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Clinical, Biochemical, and Radiological Characteristics of a Single-Center Retrospective Cohort of 705 Large Adrenal Tumors

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Abstract

Objective: To characterize large adrenal tumors (≥4 cm in diameter) and to identify features associated with malignancy.

Patients and Methods: We investigated the clinical, biochemical, and imaging characteristics in a large retrospective single-center cohort of patients with adrenal tumors of 4 cm or more in diameter during the period of January 1, 2000, through December 31, 2014.

Results: Of 4085 patients with adrenal tumors, 705 (17%) had adrenal masses measuring 4 cm or more in diameter; of these, 373 (53%) were women, with a median age of 59 years (range, 18-91 years) and median tumor size of 5.2 cm (range, 4.0-24.4 cm). Underlying diagnoses were adrenocortical adenomas (n=216 [31%]), pheochromocytomas (n=158 [22%]), other benign adrenal tumors (n=116 [16%]), adrenocortical carcinomas (n=88 [13%]), and other malignant tumors (n=127 [18%]). Compared with benign tumors, malignant tumors were less frequently diagnosed incidentally (45.5% vs 86.7%), were larger (7 cm [range, 4-24.4 cm] vs 5 cm [range, 4-20 cm]), and had higher unenhanced computed tomographic (CT) attenuation (34.5 Hounsfield units [HU] [range, 14.1-75.5 HU] vs 11.5 HU [range, −110 to 71.3 HU]; $P<.001$). On multivariate analysis, older age at diagnosis, male sex, nonincidental mode of discovery, larger tumor size, and higher unenhanced CT attenuation were all found to be statistically significant predictors of malignancy.

Conclusion: The prevalence of malignancy in patients with adrenal tumors of 4 cm or more in diameter was 31%. Older age, male sex, nonincidental mode of discovery, larger tumor size, and higher unenhanced CT attenuation were associated with an increased risk for malignancy. Clinical context should guide management in patients with adrenal tumors of 4 cm or more in diameter.

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Adrenal tumors are encountered in approximately 5% of patients undergoing cross-sectional imaging.[1-3] Prevalence varies with age, ranging from less than 0.5% in children[4,5] to 10% in elderly patients.[6-8] Most adrenal tumors are discovered incidentally on imaging performed for a reason other than suspected adrenal disease; however, at least 15% of patients with adrenal tumors present with signs and symptoms of adrenal hormonal excess.[9] In every patient with a newly discovered adrenal tumor, it is essential to determine whether the adrenal tumor is malignant and/or hormonally active.

Most incidentally discovered adrenal tumors are benign and nonfunctioning adrenocortical adenomas (ACAs).[9] Functional ACAs and pheochromocytomas (PHEOs) are diagnosed in 11% to 15% and 4% to 10% of patients with adrenal incidentalomas, respectively.[9] Malignant adrenal tumors (mainly adrenocortical carcinomas [ACCs]) are diagnosed in up to 11% of patients with adrenal incidentalomas.[7,9] However, in patients with an active extraadrenal malignancy, the likelihood of adrenal metastasis varies widely between 2% and 71% depending on the studied population, clinical presentation, and underlying malignancy.[10-13]

The imaging characteristics of the adrenal mass are helpful in determining the risk of malignancy. The intracellular lipid content can be approximated by measuring Hounsfield units (HU) on unenhanced computed tomography (CT) and with the use of chemical shift magnetic resonance imaging. Lipid-rich adrenal tumors present with low unenhanced CT attenuation and positive chemical shift on magnetic resonance imaging and are consistent with ACAs. Because most incidentally discovered adrenal tumors are lipid-rich adenomas, guidelines[9,14-16] recommend unenhanced CT as the initial imaging study to exclude malignancy. An attenuation threshold of more than 10 HU has a sensitivity of 93% to 100%, but a specificity of only 71% to 72% for detecting a malignancy.[3] Thus, after imaging, a clinically significant proportion of adrenal tumors remain indeterminate for malignancy and require additional assessment. Additional imaging modalities are often used to further characterize adrenal masses, including CT with contrast administration to assess for absolute and relative contrast washout and [^{18}F]-fluorodeoxyglucose–positron emission tomography integrated with CT to assess for metabolic activity. However, evidence on the diagnostic accuracy of these imaging modalities is limited[3]; a recent publication by our group demonstrated that [^{18}F]-fluorodeoxyglucose–positron emission tomography integrated with CT adrenal liver ratio of more than 1.8 diagnosed malignancy with a sensitivity of 87% and specificity of 84%.[17] When imaging is inconclusive, various strategies may be considered including interval imaging to assess for tumor growth, adrenalectomy, and, in selected cases, adrenal biopsy.[3,9,18,19]

