

# Clinical, Surgical, and Histopathologic Outcomes of Filipino Patients who Underwent Adrenalectomy in a Tertiary Hospital in Cebu, Philippines

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## Abstract

**Introduction:** Hormone-producing adrenal tumors, adrenal carcinomas and other adrenal diseases can be potentially cured with adrenalectomy. In the local setting, studies are often limited by a small sample size and inadequate patient data. This study aimed to determine the clinical and histopathologic characteristics and perioperative outcomes of patients who underwent adrenalectomy.

**Methods:** This is a retrospective chart review study from January 2007 to June 2017 in a tertiary hospital in Cebu City, Philippines. Clinical profiles, type of surgery, and operative outcomes were determined. Comparative analysis of clinical profile, histopathologic features, and surgical outcome was done. Descriptive as well as appropriate inferential statistical methods were used to analyze the data.

**Results:** A total of 31 patients who underwent adrenalectomy were included with the mean age of 45.7 (SD=17.1) years old and a 1:3 male to female distribution. The distribution of tumors was as follows: hormone-producing adrenal tumor (74.2%), malignant adrenal tumors (12.9%), and other benign lesions (12.9%). Among patients with hormone-producing tumors, 39.1% had catecholamine excess, 34.8% had aldosterone excess, and 26.1% had cortisol excess. Hormone-producing adrenal tumors were common at age 20 to 40 years old while malignant tumors were more common among those above 40 years old ( $p$ -value=0.023). Stage 3 hypertension ( $p$ -value=0.010) and improvement

of hypertension postoperatively ( $p$ -value=0.046) were more common among hormone-producing tumors. On the other hand, large tumor size (>4cm) ( $p$ -value=0.011), blood loss needing blood transfusion ( $p$ -value=0.001), prolonged operation ( $p$ -value=0.046), and longer hospital stay ( $p$ -value=0.002) were common among those with malignant tumors. Open adrenalectomy was associated with significant blood loss needing transfusion ( $p$ -value=0.001) and prolonged hospital stay ( $p$ -value=0.024).

**Conclusion:** Hormone-producing adrenal tumors with secondary hypertension are the most common pathology among patients who underwent adrenalectomy. They are usually seen among patients less than 40 years old, with smaller tumor size, and frequently present with higher blood pressures that improve following adrenalectomy. In contrast, adrenal carcinomas are more common among patients above 40 years old and have larger tumor size. More often they have prolonged operation time, greater blood loss, and longer hospital stay. Patients who underwent open adrenalectomy had more blood loss and had a longer hospital stay than those who underwent laparoscopic surgery.

**Keywords:** hormone-producing adrenal tumors, functioning adrenal tumors, adrenal carcinoma, adrenalectomy, adrenal-dependent secondary hypertension

## Introduction

The clinical syndromes of hormone excess from an adrenal tumor is the most common indication for adrenalectomy.<sup>1</sup> These are primary aldosteronism (Conn's syndrome), Cushing's syndrome, and pheochromocytoma.<sup>2</sup> These endocrine disorders are adrenal-dependent causes of secondary hypertension<sup>3</sup> and are potentially curable by

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removal of the affected adrenal gland. Other indications for adrenalectomy are adrenal carcinoma, symptoms due to an enlarged adrenal gland pressing on adjacent organs, and unsuccessful pituitary surgery requiring a bilateral laparoscopic adrenalectomy for Cushing's disease.<sup>4</sup>

Traditionally, the adrenal gland has been removed through open surgery, but the minimally invasive laparoscopic approach is now the operation of choice for most tumors.<sup>5</sup> Patients undergoing a laparoscopic procedure had significantly lower postoperative morbidity and shorter length of stay than patients undergoing an open procedure.<sup>6</sup> Morbidity following adrenalectomy is associated with intraoperative injury to an adjacent or contiguous structure, postoperative infection, thromboembolism, or

adrenal insufficiency. Mortality is most often associated with pulmonary emboli, sepsis, myocardial infarction or arrhythmia, or as a direct result of the underlying disease for which adrenalectomy is being performed.<sup>7</sup>

Local data on the prevalence of adrenal gland tumors are limited. This study aims to determine the clinical and histopathologic characteristics and perioperative outcome of patients who underwent adrenalectomy in a tertiary hospital.

