Original Article

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The Significance of Hounsfield Unit and Tumor Diameter in the Differentiation of Malignant and Benign Adrenal Masses

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Abstract

Aim: The Hounsfield unit (HU) used in non-contrast computed tomography (CT) imaging can predict adrenal masses. In the literature, a HU measurement of >10 on non-contrast CT has been reported to have a wide range of sensitivity (33-72%) in detecting malignancy in patients with adrenal masses, and the size of malignant masses is >4 cm in approximately 90% of cases. The current study investigated the role of the HU value and tumor diameter measured on preoperative CT imaging in the differentiation of benign and malignant masses.

Methods: Data analysis was conducted on patients undergoing adrenalectomy for adrenal masses at two different tertiary care centers between January 1, 2019 and January 1, 2023. Patients who underwent an adrenalectomy non-contrast CT scans were assessed for HU and tumor size. The patients were divided into two groups according to histopathologically confirmed benign or malignant masses. Statistical analysis, including receiver operating characteristic curve assessment, was performed to evaluate the diagnostic accuracy.

Results: The study included 108 patients, of whom 66.7% (n=72) were female and 33.3% (n=36) were male. The mean age was 51.01±14.01 years. The laparoscopic technique was used in 72 patients, the robotic technique in 17, and the open technique in 19. The mean length of hospital stay was 4 (2-37) days. The mean tumor size was 55 (10-230) mm. The mean operative time was 80 (50-180) minutes. The mean amount of intraoperative blood loss was 40 (20-300) milliliters. The surgical method, tumor diameter, operative time, amount of intraoperative blood loss, and HU value of the mass statistically significantly differed between the groups (p<0.001). We found that the cut-off values of HU and tumor diameter for distinguishing malignant masses from benign masses were 30.5 and 72.5 mm, respectively. At a cut-off value of 30.5 or above, HU had a sensitivity of 100% and a specificity of 81.6% in identifying malignant masses, whereas a sensitivity of 100% and a specificity of 88.7% were determined for malignant masses with a tumor size of 72.5 mm or above.

Conclusion: The HU value and tumor diameter were crucial for distinguishing between benign and malignant adrenal masses, enhancing diagnostic accuracy, and informing treatment decisions.

Keywords: Adrenal mass, Hounsdield unit, diameter of tumor

Introduction

Although adrenal masses are not very common in clinical practice, their prevalence increases with age, reaching 10% at the age of 70 years (1,2). On the other hand, benign adrenal masses are common, with a prevalence of 2-9% depending on the population (3). Malignant adrenal masses represent rare cancers, with an annual incidence estimated to vary between 0.5 and 2/1,000,000 cases (4,5). Approximately 10-25% of malignant adrenal masses are diagnosed incidentally (6-8). The major difficulty in diagnosis is identifying whether the lesion is benign or malignant. In the diagnostic

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evaluation of patients with adrenal masses, there are two important issues: the evaluation of hormonal activity and the determination of the possibility of malignancy (9).

Evaluation of hormonal status in adrenal masses is an important step in guiding the decision to excise the mass. Therefore, the measurement of hormones and hormone metabolites in the blood and urine has diagnostic value. In hormone-active cases, treatment is mostly surgery. The presence or suspicion of malignancy is another surgical indication. Many diagnostic imaging methods have been used to evaluate the malignant status of adrenal masses. However, despite the availability of these methods, the negative excision rate is not yet zero. Non-contrast computed tomography (CT) imaging can evaluate the condition based on the lipid content of the adrenal mass, which forms the basis for the evaluation of malignancy. The Hounsfield unit (HU) is a relative quantitative measurement of radio intensity used by radiologists in the interpretation of CT images. The absorption/attenuation coefficient of radiation within a tissue is used to create a grayscale image during CT reconstruction. HU, also known as the CT unit, is calculated based on the linear transformation of the fundamental linear attenuation coefficient of the X-ray beam (10-12). Early studies showed that HU depended on various CT parameters (13). However, the standardization of these parameters is necessary to ensure that HU becomes a reliable diagnostic measurement tool (14). HU is specific for lipid-rich lesions; therefore, it has a high specificity for adenomas (15). Nevertheless, certain benign masses poor in lipids may be misdiagnosed with the use of HU (16). Accurate diagnosis and appropriate treatment are crucial for preventing unnecessary adrenalectomies, which occur in more than 40% of cases. In a previous study, it was suggested that a tumor diameter of 4 cm and HU of 20 on non-contrast CT could have diagnostic value for malignant adrenal masses (17).