In patients with adrenal masses, the risk of malignancy is directly proportional to the size of the adrenal mass. Although several studies report sensitivities of 80% to 93%, a tumor size threshold of 4 cm is only 34% to 61% specific for the diagnosis of a malignant adrenal mass.[7,20,21] The natural history of patients with large adrenal tumors is not well studied and most evidence originates from surgical series.[7,21,22] Several guidelines recommend consideration of adrenalectomy for adrenal masses greater than 4 to 6 cm.[14-16] However, more recent guidelines on adrenal incidentalomas do not recommend an absolute size cutoff for adrenalectomy, but suggest an individualized approach with consideration of adrenalectomy in large tumors.[9] This equivocal recommendation reflects the paucity of data on the management and natural history of patients with large tumors. An alternative explanation for the lack of a consensus recommendation is that many variables tend to be considered when deciding on surgery, including HU attenuation on unenhanced CT, CT contrast washout behavior (if available), growth or stability on follow-up imaging, patient age, and comorbidities. Our objective was to improve the understanding of the characteristics of large adrenal tumors by retrospectively studying a large cohort of patients with adrenal tumors of 4 cm or more in diameter seen over a 15-year period, in order to identify features associated with malignancy.

PATIENTS AND METHODS

This was a retrospective cohort study performed at Mayo Clinic, Rochester, Minnesota, between January 1, 2000, and December 31, 2014. This study received approval from the Mayo Clinic Institutional Review Board and included only those patients who provided authorization for research. All electronic medical records of patients with adrenal tumors diagnosed during the study period were individually reviewed for inclusion criteria. Adult patients with adrenal tumor size of at least 4 cm in largest diameter were included in the study and detailed clinical, imaging, biochemical, and histopathologic data were collected. The functional status of adrenal tumors was obtained through medical record review. Overt hypercortisolism, primary hyperaldosteronism, and catecholamine excess were diagnosed on the basis of most recent guidelines.[23-25] Mild autonomous cortisol excess was defined as failure to suppress cortisol to less than or equal to 1.8 μg/dL (to convert to nmol/L, multiply by 27.59) after overnight dexamethasone administration (1 mg or 8 mg).[9]

We grouped all adrenal tumors into 5 main diagnostic categories, on the basis of histology for patients who underwent adrenalectomy and on the basis of cytology results if adrenal biopsy was performed. For patients in whom adrenalectomy or adrenal biopsy was not performed, we used information on clinical and radiological characteristics at presentation and follow-up to determine the final diagnosis.

TABLE 1. Demographic Characteristics, Clinical Presentation, and Management of Patients With Large Adrenal Tumors[a,b]

