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The efficacy of volumetric computed tomography histogram analysis in adrenal masses

Mustafa Orhan Nalbant, Ercan İnci

Department of Radiology, Bakırkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, İstanbul, Turkey

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ABSTRACT

Aims: The rate of adrenal mass detection has increased due to the development of imaging modalities. It is vital to differentiate benign adrenal adenomas from other adrenal masses in order to establish whether an active management strategy is essential. Volumetric CT histogram analysis calculates the percentage of covered pixels in the negative attenuation region. The goal of this research was to evaluate the diagnostic utility of volume histogram analysis for adrenal tumors confirmed histopathologically as well as the ideal slice thickness for CT histogram analysis to differentiate between benign and malignant lesions with a density greater than 10 Hounsfield units (HU).

Methods: The research analyzed the CT images of 127 individuals with 136 adrenal masses that were verified histopathologically after resection (57 lipid-poor adenomas, 21 pheochromocytomas, 47 metastases, and 11 adrenocortical carcinomas). For imaging, a 40-row MDCT device (Siemens Medical Solution, Erlanger, Germany) was utilized. 1 mm and 5 mm unenhanced CT images were obtained. Two separate radiologists manually assessed the Hounsfield units (HU) of the masses. The 5th to 95th percentiles of HU values, as well as the minimum, mean, and maximum values, skewness, kurtosis, and variance, were calculated. Interobserver agreement was determined by means of the interclass correlation coefficient (ICC).

Results: The HU parameters for the malignant group were all higher than those of the benign group, and the difference in the 5 mm slice thickness was more significant than the 1 mm slice thickness. The difference between HUmin (P=0.007), HUmean and HUmedian (P <0.001), 5th to 50th (P <0.001), 75th (P=0.004), 90th (P=0.016), and 95th (P=0.049) percentiles was statistically significant. The malignant group had higher skewness and kurtosis than the benign group, while the benign group had higher variance. Statistically, the disparity between the variances was significant (P=0.046). The area under the curve (AUC) of the 25th percentile of the HU value was the highest (AUC=0.932; cut-off value=15; sensitivity=90.0%; specificity=85.7%).

Conclusion: Noninvasive volumetric CT histogram analysis can detect malignant adrenal masses from benign tumors before an operation. Histogram analysis benefits from thicker slices. HUmin, HUmean, HUmedian, percentile values, and variance can identify adrenal masses.

Keywords: Adenoma, adrenal mass, computed tomography, histogram analysis, pheochromocytoma

INTRODUCTION

As imaging techniques have advanced, the rate of adrenal mass identification has climbed to 10%.[1] It is important to distinguish adenomas from pheochromocytomas, carcinomas, and metastases to determine whether an active strategy for management is required.[2] A mean density greater than 10 Hounsfield units (HU) is a straightforward method for diagnosing about two-thirds of adenomas.[3-5] The others have a density greater than 10 HU in non-contrast CT images due to containing a small amount of intracellular lipid and should be regarded as indeterminate. This group of patients may also undergo computed tomography (CT) with percentage washout measurement,[6,7] chemical-shift MRI assessment,[8] and volumetric non-contrast histogram analysis.[9]

CT histogram analysis requires intracytoplasmic lipid concentrations below 0 HU. Histograms can show the attenuation values of each pixel in a region of interest over an adrenal adenoma. Negative and positive CT attenuation values are shown on the x-axis. Pixel frequency is on the y-axis. There is currently no consensus regarding the ideal CT monitoring criteria. One of the many adjusting factors is slice thickness, which increases CT image noise but improves clarity and spatial resolution.

This study aimed to determine the value of volumetric CT histogram analysis for the diagnosis of adrenal tumors confirmed histologically after surgery as well as the optimal slice thickness for CT histogram analysis to distinguish between benign (lipid-poor adenomas and pheochromocytomas) and malignant (adrenal

Corresponding Author: Mustafa Orhan Nalbant, musnalbant88@hotmail.com

carcinomas and metastases) masses with an unenhanced attenuation of greater than 10 HU.

METHODS

This retrospective study was carried out with the permission of University of Health Sciences, Bakırkoy Dr. Sadi Konuk Training and Research Hospital. Ethics Committee (Date: 09.01.2023, Decision No: 2023/06). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Study Population

We analyzed the patients for those who required operations at our facility between June 2015 and November 2022. These were the inclusion criteria for the research: (a) patients diagnosed postoperatively; (b) patients who underwent an unenhanced CT scan prior to surgery; (c) patients with histologically confirmed adrenal adenoma, pheochromocytoma, adrenal carcinomas, and metastases. CT scans were conducted to obtain contrast-enhanced series along with non-contrast series for the purpose of excluding alternative pathologies.