This study aimed to investigate the role of tumor diameter and HU values measured on CT in differentiating malignant and benign masses by retrospectively examining the data of patients who underwent adrenalectomy.

Methods

Compliance with Ethical Standards

The study was initiated after receiving approval from the University of Health Sciences Turkey, Antalya Training and Research Hospital, Clinical Research Ethics Committee (approval no.: 16/21, date: November 23, 2023) and administrative approval from our institution. The data of patients who underwent surgery for adrenal masses at two different tertiary care centers from January 1, 2019, to January 1, 2023 were retrospectively screened.

Study Design

Patients who underwent adrenalectomy and had adrenal masses proven to be benign or malignant by histopathology were included in the study. Our study includes data from patients who underwent adrenalectomy at two centers between January 1, 2019 and January 1, 2023. Nevertheless, patients with metastatic masses, those receiving intensive care, and those aged 18 years were excluded from the study. Further excluded from the study were patients with additional malignancies, pregnant and breastfeeding women, and patients with a current or recent (<6 months) history of taking drugs known to alter steroid synthesis or metabolism. All demographic and clinical data, including sex, age, surgical procedure, and postoperative outcomes, were obtained from the institutional database. All patients were screened in terms of 24 h urine metanephrine, normetanephrine, pheochromocytoma, and hypercortisolism (1 mg dexamethasone test and adrenocorticotropic hormone test). Hypertensive patients were additionally screened for excess aldosterone production (aldosterone-to-renin ratio and 24-hour urinary aldosterone). CT findings were re-evaluated by a radiologist. The size of the adrenal gland masses was measured. To determine the HU values, a circular area was placed on the adrenal mass, and the average value was recorded. The longest diameter of the adrenal mass was measured on an image showing the maximum cross-sectional area.

A total of 119 patients were evaluated. Eight patients under 18 years of age and three patients who died in the intensive care unit were excluded from the study. The sample consisted of 108 patients. The patients were divided into two groups: benign and malignant.

Statistical Analysis

The normality of the distribution of the data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Parametric data are expressed as mean ± standard deviation, and non-parametric data as median (minimum-maximum). The independent samples t-test was used to compare parametric data, whereas the Mann-Whitney U test was used to compare non-parametric data. A chi-square or Fisher's exact test was used to analyze categorical data. The optimal cut-off values of the predictive factors were determined using receiver operating characteristic (ROC) curves. In the ROC analysis, the value with the highest sensitivity and specificity was deemed the cut-off value.

Results

Patients' Demographic Characteristics

The mean age of the patients was 51.01±14.01 years. Thirty-six (33.3%) patients were male, and 72 (66.7%) were female. The pathology result was benign in 98 (90.7%) patients (benign adrenal adenoma in 49.1%, benign pheochromocytoma in 17.6%, benign myelolipoma in 9.3%, and other benign pathologies in 14.7%) and malignant in 10 (9.3%) patients (malignant pheochromocytoma in two and malignant adrenocortical carcinoma in eight). Right adrenalectomy was performed on 54 (50%) patients, open adrenalectomy on 19 (17.6%), laparoscopic adrenalectomy on 72 (66.7%), and robotic adrenalectomy on 17 (15.7%). While 55 (50.9%) patients had no comorbidities, nine (8.3%) patients had Cushing's syndrome, 21 (19.4%) had hypertension, 14 (13%) had diabetes mellitus, and nine (8.4%) had multiple comorbidities (diabetes mellitus, hypertension, and chronic renal failure). The mean length of hospital stay was 4 (2-37) days. The mean tumor size was 55 (10-230) mm. The mean operative time was 80 (50-180) minutes. The mean amount of intraoperative blood loss was 40 (20-300) milliliters. The laboratory data of the patients is shown in Table 1.

Radiological Evaluation

In the non-contrast abdominal CT sections of the cases in which a mass was detected in the adrenal gland, a region of interest (ROI) was placed in the most homogeneous area of the lesion in the gland, and density (HU) measurements were performed by placing a ROI in the middle portion of the spleen (Figures 1, 2). Preoperative CT images were evaluated by a specialist radiologist (HP). Tumor size was defined as the maximum axial plane diameter. Hounsfield units were measured from non-contrast images by placing a single circular ROI over the tumor. The ROI covered the largest possible area of the tumor plane while avoiding necrosis, hemorrhage, and calcifications.

Group Comparisons

When comparing the groups, no statistically significant differences were found in age, sex, tumor side, presence of comorbidities, glucose, potassium, neutrophil count, lymphocyte count, or length of hospital stay (p>0.05). Although the neutrophil-to-lymphocyte ratio, which is known to be a link between inflammation and cancer, was higher in the malignant group, the difference was not statistically significant (p>0.05). Surgical method, tumor diameter, operative time, amount of intraoperative blood loss, and the HU value of the mass significantly differed between the malignant and benign groups (p<0.05) (Table 2).