## Methods

This is a retrospective chart review of Filipino patients who underwent adrenalectomy in a tertiary hospital in Cebu city. All adult patients, 18 years old and above, who underwent adrenalectomy from January 2007 to June 2017 were included in the study. Only in-hospital data were included and data after discharge were beyond the scope of this study.

The complete list of patients was retrieved from hospital medical records, surgical logbooks, and histopathology logbooks. A data collection form was used to gather data, which included patient’s clinical data, diagnosis, imaging, histopathology, treatment, surgical procedure, post-operative monitoring, and clinical outcomes.

Patients’ diagnoses were categorized as hormone-producing tumor, malignant, and other benign lesion and paired with their final histopathology as used by other studies.<sup>1</sup> Hormone-producing tumors were sub-classified as to having aldosterone excess, catecholamine excess, and cortisol excess. Imaging studies were also retrieved and noted for the site of tumor, size of tumor with its largest measurement.

Patients’ categorical data was expressed in frequency and percentages while those continuous profiles were described in mean and standard deviation. In testing associations among categorical profiles, Chi square test with 2x2 Fischer Exact test adjustment was employed in testing associations among patients’ profiles and outcomes. Moreover, comparing mean values and standard deviation as stratified by patients’ profiles and outcomes, Mann Whitney U test or Kruskal Wallis Test was employed due to an expected non-parametrical distribution. Any associated p-value lesser than 0.05 alpha ( $\alpha$ ) was considered significant. IBMSPSS version 21 was used as statistical software.

## Results

A total of 31 patients who underwent adrenalectomy from January 2007 to June 2017 were included in this study. The mean age was 45.7(SD=17.1) years old; the youngest

**Table I. Clinical profiles of patients who underwent adrenalectomy (n=31)**

Characteristics of patients	n (%)
<b>Incidentaloma</b>	
Yes	18 (58.1%)
No	13 (41.9%)
<b>Hypertension</b>	
Stage of hypertension	
1	5 (16.2%)
2	14 (45.2%)
3	10 (32.2%)
<b>Hypertensive medications:</b>	
Angiotensin converting enzyme inhibitors/Angiotensin Receptor Blocker: Losartan, Imidapril, Candesartan, Irbesartan	11 (35.5%)
Calcium Channel Blockers: Amlodipine, Felodipine, Verapamil	23 (74.2%)
Beta blocker: Atenolol, Metoprolol	10 (32.3%)
Alpha blocker: Terazosin	9 (29.0%)
Spironolactone	9 (29.0%)
<b>Other co-morbid illness:</b>	
None	21 (67.7%)
Diabetes mellitus type II	3 (9.7%)
Cholelithiasis	1 (3.2%)
Post thyroidectomy	2 (6.5%)
Renal cancer	2 (6.5%)
Colon cancer	1 (3.2%)
Chronic kidney disease	1 (3.2%)
<b>Imaging characteristics (CT-Scan)</b>	
Imaging impression of the adrenal gland	
Normal	3 (9.7%)
Adrenal adenoma	15 (48.4%)
Adrenal carcinoma	8 (25.8%)
Pheochromocytoma	5 (16.1%)
Others	0 (0.0%)
Site of tumor	
Right	13 (41.9%)
Left	18 (58.1%)
Tumor size (largest measurement)	
0 (no tumor)	3 (9.7%)
0.1 – 4 cm	17 (54.8%)
≥4 cm	11 (35.5%)
<b>Types of surgery</b>	
Open adrenalectomy	17 (54.8%)
Laparoscopic adrenalectomy	14 (45.2%)

was 22 years old and the oldest was 74 years old. Majority were females (77.4%) with male-to-female ratio of 1:3. The clinical characteristics of the patients included in the analysis is shown in Table I. Majority of cases (58.1%) were considered incidentalomas with pre-operative impression of adrenal adenoma (48.4%), followed by adrenal carcinoma (25.8%) and pheochromocytoma (16.1%).

