ORIGINAL ARTICLE

Effect of Laparoscopy on the Indications for Adrenalectomy

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Background: Laparoscopic adrenalectomy is now the criterion standard for removal of most benign adrenal lesions and may be used for malignant lesions as well. At the same time, improved imaging has led to an increase in the number of incidentally detected adrenal masses. The aim of this study was to determine whether the introduction of laparoscopy has changed the indications for adrenalectomy.

Design: Retrospective cohort study of patients operated on for primary adrenal disease between September 1, 1987, and August 17, 2007.

Setting: Academic hospital.

Patients: Sixty-six patients treated before (group 1) and 203 treated after (group 2) introduction of laparoscopic adrenalectomy.

Main Outcome Measures: Patient characteristics, comorbidity, tumor size, indication, and time between diagnosis and surgery.

Results: Group 2 had more patients in American Society of Anesthesiologists class III with gastrointestinal and metabolic-endocrine comorbidities. Tumor size did not change, and, despite an increase in the number of adrenalectomies, indications for surgery remained consistent over time.

Conclusion: Despite an increased volume of procedures, the introduction of laparoscopic adrenalectomy in our hospital did not change the indications for surgical intervention.

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THE USE OF LAPAROSCOPY FOR adrenalectomy has rapidly increased during the past decade. The first such procedure in our hospital was performed in 1997, and by 1999 almost two-thirds of the adrenalectomies were being done laparoscopically. Laparoscopic adrenalectomy (LA) is associated with less morbidity and shorter postoperative length of stay than an open approach and is now the criterion standard for removal of most benign adrenal lesions.[1-3] It has been suggested that LA can also be used in resection of large adrenal tumors and malignant lesions.[4-6] At the same time as the laparoscopic revolution, there has been enormous growth in the use of computed tomography and magnetic resonance imaging, leading to a substantial increase in the number of incidentally detected, clinically nonevident adrenal masses. This trend will probably continue with improving technology, as there remains a discrepancy between the prevalence of incidentalomas noted by computed tomography and the prevalence found in autopsies.[7]

See Invited Critique at end of article

The 2002 National Institutes of Health consensus statement emphasized removing an adrenal tumor if it exceeds 6 cm, if there is suspicion of malignancy based on imaging studies, or if there is evidence of a hormone-secreting adenoma or pheochromocytoma.[8] Other thresholds for surgery have also been suggested.[9-12] Evidence in favor of either surgery or a conservative approach is lacking for patients with smaller lesions or subclinical hyperfunction. In many instances, the treating physician faces uncertainty about the actual diagnosis and the patient and physician must make an educated decision about proceeding, sometimes with uncertain indications. With the perceived benefits of laparoscopic resection, it may be easier for a surgeon and more acceptable for a patient to undergo adrenalectomy. There are suggestions that indications have changed, but the literature is not conclusive.[13-17] Early intervention avoids an extensive follow-up period, reduces the number of high-cost imaging

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Table 1. Laboratory Values Used to Diagnose Hypersecretion

Measure	Elevated Level
Plasma aldosterone (upright), ng/dL	
8-9:59 AM	>28
10 AM–6 PM	>21
Aldosterone to renin ratio	>30
Plasma cortisol, µg/dL	
8 AM–11:59 AM	>25
Noon–7:59 PM	>15
8 PM–7:59 AM	>10
Urine free cortisol, µg/24 h	>70
Dexamethasone suppression test	
8 AM plasma cortisol, µg/dL	≥5
Timed urine metanephrine, mg/24 h	
Males ≥18 y	>0.26
Females ≥18 y	>0.18
Timed urine normetanephrine, µg/24 h (males and females)	
18-29 y	>390
30-39 y	>419
40-49 y	>451
50-59 y	>484
60-69 y	>521
≥70 y	>560
Timed urine epinephrine, µg/24 h	>24
Timed urine norepinephrine, µg/24 h	>100

SI conversion values: To convert plasma aldosterone to picomoles per liter, multiply by 27.74; plasma cortisol to nanomoles per liter, multiply by 27.588; urine metanephrine to micromoles per day, multiply by 5.07.

studies, and reduces psychological stress on the patient. However, it may result in overtreatment, as most incidentalomas are small, benign, nonfunctional, and not likely to grow rapidly or become functional during either short-term or long-term follow-up.[10,18,19]

The objective of this study was to identify the impact of the introduction of laparoscopy on the indications for adrenalectomy and assess the changes in the volume of procedures over time in a single academic institution.