ROC Analysis of Variables

ROC curve analysis was performed for HU and tumor diameter to differentiate between benign and malignant masses. In this analysis, the area under the curve value of HU was found to be 0.863 [95% confidence interval (CI): 0.796-0.931] (p<0.001), and that of tumor diameter was 0.978 (95% CI: 0.950-1) (p<0.001) (Figure 3). The cut-off value was determined to be 30.5 mm for mass HU and 72.5 mm for tumor diameter. After dichotomizing the data according to these cut-off values, malignancy was identified in 10 of the 28 patients with a mass density >30.5 HU and in 10 of the 21 patients with a tumor diameter >72.5 mm. Upon combining the two cut-off values, all 10 patients with malignancy were observed to

Table 1. Demographic and laboratory data of the patients

Variables		n=108 (100%)
Age (years)		51.01±14.01
Sex	Male	36 (33.3%)
	Female	72 (66.7%)
Tumor side	Right	54 (50%)
	Left	54 (50%)
Surgery type	Open	19 (17.6%)
	Laparoscopic	72 (66.7%)
	Robotic	17 (15.7%)
Comorbidity	None	55 (50.9%)
	Cushing's syndrome	9 (8.3%)
	HT	21 (19.4%)
	DM	14 (13%)
	DM + HT/CRF	9 (8.4%)
Pathology	Benign	98 (90.7%)
	Malign	10 (9.3%)
Tumor histology	Malignant pheochromocytoma	2 (1.9%)
	Malign adrenocortical carcinoma	8 (7.4%)
	Benign adrenal adenoma	53 (49.1%)
	Benign pheochromocytoma	19 (17.6%)
	Benign myelolipoma	10 (9.3%)
	Others	16 (14.7%)
Hospital stay (days)		4 (2-37)
Tumor diameter (mm)		55 (10-230)
Glucose (mL/dL)		106.5 (69-356)
K+		4.3±0.83
Lymphocyte count		1.9 (0.55-4.77)
Neutrophil count		5.64 (1.3-19.72)
NLR		2.27 (0.66-23.33)
Operative time (min)		80 (50-180)
Blood loss (mL)		40 (20-300)
Mass HU		16.37 (-95.36-85)
Spleen HU		48.99 (20.14-140)

K+: Potassium, DM: Diabetes mellitus, HT: Hypertension, CRF: Chronic renal failure, NLR: Neutrophil-to-lymphocyte ratio, HU: Hounsfield unit

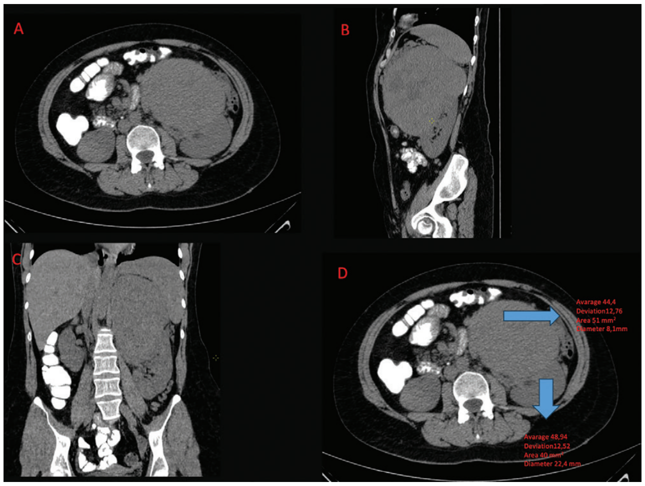

Figure 1. The diagnostic assessment of a malign lesion located in the left adrenal gland is supported by axial (A), sagittal (B), and coronal (C) plane images. Additionally, measurements of Hounsfield units from both the adrenal lesion and the spleen are provided in the axial section (D)

