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Nationwide review of hormonally active adrenal tumors highlights high morbidity in pheochromocytoma

Punam P. Parikh, MD, Gustavo A. Rubio, MD, Josefina C. Farra, MD, and John I. Lew, MD, FACS*

Division of Endocrine Surgery, DeWitt Daughtry Family Department of Surgery, Leonard M. Miller School of Medicine, University of Miami, Miami, Florida

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ABSTRACT

Background: Adrenal adenomas are benign tumors often discovered incidentally, and >70% are hormonally inactive. The remaining subset may produce excess aldosterone, cortisol, or catecholamine. Perioperative outcomes after adrenalectomy for such "hormonally active" tumors remain unclear. This study examines in-hospital outcomes after unilateral adrenalectomy for hormonally active tumors.

Methods: A retrospective review was performed using the Nationwide Inpatient Sample (2006-2011) to identify patients undergoing unilateral adrenalectomy for hormonally active or inactive tumors. Malignant adrenal tumors were excluded. Demographics, comorbidities, and postoperative complications were evaluated by univariate analysis, using two-tailed Chi-square and t-tests and multivariate logistic regression.

Results: Of 27,312 patients who underwent adrenalectomy, 78% ($n = 21,279$) had hormonally inactive and 22% ($n = 6033$) had hormonally active adrenal tumors. Among the latter, 65% ($n = 4000$) had primary hyperaldosteronism (Conn's syndrome), 33% ($n = 1996$) had hypercortisolism (Cushing's syndrome), and 1.4% ($n = 85$) had pheochromocytoma. Patients with pheochromocytoma had higher rate of comorbidities including congestive heart failure, chronic lung disease, and malignant hypertension compared with remaining hormonally active tumors (12% *versus* 4%, 18% *versus* 11%, 6% *versus* 2%; $P < 0.01$). For patients with pheochromocytoma *versus* other hormonally active tumors, mean length of stay was 5 *versus* 3 d and total in-hospital cost was $50,000 *versus* $41,000 ($P < 0.01$). On multivariate analysis, pheochromocytoma had an independently higher risk for intraoperative blood transfusion (4.2, 95% confidence interval [CI] 2.4-7.2), postoperative cardiac (7.6, 95% CI 2.8-20.2), and respiratory (1.9, 95% CI 1.0-3.3) complications.

Conclusions: Patients with pheochromocytoma have high rates of preoperative comorbidities, postoperative cardiopulmonary complications, and longer and more costly

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* *Corresponding author*. DeWitt Daughtry Family Department of Surgery, University of Miami Leonard M. Miller School of Medicine, 1120 NW 14th St, 4th Floor, Miami, FL 33136. Tel.: +1 (305) 243 4444; fax: +1 (305) 243 4221.
E-mail address: Pparikh@med.miami.edu (P.P. Parikh).

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hospitalizations. Such high-risk patients should undergo appropriate preoperative medical optimization in preparation for adrenalectomy.

Introduction

A growing number of adrenal adenomas or masses are incidentally discovered on 1%-5% of all abdominal cross-sectional imaging studies performed for other diagnostic reasons unrelated to the adrenal gland.[1] Once such an adrenal adenoma or "incidentaloma" is discovered, there is an impetus to evaluate functional status and malignant potential of the adrenal mass. Although such adrenal tumors remain hormonally inactive >70% of the time, the remaining subsets of adrenal masses are commonly associated with excess catecholamine, aldosterone, or cortisol production.[1]

Medical management of such hormonally active adrenal tumors is contingent on biochemical evaluation that includes elevated urinary metanephrines for pheochromocytoma, increased aldosterone to plasma renin activity for primary hyperaldosteronism (Conn's syndrome), and excess cortisol secretion after dexamethasone suppression test for hypercortisolism (Cushing's syndrome).[2] For definitive management, surgical resection is generally recommended for not only hormonally active adrenal tumors but also for those tumors that are large (>4 cm) or rapidly growing because of underlying malignancy.[3]