Variable	Total	Pheochromocytoma	ACA	Other benign tumors	ACC	Other malignant tumors	*P* value (overall)	*P* value (ACC vs other malignancy)
No. (%)	705	158 (22)	216 (31)	116 (16)	88 (13)	127 (18)		
Sex: female, No. (%)	373 (53)	84 (53)	134 (62)	55 (47)	56 (64)	44 (35)	<.001[c]	<.001[c]
Age at diagnosis (y), median (range)	59 (18 to 91)	53 (18 to 87)	61 (25 to 91)	54 (20 to 84)	50 (19 to 85)	66 (18 to 88)	<.001[c]	<.001[c]
Mode of discovery, No. (%)							<.001[c]	<.001[c]
Incidental	472 (67)	86 (54)	184 (85)	104 (90)	37 (42)	61 (48)		
Hormone excess	107 (15)	62 (39)	18 (8)	0 (0)	27 (31)	0 (0)		
Cancer staging	61 (9)	3 (2)	6 (3)	3 (3)	5 (6)	48 (38)		
Mass effect	51 (7)	6 (4)	6 (3)	9 (7)	18 (20)	12 (9)		
B symptoms	14 (2)	1 (1)	2 (1)	0 (0)	1 (1)	6 (5)		
Location of adrenal tumor, No. (%)							<.001[c]	<.001[c]
Right	297 (42)	76 (48)	81 (38)	53 (46)	43 (49)	45 (35)		
Left	304 (43)	69 (44)	96 (44)	51 (44)	45 (51)	44 (35)		
Bilateral	104 (15)	13 (8)	39 (18)	12 (10)	0 (0)	38 (30)		
Adrenal mass diameter (cm), median (range)	5.2 (4 to 24.4)	5.2 (4.0 to 20)	4.5 (4 to 17)	6.9 (4 to 20)	10.9 (4 to 24.4)	5.4 (4.0 to 18.6)	<.001[c]	<.001[c]
Unenhanced CT attenuation (HU), median (range)	27 (−110 to 76)	33 (18 to 60)	11 (−64 to 71)	13 (−110 to 55)	35 (18 to 76)	34 (14 to 56)	<.001[c]	.70
Available in No. (%)	360 (51)	63 (40)	138 (64)	70 (60)	41 (47)	48 (38)		
Adrenal biopsy, No. (%)	103 (15)	13 (8)	15 (7)	10 (9)	19 (22)	46 (36)	<.001[c]	.02[c]
Adrenalectomy, No. (%)	457 (65)	155 (98)	118 (55)	57 (49)	77 (88)	50 (39)	<.001[c]	<.001[c]

[a]ACA = adrenocortical adenoma; ACC = adrenocortical carcinoma; CT = computed tomography; HU = Hounsfield unit.
[b]Range was defined as minimum to maximum value.
[c]Indicates statistical significance with *P* values <.05.

Radiological Assessment

All radiology reports of cross-sectional imaging were reviewed. In addition, an experienced radiologist personally reviewed unenhanced CT images. A CT linear measurement tool was used to determine the largest diameter of the adrenal mass in the axial plane. To determine the CT attenuation values, an oval region-of-interest cursor was used. The region of interest covered two-thirds to three-quarters of the adrenal mass. The mass boundary, calcifications, and areas of necrosis were avoided.

Statistical Analyses

A descriptive summary analysis of patients' baseline characteristics was performed using JMP, version 10.0.0 (SAS Institute). The findings are presented as frequencies (percentages) for the categorical variables and median (ranges) for the continuous variables. Differences between categorical variables were assessed using the Pearson χ^2 test. Differences between continuous variables were assessed using the Wilcoxon/Kruskal-Wallis test. Logistic regression was used to differentiate malignancy groups on the basis of predefined predictors. A P value of less than .05 was considered statistically significant.

RESULTS

Patients

During the 15-year study period, 4085 patients with adrenal tumors were evaluated at Mayo Clinic in Rochester, MN; 705 (17%) patients had a maximum adrenal tumor diameter of 4 cm or more (median size, 5.2 cm; range, 4.0-24.4 cm). Patients were diagnosed with an adrenal tumor at a median age of 59 years (range, 18-91 years), 373 (53%) patients were women, and the vast majority were white (n=631 [90%]) (Table 1).

Overall, 215 (31.0%) patients were found to have a malignant adrenal mass (13.0% ACC and 18.0% other malignant tumors). Adrenocortical adenoma was diagnosed in 216 (30.6%) patients, PHEO in 158 (22.4%), and other benign adrenal tumors (myelolipoma, cyst, ganglioneuroma) in 116 (16.4%) patients. Patients with ACA and malignant tumors other than ACC were diagnosed at an older age than were patients with ACC, other benign tumors, and PHEO ($P<.001$) (Table 1). Adrenocortical adenoma, ACC, and PHEO were more commonly diagnosed in women, whereas other benign or malignant tumors were more frequently diagnosed in men. No patient with ACC had bilateral adrenal disease, but 30% of patients with other malignant tumors presented with bilateral disease (Table 1). Adrenocortical carcinomas had the largest median tumor size (10.9 cm [range, 4.0-24.4 cm]), followed by benign tumors other than ACA (6.9 cm [4.0-20.0 cm]), malignant tumors other than ACC (5.4 cm [4.0-18.6 cm]), PHEO (5.2 cm [4.0-20.0 cm]), and ACA (4.5 cm [4.0-17.0 cm]) ($P<.001$). Compared with benign tumors, malignant tumors were less frequently