The hormone-producing adrenal tumor comprised majority of the cases (74.2%), while malignant adrenal tumors and other benign lesions constituted 12.9% each. Table II shows the histopathologic report and the corresponding percentage distribution of hormone production. Among

**Table II. Proportions of patients with hormone-producing adrenal tumor, malignant adrenal tumors, and other benign lesions according to final histopathology**

Histopathology	Hormone-Producing Adrenal Tumor n = 23 (%)			Malignant Adrenal Tumor n=4 (%)	Others n=4 (%)
	Aldosterone Excess 8 (34.8%)	Catecholamine Excess 9 (39.1%)	Cortisol Excess 6 (26.1%)		
Adenoma	8 (100%)		4 (66.7%)		
Pheochromocytoma		6 (66.7%)			
Hyperplasia		1 (11.1%)	2 (33.3)		1 (25%)
Myelolipoma		1 (11.1%)			
Benign Cyst		1 (11.1%)			
Adrenocortical Carcinoma				2 (50%)	
Metastatic				2 (50%)	
Myxoid Neoplasm					1 (25%)
Hemorrhagic Infarction					1 (25%)
Normal					1 (25%)

those hormone-producing adrenal tumors, majority were catecholamine (39.1%), followed by aldosterone (34.8%), and cortisol (26.1%). Correlating hormone produced with histopathology report, pheochromocytoma (66.7%) constitutes majority of those cases diagnosed with catecholamine production. All aldosterone producing tumor, were proven to be adrenal adenoma (100%). And among those with cortisol excess, 66.7% were due to adrenal adenoma and 33.3% had hyperplasia. Characteristics of malignant tumors are also listed in Table II.

Perioperative outcome characteristic of patients are listed in Table III. After adrenalectomy, blood pressure improved in most of the hypertensive patients (82.8%) where hypertensive medications had been discontinued in 51.7% and 31% had dose reduction. There was no reported mortality, no incidence of nosocomial infection, re-operation, and conversion from laparoscopic to open adrenalectomy noted in this study.

Comparative analysis of patients' clinical profile correlated with histopathologic feature of adrenal adenoma versus malignant tumors are shown in Table IV. A significant number of patients who had hormone-producing adrenal adenoma were aged 20 to 40 years old while those with malignant tumor and other benign lesions were above 40 years old ( $p$ -value=0.023). Tumor types were not significantly associated to a specific sex. Stage 3 hypertension was associated in patients with hormone-producing tumors ( $p$ -value=0.010).

Tumor size of greater than 4cm (min-max: 5.8-20.9) is associated with malignancy while hormone-producing adrenal adenoma tumors were usually less than four centimeters ( $p$ -value=0.011). On the other hand, half of the patients with other benign lesions also had tumor size of >4cm. Tumors were evenly distributed between left and right among those with hormone producing tumors and carcinoma, while other benign lesions were all noted in the left adrenal gland.

**Table III. Outcomes of patients who underwent adrenalectomy**

Outcomes	Descriptive n=31(%)	Mean (SD)
<b>Perioperative Complications</b>		
<b>Blood Loss Needing Transfusion (ml)</b>		
Yes	9 (29.0%)	349.1 (480.9)
No	22 (71.0%)	
<b>Blood Pressure Intraoperative</b>		
Stable Blood Pressure	21 (67.7%)	
Hypertension Needing IV Hypertensive Drug	8 (25.8%)	
Hypotension Needing Inotropes	2 (6.5%)	
<b>Operative Time</b>		
<3 hours	15 (48.4%)	3.1 (1.3)
≥3 hours	16 (51.6%)	
ICU Admission	9 (29.4%)	
<b>Hospital Stay</b>		
≤4 days	19 (61.3%)	5.7 (5.1)
>4 days	12 (38.7%)	
<b>Improvement of Hypertension</b>		
A. Improved:	24 (82.8%)	
Discontinued Medications	15 (51.7%)	
Reduced Medications	9 (31.0%)	
B. No Improvement	5 (17.2%)	
V. Death	0 (0.0%)	
VI. Others: Nosocomial Infection, Re-operation, Conversion from Laparoscopic to Open Adrenalectomy	0 (0.0%)	

Substantial blood loss needing blood transfusion intraoperatively was noted in all patients with carcinoma (100%), less likely for hormone-producing tumors (13%) and other benign lesions (50%) ( $p$ -value=0.001). The duration of operation for those patients with malignant tumor was prolonged to above three hours ( $p$ -value=0.046). The type of tumor had no association in the admission to the intensive care unit (ICU) but patients with adrenal carcinoma had significantly longer hospital stay ( $p$ -value=0.002). Improvement of hypertension postoperatively was significantly seen in those patients with hormone-producing tumors ( $p$ -value=0.046) than in patients with malignant tumors and other benign lesions.