METHODS

We performed a retrospective cohort study that included all patients older than 16 years who underwent adrenalectomy for a primary adrenal lesion at our hospital from September 1, 1987, through August 17, 2007. Any patient who underwent an adrenalectomy in conjunction with another procedure or who had a nonprimary adrenal issue was excluded. Patients were divided into 2 groups. The first had surgery between September 1, 1987, and May 10, 1997. This is the period during which all adrenalectomies were performed in an open fashion. The patients in the second group were operated on from May 11, 1997, through August 17, 2007, after the introduction of LA, but this group included patients operated on in both open and laparoscopic fashion.

Electronic medical records and medical charts were used to gather information. We specifically looked at the reason for the initial imaging study (adrenal disease suspected or incidental finding), the interval (in days) between diagnosis and operation, and the size of the adrenal tumor on each subsequent scan. Since not all imaging studies reported tumor size in more than 1 dimension, we took the largest measured dimension.

To try to definitively confirm secreting tumors, we gathered laboratory tests when the information was available. We used urine and plasma catecholamine levels to establish the diagnosis of pheochromocytoma. The tests for primary aldosteronism were aldosterone plasma levels and aldosterone to renin ratio, 24-hour urine aldosterone excretion following a high-sodium diet, and aldosterone levels from venous sampling. The overnight dexamethasone suppression test, plasma cortisol level, and 24-hour urine cortisol excretion were used to diagnose hypercortisolism. Plasma testosterone level was used to diagnose hyperandrogenism. Levels considered to represent positive laboratory results are given in **Table 1**.

Once we ascertained the size of the tumor and assessed the possibility of hormone production, we correlated this against the type of operation (laparoscopic or open) and the final pathology report, which included the size of the tumor and the histologic diagnosis. Again, for tumor size we used the largest measured dimension. We considered the following as straightforward indications for surgery: if the tumor was larger than 5 cm on an imaging study, if the tumor was positively secreting hormones on the basis of the results of proper laboratory tests (Table 1), and if there was a strong suggestion of pheochromocytoma or malignancy based on imaging studies (hyperintense T2-weighted magnetic resonance imaging signal, irregular aspect, metastases visible, or lymphadenopathy) or results of biochemical laboratory tests. Enlargement of the adrenal mass alone during the follow-up period was not considered an indication for surgery if the tumor did not exceed 5 cm.

Categorical variables were compared between the 2 groups by χ^2 tests, while 2-sample *t* tests or Wilcoxon rank sum tests, as appropriate, were used for continuous variables. Linear and logistic regression models were used to compare outcomes between the 2 periods controlling for American Society of Anesthesiologists (ASA) class and comorbidities. A 2-sided $P \leq .05$ was considered statistically significant. All analyses were conducted with SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

A total of 295 patients underwent adrenalectomy for primary adrenal disease between September 1, 1987, and August 17, 2007. Twenty-four patients were excluded because they were younger than 16 years, and 2 patients were excluded because insufficient information could be retrieved. A total of 269 patients were included in our study.

Table 2 gives the patient characteristics at the time of operation. Sixty-six patients (24.5%) were operated on up to May 10, 1997 (group 1), averaging 6.8 cases per year. Two hundred three patients (75.5%) were operated on after that date (group 2), averaging 19.8 cases per year. This represents an almost 3-fold increase in the number of adrenalectomies over the first period. The 2 groups were similar in terms of age (mean [SD], 50 [14] and 52 [14] years in groups 1 and 2, respectively) and sex (62.1% female vs 66.5% female) distributions. All operations were performed in an open fashion in group 1 compared with 71 (35.0%) of the operations in group 2. Six of the laparoscopic cases were converted to an open approach but were kept in the laparoscopic group on an intention-to-treat basis. The 2 groups differed in ASA class distribution and comorbidities. A higher proportion of patients in group 2 were in ASA class III ($P = .04$), and there were more patients with metabolic-endocrine or gastrointestinal comorbidity in group 2 ($P = .002$ and $P = .008$, respectively).