TABLE 2. Accuracy of Tumor Size and Unenhanced CT Attenuation for the Diagnosis of a Malignant Adrenal Mass[a,b]

Tumor size/unenhanced CT attenuation	No.	Sensitivity	Specificity	PPV	NPV
Tumor size ≥6 cm	547	61%	71%	57%	74%
Unenhanced CT attenuation ≥10 HU	297	100%	46%	44%	100%
Unenhanced CT attenuation ≥20 HU	297	98%	64%	54%	98.5%

[a]CT = computed tomography; HU = Hounsfield units; NPV = negative predictive value; PPV = positive predictive value.
[b]Pheochromocytomas were excluded from this analysis.

TABLE 3. Clinical Presentation of Patients With Large Adrenal Tumors Based on Surgical or Conservative Management[a,b]

Variable	Adrenalectomy	Conservative management	P value[c]
No. (%)	457 (65)	248 (35)	
Sex: female, No. (%)	26 (57)	111 (45)	.001
Age at diagnosis (y), median (range)	55 (18-87)	64 (18-91)	<.001
Mode of discovery, No. (%)			<.001
Incidental	290 (63)	182 (73)	
Hormone excess	95 (21)	12 (5)	
Cancer staging	30 (7)	31 (13)	
Other[d]	42 (9)	23 (9)	
Evaluated by endocrinologist: yes, No. (%)	392 (86)	170 (69)	<.001
Diagnosis, No. (%)			<.001
Adenoma	118 (55)	98 (45)	
Pheochromocytoma	155 (98)	3 (2)	
Other malignant	50 (39)	77 (61)	
Other benign	57 (49)	59 (51)	
ACC	77 (88)	11 (12)	
Adrenal mass diameter (cm), median (range)	5.5 (4-24.4)	5 (4-15.3)	<.001
Bilateral, No. (%)	44 (10)	60 (24)	<.001

[a]ACC = adrenocortical carcinoma.
[b]Range was defined as minimum to maximum value.
[c]Indicates statistical significance.
[d]Other: mass effect and B symptoms.

TABLE 4. Demographic Characteristics and Clinical, Imaging, and Biochemical Presentation of Patients With Large Adenomas[a,b]

Variable	All adenomas	Adrenalectomy	Conservative management	*P* value (adrenalectomy vs conservative)
No. (%)	216	118 (55)	98 (45)	
Sex: female, No. (%)	134 (62)	78 (66)	56 (57)	.18
Age at diagnosis (y), median (range)	61 (25 to 91)	58 (25 to 87)	63 (28 to 91)	.003[c]
Mode of discovery, No. (%)				.22
Incidental	184 (85)	102 (86)	82 (84)	
Hormone excess	18 (8)	12 (10)	6 (6)	
Other[d]	14 (7)	4 (4)	10 (10)	
Evaluated by endocrinologist: yes, No. (%)	181 (84)	103 (87)	78 (80)	.13
Location, No. (%)				.08
Right	81 (38)	48 (40)	33 (34)	
Left	96 (44)	55 (47)	41 (42)	
Bilateral	39 (18)	15 (13)	24 (24)	
Adrenal mass diameter (cm), median (range)	4.5 (4 to 17)	4.8 (4 to 17)	4.4 (4 to 11.8)	.04[c]
Unenhanced CT attenuation (HU), median (range)	Available for 138 patients: 10.5 (−63.8 to 71.3)	Available for 69 patients: 14 (−64 to 71)	Available for 69 patients: 9 (−19 to 60)	.06
Unenhanced CT attenuation (HU category), No. (%)	Available for 138 patients:	Available for 69 patients:	Available for 69 patients:	.04[c]
≤10 HU	68 (49)	28 (41)	40 (58)	
>10 HU	70 (51)	41 (59)	29 (42)	
Hormonal excess, No. (%)				.002[c]
No hormonal excess	111 (51)	46 (39)	65 (66)	
Overt cortisol excess	11 (5)	9 (7.6)	2 (2)	
Mild cortisol excess	88 (41)	59 (50)	29 (30)	
Hyperaldosteronism	5 (2)	3 (2.5)	2 (2)	
Androgen excess	1 (0.5)	1 (0.9)	0 (0)	