The database included a total of 361 patients. The exclusion criteria are summarized in **Table 1**. Lastly, 127 patients with 136 lesions were analyzed. The research group consisted of 49 men and 78 women. In 69 cases, the lesions were on the left side; in 49 cases, on the right side; and in nine patients, on both sides. There were 57 lipid-poor adenomas, 21 benign pheochromocytomas, 47 metastases, and 11 carcinomas in the study cohort.

CT Examination

Using a 40-row MDCT scanner, the images were obtained (Siemens Medical Solution, Erlanger, Germany). The imaging was performed utilizing a variety of protocols with standard settings. In a supine position, a standard CT protocol for the abdomen was executed with. The effective mAs was regulated by Siemens' "CARE dose" at 120 kV. The rotational speed of the gantry was 0.5 seconds, the collimation was 1 millimeter, and the pitch was 1.2. Individually adjusting the field of view (FOV) to encompass the body, and the matrix was 512 x 512. Image thickness of 5 mm was used for multiplanar reconstruction.

Image Analysis

The unprocessed CT raw data were transferred from the picture archiving and communication system (PACS) to a personal computer and analyzed with the open-source LIFEx 7.2.0 voxel tool (https://lifesoft.org). All images were separately evaluated by two radiologists, who were blind to the medical data and histologic results and had 11 and 8 years of abdominal imaging experience, respectively. In each segment, they manually drew the ROI encompassing the lesion (**Figure 1**). Each ROI was automatically combined into a volumetric ROI comprising voxel data for the entire tumor. Then, a volumetric HU map was created. The 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of HU values were determined, along with the minimum, mean, and maximum values, as well as the skewness, kurtosis, and variance. The area under the curve (AUC) was calculated for all parameters. The nth percentile was the point on the histogram where n percent of the voxel values were detected on the left. Positive skewness reflects the deviation of the distribution's median from its mean value. Kurtosis represents the peakiness of the histogram distribution, with high kurtosis characterized by a noticeable peak near the mean, a quick drop, and heavy tails.

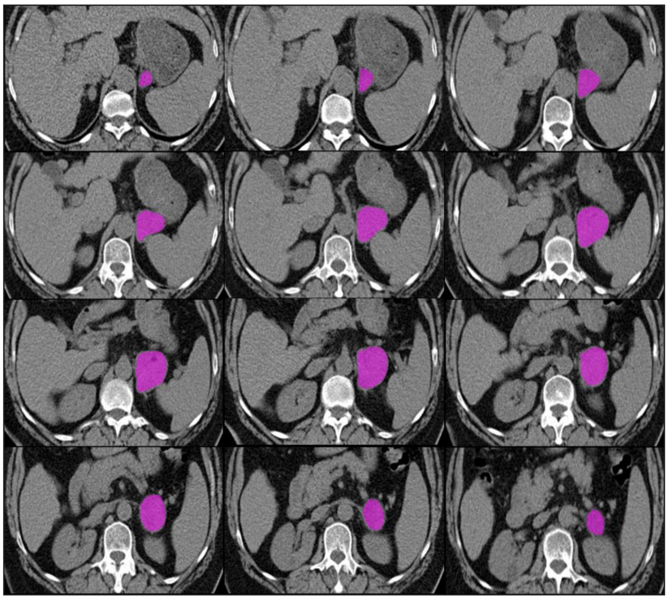

Figure 1. An example of volumetric CT histogram analysis. The whole lesion was manually evaluated as an area of interest (ROI) in each slice of the unenhanced CT images.

Statistical Analysis

IBM SPSS 25.0 was utilized to conduct the analysis (Chicago, IL, United States). From the data set obtained by combining the HU values of each patient, histograms of the groups were generated. Histograms revealed a difference in the distribution of all patient measurements. Using these measurements, statistical values such as minimum, median, mean, maximum, standard deviation, skewness, kurtosis, and percentiles were computed for each patient group, and the variations in the resulting descriptive statistics were depicted graphically. These group statistics were computed for individuals. Using the t-test for independent samples, it was determined whether these statistics derived from individuals differed between groups. On the basis of individual data, receiver operating characteristic (ROC) curves were generated, and the threshold value for the obtained statistics was computed. Sensitivity and specificity values for threshold values were calculated.

