MDCT combined parameters in characterization of adrenal masses in cancer patients; A prospective study in South Egypt Cancer Institute

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Abstract

Objective:
to evaluate the role of combined MDCT parameters in distinguishing benign from malignant adrenal masses in well known oncological patients.

Methods:
CT protocol included pre-contrast scan, venous and delayed contrast-enhanced scans assessing the mass size, pre contrast attenuation, histogram & post contrast absolute and relative percentage washout .Statistical analysis of the data was done.

Results:
The study included 40 patients with 44 adrenal masses. Adrenal masses included 7 lipid rich, 6 lipid poor adenomas, 7 neuroblastomas and 24 metastases. Combined CT parameters including the size (2.25 cm as cut off value), pre contrast attenuation value (<10 HU as cut off value), the 10% negative pixels mean attenuation threshold value for unenhanced CT scan, post contrast absolute percentage washout of 60% and relative percentage washout at 15 min delay were calculated, they yielded a valuable diagnostic protocol with an accuracy of 91.3 %, sensitivity of 100% and specificity of 93.55% for distinguishing the nature of adrenal masses.

Conclusion:
Combining the studied CT parameters yielded a powerful diagnostic protocol in distinguishing benign from malignant adrenal masses.

Key words: Adrenal adenoma, histogram analysis, absolute percentage washout, relative percentage washout.

Introduction

Incidental discovery of adrenal masses is common in abdominal computed tomography (CT), occurring in up to 5% of patients. Most adrenal masses are adenomas. However, in a patient with a known extra-adrenal neoplasm the finding of an adrenal mass is problematic so the diagnosis or exclusion of an adrenal metastasis is essential to determine appropriate therapy for the primary tumor.(1)

On unenhanced CT , size, density and histogram analysis were calculated, among of these parameters ,the presence of macroscopic fat confirms the diagnosis of a benign myelolipoma while an attenuation of less than 10 Hounsfield units (HU) suggests the diagnosis of benign adrenal adenoma and further testing is not required (2).

While the CT histogram analysis plots the attenuation value of each pixel in the region of interest (ROI) with respect to its frequency.(3)

Multiphase contrast enhanced CT (MPCT) protocols in adrenal imaging is used to evaluate the biological behavior of the mass and its pattern of enhancement and washout.(4)

Aim of the work of our study is to evaluate the role of multi detector computed tomography combined parameters in the characterization of adrenal masses in well known oncological patients.

Patients and methods

2.1 .Patients and masses

This prospective study was conducted at South Egypt Cancer Institute at radio diagnosis department, Assuit University after approval of local ethical committee of faculty of medicine, Assuit University. The study included 40 patients [16 males (40%) & 24 females (60 %)] with mean age 49.88 year with range: 1-76 (table 1), with known cancer of variable sites of origin and had supra renal masses discovered during metastatic work up or by CT.

Patients had undergone the dedicated CT protocol for evaluating adrenal masses. Patients with adrenal cysts, calcifications or hemorrhage were excluded from the study (for not interfering with the pre and post contrast attenuation values calculations of the ROI). Also patients with contraindication to be exposed to ionized radiation were excluded.

2.2. CT scan technique

The CT examinations were performed by 16 multi detector scanners (GE Healthcare, Bright speed, WI, USA) with 2.5 slice collimation, 3 mm slice thickness, 1.5 reconstruction intervals, a kV of 140, 200–300 mA and 0.8-s gantry rotation time. Starting with pre contrast images ,then post contrast images (portal phase) were obtained by administration of IV contrast (Ultravist 300) was given as 1.5-2 mg/kg at a rate of 4 mL/s using an automatic pump injector (Angiomat 6000; Liebel-Flarsheim) via an antecubital vein, scanning was initiated 60 s after the start of the injection. Delayed images were also obtained 15 min later. Images were transferred to the workstation (ADW version 4.6).

2.3. Image interpretation and analysis

On the pre contrast imaging, the supra renal mass size, shape and density were assessed (figure 1). Masses <2.25 cm were presumed to be benign while masses >2.25 cm were presumed to be malignant. A threshold value of <10 HU on the pre contrast CT scans was chosen for distinguishing benign lesions (e.g. adenomas) from indeterminate lesions(5).