[a]CT = computed tomography; HU = Hounsfield units.
[b]Range was defined as minimum to maximum value.
[c]Indicates statistical significance with *P* values <.05.
[d]Other: cancer staging, mass effect, and B symptoms.

diagnosed incidentally (45.5% vs 86.7%), were larger (7 cm [range, 4-24.4 cm] vs 5 cm [range, 4-20 cm]), and had higher unenhanced CT attenuation (34.5 HU [range, 14.1 to 75.5 HU] vs 11.5 HU [range, −110 to 71.3 HU]; *P*<.001). Unenhanced CT attenuation (>10 HU) had 100% sensitivity but only 46% specificity for detecting malignancy. An unenhanced CT attenuation cutoff of more than 20 HU had similar sensitivity but better specificity, albeit still low at 64% (Table 2).

Mode of Adrenal Mass Discovery

Regardless of tumor type, most adrenal masses were diagnosed incidentally (n=472 [67%]) (Table 1). Cross-sectional imaging obtained because of clinical and/or biochemical presentation with adrenal hormonal excess was the second most common mode of discovery for PHEO (39%), ACC (31%), and ACA (8%). Cancer staging/surveillance imaging was the second most frequent mode of discovery (38%) for malignant tumors other than ACC (Table 1).

Patients with incidentally discovered adrenal masses had lower rates of malignancy (21% vs 50%; *P*<.001), were older at the time of diagnosis (median, 60 years [range, 19-88 years] vs 54 years [range, 18-91 years]; *P*<.001), and presented with smaller tumors than did patients whose tumors were discovered because of symptoms or during cancer staging (median, 5.0 cm [range, 4.0-20.0 cm] vs 6.0 cm [range, 4.0-24.4 cm]; *P*<.001) (Supplemental Table 1, available online at http://mcpiqojournal.org/).

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TABLE 5. Multivariate Analysis—Predictors of a Malignant Adrenal Mass[a]

Any malignant mass				
	All patients[b] (n=547)		Only for patients with unenhanced HU measurements available[b] (n=297)	
Variable	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Sex (male vs female)	1.57 (1.04-2.37)	.03[c]	1.45 (0.72-2.95)	.29
Age at diagnosis (each decade increase)	1.2 (1.04-1.37)	.01[c]	1.08 (0.86-1.4)	.49
Mode of discovery (nonincidental vs incidental)	6.99 (4.5-10.99)	<.001[c]	5.92 (2.7-13.4)	<.001[c]
Adrenal mass size (each 1-cm increase)	1.2 (1.14-1.3)	<.001[c]	1.3 (1.17-1.48)	<.001[c]
Unenhanced CT attenuation (each 1-HU increase)			1.08 (1.06-1.1)	<.001[c]
Other malignancy				
	All patients[b] (n=547)		Only for patients with available work-up for adrenal glucocorticoid production[b] (n=393)	
Variable	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Sex (male vs female)	2.4 (1.5-3.9)	.002[c]	1.8 (0.95-3.4)	.07
Age at diagnosis (each decade increase)	1.45 (1.2-1.7)	<.001[c]	1.6 (1.3-2.1)	<.001[c]
Mode of discovery (nonincidental vs incidental)	7.8 (4.7-13)	<.001[c]	5.5 (2.8-11)	<.001[c]
Adrenal mass size (each 1-cm increase)	1.1 (0.98-1.15)	.17	0.9 (0.8-1)	.05[c]
Hypercortisolism (vs normal cortisol production)			0.2 (0.1-0.4)	<.001[c]
ACC				
	All patients[b] (n=547)		Only for patients with available work-up for adrenal glucocorticoid production[b] (n=393)	
Variable	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Sex (male vs female)	0.53 (0.29-0.95)	.03[c]	0.79 (0.37-1.6)	.52
Age at diagnosis (each decade increase)	0.83 (0.69-0.99)	.04[c]	0.83 (0.67-1.02)	.08[c]
Mode of discovery (nonincidental vs incidental)	2.48 (1.4-4.4)	.002[c]	2.9 (1.4-5.9)	.003[c]
Adrenal mass size (each 1-cm increase)	1.36 (1.27-1.47)	<.001[c]	1.5 (1.37-1.68)	<.001[c]
Hypercortisolism (vs normal cortisol production)			3.5 (1.7-7.6)	<.001[c]