RESULTS

Demographic Information

A total of 75 cases with 78 adrenal masses (57 lipid-poor adenomas and 21 pheochromocytomas) were enrolled in the benign group (**Figures 2** and **3**), and 52 cases with 58 adrenal masses (47 metastases and 11 adrenocortical carcinomas) were included in the malignant group (**Figure 4**). In total, 49 men and 78 women, with a mean age of 55.44±12.14 years, were included in the study. The percentage of women in the benign group was higher than in the malignant group (p=0.010). The mean age of the patients in the malignant group was higher than that in the benign group (p=0.014) (**Table 1**).

Table 1. Data of the patients excluded from the study

Patients Excluded From the Study	**n**
Patients without an unenhanced CT scan	77
Patients whose unenhanced CT image was compatible with an adenoma	114
Poor image quality	12
Patients with direct adrenal gland infiltration by renal cell carcinomas	4
Pathologically confirmed other than adrenal adenoma, pheochromocytoma, and malignancies	
Myelolipoma	14
Granulomatous disease	5
Abscess	3
Hemangioma	1
Ganglioneuroma	1
Patients with malignant pheochromocytoma	3

CT: computed tomography

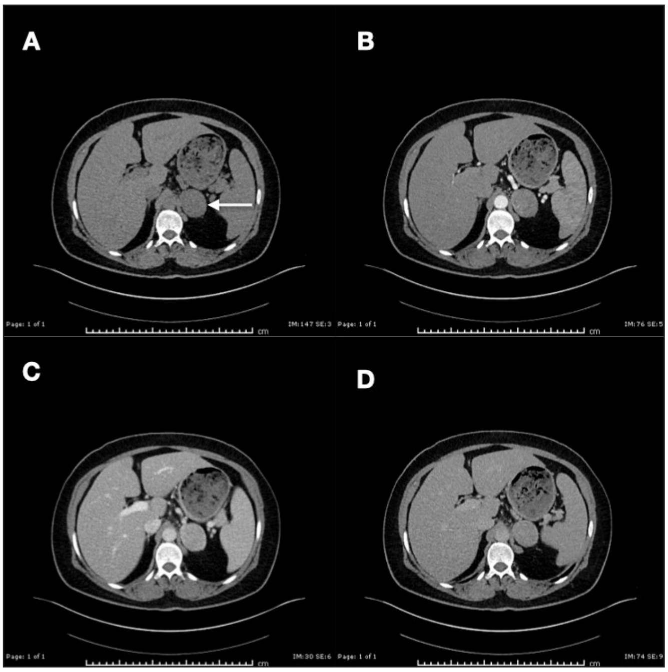

Figure 2. Lipid-poor adenoma in a 39-year-old male patient. On unenhanced CT images, a hyperdense mass was detected in the left adrenal gland (white arrow) (a). The contrast-enhanced series displayed substantial enhancement (b–d).

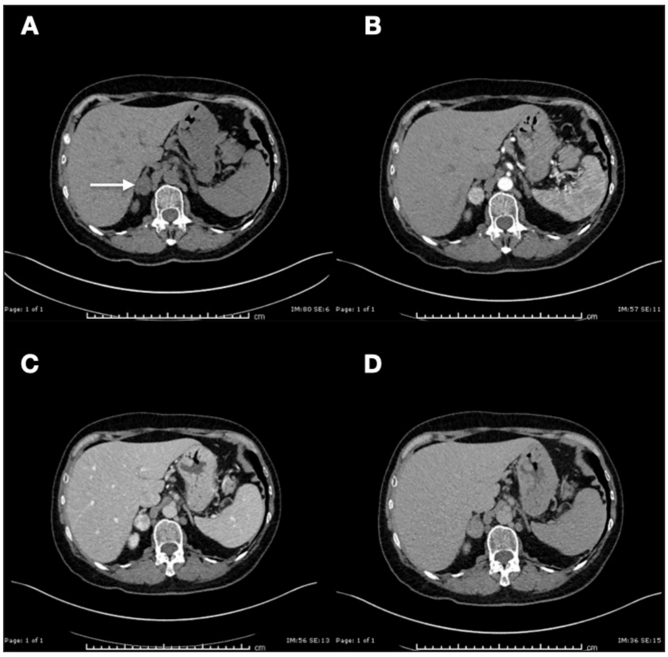

Figure 3. Pheochromocytoma in a 42-year-old female patient. A heterogeneous hyperdense mass was observed in the right adrenal gland (white arrow) on unenhanced CT images (a). In the contrast-enhanced series, the early phase (b,c) shows rapid enhancement of the mass and wash-out in the delayed phase (d).