CT histogram analysis measurements were performed on the pre contrast imaging by placing a circular or ovoid region of interest (ROI) on the adrenal mass including as much of the mass as possible but excluding the outer edges to avoid partial volume effects. The mean attenuation over the ROI was recorded. The CT histogram curve was acquired from the ROI using software application on the workstation where a graph of the number of pixels on the y-axis versus the pixel attenuation on the x-axis was obtained from the ROI. Histogram analysis included recording the total number of pixels, number of negative pixels with attenuation less than 0 HU, and the resulting percentage of negative pixels in each ROI (figure 2).

CT pixel mapping was performed on pre contrast imaging by placing a rectangular ROI on the mass and including as much as possible of it then choose pixel report from the software to detect negative CT attenuation within the mass (figure 3). The threshold values of 10% negative pixels on unenhanced CT images were recorded.

On the venous and delayed imagings , density of the supra renal mass were assessed (figure 4) and the absolute(APW) and relative percentage wahout(RPW) were calculated as follows: APW = 100 x ([VA-DA]/ [VA-PCA]), where VA is attenuation on contrast-enhanced scans, DA is attenuation on delayed contrast-enhanced scans & PCA is pre-contrast attenuation. The relative percentage washout (RPW) was calculated as follows: RPW= 100 x ([VA-DA]/VA),

2.4. Statistical analysis

The recorded data were entered into an Excel worksheet. Sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), and accuracies were calculated for the mass size, the pre-contrast & post-contrast CT analysis and for the combined CT parameters used for the differentiation of benign & malignant adrenal masses. The P-values by Chi-square test were also determined (>0.05 = non-significant, <0.05 = significant, & <0.01 = highly significant). Cut off value of benign and malignant lesions were determined by using ROC curve.

2.5. Proof of diagnosis
Pathologic proof of diagnosis was able to confirm malignancy in seven patients (neuroblastomas).The five lesions that did not meet the criteria of malignancy on adrenal washout study showed either increased size on follow up imaging, or had appeared recently during their routine follow up study and therefore, were presumed to be malignant on the basis of imaging stability(6). None of the adenomas had increased in size on follow up study during 6 months. Change in size of mass was evaluated by RECIST(7).

Results

Forty four adrenal masses were detected in 40 patients; they included 13 benign masses 29.5 % (7 lipid rich & 6 lipid poor adenomas), 31 malignant masses 70.5 %(7 neuroblastomas and 24 adrenal metastases) (table 2).

3.1. Individual CT parameters
3.1.1. Size
Using 2.25 cm as cut off value by calculating the sensitivity, specificity ,accuracy and ROC curve ,16 masses (8 adenomas, 8 malignant masses) were < 2.25cm (36.4 %) and 28 masses (5 adenomas, 23 malignant masses) were > 2.25 cm (63.6 %).). Eighteen malignant masses had small sizes but their washout was consistent with malignant behavior. They were proved to be malignant by histopathology & by increasing size on follow up imaging. We concluded that size has 92.31 % sensitivity, 41.49% specificity and 43.18 % accuracy in the differentiation of benign & malignant adrenal masses.

3.1.2. Pre contrast mean attenuation values
All the lipid rich adenomas (100%) on unenhanced CT had low attenuation values <10 HU (figure 5) .The six lipid poor adenomas had attenuation values >10 HU. All malignant masses (metastases and neuroblastomas) had attenuation >10 HU ranging from 35 to 54 HU with accuracy of 86.36 % & 100% specificity.
3.1.3. Pre contrast histogram

All lipid rich & five lipid poor adenomas had > 10% negative pixels on histogram ranging from 14 % to 59.5 % (12 of 13 adenomas, 92.3 %). One lipid poor adenomas had < 10 % negative pixels on the histogram (1of 13 adenomas, 7.69 %).Six of the malignant masses had < 10% negative pixels. Three had > 10% negative pixels (20 %). The other twenty two did not show any negative pixels. We obtained 90.91% accuracy, 90.32% specificity and 92.31% sensitivity (figure 6).