Delayed resection, or lack thereof, permits autonomous hormonal secretion by active adrenal tumors. Such biochemical activity increases risk for metabolic and cardiovascular diseases, including diabetes and hypertension, compared with hormonally inactive adrenal tumors.[4] Furthermore, studies also demonstrate that patients with hormonally inactive adrenal tumors have a significantly higher risk for metabolic disease than those patients without an adrenal mass.[4] These findings prompt consideration of whether the classification of hormonally inactive adrenal tumors is simply prefatory to the continuum of hormonally active tumors.[4]

Although hormonally active adrenal tumors may be associated with metabolic disease, current comparison of disease severity among patients with pheochromocytomas, Conn's or Cushing's syndrome is unknown. Specifically, perioperative outcomes after adrenalectomy for hormonally active adrenal tumors remain unclear. This study examines patient comorbidities and in-hospital outcomes after unilateral adrenalectomy in patients with hormonally active, benign adrenal tumors. The authors hypothesize that patients with hormonally active adrenal adenomas have more associated comorbidities and perioperative complications compared with those patients with hormonally inactive, benign adrenal tumors.

Methods

A retrospective cross-sectional analysis using data from the Health Care Utilization Project Nationwide Inpatient Sample (HCUP-NIS) from 2006 to 2011 was performed. HCUP-NIS is the largest publicly available inpatient database maintained by the United States Agency for Healthcare Research and Quality. This database includes a 20% stratified sample of all discharges from nonfederal hospitals, resulting in approximately 8 million records per year. Patient cases are weighted appropriately to project national estimates for analyses. This large sample size allows for analysis of rare conditions including pheochromocytoma, Conn's and Cushing's syndrome, and their related perioperative outcomes.

Clinical and pathologic data of 27,312 consecutive patients who underwent adrenalectomy for hormonally active or inactive adrenal tumors were analyzed. All patients underwent unilateral adrenalectomy in a laparoscopic or open fashion performed by an endocrine surgeon, general surgeon, or urologist. The first cohort included all patients with a diagnosis of pheochromocytoma, Conn's or Cushing's syndrome. In current clinical practice, such patients typically undergo adrenalectomy because of clinical sequelae related to the respective hormonally active adrenal tumor. As a comparison, the second cohort included all patients with a hormonally inactive adrenal adenoma or an "incidentaloma." Such patients typically undergo adrenalectomy for incidentalomas that are ≥4 cm by imaging studies, suspicious for malignancy by radiographic features, and/or patient preference.

Unilateral adrenalectomies were identified using International Classification of Diseases, Ninth Revision (ICD-9) codes 0721, 0722, and 0729. Patients with a primary diagnosis of pheochromocytoma (ICD-9 255.6), Conn's syndrome (ICD-9 255.10, 255.12), and Cushing's syndrome (ICD-9 255.0) were compared with each other and the remaining cohort of patients with hormonally inactive adrenal tumors with an indication for unilateral adrenalectomy. All operative cases revealing primary adrenal malignancy or metastatic adrenal disease on final pathology were excluded (ICD-9 1940 and 1987, respectively).

Patient characteristics including demographic, socioeconomic, and comorbidities were recorded and compared between the aforementioned cohorts. Variables available from HCUP-NIS included age, sex, race, payer type, and admission status (elective *versus* nonelective). Comorbidities including history of diabetes mellitus type 2 (DMT2), hypertension, congestive heart failure (CHF), chronic lung disease (CLD), kidney failure, and obesity were also recorded. Dependent variables included in-hospital complications, length of stay, and total hospital charges. Perioperative complications were identified using ICD-9 diagnostic codes, with the exception of in-hospital death, which is reported in HCUP-NIS. Perioperative complications analyzed included intraoperative vascular, spleen or liver injury, and blood transfusion. Postoperative outcomes included wound complications such as seroma, infection, nonhealing, or dehiscence. Endocrine complications included adrenocortical insufficiency and malignant