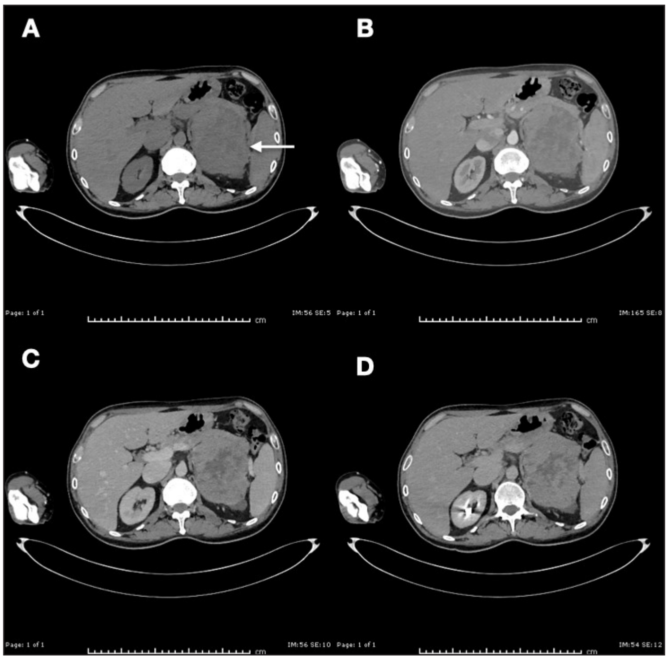

Figure 4. Adrenocortical carcinoma in a 54-year-old female patient. A massive heterogeneous hyperdense mass was observed in the left adrenal gland (white arrow) on unenhanced CT images (a). Heterogeneous progressive enhancement was seen in the contrast-enhanced series (b–d).

Interobserver Agreement

Using the interclass correlation coefficient (ICC), the agreement between the observers was assessed. The ICCs for each parameter exceeded 0.80, showing almost perfect agreement.

Results and Diagnostic Performance of CT Histogram Parameters **Figures 5** and **6** display the histogram curves pertaining to the benign and malignant groups. HUmin, HUmean, HUmedian, HUmax, 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles were all higher for the malignant group than for the benign group. The difference in the 5 mm slice thickness was more substantial than the 1 mm slice thickness (**Tables 2** and **3**). There was a significant difference in HU values between HUmin (p=0.007), HUmean (p <0.001), HUmedian (p <0.001), 5th (p <0.001), 10th (p <0.001), 25th (p <0.001), 50th (p <0.001), 75th (p=0.004), 90th (p=0.016), and 95th (p=0.049) percentiles in the 5 mm slice thickness (**Table 3**).

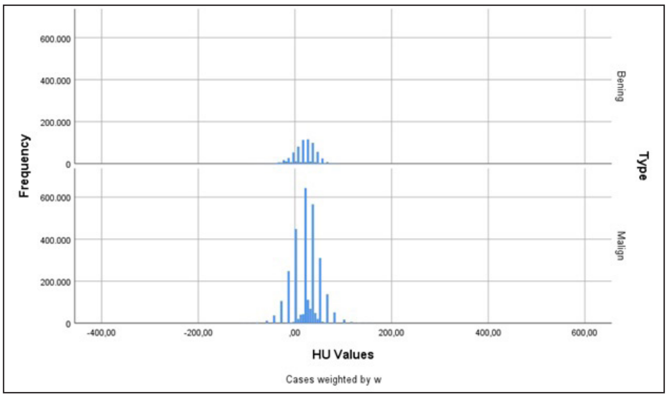

Figure 5. The histogram curve depicting the distribution of data for both the benign and malignant groups was generated based on a section thickness of 1 mm.