Table 2. Patient Characteristics[a]

Characteristic	No. (%) Group 1 (n=66)	Group 2 (n=203)	P Value
Age, y, mean (SD)	50 (14)	52 (14)	.48
Sex, F	41 (62.1)	135 (66.5)	.52
ASA class			
I	6 (9.1)	14 (6.9)	.04[b]
II	53 (80.3)	144 (70.9)	
III	6 (9.1)	45 (22.2)	
IV	1 (1.5)	0 (0)	
Comorbidity			
Metabolic-endocrine	17 (25.8)	97 (47.8)	.002[b]
Gastrointestinal	5 (7.6)	45 (22.2)	.008[b]
Respiratory	5 (7.6)	31 (15.3)	.11
Musculoskeletal	4 (6.1)	28 (13.8)	.09

Abbreviation: ASA, American Society of Anesthesiologists.
[a]Patients in group 1 underwent surgery between September 1, 1987, and May 10, 1997, before the initiation of laparoscopic adrenalectomy; group 2, between May 11, 1997, and August 17, 2007, after the initiation of laparoscopic adrenalectomy.
[b]Statistically significant.

Table 3 shows the main outcomes. There was no significant difference in the assessed appropriateness of surgical indication between the 2 periods. In group 1, 59 cases (89.4%) had an easily identifiable indication for surgery and 7 (10.6%) had indications that did not meet our defined criteria. Group 2 had 182 cases (89.7%) with a clear indication and 21 (10.3%) that did not meet our defined criteria ($P=.95$). The 2 patient groups were similar in terms of tumor size and proportion of incidentally discovered tumors.

The second period was then divided into two 5-year intervals (May 11, 1997, through December 31, 2002, and January 1, 2003, through August 17, 2007). A large increase in volume, from 81 to 122 procedures, was seen between the 2 intervals. A new surgeon had been hired in 2002 and accounted for 5 of the 81 cases in the first time interval and 52 of the 122 procedures in the second. When these cases were excluded, the number of procedures was not significantly different between the two 5-year intervals, with 76 cases in the first and 70 cases in the second. There were no differences in indications or postoperative diagnosis between the first and second halves of the second period. Tumor size was significantly different between the two 5-year intervals, with a mean of 5.6 cm in the first and 4.4 cm in the second 5 years ($P=.02$).

In group 2, 4 patients were operated on for tumor enlargement, but these tumors did not reach the 5.0-cm threshold set as our criterion for resection. There was a significant difference in tumor size between the open and laparoscopic cohorts of group 2. The mean tumor size was 7.2 cm for open resection and 3.6 cm for laparoscopy ($P<.001$). Tumor size information was lacking in pathology reports of 3 patients. Two were excluded from the size analysis and one was assigned a size on the basis of the most recent imaging study. Group 2 had a longer time interval between the day the diagnosis was made on an imaging study and the day of surgery (median, 91 vs 39.5 days; $P=.006$). For this analysis, 4 patients were excluded because the exact date of the imaging study could not be found.

Table 3. Main Outcomes[a]

Outcome	No. (%) Group 1 (n=66)	Group 2 (n=203)	P Value
Indication for surgery			
Clear/straightforward	59 (89.4)	182 (89.7)	.95
Questionable	7 (10.6)	21 (10.3)	
Pathology tumor size, cm, mean (SD)	5.2 (3.0)	4.9 (3.7)	.42
Reason for imaging study			
Suspected adrenal tumor	34 (51.5)	84 (41.4)	.16
Incidental finding	32 (48.5)	118 (58.1)	
Unclear	0	1 (0.5)	
Days between diagnosis and operation, median (Q1/Q3)	39.5 (32/168)	91.0 (40/210)	.006[b]

Abbreviations: Q1, quartile 1; Q3, quartile 3.
[a]Patients in group 1 underwent surgery between September 1, 1987, and May 10, 1997, before the initiation of laparoscopic adrenalectomy; group 2, between May 11, 1997, and August 17, 2007, after the initiation of laparoscopic adrenalectomy.
[b]Statistically significant.