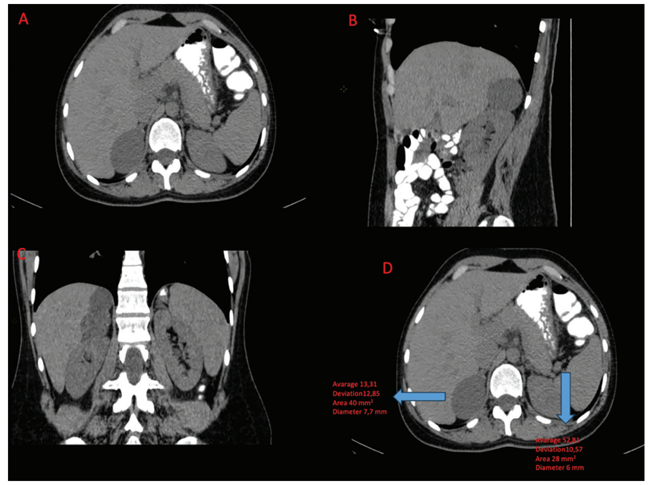

Figure 2. The diagnostic assessment of a benign lesion located in the right adrenal gland is supported by axial (A), sagittal (B), and coronal (C) plane images. Additionally, measurements of Hounsfield units from both the adrenal lesion and the spleen are provided in the axial section (D)

Table 2. Comparison of groups in terms of demographic and laboratory data

Variables		**Benign group (n=98)**	**Malignant group (n=10)**	**p-value**
Age (years)		51.32±13.53	48±18.81	0.479
Sex	Male	35	1	0.160
	Female	63	9	
Tumor side	Right	50	4	0.507
	Left	48	6	
Surgery type	Open	10	9	**<0.001**
	Laparoscopic	71	1	
	Robotic	17	0	
Comorbidity	None	50	5	0.833
	Cushing's syndrome	9	0	
	HT	19	2	
	DM	12	2	
	DM + HT/CRF	8	1	
Tumor diameter (mm)		50 (10-140)	140 (75-230)	**<0.001**
Glucose (mL/dL)		105.5 (69-356)	133.5 (95-326)	**0.040**
K+		4.3±0.56	4.33±0.82	0.902
Lymphocyte count		2 (0.55-4.77)	1.37 (0.92-3.5)	0.092
Neutrophil count		5.64 (1.3-19.72)	5.59 (3.2-10.64)	0.791
NLR		2.59 (0.66-23.33)	3.05 (1.71-9)	0.118
Operative time (min)		80 (50-140)	95 (90-180)	**<0.001**
Blood loss (mL)		40 (20-150)	85 (40-300)	**<0.001**
Hospital stay (days)		4 (2-37)	5.5 (2-15)	**0.049**
Mass HU		15.74 (-95.36-85)	38 (31-60.21)	**<0.001**
Spleen HU		47.72 (20.14-140)	67.5 (37-120)	**0.011**

K+: Potassium, DM: Diabetes mellitus, HT: Hypertension, CRF: Chronic renal failure, NLR: Neutrophil-to-lymphocyte ratio, HU: Hounsfield unit have a density of >30.5 HU and a diameter of >72.5 mm (Table 3). None of the patients with benign masses had a density >30.5 HU or a tumor diameter >72.5 mm.

Discussion

Imaging methods must be used to distinguish between malignant and benign lesions (18). However, adenomas often contain sufficient intracytoplasmic fat to produce lower attenuation values. Consequently, the density decreases with an increasing lipid mass ratio. Although the lipid ratio is high in benign cases, it is lower in malignant cases. In the literature, no cases of adrenal malignancies have been reported to have a density value of 0 HU. Cases with a density of 4-20 HU should raise strong suspicion (19). The size of the lesion and a history of cancer are important factors in determining whether the mass is benign. While the incidence of carcinoma is 2% in masses smaller than 4 cm, it reaches 6% in masses larger than 4-6 cm and 25% in those larger than 6 cm (20). According to various guidelines and recent publications, a small mass size and high lipid content (<4 cm size and <10 HU attenuation value) are considered markers of a benign lesion. Nevertheless, up to 30% of adrenal masses fail to satisfy well-established criteria for a benign lesion, and new approaches are needed. Recently, image-based texture analysis on CT has been employed to differentiate between benign and malignant tumors by obtaining quantitative parameters that can be useful for measuring the presence of necrosis, hemorrhage, calcification, and intracellular lipid content (20-22). It is considered that tissue analysis of adrenal masses on CT will obviate the need for contrast material injection in these patients, thereby reducing the risk of allergic reactions and negative effects on renal function (23,24).

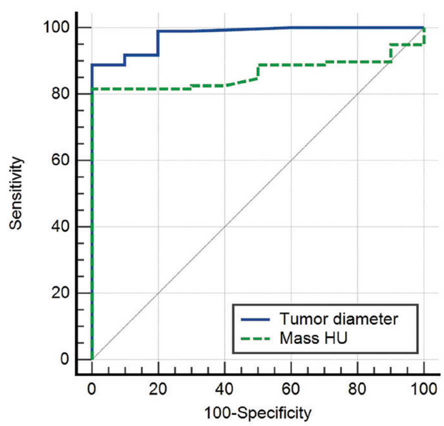

Figure 3. Results of receiver operating characteristic analysis of Hounsfield unit and tumor diameter for the differentiation of benign and malignant masses

HU: Hounsfield unit

The precise and effective characterization of adrenal masses using noninvasive imaging is a crucial element in the algorithm for assessing cancer or malignancy risk (15,25-28).