<b>Table IV. Comparative analysis of patients clinical profile and outcomes according to patients diagnosis</b>				
Characteristics of Patients	Hormone-Producing Adrenal Tumor n=23 (%)	Malignant Adrenal Tumor n=4 (%)	Others n=4 (%)	p-value
Demographics:				
Age (years)				
20 – 40	13 (52.2%)	0 (0.0%)	0 (0.0%)	0.023*
41 – 60	8 (34.8%)	2 (50.0%)	2 (50.0%)	
> 60	3 (13.0%)	2 (50.0%)	2 (50.0%)	
Gender				
Female	19 (82.6%)	3 (75.0%)	2 (50.0%)	0.395
Male	4 (17.4%)	1 (25.0%)	2 (50.0%)	
Incidentaloma				
Yes	13 (56.5%)	2 (50.0%)	3 (75.0%)	0.858
No	10 (43.5%)	2 (50.0%)	1 (25.0%)	
Stage of Hypertension				
No hypertension	0 (0.05)	1 (25.0%)	1 (25.0%)	0.010**
Stage 1	2 (8.7%)	1 (25.0%)	2 (50.0%)	
Stage 2	11 (47.8%)	2 (50.0%)	1 (25.0%)	
Stage 3	10 (43.5%)	0 (0.0%)	0 (0.0%)	
Imaging Characteristics (CT-Scan)				
Tumor Size (largest measurement)				
0 (normal)	2 (8.7%)	0 (0.0%)	1 (25.0%)	0.011*
0.1 – 4.0 cm	16 (69.6%)	0 (0.0%)	1 (25.0%)	
>4 cm	5 (21.7%)	4 (100%)	2 (50.0%)	
Site of Tumor				
Right	10 (43.5%)	2 (50.0%)	0 (0.0%)	0.356
Left	13 (56.5%)	2 (50.0%)	4 (100%)	
Type of Surgery				
Laparoscopic	13 (56.5%)	0 (0.0%)	1 (25.0%)	0.101
Open	10 (43.5%)	4 (100%)	3 (75.0%)	
Perioperative Outcomes				
Blood Loss Needing Transfusion				
No	20 (87.0%)	0 (0.0%)	2 (50.0%)	0.001**
Yes	3 (13.0%)	4 (100%)	2 (50.0%)	
Blood Pressure Intraoperative				
Stable BP	16 (69.6%)	2 (50.0%)	3 (75.0%)	0.648
Low BP needing inotropes	1 (4.3%)	1 (25.5%)	0 (0.0%)	
High BP needing IV hypertensive meds	6 (26.1%)	1 (25.5%)	1 (25.5%)	
Operation Duration				
<3 hours	14 (60.9%)	0 (0.0%)	1 (25.0%)	0.046*
≥3 hours	9 (39.1%)	4 (100.0%)	3 (75.0%)	
ICU				
No	16 (69.6%)	2 (50.0%)	4 (100.0%)	0.371
Yes	7 (30.4%)	2 (50.0%)	0 (0.0%)	
Hospital Stay				
≤4 days	18 (78.3%)	0 (0.0%)	1 (25.0%)	0.002**
> 4days	5 (21.7%)	4 (100%)	3 (75.0%)	
Improvement of Hypertension	21 (91.3%)	1 (33.3%)	2 (66.7%)	0.046*
Improved:				
Discontinued Medications	13 (56.5%)	1 (33.3%)	1 (33.3%)	0.083
Reduced Medications	8 (34.8%)	0 (0.0%)	1 (33.3%)	
No Improvement	2 (8.7%)	2 (66.7%)	1 (33.3%)	
Other Co-morbid Illness:				
No	16 (69.6%)	3 (75.0%)	2 (50%)	0.856
Yes	7 (30.4%)	1 (25.0%)	2 (50%)	