3.1.4. Absolute percentage washout (APW)
APW threshold of 60% was accurate in diagnosing 13 benign masses “all benign masses” & 22 malignant masses “22 out of 31 masses” .By using an APW of 60 % at 15 min delay post contrast, a sensitivity of 100%, a specificity of 70.97% & an accuracy of 79.55% were calculated. Nine of the malignant masses were misdiagnosed because they did not meet the malignant criteria of APW (i.e < 60%), however they show no negative pixels on histogram & had malignant features by other CT parameters & histopathology.

3.1.5. Relative percentage washout (RPW)
RPW threshold of 40% was accurate in diagnosing 13 benign masses “all benign masses” & 29 malignant masses “29 out of 31 masses”. By using an RPW of 40 % at 15 min delay post contrast, a sensitivity of 100%, a specificity of 93.55% & an accuracy of 95.45% were calculated. Two of the malignant masses were misdiagnosed because they did not meet the malignant criteria of RPW (i.e < 40%), however they show no negative pixels on histogram & had malignant features by other CT parameters & histopathology.

3.2. Value of combined CT parameters
The combined CT parameters succeeded in diagnosing 42 (95.45%) of the total 44 masses (table 3). The combination of pre contrast study parameters and the post contrast washout analysis (APW and RPW) were highly significant CT parameters for the differentiation of benign & malignant adrenal masses (figure 7 and 8) with 100% sensitivity,93.55% specificity,91.3% accuracy and diagnostic value of <0.001(table 4). The size had the lowest statistical diagnostic values (0.026) & the pre contrast attenuation had the highest values obtained among the studied CT parameters.

Discussion

The adrenal glands are a common site for metastatic disease. Virtually any primary malignancy can spread to the adrenals .(8)
CT readily characterizes benign adrenal masses, such as lipid rich adenomas, myelolipomas, adrenal cysts

and adrenal hemorrhage as they have characteristic diagnostic imaging findings such as intra lesional fat, water or blood. A small minority of adrenal masses is difficult to be characterized and remains indeterminate. These include lipid poor adenomas, adrenal metastases, adrenal carcinomas, and pheochromocytomas . Kamiyama et al. reported that combining the diagnostic parameters of the CT protocol can yield the best diagnostic results. (5)

In the current study, the size criterion (using < 2.25 as cut off value for differentiation benign from malignant masses) yielded the lowest sensitivity (61.45%), specificity (74.19%) &accuracy (70.45%) as compared to other studied CT parameters. This was comparable to 98% sensitivity & 53% specificity in Kamiyama et al. study(used < 4 cm as cut off value for differentiation)(5). Korobkin et al.(9) compared the quantity of lipid in resected adrenal adenoma specimens with in vivo CT attenuation and found an inverse linear relationship between the percentage of lipid-rich cells and the unenhanced mean CT attenuation. (10)

Boland et al.(11) in 1998 performed a meta-analysis of 10 studies demonstrating that if a threshold attenuation value of 10 HU was adopted, the specificity was 98% but the sensitivity increased to 71% , therefore, 10 HU is the most widely used threshold attenuation value for the diagnosis of an adrenal adenoma. In the current study, the same threshold was used with comparable results: 53.85% sensitivity, 100% specificity & 86.36% accuracy for the total adrenal masses & 100% statistical indices for lipid rich adenomas.

In agreement with Blake et al.(12) study, any lesions with pre contrast attenuation greater than 43 HU should be regarded with suspicion considered malignant, regardless of its washout profile. In the current study, eight malignant lesions had pre contrast attenuation values greater than 43HU (25.8 % of malignant masses), whereas none of the benign lesions had pre contrast attenuation values greater than 43 HU.

CT histogram analysis can characterize the composition of lesions that are composed of heterogeneously distributed tissues. Bae et al.(13)found that at least one negative pixel was present in 14 of 16 adenomas with a mean attenuation of greater than 10 H on unenhanced CT. He proposed using a threshold of at least 10% negative pixels for diagnosis of an adenoma. Comparatively, we showed an overall sensitivity of 80%, specificity of 87.50% and accuracy of 90.91% when a threshold of 10% negative pixels was applied.

