. The right-sided gland was severely adherent to the liver. During the dissection, a 1-cm diaphragmatic tear was created, and the procedure was converted to laparotomy. The diaphragmatic injury was repaired without difficulty, and the contralateral side was resected via laparoscope. A second diaphragmatic injury was encountered, also in the Cushing's syndrome group, in a 25 year old woman undergoing right adrenalectomy for a functional adenoma. The right adrenal gland was severely adherent to the diaphragm, and mobilization created a 2-mm diaphragmatic tear, which was successfully repaired laparoscopically. Both patients with iatrogenic diaphragmatic injury had uneventful postoperative courses. A postoperative right-sided pneumothorax was diagnosed in a 62 year old woman undergoing bilateral adrenalectomy for Cushing's syndrome. She remained asymptomatic postoperatively, and the pneumothorax resolved before discharge. The preceding three complications occurred in our first 25 cases.

One postoperative death occurred in the case of a 62 year old woman with Cushing's syndrome who underwent bilateral adrenalectomy. Preoperatively, she had declined the use of blood products. Postoperatively, she became hypotensive, with a hematocrit of 17%. Reoperation was performed via laparotomy and 500 ml of blood was noted in the right upper quadrant. Bleeding from the Hasson cannula site was cauterized, and the patient was taken to the surgical intensive care unit.

Table 2. Complications of laparoscopic adrenalectomy

	Complication	Frequency
Major complications (n = 9)		
	Death	1
	Addisonian crisis	1
	Right diaphragm injury	2
	Arrhythmia	2
	Hypertension	1
	Incisional hernia	1
	Pneumothorax	1
Minor complications (n = 5)		
	Ileus	2
	Epistaxis	1
	Port-site hematoma	1
	Urinary retention	1

Despite reoperation, the patient succumbed to multisystem organ failure and died on postoperative day 6. Nine major complications and five minor complications are summarized in Table 2.

Univariate analysis

The primary outcome of this study was postoperative improvement or cure with antihypertensive medication use. According to simple proportions at the end of the follow-up period, the percentage of patients with improvement or cure was 75% for Conn's syndrome, 27% for Cushing's syndrome, 88% for pheochromocytoma, and 54% for Other tumors. Accounting for follow-up time, unadjusted rate ratios showed a trend toward improvement or cure in the Cushing's syndrome and pheochromocytoma groups, as compared with the other tumor group. This trend, however, did not reach statistical significance using the 95% confidence interval approach (Table 3).

To analyze the probability of postoperative improvement or cure with antihypertensive medication use in the setting of variable follow-up time, hazard curves were constructed (Fig. 2). At 12 months of follow-up evaluation, a 50% probability of improvement or cure was observed in the pheochromocytoma group, as compared with all the Other groups ($p < 0.05$, log-rank test). The Conn's syndrome group, the Cushing's syndrome group, and the Other tumor groups had a 50% probability of improvement or cure at 35 to 45 months of follow-up evaluation. By 72 months of follow-up evaluation, a 75% probability of improvement or cure was observed in all the groups. In the univariate Cox proportional hazards model, the likelihood for improvement or cure was higher in the pheochromocytoma group than in the other tumor group (Table 4). Furthermore, pheochromocytoma patients demonstrated a higher likelihood for improvement or cure than the patients with Conn's syndrome (hazard ratio, 3.78; 95% confidence interval [CI], 1.56–9.12; $p < 0.05$) or Cushing's syndrome (4.22; 95% CI, 1.35–13.14; $p < 0.05$). A trend for improvement or cure was observed in the Conn's syndrome group, as compared with the Cushing's syndrome group (hazard ratio 1.12; 95% CI, 0.41–3.04; $p = 0.55$) and the Other tumor group (hazard ratio 1.17 95% CI, 0.51–2.68; $p = 0.83$), which did not reach statistical significance.

Multivariate analysis

In the multivariate analysis, a Cox proportional hazards model was constructed, which included covariates of race, sex, age, disease entity, maximum tumor dimension, and previous abdominal operations. As in the univariate analysis, the hazard ratio for improvement or cure was highest in the pheochromocytoma group compared with all the other groups. The patients with Conn's syndrome had a slightly higher hazard ratio in the multivariate model (1.18 vs the univariate hazard ratio of 1.17), but improvement or cure did not differ with that of the Other tumor group (Table 4).