[a]CT = computed tomography; HU = Hounsfield units.
[b]Pheochromocytomas were excluded from this analysis.
[c]Indicates statistical significance with *P* values <.05.

Adrenalectomy in Patients With Adrenal Tumors

Adrenalectomy was performed in 457 (65%) patients with large adrenal tumors. Adrenalectomy was performed in 88% of patients with ACC and 98% of patients with PHEO. The remainder of patients with ACC and PHEO chose nonsurgical or palliative care approaches because of poor functional status or incurable metastatic disease (Table 3). The rate of adrenalectomy was higher in patients with tumors of more than 6 cm in diameter, mainly due to a higher prevalence of ACCs and large myelolipomas (Supplemental Table 2, available online at http://mcpiqojournal.org/).

Just over half (55%) of patients with large adenomas were treated surgically (Table 4). In contrast to patients with large adenomas who were treated conservatively, patients with adenomas treated with adrenalectomy were younger (median, 58 years [range, 25-87 years] vs 63 years [range, 28-91 years]; *P*=.003), had slightly larger adrenal tumors (median, 4.8 cm [range, 4.0-17.0 cm] vs 4.4 cm [range, 4.0-11.8 cm]; *P*=.04), were more frequently diagnosed with hormonal excess (61% vs 34%; *P*=.002), and had a higher prevalence of indeterminate

imaging characteristics (tumor CT attenuation >10 HU in 59% vs 42% of patients; P=.04) (Table 4).

Features Associated With Malignant Adrenal Masses

To identify characteristics associated with malignancy, we performed a multivariate analysis of a cohort of patients after excluding PHEOs (n=547). Male sex (odds ratio [OR], 1.57 [95% CI, 1.04-2.37]), older age at diagnosis (OR, 1.2 for each decade increase [95% CI, 1.04-1.37]), nonincidental mode of discovery (OR, 6.99 [95% CI, 4.5-10.99]), and tumor size (OR, 1.2 for each 1-cm increase in size >4 cm [95% CI, 1.14-1.3]) were significant predictors of malignancy. Multivariate analysis of the subgroup of patients with available measurements of tumor attenuation on unenhanced CT (n=297) revealed that tumor CT attenuation (OR, 1.08 for each 1-HU increase [95% CI, 1.06-1.1]), tumor size (OR, 1.3 for each 1-cm increase in tumor size >4 cm [95% CI, 1.17-1.48]), and nonincidental mode of discovery (OR, 5.92 [95% CI, 2.7-13.4]) were statistically significant predictors of malignancy (Table 5).

Because patients with ACC present differently than patients with other malignant adrenal tumors, we performed a multivariate analysis of features predictive of ACC vs non-ACC. Female sex (OR, 0.53 for male vs female [0.29-0.95]), younger age of diagnosis (OR, 0.83 for each decade increase [0.69-0.99]), nonincidental mode of discovery (OR, 2.48 [1.4-4.4]), and size (OR, 1.36 for each 1-cm increase [1.27-1.47]) were significant predictors of ACC. A subgroup analysis of patients with available work-up for hypercortisolism (n=393) revealed that the presence of cortisol excess was a significant predictor of ACC (OR, 3.5 [1.7-7.6]; P<.001). In contrast, for patients with malignant tumors other than ACC, male sex (OR, 2.4 [1.5-3.9]) and older age at the time of diagnosis (OR, 1.45 [1.2-1.7]) were significant predictors of malignancy, whereas size was not (P=.17), likely reflecting earlier adrenal mass detection due to (P<.001) cancer staging/surveillance imaging (Table 5).