**Table V. Comparative analysis of patients clinical profile and outcomes according to hormone-producing tumors**

Characteristics of Patients	Primary Aldosteronism n=8 (%)	Catecholamine Excess n=9 (%)	Cushing's Syndrome n=6 (%)	p-value
Demographics:				
Age (years)				
20 – 40	3 (37.5%)	4 (44.4%)	4 (66.7%)	0.934
41 – 60	4 (50.0%)	4 (44.4%)	1 (16.7%)	
> 60	1 (12.5%)	1 (11.1%)	2 (33.3%)	
Gender				
Female	7 (87.5%)	7 (77.8%)	5 (83.3%)	1
Male	1 (12.5%)	2 (22.2%)	1 (16.7%)	
Incidentaloma				
Yes	4 (50%)	8 (88.9%)	1 (16.7%)	0.017*
No	4 (50%)	1 (11.1%)	5 (83.3%)	
Stage of hypertension				
Stage 1	1 (12.5%)	1 (11.1%)	0 (0.0%)	0.96
Stage 2	4 (50.0%)	5 (55.6%)	2 (33.3%)	
Stage 3	3 (37.5%)	3 (33.3%)	4 (66.7%)	
Imaging characteristics (CT-scan)				
Tumor size (largest measurement)				
0 (normal)	0 (0.0%)	0 (0.0%)	2 (33.3%)	0.053
0.1 – 4.0 cm	7 (87.5%)	5 (55.6%)	4 (66.7%)	
>4 cm	1 (12.5%)	4 (44.4%)	0 (0.0%)	
Site of tumor				
Right	3 (37.5%)	4 (44.4%)	3 (50.0%)	1
Left	5 (62.5%)	5 (55.6%)	3 (50.0%)	
Type of surgery				
Laparoscopic	5 (62.5%)	5 (55.6%)	4 (66.7%)	1
Open	3 (37.5%)	4 (44.4%)	2 (33.3%)	
Perioperative outcomes				
Blood loss needing transfusion				
No	7 (87.5%)	7 (77.8%)	6 (100%)	0.756
Yes	1 (12.5%)	2 (22.2%)	0 (0.0%)	
Blood pressure intraoperative				
Stable BP	6 (75.0%)	7 (77.8%)	3 (50.0%)	0.454
Low BP needing inotropes	0 (0.0%)	1 (11.1%)	0 (0.0%)	
High BP needing IV hypertensive meds	2 (25.0%)	1 (11.1%)	3 (50.0%)	
Operation duration				
<3 hours	6 (75.0%)	5 (55.6%)	4 (66.7%)	0.647
≥3 hours	2 (25.0%)	4 (44.4%)	2 (33.3%)	
ICU				
No	5 (62.5%)	7 (77.8%)	4 (66.7%)	0.856
Yes	3 (37.5%)	2 (22.2%)	2 (33.3%)	
Hospital stay				
≤4 days	7 (87.5%)	7 (77.8%)	4 (66.7%)	0.82
>4 days	1 (12.5%)	2 (22.2%)	2 (33.3%)	
Improvement of hypertension				
Improved	8 (100%)	7 (77.8%)	6 (100%)	1
Discontinued medications	6 (75.0%)	5 (55.6%)	2 (33.3%)	
Reduced medications	2 (25.0%)	2 (22.2%)	4 (66.7%)	
No Improvement	0 (0.0%)	2 (22.2%)	0 (0.0%)	