Table 4. Secondary Outcomes[a]

Postoperative Diagnosis	No. (%) Group 1 (n=66)	Group 2 (n=203)
Nonactive adenoma	11 (16.7)	35 (17.2)
Aldosterone secreting	10 (15.2)	30 (14.8)
Cortisol secreting	4 (6.1)	24 (11.8)
Cortisol and aldosterone secreting	2 (3.0)	8 (3.9)
Testosterone secreting	0	2 (1.0)
Pheochromocytoma	23 (34.8)	59 (29.1)
Malignant neoplasm	8 (12.1)	27 (13.3)
Other	7 (10.6)	18 (8.9)
Unknown	1 (1.5)	0

[a]Patients in group 1 underwent surgery between September 1, 1987, and May 10, 1997, before the initiation of laparoscopic adrenalectomy; group 2, between May 11, 1997, and August 17, 2007, after the initiation of laparoscopic adrenalectomy. There was no significant difference in distribution of postoperative diagnoses ($P=.43$).

Postoperative diagnoses are shown as secondary outcomes in **Table 4**. There was no difference in distribution of postoperative diagnoses. **Table 5** shows the final pathological findings of the patients who underwent adrenalectomy for incidentaloma. There was no difference in tumor size or postoperative diagnosis between the 2 groups for the incidentally discovered tumors. Of the lesions that were diagnosed after adrenal disease was suspected, 23 of 34 (68%) turned out to be hormonally active adenomas or pheochromocytomas in group 1 vs 61 of 85 (72%) in group 2, and there was no significant difference ($P=.19$).

When adjusted for the imbalanced factors (ASA distribution, metabolic-endocrine, and gastrointestinal comorbidity), the differences in indication, tumor size, reason for imaging study, and postoperative diagnosis remained not significant and the difference in the time

Table 5. Tumor Size and Postoperative Diagnosis for Incidentalomas[a]

Postoperative diagnosis	No. (%) Group 1 (n=32)	Group 2 (n=118)	P Value
Nonactive adenoma	8 (25)	27 (22.9)	.91
Aldosterone secreting	1 (3.1)	10 (8.5)	
Cortisol secreting	3 (9.4)	15 (12.7)	
Cortisol and aldosterone secreting	1 (3.1)	1 (0.8)	
Testosterone secreting	0	1 (0.8)	
Pheochromocytoma	11 (34.4)	36 (30.5)	
Malignant neoplasm	5 (15.6)	16 (13.6)	
Other	3 (9.4)	12 (10.2)	
Tumor size, cm, mean (SD)	5.6 (2.6)	5.6 (3.8)	.42

[a] Patients in group 1 underwent surgery between September 1, 1987, and May 10, 1997, before the initiation of laparoscopic adrenalectomy; group 2, between May 11, 1997, and August 17, 2007, after the initiation of laparoscopic adrenalectomy.

interval between diagnosis and surgery remained statistically significant ($P = .004$).

COMMENT

Since the early 1990s, the use of laparoscopy for removal of benign and malignant adrenal tumors has steadily increased because of its superiority over open adrenalectomy in terms of morbidity and length of stay.[1-3] These advantages, along with a better cosmetic result, have made it more acceptable for patients and physicians to take the step to surgery. The National Institutes of Health has set a threshold for surgery at 6 cm and advises surgery for hormone-producing tumors and lesions suggestive of malignancy; however, the size threshold is subject to debate.[8-12]

With improving quality and wider availability of imaging techniques such as magnetic resonance imaging and computed tomography, there has been an increase in the number of incidentally found, clinically silent adrenal masses.[7-9] Adrenal incidentalomas are likely to be small, benign, and nonfunctional during follow-up and therefore are unlikely to meet criteria for resection.[10,17,18] Patients and physicians must choose either surgery early in the process or extensive and costly follow-up with possible diagnostic uncertainty. Better surgical results with LA and an increased availability of laparoscopy, combined with an increased prevalence of incidentalomas, have raised concern that the threshold for adrenalectomy may have been lowered. The sparse literature available is not conclusive about possible changes in indications for adrenalectomy.[13-17]

There has been a documented increase in the number of adrenalectomies over time.[13-17] The 3-fold increase we found in our institution is substantially larger than the national trend between 1988 and 2000.[17] As the early and later groups had equal proportions of incidentalomas, we can say that part of the increase in adrenalectomies in our hospital was due to more widespread use of improved imaging techniques. Furthermore, in 2002, a new endocrine surgeon was hired, bringing his referral pattern with him and accounting for 57 adrenalectomies. While this accounts for a significant portion of the increased volume, there was still a 2-fold increase in volume without these cases. This reflects a combination of increased use of imaging and our increased growth as a referral center for endocrine disease.