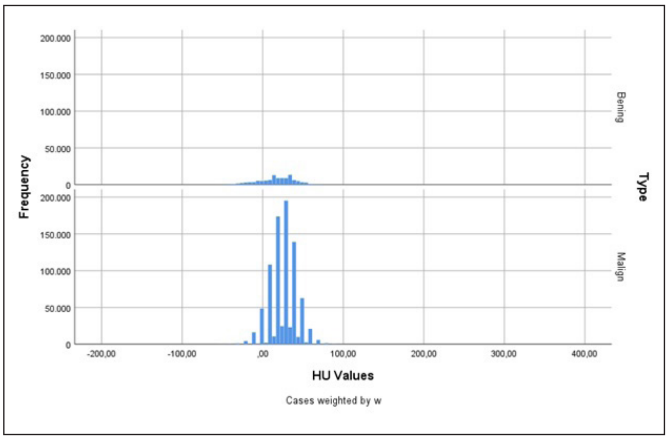

Figure 6. The histogram curve depicting the distribution of data for both the benign and malignant groups was generated based on a section thickness of 5 mm.

Table 2. Demographic data of patients

		Bening	Malign	p
		n (%) / mean±s.d.	n (%) / mean±s.d.	
Age		53.19±13.10	58.69±10.76	0.014a
Sex	Male Female	22 (29.3) 53 (70.7)	27 (51.9) 25 (48.1)	0.010b

aMann Whitney U Test; bChi-squared test

Table 3. Comparisons of HU histogram parameters between benign and malignant adrenal masses in 1 mm slice thickness

HU	Malignant	Bening	Total	p	Significance Level
Mean	29.07±6.98	8.86±16.62	17.28±16.7	0.002	99%
Std. deviation	20.46±10.16	26.8±12.95	24.16±12.06	0.128	-
Median	29.0±7.48	9.21±16.83	17.46±16.77	0.003	99%
Minimum	-83.2±51.21	-131.86±55.14	-111.58±57.84	0.057	-
Maximum	152.5±158.34	146.21±105.54	148.83±126.95	0.930	-
Kurtosis	0.98±1.55	1.51±1.53	1.29±1.52	0.266	-
Skewness	-0.22±0.44	-0.18±0.35	-0.2±0.38	0.464	-
5th	-4.8±21.58	-34.36±25.61	-22.04±27.83	0.007	99%
10th	3.7±18.19	-24.0±22.53	-12.46±24.72	0.007	99%
25th	16.4±12.68	-8.43±18.66	1.92±20.4	0.003	99%
50th	29.0±7.48	9.21±16.83	17.46±16.77	0.003	99%
75th	41.6±6.1	26.36±20.04	32.71±17.34	0.037	95%
90th	53.6±9.61	41.57±24.34	46.58±20.19	0.177	-
95th	62.0±13.76	52.07±28.79	56.21±23.82	0.278	-

HU, Hounsfield unit

Table 4. Comparisons of HU histogram parameters between benign and malignant adrenal masses in 5 mm slice thickness

HU	Malignant	Bening	Total	p	Significance Level
Mean	29.54±7.24	7.81±16.50	16.86±17.15	<0.001	99%
Std. deviation	15.77±6.81	20.15±6.06	18.32±6.61	0.046	95%
Median	30.8±7.07	8.5±16.21	17.79±17.15	<0.001	99%
Minimum	-46.3±36.7	-87.81±32.8	-70.46±39.63	0.007	99%
Maximum	113.6±97.55	86.07±42.34	97.54±70.21	0.837	-
Kurtosis	1.22±1.74	1.19±1.44	1.20±1.53	0.447	-
Skewness	-0.24±0.49	-0.34±0.42	-0.3±0.44	0.412	-
5th	4.1±15.91	-26.07±18.5	-13.5±22.88	<0.001	99%
10th	9.1±13.81	-17.0±17.4	-6.13±20.46	<0.001	99%
25th	20.3±9.74	-4.71±16.63	5.71±18.77	<0.001	99%
50th	30.8±7.07	8.5±16.21	17.79±17.15	<0.001	99%
75th	39.6±6.36	20.71±17.69	28.58±16.83	0.004	99%
90th	48.6±6.47	32.36±18.82	39.13±16.84	0.016	95%
95th	53.96±9.72	38.63±19.38	45.01±17.57	0.049	95%

HU, Hounsfield unit

The skewness and the kurtosis were larger in the malignant group as compared to the benign group; however, there was no statistically significant difference. The variance was higher in the benign group, and the difference was statistically significant (p=0.046) (**Table 3**).