DISCUSSION

We found that patients with adrenal tumors of at least 4 cm in diameter represent a heterogeneous group with an overall malignancy rate of 31%. We found that older age at the time of discovery of an adrenal mass, male sex, nonincidental mode of discovery, larger tumor size, and indeterminate imaging characteristics are predictors of a malignant adrenal mass. However, there are important differences in presentation and risk factors for ACC vs other malignant tumors, most notably sex (64% vs 35% women), age at diagnosis (median of 50 vs 66 years), and the presence of bilateral adrenal tumors (0% vs 30%). Although the absence of adrenal hormonal excess does not exclude ACC, the presence of hypercortisolism is strongly indicative of ACC over other malignant adrenal masses. Active extraadrenal malignancy is an important factor because more than a third of malignant adrenal lesions other than ACC were metastases discovered during cancer staging imaging for an extraadrenal primary malignancy.

Larger tumor size has previously been reported to be associated with malignancy. In a multicenter survey of 1096 patients with incidentally discovered adrenal tumors, a tumor size threshold of at least 4 cm distinguished ACC from benign adrenal tumors with a sensitivity of 93% but a specificity of only 42%.[7] In concordance with our findings, using a higher threshold of at least 6 cm resulted in a higher specificity (73%) but a lower sensitivity (74%).[7] The reason for suboptimal accuracy of size alone as a predictor of malignancy is the high rate of ACAs and other benign tumors among adrenal tumors of at least 4 cm in diameter (false-positives). Furthermore, adrenal metastases are usually detected during imaging for cancer staging, before clinically significant growth occurs (false-negatives).

Of all adrenal tumors evaluated during the study period, we found that the prevalence of adrenal tumors of at least 4 cm in diameter was 17%. In a multicenter Italian study of adrenal incidentalomas published in 2000, at least one-third of patients had adrenal tumors of at least 4 cm in diameter.[20] Higher frequency of imaging and improved quality of cross-sectional imaging could explain the significantly lower prevalence in our study and the even lower frequencies reported in another study.[2]

In our study, we found that all malignant adrenal tumors demonstrated an unenhanced CT attenuation of more than 10 HU (100% sensitivity). However, approximately only half of benign adrenal tumors had tumor CT

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attenuation of less than 10 HU (46% specificity). An unenhanced CT attenuation threshold of at least 20 HU had similar sensitivity of 98% but slightly higher specificity (64%) for malignancy. In a recent systematic review on the accuracy of imaging characteristics for the diagnosis of a malignant adrenal mass, an unenhanced CT attenuation threshold of at least 10 HU demonstrated a high sensitivity but a low specificity.[3] A study on surgical series of consecutive patients with adrenal tumors of any size demonstrated similar findings of noncontrast CT attenuation cutoffs of both 10 and 20 HU in the diagnosis of "nonadenomas."[21]

Pheochromocytomas were diagnosed in 22% of our cohort patients, with approximately half being discovered incidentally (54%). Thus, it is essential to biochemically exclude PHEO, especially in an adrenal mass with indeterminate imaging characteristics. The prevalence of PHEO in patients with incidentally discovered adrenal tumors of any size was previously reported to be 4.2%.[7] Other data derived from surgical series are difficult to compare with our cohort of patients, especially considering the differences in tumor size cutoff.[7,20] In our cohort, all 158 PHEOs with available unenhanced CT images demonstrated attenuation of more than 10 HU. This finding is consistent with another study,[21] in which the mean unenhanced HU was 38.6±8.2 and all 63 PHEOs demonstrated unenhanced CT attenuation of more than 10 HU. On the basis of our findings, we conclude that when a homogeneous adrenal mass of more than 4 cm in diameter has an unenhanced CT attenuation of less than 10 HU, biochemical testing for PHEO is not needed.