Whereas we saw a vast increase in adrenalectomies over time, the feared lowering of the threshold for surgery did not occur. With data available from imaging and laboratory studies, we looked critically at the indications for surgery to determine whether more operations were performed with a questionable indication after LA became available. It is reassuring that the introduction of LA in our hospital did not lead to more unnecessary surgery and that the indications for surgical intervention did not change.

Patients in the group treated later (group 2) had a significantly longer interval between the initial diagnostic imaging and surgery. We hope this implies that, after the introduction of LA, referral for or the decision to proceed with surgery took place after a longer and more thorough workup than before. Furthermore, mean tumor size remained the same during the 2 periods. This is consistent with other studies.[13,14] The distribution of postoperative histologic diagnoses remained the same over time.

Interestingly, we found a higher number of patients in ASA class III and more patients with endocrine-metabolic gastrointestinal comorbidity in the later group. It may be owing to the availability of laparoscopy that the surgeons in our hospital were willing to perform the operation on patients who were slightly sicker, possibly accounting for a percentage of the increase in the number of adrenalectomies.

This study has its weaknesses. In general, data would have been more accurate had we performed a prospective study instead of a retrospective one, since that would have overcome the difficulties of retrieving data from 2 decades ago. Also, to define whether there was an indication for surgery, we had to choose somewhat arbitrary cutoff values for laboratory results and tumor size on imaging. With different reference values and tumor sizes, our results may have been different; however, we were consistent and used the same cutoff values and sizes for the 2 periods. Therefore, the results are still useful for comparison. Furthermore, we primarily looked at potential changes in indications for surgery but did not look at the postoperative clinical results, and hence we cannot comment on changes in outcomes over time. Finally, the small number of patients and the large difference in size between the 2 groups make it difficult to identify small changes as significant.

The introduction of LA in our hospital occurred concurrently with a 3-fold increase in adrenalectomies, probably as a result of more widespread use of imaging modalities and the growth of our hospital as an endocrine referral center. It is reassuring to demonstrate that there was no change in the indications for adrenalectomy with the advent of laparoscopy.

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Author Contributions: Dr Berger had full access to all 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:* Henneman and Berger. *Acquisition of data:* Henneman. *Analysis and interpretation of data:* Chang and Hodin. *Drafting of the manuscript:* Henneman. *Critical revision of the manuscript for important intellectual content:* Henneman, Chang, Hodin, and Berger. *Statistical analysis:* Chang. *Obtained funding:* not applicable. *Administrative, technical, and material support:* Hodin and Berger. *Study supervision:* Berger.
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INVITED CRITIQUE

The indications for adrenalectomy were developed before the introduction of laparoscopy. Tumors larger than 5 cm, tumors between 3 and 5 cm with worrisome features or in young patients who would require prolonged follow-up, and functioning tumors are generally accepted reasons to recommend adrenalectomy. In this article, Henneman and others reviewed their 20-year experience with adrenal surgery to determine whether the indications for operation have changed with the introduction of LA at their center. They conclude that the indications for surgery have remained constant during the study period. However, the authors note a dramatic increase in the number of adrenalectomies performed, from 66 cases to 203 cases after the introduction of LA. The laparoscopic era was further divided into 5-year intervals. An increase from 81 cases in the first 5-year period to 122 cases in the latter period was noted. The authors state that the recruitment of an endocrine surgeon with experience in LA might explain the increase in the latter 5 years. They also note that increased imaging, which has identified more adrenal incidentalomas, and greater emphasis placed on endocrine disease at their center are other possible reasons for the growth.

The data the authors present seem to suggest to us that the indications for adrenalectomy may have broadened somewhat during the study. First, the large increase in the number of operations during the study period is not completely explained by the factors that the authors suggest are causative. Second, the mean tumor size decreased significantly in the laparoscopic era from 5.6 cm in the first 5 years to 4.4 cm in the second 5 years. The ASA classification also changed between the pre- and post-LA eras, with 9% of patients in the first 10 years being in class III, while 22% were in class III in the second period. Both of these latter findings suggest a trend toward recommending operations to patients who might have previously been observed.

The indications for adrenalectomy have served patients well, with the most benefit being provided to those who really need an operation and a major risk being avoided by those who do not need an operation. Broadening the indications for adrenalectomy because of the minimally invasive nature of laparoscopy will not increase overall benefit to patients but will only subject more to unnecessary risk.

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