A German study concluded that a HU threshold greater than 21 provides the highest diagnostic accuracy for identifying adrenocortical carcinoma, with a sensitivity of 96% and a specificity of 80% in statistical tests (29). The radiological features of early, small adrenocortical carcinomas are rarely reported in the literature and can easily be overlooked (30) In the research conducted by Schloetelburg et al. (31), it was observed that more than 20% of benign lesions exhibited dimensions exceeding 4 cm, while over 45% of malignant lesions were measured to be less than 4 cm, including a mere 1.7 cm adrenocortical carcinoma.

In a comprehensive study conducted in Korea, ROC curve analysis was used to distinguish malignant lesions from benign lesions, and the optimal cut-off value of mass size was determined to be 3.4 cm (sensitivity: 100%; specificity: 95.0%), whereas that of pre-contrast HU was

Table 3. Characteristics of the data dichotomized according to cut-off values for malignant and benign masses

Variable			Benign group	Malignant group	
Mass HU	<30.5		80	0	Sensitivity: 100% Specificity: 81.6% PPV: 35.7% NPV: 100%
	≥30.5		18	10	
Tumor diameter	<72.5		87	0	Sensitivity: 100% Specificity: 88.7% PPV: 47.6 NPV: 100%
	≥72.5		11	10	
Mass HU and tumor diameter	<30.5	<72.5	69	0	
		≥72.5	11	0	
	≥30.5	<72.5	18	0	
		≥72.5	0	**10**	

HU: Hounsfield unit, PPV: Positive predictive value, NPV: Negative predictive value

19.9 HU (sensitivity: 100%; specificity: 67.4%). The authors suggested that a diameter of 3.4 cm and a density of 20 HU could be used for benign-malignant differentiation in patients with non-functional adrenal masses, regardless of the change in mass size (32).

Kostiainen et al. (33) found that on non-contrast CT, adrenal malignant tumors were >20 HU and the tumor diameter was 92 (20-196) mm, suggesting that malignancy could not be excluded only based on the small size of the tumor. In another study, Torresan et al. (34) reported the mean mass size to be 62.3 (±35.2) mm for adrenal carcinomas and 56.6 (±42.4) mm for adrenal adenomas, and the mean HU values to be 33.4 and 20.2, respectively. In other studies conducted to differentiate between benign and malignant masses, a cut-off value of 20 HU has been recommended (35,36).

Study Limitations

There were some limitations to this study. First, the retrospective design may introduce selection and information biases, affecting the generalizability of the findings. Second, the sample size is relatively small, which may limit the statistical power and robustness of the conclusions. Third, the study was conducted at only two centers, which may not represent broader clinical practices. In addition, in developing countries, malignant diseases may be delayed due to social reasons and differences in CT scanning protocols, which may affect the comparison of results. Variations in CT imaging protocols and radiological assessments could influence the consistency of HU measurements. Finally, due to the rarity of malignant adrenal masses, there is an inherent imbalance in the number of benign versus malignant cases, potentially skewing the results. Future prospective studies with larger, more diverse cohorts and standardized imaging protocols are necessary to validate these findings.

Conclusion

Parameters such as the HU value and tumor diameter can differentiate benign from malignant adrenal masses, thereby aiding in diagnosis and treatment. However, there is a need for prospective studies with higher patient volumes.

Ethics

Ethics Committee Approval: The study was initiated after receiving approval from the University of Health Sciences Turkey, Antalya Training and Research Hospital, Clinical Research Ethics Committee (approval no.: 16/21, date: November 23, 2023).

Informed Consent: The data of patients who underwent surgery for adrenal masses at two different tertiary care centers from January 1, 2019, to January 1, 2023 were retrospectively screened.

Authorship Contributions

Surgical and Medical Practices: H.O., M.Y., S.Y., Concept: H.O., A.S.A., Design: R.C.C., Data Collection or Processing: T.C.Y., R.C.C., M.Y., Analysis or Interpretation: R.C.C., S.C., M.Y., S.Y., Literature Search: H.O., O.C., A.S.A., Writing: H.O.

Conflict of Interest: No conflicts of interest were declared by the authors.

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