Adrenocortical adenomas were found in 31% of our cohort patients. Most patients with ACAs were discovered incidentally (85%); however, half of the patients demonstrated biochemical evidence of adrenal hormonal excess. In patients with functioning adrenal tumors, overt and mild cortisol excess were most common, whereas primary aldosteronism was documented in only 5 patients. Almost half of the patients with nonfunctioning adenomas were treated surgically. In concordance with our findings, a surgical series[9] of patients with adrenal tumors reported that 52% to 75% of patients undergoing adrenalectomy were diagnosed with a nonfunctioning adrenal tumor. Therefore, it is likely that many patients undergo an adrenalectomy unnecessarily. The decision to proceed with adrenalectomy likely reflects the uncertainty of diagnostic evaluation due to suboptimal accuracy of available imaging tests and the concern for malignancy due to size and/or tumor attenuation. A new diagnostic modality expected to be introduced into clinical practice soon is urine steroid metabolomics; this test has demonstrated 90% sensitivity and specificity in a proof-of-concept study,[26,27] with prospective validation underway.

Strengths and Limitations

This is a large study addressing a population of patients with large adrenal tumors, which to date has not been well characterized. The retrospective nature meant that not all variables were available for all patients, which also reflects the heterogeneity in the management of patients with large adrenal tumors. Enrollment of all consecutive patients with large adrenal tumors over a 15-year period allowed for a thorough study of patients who were managed medically. Although this is a single-institution referral center and our study may overestimate the prevalence of malignant adrenal tumors, it is reflective of the current standard of care to refer such patients to a center with adrenal expertise. In addition, a subgroup analysis of incidentally discovered large adrenal tumors is likely generalizable to other institutions.

Clinical Implications

It is important to note that in a third of the patients with malignant adrenal tumors, the diagnostic evaluation and management differed on the basis of etiology. We recommend that the management of patients with large adrenal tumors should be individualized to the patient's circumstances and presentation, taking into account patient age, sex, mode of discovery, imaging phenotype including unenhanced CT tumor attenuation, rate of tumor growth and size, hormonal activity, and comorbidities. An active or previously diagnosed extraadrenal malignancy should raise the suspicion for metastases.

In our cohort of patients with large adrenal tumors, we have observed that all ACCs, malignant

tumors other than ACCs, and PHEOs of at least 4 cm demonstrated unenhanced CT attenuation of more than 10 HU. Therefore, in homogeneous adrenal tumors with unenhanced CT attenuation of less than 10 HU, additional diagnostic tests to establish the diagnosis of malignancy or PHEO are unnecessary given the low likelihood of their presence. In contrast, when unenhanced CT attenuation is more than 10 HU in large adrenal tumors, further diagnostic tests and adrenalectomy need to be considered.

CONCLUSION

Large adrenal tumors are most frequently diagnosed incidentally and encompass a heterogeneous group. Tumor size alone is not a reliable determinant of malignancy. The overall prevalence of malignancy in patients with adrenal tumors of at least 4 cm in diameter was 31%. Risk of malignancy was associated with age at diagnosis, male sex, nonincidental mode of discovery, larger tumor size, and indeterminate imaging characteristics. All ACCs, PHEOs, and malignant adrenal tumors other than ACC demonstrated unenhanced CT attenuation of more than 10 HU, which supports the concept that malignancy and PHEO can be excluded with certainty in patients with adrenal tumors with unenhanced CT attenuation of less than 10 HU. We suggest that clinical context, hormonal assessment, and image phenotype can together determine the need for adrenalectomy in patients with adrenal tumors of at least 4 cm in diameter. Patients with large adrenal tumors should be managed by an expert multidisciplinary team that includes endocrinologists, radiologists, and adrenal surgeons.

Abbreviations and Acronyms: **ACA** = adrenocortical adenoma; **ACC** = adrenocortical carcinoma; **CT** = computed tomography; **HU** = Hounsfield units; **OR** = odds ratio; **PHEO** = pheochromocytoma

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