**Table VI. Comparative analysis of patients clinical profile and operative outcomes according to type of surgery**

Patients Characteristics	Laparoscopic Adrenalectomy n=14 (%)	Open Adrenalectomy n=17 (%)	p-value
<b>Demographics</b>			
Age (years)			
20 – 40	7 (50.0%)	5 (29.4%)	0.271
41 – 60	3 (21.4%)	9 (52.9%)	
> 60	4 (28.6%)	3 (12.6%)	
Gender			
Female	13 (92.9%)	11 (64.7%)	0.094
Male	1 (7.1%)	6 (35.3%)	
<b>Diagnosis</b>			
Hormone-producing adrenal tumor	13 (92.9%)	10 (58.8%)	0.101
Malignant adrenal tumors	0 (0.0%)	4 (23.5%)	
Other benign	1 (7.1%)	3 (17.6%)	
<b>Stage of Hypertension</b>			
No hypertension	0 (0.0%)	2 (11.8%)	0.151
Stage 1	1 (7.1%)	4 (23.5%)	
Stage 2	6 (42.9%)	8 (47.1%)	
Stage 3	7 (50.0%)	3 (17.6%)	
<b>Imaging characteristics (CT-scan)</b>			
Tumor size			
0	2 (14.3%)	1 (5.9%)	0.337
0.1 – 4.0 cm	9 (64.3%)	8 (47.1%)	
>4 cm	3 (21.4%)	8 (47.1%)	
Site of tumor			
Right	7 (50%)	5 (29.4%)	0.246
Left	7 (50%)	12 (70.6%)	
<b>Perioperative outcomes</b>			
Blood loss needing transfusion			
No	14 (100.0%)	8 (47.1%)	0.001**
Yes	0 (0.0%)	9 (52.9%)	
Unstable BP intraoperative			
Stable BP	10 (71.4%)	11 (64.7%)	0.845
Low BP	1 (7.1%)	1 (5.9%)	
High BP	3 (21.4%)	5 (29.4%)	
Operation duration			
<3 hours	9 (64.3%)	6 (35.3%)	0.156
≥3 hours	5 (35.7%)	11 (64.7%)	
ICU			
No	11 (78.6%)	11 (64.7%)	0.329
Yes	3 (21.4%)	6 (35.3%)	
Hospital stay			
≤4 days	13 (85.7%)	7 (41.2%)	0.024*
>4 days	3 (14.3%)	10 (58.5%)	
Improvement of hypertension			
Improved	14 (100.0%)	9 (60.0%)	0.017*
Discontinued medications	9 (64.3%)	6 (40.0%)	
Reduced medications	5 (35.7%)	3 (20.0%)	
No Improvement	0 (0.0%)	6 (40.0%)	
Other co-morbid illness			
No	9 (64.3)	12 (70.6%)	0.154
Yes	5 (35.7%)	5 (29.4%)	

There is no reported statistically significant difference between the clinical profile of patients and the syndromes reported, except for the incidentalomas which was shown to be associated with catecholamine-producing tumors as shown in Table V.

Comparing the outcome of open adrenalectomy compared to laparoscopic adrenalectomy, Table VI showed that patients who underwent open adrenalectomy had significantly prolonged hospital stay ( $p$ -value=0.024); and blood loss needing transfusion ( $p$ -value=0.001), compared to patients who underwent laparoscopic surgery.

## Discussion

This review of 31 cases from 2007 - 2017 of adrenalectomy showed that hormone-producing adrenal tumor comprises the majority of cases (74.2%) while malignant adrenal tumors were only 12.9%. This was also observed by the study of Hsun-Shuan Wang et al.<sup>8</sup> Other benign cases of myxoid adrenal neoplasm and hemorrhagic infarction, which are very rare<sup>10,11</sup> were also noted.

### Hormone-producing adrenal tumors

The prevalence of hormone-producing adrenal tumors in the general population is low.<sup>9,14</sup> Primary aldosteronism has a prevalent rate of 5-10% of among hypertensive patients. It is considered the most common and important cause of endocrine hypertension.<sup>3</sup> These hormone-producing adrenal tumors occur in middle-aged adults<sup>15</sup> with 1:1 male to female ratio. They are diagnosed usually at 30 to 60 years old.<sup>3,16</sup> In this study, 87% were under 60 years old and majority belongs to 20-40 years age group (52%) consistent with previous studies. The female to male ratio in this study was 3:1 and this is due to the significant number of incidentalomas (58.1%) which are more frequently seen in females.<sup>17</sup> This could be partly explained by the higher rate of diagnostic abdominal procedures recommended for women than men.<sup>12</sup> This findings were also noted in the study of Cho YY et al.<sup>18</sup>

For the tumor sizes on imaging, hormone-producing adenoma are generally measure less than four centimeter for primary aldosteronism and Cushing's syndrome.<sup>19</sup> Conversely, symptomatic pheochromocytomas usually present with larger mass >4cm, although frequently smaller (<3cm)<sup>19</sup> if incidentally discovered. In this study, tumor size of less than four centimeter is significantly associated in hormone-producing tumors compared to adrenal carcinoma and other benign lesions. Even though majority were pheochromocytomas, they were mostly discovered incidentally in this study.