Discussion

The principal finding of this study was that laparoscopic adrenalectomy is an effective procedure for traditional indications (Conn's syndrome, Cushing's syndrome, Other tumors) and for pheochromocytoma. In addition, data from the current study suggest that the improvement or cure with antihypertensive medication use may take place over a longer period than previously appreciated.

Numerous recent laparoscopic adrenalectomy cohort studies and case series populate the literature. Most of these studies do not examine postoperative antihypertensive medication use [7, 9, 10, 13, 15, 18, 19]. In a multicenter cohort analysis, Terachi et al. [18] presented 370 cases of minimally invasive adrenalectomies with a 6% postoperative complication rate, but no medication follow-up management. A recent nonrandomized prospective study of laparoscopic and open adrenalectomy in 150 patients noted fewer complications in the laparoscopic group (9%) than in the open group (21%), supporting the choice of laparoscopic resection. However, antihypertensive medication use was not evaluated [13]. Other studies with follow-up periods ranging from 0 to 24 months reported similar results with no medication-specific outcomes [7, 9, 10, 15, 19].

Few studies have systematically examined antihypertensive medication use after laparoscopic adrenalectomy, and none have performed analyses accounting for variable follow-up time [3–5, 8, 12]. In a series of 111 resections with a median follow-up period of 14 months, Bonjer et al. [3] reported a 69% improvement or cure rate for patients with Conn's syndrome. For both Conn's syndrome and pheochromocytoma patients, Lezoche et al. [12] described improvement (52%) or cure (48%) for a subset of patients with only one preoperative antihypertensive medication. Brunt et al. [4] and Filipponi et al. [5] both reported laparoscopic adrenalectomy cohorts with a 92% to 100% improvement or cure rate for Conn's syndrome and pheochromocytoma patients as early as 3 months after resection. For another large series, Henry et al. [8] described 169 laparoscopic

Table 3. Incidence rates and rate ratios of postoperative improvement or cure with antihypertensive medication use

	Conn's syndrome	Cushing's Syndrome	Pheochromocytoma	Other tumors
Incidence rate[a]	25.5	34.5	58.8	30
Incidence rate ratio	0.85	1.15	1.96	1
95% Confidence interval	0.45–1.60	0.58–2.27	0.91–4.24	Ref[b]
p Value	0.31	0.35	0.05	Ref[b]

[a] Incidence rates describe occurrences of improvement or cure with antihypertensive medication use per 1,000 person-months of follow-up evaluation
[b] Reference group is the group used as the denominator in the calculation of rate ratios, standard errors, 95% confidence intervals, and *p* values

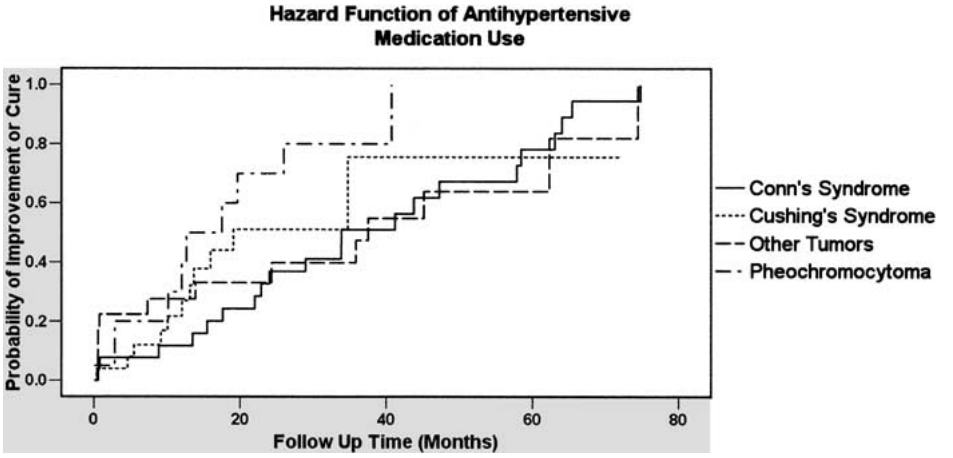

Fig. 2. Hazard function of primary outcome and follow-up data. Probability of improvement or cure is plotted versus months of follow-up evaluation. The pheochromocytoma curve differs from that for all other groups ($p < 0.05$, log-rank test).