In the current study we found that 83.3% of the lipid-poor benign nodules contained more than 10% negative pixels on unenhanced CT. Performance sensitivity by histogram analysis is substantially higher for the subset of lipid-poor adenomas measuring between 10 and 20 HU, presumably owing to their higher intracellular lipid content.(14)

Characterization of adrenal masses using contrast enhanced CT utilizes the different physiological perfusion patterns of adenomas and metastases. Attenuation values of adrenal masses obtained 60 s after contrast medium injection show too much overlap between adenomas and malignant lesions to be of clinical value(6). However, the percentage of contrast washout between initial enhancement (at 60 seconds) and delayed enhancement (at 15 min) can be used to differentiate adenomas from malignant lesions. It has been demonstrated that washout of contrast from adenomas occurs much faster than from metastases. Both lipid rich and lipid poor adenomas behave similarly, as this property of adenomas is independent of their lipid content (15). The APW of an adrenal mass may seem to be a more accurate calculation of de-enhancement because the pre contrast attenuation value is included in the calculation of APW.(5).

In agreement with Caoili et al.(16), in the current study, an APW of 60 % at 15 min delay post contrast showed sensitivity of 100 %, specificity of 70.97 % & accuracy of 79.55 %.

In Kamiyama et al. study(5), they concluded that a combination of the unenhanced and dynamic enhanced CT protocol parameters can yield a high diagnostic accuracy in the differentiation of adrenal adenomas from non adenomas. Combining the CT parameters studied in the current study yielded a valuable diagnostic protocol with an accuracy of 91.3% for distinguishing the nature of adrenal masses.The majority of the adrenal masses was not pathologically proved and required follow-up imaging for characterization. This has been an accepted method of classifying benign and malignant lesions in previous studies (12, 17). Size stability during a 6 month follow up to confirm adenomas and growth of the mass within 6 months or shrinkage after chemotherapy to confirm metastases was used in most studies as in Blake et al.(12), Kamiyama et al.(5), & Halefoglu et al.(18)studies. In the current study, 6 months of stability was used for the exclusion of adrenal metastasis as the patients' population was known with cancer of variable origins. Yet, none of the adenomas had increased in size on follow up study during the first 6 months & they were presumed to be benign on the basis of their imaging stability on follow up. Therefore,6 months of follow up is a sufficient period.(19)

Summary and conclusion

In conclusion, benign adrenal masses are common even in patients with cancer. Most of these masses are lipid rich adenomas and these can be confirmed on unenhanced CT with an attenuation value of less than 10 HU & a histogram threshold of more than 10% negative pixels. Histogram analysis is more accurate than pre contrast attenuation in detecting intra lesion fat content & is considered a useful tool in diagnosing lipid rich adenomas. The APW and RPW values are accurate discriminators of the nature of adrenal masses whether benign or malignant especially for the intermediate density masses. In the current study, the washout profile supersedes the pre contrast attenuation value of less than 10 HU and 10 % negative pixels on histogram analysis in the evaluation of an adrenal mass. Size is the lowest CT parameter discriminator with considerable overlap between benign & malignant lesions. Combining the studied CT parameters yielded a powerful diagnostic protocol in distinguishing benign from malignant adrenal masses.

List of abbreviations

APW Absolute percentage washout
DA Delayed attenuation
HU Housefield unit
IV Intravenous contrast
KV Kilovolt
mA Milli amber
MDCT Multi detector computed tomography
MPCT Multiphase contrast enhanced CT

NPV Negative predictive value
PCA Pre contrast attenuation
PDV Positive predictive value
RECIST Response evaluation criteria in solid tumors
ROI Region of interest
RPW Relative percentage washout
VA Venous attenuation

Declaration of Conflicting Interests
None.
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Table 1: Demographic data of the studied patients

	No. (n= 40)	%
Age: (years)		
< 40	10	25
40 – 60	12	30
> 60	18	45
Mean ± SD; Median (Range)	49.88 ± 24.77; 57.0 (1.0 – 76.0)	
Sex:		
Male	16	40
Female	24	60

Table 2: primary sites of the tumors

Diagnosis	No. (n= 21)	%
Neuroblastoma	5	23.8
Lung cancer	4	19.0
Cancer breast	1	4.8
Cancer cardia	1	4.8
cancer pancreas in post-operative status	1	4.8
Cancer stomach underwent distal gastrectomy	1	4.8
Ewing's sarcoma (pelvic mass)	1	4.8
Intestinal lymphoma	1	4.8
left ovarian adenocarcinoma	1	4.8
Metastatic cancer pancreas	1	4.8
Ovarian cancer	1	4.8
Thymic carcinoma	1	4.8