The ROC curve indicated the effectiveness of HU histogram parameters in the diagnosis of adrenal masses (**Figure 7**), with the AUC of the 25th percentile of the HU value being the greatest (0.932). Under the cut-off value of 15, the sensitivity and specificity were, respectively, 90.0% and 85.7%. Following diagnostic effectiveness was the 5th percentile of the HU value (AUC=0.925). Below the threshold value of 0.5, the sensitivity and specificity were 90% and 92%, respectively. AUC was also greater for the HUmedian and the 50th percentile (AUC=0.921) of the HU value. Under the threshold value of 27.5, the sensitivity and specificity were 80% and 92%, respectively. **Table 4** summarizes the ROC results for every parameter.

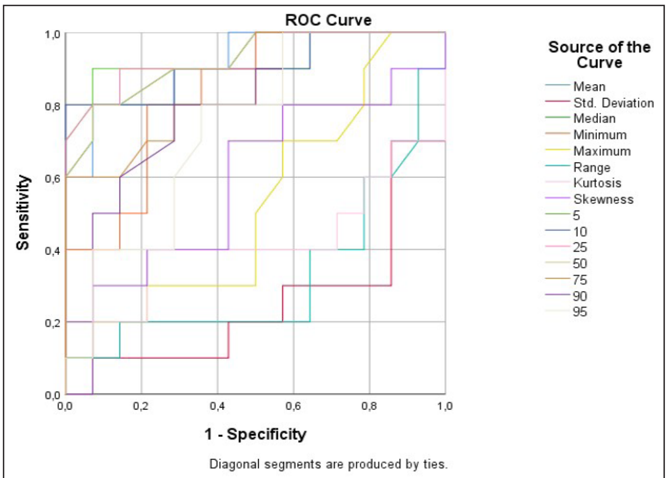

Figure 7. The ROC (receiver operating characteristic) curve (a) represents all histogram parameters. There was a significant difference in HU values between HUmin (P=0.007), HUmean (P <0.001), HUmedian (P <0.001), 5th (P <0.001), 10th (P <0.001), 25th (P <0.001), 50th (P <0.001), 75th (P=0.004), 90th (P=0.016), and 95th (P=0.049) percentiles. The AUC (area under the curve) was correspondingly 0.829, 0.914, 0.921, 0.925, 0.907, 0.932, 0.921, 0.854, 0.793, and 0.739.

DISCUSSION

Adrenal focal masses present a significant difficulty in the daily routine. If either identified incidentally or at the endocrinologist's request, all differential diagnosis options must be thoroughly investigated.[10] Each incidentaloma must always be evaluated for secretory hormonal activity and malignant malignancy.[3] The choice is crucial for individuals with confirmed extra-adrenal malignancies. The therapy and prognosis for adenomas and metastases are very different. The goal of the assessment is to correctly identify benign lesions without further study, saving the patient from ionizing radiation, contrast media, uncertainty, and follow-up exams.

A CT scan can help determine the biological nature of lesions and differentiate between common adrenal pathologies. The non-contrast density of adenomas is usually low due to the high lipid content, whereas the attenuation of carcinomas and metastases is higher. Commonly, 10 HU of unenhanced attenuation is recognized as the threshold.[4,5] The simplicity of this assessment is a major benefit, as it can be conducted even when the CT imaging was not intended to examine the adrenal masses. However, around one-third of the adenomas have mean density values higher than 10 HU, which are regarded "lipid-poor", and they pose a substantial dilemma for why they cannot be consistently distinguished from other adrenal tumors.

A CT histogram analysis is an alternative technique for analyzing the initial unenhanced CT image.[9] The volumetric CT histogram has been utilized in research including both malignant and benign processes.[11-15] This study represents a novel contribution to the existing literature, as it is the first to ascertain HUmin, HUmean, HUmedian, HUmax, and percentile values of HU, alongside standard deviation, skewness, and kurtosis with different slice thicknesses.