Table 4. Cox proportional hazards regression for postoperative improvement or cure with antihypertensive medication use

	Conn's syndrome	Cushing's syndrome	Pheochromocytoma	Other tumors
Univariate hazard ratio	1.7	1.04	4.41	1
Univariate 95% confidence interval	0.51–2.68	0.34–3.25	1.58–12.3	Ref[a]
p value	0.71	0.94	0.005	Ref[a]
Multivariate hazard ratio[b]	1.18	1.08	4.87	1
Multivariate 95% confidence interval	0.32–4.39	0.31–3.73	1.61–14.7	Ref[a]
p value	0.80	0.91	0.005	Ref[a]

[a] Other tumors used as the reference group
[b] Multivariate model adjusted for race, sex, age, maximum tumor dimension, and previous abdominal operations

adrenalectomies performed for varied indications, with mean length of hospital stay of 5.4 days. In this series, 61 patients underwent resection for Conn's syndrome, 41 for Cushing's syndrome, 29 for pheochromocytoma, and 37 for nonfunctioning tumors. A mean follow-up of 27 months was obtained, with all patients reportedly cured of the underlying endocrinopathy. However, no methodology was given for medication follow-up management. These studies agree well with open resection improvement or cure using simple proportions of 76% to 85%, with follow-up periods ranging from 42 months to 9 years [14, 17]. Although the results for these studies are encouraging, significant bias may exist in the simple reporting of "percentage cured or improved" in the setting of extremely variable follow-up time. As such, the inevitability of inconsistent follow-up (in prospective and retrospective cohorts alike) must be taken into consideration in analyses.

In the current cohort, the patients with pheochromocytoma were more likely to have improvement or cure of antihypertensive medication therapy than patients with other disease entities. According to simple proportions, 88% of the patients reduced or eliminated antihypertensive therapy. This agrees with a prior study of 39 patients with pheochromocytoma who underwent laparoscopic resection with 92% success [11]. To account for variable follow-up times, incidence rates, hazard function curves, and Cox proportional hazards regression models were calculated. The incidence rate ratio for improvement or cure (1.96) approached significance (95% CI, 0.91–4.24; $p = 0.05$), as compared with the Other tumor reference group. A sizable proportion of truly functional tumors, which did respond to resection, may have populated the Other tumor group, driving the association toward a hazard ratio of 1 (i.e., indicating no difference). However, the multivariate model did predict

a significant likelihood (hazard ratio, 4.9) for improvement or cure for the patients with pheochromocytoma, as compared with all the other disease entities when adjustments were made for race, sex, age, maximum tumor dimension, and previous abdominal operations. Interestingly, approximately 1 year was needed before 50% of the patients with pheochromocytoma had improvement or cure with their antihypertensive regimen. We did not observe more than a 90% improvement or cure rate in our pheochromocytoma group because of one patient found to have an extraadrenal pheochromocytoma after initial laparoscopic resection and because of the nature of our analysis. Comparisons of these data and the time course with those of previous work are difficult because variable follow-up time has not been incorporated into the analyses of prior studies. Furthermore, an examination of simple proportions cannot take into account the confounding factors that may have an impact on antihypertensive use such as race, sex, age, tumor size, or history of prior abdominal operations. Thus, the use of simple proportions alone as an outcome measure results in more bias than the use of analyses that incorporate variable follow-up time and adjust for confounding factors. In our analysis, we were able to account for variable follow-up time, and we used a multivariate model to control for confounding elements.

For patients in the Conn's syndrome, Cushing's syndrome, and Other tumor groups, improvement or cure probabilities over time were similar, as reflected by the hazard function curves (Fig. 2). No differences in improvement or cure were evident in the multivariate Cox proportional hazards model between these groups. Nevertheless, the patients with Conn's syndrome and the Other tumor group showed increased probabilities toward improvement or cure over time (Fig. 2). Our results show a longer period until improvement or cure for patients with Conn's syndrome than was expected. However, as time progressed (beyond 35–45 months), the probability of improvement or cure increased. This pattern was observed also in the Other tumor group and, to a lesser extend, in the Cushing's syndrome group. The hazard function was less robust at later time points because fewer patients were available for the calculation of outcomes. Follow-up evaluation beyond 24 months was available for 17% of the pheochromocytoma group, 56% of the Conn's syndrome group, 20% of the Cushing's syndrome group, and 38% of the Other tumor group. Although the patients with Cushing's syndrome initially displayed an increased probability of improvement or cure over time, this group's antihypertensive regimen persisted after resection. Of the 30 patients in the Cushing's syndrome group, 6 (20%) continued to receive steroid therapy at their latest individual follow-up times. No patients in the remaining groups received steroid therapy during the study period. Steroid use likely confounded the measurement of improvement or cure with antihypertensive medication use in the Cushing's syndrome group. Furthermore, the goal of operative therapy in this group was not improvement or cure of antihypertensive medication use.