Undifferentiated carcinoma of left inguinal LN	1	4.8
Unknown	1	4.8

Table 3: value of combined CT parameter

	Benign (n= 13)		Malignant (n= 31)		P-value
	No.	%	No.	%	
Size:					0.024*
≤ 2.25	8	50	8	50	
> 2.25	5	17.9	23	82.1	
Non-contrast attenuation HU:					<0.001*
< 10	7	100.0	0	0.0	
≥ 10	6	16.2	31	83.8	
APW:					<0.001*
< 60%	0	0.0	22	100.0	
≥ 60%	13	59.1	9	40.9	
RPW:					<0.001*
< 40%	0	0.0	29	100.0	
≥ 40%	13	86.7	2	13.3	
Pixel report and its significance:					<0.001*
< 10%	1	3.4	28	96.6	
≥ 10%	12	80.0	3	20.0	

Table 4: statistical values of combined CT parameter

Sensitivity	Specificity	+PV	-PV	Accuracy	Chi-square	P-Value
100	93.55	86.67	100	91.3	35.673	<0.001

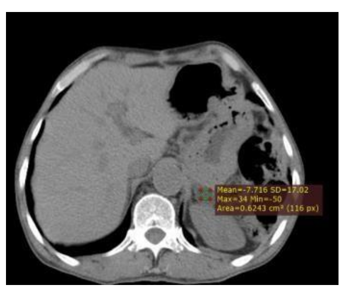


Figure (1): pre contrast phase showing left supra renal mass size and density in known patient of pancreatic cancer

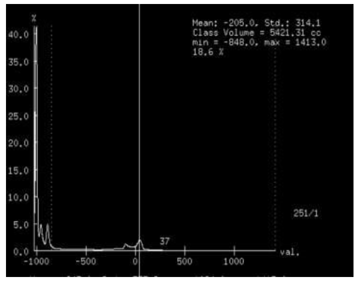


Figure (2): CT histogram of a patient with neuroblastoma showing range of attenuation and class volume

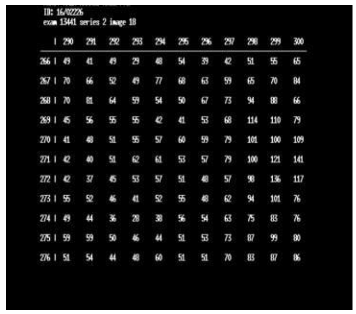


Figure (3): pixel report of a pathologically proven neuroblastoma, showing no negative pixel within the mass

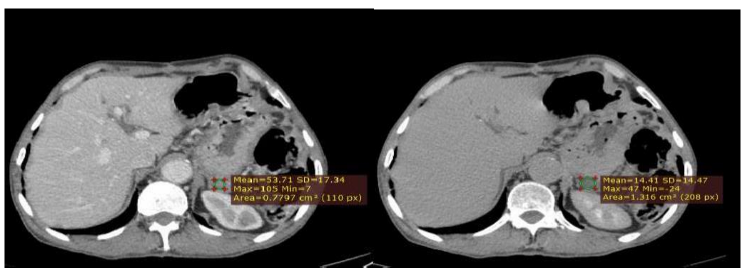
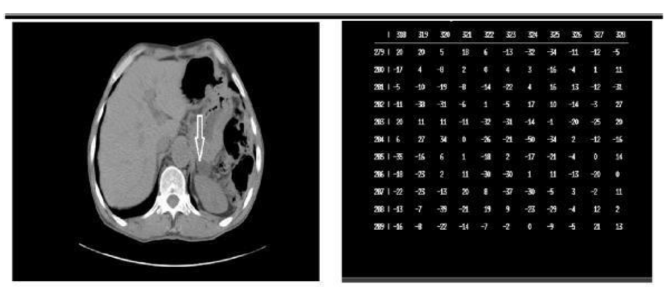


Figure (4): venous and delayed phases showing left supra renal mass density in known patient of pancreatic cancer



A **B**

Figure 5: Lipid rich adenoma: 72 years old man with a history of cancer pancreas and left adrenal spherical mass 2 cm in diameter. The arrow in (A) demonstrates a mean pre contrast density of -8.4 HU. The pixel report (B) had > 10% negative pixels. The APW was 78.9% and RPW was 66.8%.