Primary aldosteronism is commonly caused by an adrenal adenoma, unilateral or bilateral adrenal hyperplasia, or in rare cases by the inherited condition of glucocorticoid-

remediable aldosteronism.<sup>20</sup> In this study, patients with aldosterone excess syndrome all had adenoma on final histopathology. For those patients with catecholamine excess, pheochromocytoma were documented by biopsy on majority of patients (66.7%). Other rare causes were functioning adrenal cyst, myelolipoma, and hyperplasia that are documented only on case reports.<sup>21,22,23</sup> And for those patients with cortisol excess, ectopic ACTH-secreting neoplasms and the ACTH-independent forms of Cushing syndrome (e.g., adrenal adenoma, adrenal carcinoma, and adrenal nodular hyperplasia) are responsible for 15% of the endogenous cases.<sup>9</sup> In this study, adrenal adenoma (66.7%) and hyperplasia (33.3%) were the final histopathology presenting with Cushing's syndrome.

### Malignant adrenal tumor

Among the non-functioning adrenal mass, malignant adrenal tumor could be metastatic (19%) or adrenocortical carcinoma (10%).<sup>24</sup> In the study of Ong-Ramos et al.<sup>25</sup> among Filipino patients, half of the adrenal cancers were due to adrenocortical carcinoma followed by metastases to the adrenals and adrenal neuroblastoma. The mean age at diagnosis was 45.5 years old. In this study, half were adrenocortical carcinoma and half were metastasis. They were all non-functioning and were common above 40 years old. This older age group was significantly associated with patients with malignant tumors and other benign lesions compared to hormone-producing tumors in this study. Although majority of patients (75%) had hypertension, essential hypertension is common in this age group and not due to secondary causes.<sup>9</sup> In one of the cases of malignant tumor with hypertension, antihypertensive medications were discontinued because of hypotension secondary to significant blood loss during the operation.

The incidence of adrenocortical carcinomas in all adrenal tumors measuring less than or equal to four centimeters is two percent, while six percent in tumors ranging from 4.1-6 cm, and 25% for tumors greater than six centimeters.<sup>24</sup> The tumor size of metastatic adrenal carcinomas varies.<sup>19</sup> A study among Filipino patients<sup>25</sup> with adrenal carcinoma observed a mean tumor size of two centimeters and largest measurement of 6.5 cm. In this study, malignant tumor sizes were all above four centimeters with a largest size noted of 20.9cm. Tumor size of more than 4.0 cm was significantly associated with malignancy in this study.

Adrenocortical carcinoma is a very rare disease with an incidence believed to be one to two per million per year and a 2.5:1 female to male ratio,<sup>25</sup> but valid data are still lacking.<sup>26</sup> In this study, only four cases of adrenocortical carcinoma were noted, with 50% metastatic from colon and renal cancer. Similarly, the study of Ong-Ramos et al.<sup>25</sup> noted metastatic adrenocortical carcinoma from renal cancer and gastrointestinal carcinoma and lung in another study.<sup>27</sup>

## Other benign adrenal lesions

In this study, other benign adrenal lesions include tumors that were non-functioning and non-malignant as well. These cases were documented either by work-up with imaging intended for other disease entities, i.e. incidentalomas. These are myxoid neoplasm, hemorrhagic infarction, and hyperplasia that were proven not malignant in the final histopathology. The indication for surgery was size of above three centimeters. Since the risk of malignancy in incidentalomas increases in 43–100% for masses larger than three centimeters<sup>29</sup> surgery was recommended.<sup>5</sup>