Table 5. ROC results of HU metrics histogram parameters in 5 mm slice thickness

Test Result Variable(s)	AUC	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% confidence interval		Cut off	Sensitivity	Specificity
				Lower Bound	Upper Bound			
Mean	0.914	0.058	0.001	0.801	1.000	26.5	0.800	0.929
Std. deviation	0.257	0.112	0.046	0.038	0.477	32.5	0.100	1.000
Median	0.921	0.056	0.001	0.812	1.000	27.5	0.800	0.929
Minimum	0.829	0.084	0.007	0.664	0.993	-69.5	0.800	0.786
Maximum	0.525	0.123	0.838	0.285	0.765	75.5	0.700	0.429
Kurtosis	0.407	0.132	0.447	0.149	0.665	1.2	0.400	0.786
Skewness	0.600	0.124	0.412	0.357	0.843	-0.2	0.700	0.571
5th	0.925	0.065	0.000	0.798	1.000	0.5	0.900	0.929
10th	0.907	0.069	0.001	0.771	1.000	9.5	0.800	1.000
25th	0.932	0.054	0.000	0.826	1.000	15.0	0.900	0.857
50th	0.921	0.056	0.001	0.812	1.000	27.5	0.800	0.929
75th	0.854	0.079	0.004	0.699	1.000	34.5	0.800	0.714
90th	0.793	0.094	0.016	0.608	0.978	45.0	0.800	0.714
95th	0.739	0.102	0.0498	0.540	0.939	48.5	0.800	0.643

AUC, area under the curve

Many publications have verified the method; however, most of them involved a limited number of cases, only a fraction of the tumors were histopathologically validated, and only a negative pixel percentage was calculated.[16-19] Our work employed volumetric histogram analysis instead of single CT image histograms. Whole-lesion volumetric histogram evaluation is utilized to examine the distribution of HU values of the entire lesion and avoids the subjectivity of ROI placement to assure repeatability and calculation precision. This method records the HU values of the entire tumor and may eliminate sampling bias. Szász et al.[20] aimed to determine the appropriate threshold with the volumetric CT histogram analysis of adrenal lesions. However, they only calculated the percentage of negative pixels and concluded that a threshold of 10% of negative pixels yielded a sensitivity of 82.9% and a specificity of 98.2%. In our study, the significance of difference, sensitivity, and specificity increased with lower percentile values.

It is also vital to note that increasing CT image noise leads to a greater distribution of CT values.[21] CT images are reconstructed using a wide variety of slice widths; a thinner slice results in a reduced voxel size and a greater noise level.[22] Although slice thickness affects the HU values, the link between noise and histogram analysis is only hypothesized or addressed in general terms in the published studies. They utilized a wide variety of slice thicknesses from 1 to 8 mm, and it is unknown how these variations may have affected the histogram analysis results.[16-19,23,24] Just one study determined the appropriate slice thickness of CT images, but only for negative voxels. Utilizing a slice thickness of 5 mm and 10% negative voxels, they attained 53.0% sensitivity, 98.8% specificity, and the highest positive predictive value (PPV).[25] We found in our study that a thicker slice thickness is more substantial.

In a study with histologically verified adrenal masses using non-contrast density, at a threshold value of 5%, sensitivity was 78.0–81% and specificity was 67.1–76.3%; at a threshold value of 10%, sensitivity was 69.5–72.4% and specificity was 85.5–89.5%.[24]

Clark et al.[26] recommended using an algorithm based on noise correction to identify adrenal masses. Their formula estimates and eliminates noise using slice thickness, mean density, pitch, standard deviation, tube voltage, and tube current.

The histological verification of all masses is a key benefit over previous research, with the exception of Szász et al.[20] and Remer et al.[24] CT wash-out rates, chemical shift MRI, and PET/CT tracer accumulation were employed to diagnose previous CT histogram analysis studies. Consequently, wash-out rate measurements may produce false-positive results with these techniques for adrenal masses.[27-29] Likewise, the specificity of PET/CT and MRI may not be enough, making histology the only totally valid reference standard.[10] Additionally, we assessed various slice thicknesses and utilized volumetric histogram analysis to eliminate sampling bias. Unlike previous studies, numerous characteristics, including percentile values, minimum, mean, and maximum values, as well as variance, kurtosis, and skewness of histogram analysis, were assessed.

Our study had some limitations. Patient selection was based on a potentially biased retrospective analytic technique. A variety of CT protocols for the evaluation of abdominal organs were studied. Our study did not examine the patients with diagnostic doubt in their adrenal mass or the extent to which CT histogram analysis might resolve this uncertainty.

CONCLUSION

Before the surgical intervention, noninvasive volumetric CT histogram analysis may assist in distinguishing malignant adrenal masses from benign tumors. Greater slice thicknesses can yield more useful data for histogram analysis. For distinguishing adrenal masses, HUmin, HUmean, HUmedian, percentile values, and variance can be used as references.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital. Ethics Committee (Date: 09.01.2023, Decision No: 2023/06).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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