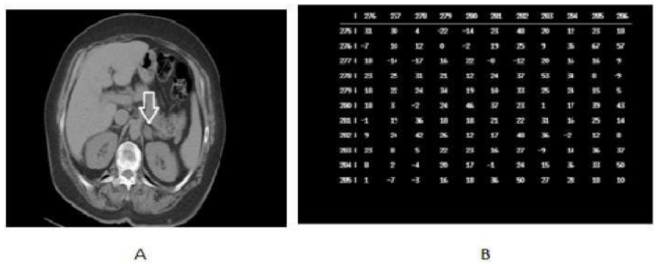


Figure 6: Lipid poor adenoma: 63 years old woman with a history of lymphoma and left adrenal spherical mass 1.5 cm in diameter. The arrow in (A) demonstrates a mean pre contrast density of 22.7 HU. The pixel report (B) had > 10% negative pixels. The APW was 65.89% and RPW was 43.26%.

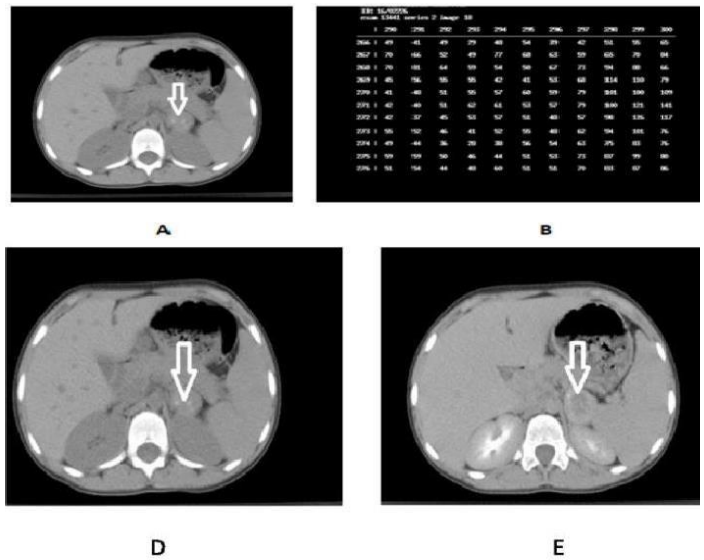


Figure 7: left adrenal neuroblastoma: 7 years old child with left adrenal spherical mass 5.5 cm in diameter. A, B, C and D are pre contrast, pixel report, venous phases and delayed phases respectively. The arrow in (A) demonstrates a mean pre contrast density of 51.6 HU. The pixel report (B) had no negative pixels. The APW was 19.8% and RPW was 6.8%.

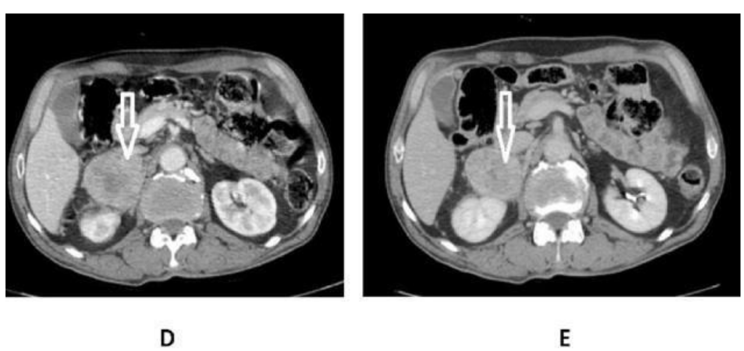


Figure 8: Right adrenal metastatic lesion: 65 years old man with history of left lung cancer and right adrenal spherical mass 3 cm in diameter. A, B, C and D are pre contrast, pixel report, venous phases and delayed phases respectively. The arrow in (A) demonstrates a mean pre contrast density of 44.5 HU. The pixel report (B) had < 10% negative pixels. The APW was 79% and RPW was 25.8%.