The Other tumor group consisted of patients considered to be nonfunctional on the basis of preoperative evaluation. Patients with pheochromocytoma had a nearly fivefold increased chance of improvement or cure after resection, as compared with the other group in the multivariate Cox proportional hazards model. However, no difference was detected between the other group and Conn's syndrome patients. Of patients on antihypertensive therapy deemed to have nonfunctional lesions in the Other tumor group, 54% had improvement or cure with their regimen according to simple proportions. The lack of difference in outcomes between the Other tumor group and the patients with Conn's syndrome was largely attributable to the high response of the Other tumor group (the comparison group in this study) after resection. In addition, this study likely did not have the statistical power necessary to detect a difference between these groups when so many Other tumor patients responded positively after resection. Although all the patients underwent complete biochemical screens to exclude functional tumors, it is inevitable that some adrenal tumors deemed to be nonfunctional by current standards of measure actually may have been functional at a subclinical level at the time of the workup.

The notion of "subclinical hyperfunctioning adenomas" is supported by the 2002 National Institutes of Health state-of-the-science statement on clinically inapparent adrenal masses [2]. Thus, these patients may show improvement in antihypertensive medication use after resection, but may have nonfunctional diagnoses. Furthermore, secular trends in the improvement of medical antihypertensive therapy may contribute to the apparent improvement seen in the other tumor group (and all groups analyzed in this study). Hypertension previously controlled by multiple drugs may now be controlled by more potent, newer, single medications. This would affect our primary outcome of the number of antihypertensive medications after resection. It is also possible that preoperative evaluations have been constrained by changes in the health care system, eschewing complicated and lengthy biochemical assessments. Enlarging the Other tumor group with patients such as these would reduce the true difference in comparisons using this group as the reference group in the analysis. Factors that have been associated with the elimination of antihypertensive medications after resection for patients with Conn's syndrome include a family history of hypertension in no more than one first-degree relative and the use of fewer than three agents [16]. In our cohort, 52% of Conn's syndrome patients receiving antihypertensive therapy were taking three or more agents. No reliable method of obtaining patients' family history of hypertension was available. The prevalence of essential hypertension also may have contributed to the inability to improve antihypertensive medication use after adrenal resection.

Several limitations of this study are apparent. First, our relatively low number of patients with pheochromocytoma reduced the power of analyses in this group. Because the effect for this particular group was larger (and faster) than for other groups, we were able to detect postoperative improvement or cure with antihyperten-

sive medication use even with our limited numbers. Second, the retrospective nature of this study incurred its own limitations including incomplete data and selection bias. Although follow-up evaluation was available for 90% of the cohort, improved long-term follow-up data would have been achieved with a higher ($>75\%$) questionnaire response rate. An element of recall bias was present in the questionnaire. However, this was minimized by requesting only current medication use by the patients. Third, a count tabulating the number of antihypertensive medications may have been an oversimplification of relative potencies among individual agents thus possibly confounding our results. Nevertheless, all groups showed a decrease in antihypertensive medication use after resection. Finally, the use of the Other tumor group (with a sizable proportion of patients improved or cured after resection) as the comparison group minimized differences between disease entities that would otherwise have been detected.

In this study, laparoscopic adrenalectomy was shown to be effective for patients with benign adrenal tumors, including pheochromocytoma. Surgeon experience and skill rather than strict size limitations likely dictate appropriate candidates for laparoscopic resection. Adjunct techniques, such as hand-assisted laparoscopy, may be required for successful resection. The analyses performed incorporated variability in follow-up time and showed postoperative improvement or cure for functional adrenal tumors, especially pheochromocytoma. This effect was seen over a longer time than previously observed. Additional studies designed to evaluate time until improvement with antihypertensive medication use are warranted.

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