## Operative outcomes

Before the advent of laparoscopic approach, open adrenalectomy was performed for surgically amenable adrenal diseases.<sup>7</sup> However, morbidity can be as high as 40%, and mortality at two to four percent.<sup>6,7</sup> Thus, laparoscopic technique has become the treatment of choice and has replaced open surgery for the removal of adrenal tumors.<sup>15</sup> This approach demonstrates decreased morbidity with the smaller incisions and shorter postoperative recovery time.<sup>15,16</sup>

The absolute contraindications to the laparoscopic technique include non-correctable coagulopathy, cranial hypertension, and cardiac and respiratory disorders that preclude a laparoscopic approach.<sup>29</sup> Relative contraindications include large tumors and suspected adrenocortical cancer. There is no absolute size criterion for determining which tumors can be resected by this approach and depends on technical and institutional experience.<sup>29</sup>

In this study, more patients underwent open adrenalectomy than laparoscopic approach. The preferred type of surgery done according to the specific type of tumor did not reach statistical significance although all of adrenal carcinomas underwent open adrenalectomy. The availability of instruments and expertise of surgeons could be the factors in our institution.

Intraoperative transfusion was independently and incrementally associated with significant morbidity and mortality after laparoscopic and open adrenalectomy.<sup>30</sup> Age, open surgery, preoperative anemia, and prolonged operative time are associated with an increased need for blood transfusions.<sup>30</sup> In this study, blood loss needing transfusion was significantly associated in those patients with adrenal carcinoma. It was also associated with open adrenalectomy. This was the group of patients who were with older age (>40 years old) and with larger tumor size (>4cm).

Hormone-producing adrenal tumors present a unique challenge requiring good pre-operative evaluation and perioperative hemodynamic control.<sup>30</sup> Relevant intraoperative increases in blood pressure occur in these

patients necessitating specific precautionary measures during anesthesia.<sup>31,32,33</sup> In this study, only few cases had unstable blood pressure intraoperative and had no predilection to specific type of tumor or type of surgery.

The longer operation duration, intensive care admission, and longer duration of hospital stay brings higher morbidity or mortality and higher costs.<sup>1,8</sup> The reported risks factors include open surgery, size of tumor, malignancy, and syndrome of hormone excess.<sup>1,6,8</sup> In this study, prolonged operation duration and hospital stay were indeed associated with adrenal carcinoma and open adrenalectomy.

Other operative complications such as local infection, pneumothorax, laceration of viscus, and re-operation were rarely noted in the study of Thompson et. al.<sup>1</sup> No noted death in the same study among 659 patients. In this study, there was no incidence of nosocomial infection, re-operation, conversion from laparoscopic to open adrenalectomy and death. This signifies that adrenalectomy is a safe procedure especially with laparoscopic approach.

Hypertension is the most common manifestation among hormone-producing adrenal tumors<sup>34</sup> Adrenalectomy may cure their hypertension or improved their management in those patients with underlying essential hypertension<sup>3,14,35</sup> A study among Filipino patients with functioning nodules who underwent laparoscopic adrenalectomy<sup>34</sup> reported a marked improvement of hypertension either discontinued or reduced their medications. In this study, improvement of hypertension postoperatively was associated with those patients who had hormone-producing tumors, and this signifies success of the surgery. This finding was also associated with patients who underwent laparoscopic approach because of more patients (92.9%) with functioning tumor in the laparoscopic group.

## Conclusion

Our study showed that hormone-producing adrenal tumor comprises the majority of cases (74.2%) while malignant adrenal tumors were seen in 12.9%. Hormone-producing tumors were common at age 20 to 40 years old while malignant tumors were more common among those above 40 years old. The larger tumor size (>4cm), blood loss needing blood transfusion, prolonged operation, and longer hospital stay were common among those with malignant tumors.

## Limitations

The study data was taken from previous records analyzed retrospectively. Other important findings may have not been recorded. The study does not identify outcomes for the individual surgeon, which may affect the results.



## Recommendations

A prospective study may be beneficial to ensure completeness of data and can include biochemical or hormonal evaluation and outcome of individual surgeons. Due to rarity of this disease, multicenter study is also recommended to have bigger sample size. Long-term outcomes of patients who underwent adrenalectomy can also be studied.

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