

# Lipid-Poor Adrenal Lesion: Differentiation of Benign from Malignant Disease by Using Imaging Features on Routine Contrast-Enhanced CT

Shanigarn Thiravit, M.D.\*, Natee Ruangpaisanbamrung, M.D.\*\*\*, Voraparee Suvannarerg, M.D.\*, Phakphoom Thiravit, M.D.\*

\*Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, \*\*Bangkok Hospital Chanthaburi, Chanthaburi 22000, Thailand.

## ABSTRACT

**Objective:** To assess the effectiveness of CT imaging features of lipid-poor adrenal lesions on routine contrast-enhanced CTs in differentiating benign from malignant masses.

**Methods:** A retrospective study was performed on 84 lipid-poor adrenal lesions (HU >10 on unenhanced CT scans), which were sized 1-4 cm, had a proven final diagnosis, and were detected during routine contrast-enhanced MDCT studies. Of those, 58 were found in patients with an underlying extra-adrenal malignancy. Two authors determined the morphological features according to their shape, margin, density on unenhanced images, and enhancement pattern. The sensitivity, specificity, and positive and negative predictive values were also calculated for each feature which suggested benignancy, plus a combination of those features.

**Results:** There were 46 (55%) benign and 38 (45%) malignant adrenal masses. The low-density feature (10-20 HU on unenhanced CT images) indicated as benign with a high specificity of 92%, even in patients with known malignancy. The other features (round/oval shape, smooth margin, and homogenous enhancement) showed a high sensitivity (75%-85%) but a low specificity (39%-56%) in predicting benignity. The combined features for presumed benignancy could predict a benign mass with the highest specificity of 95%.

**Conclusion:** The small, lipid-poor, adrenal masses detected by routine contrast-enhanced CTs are likely to be benign when their internal density on unenhanced images is not higher than 20 HU and/or, especially, when a combination of all morphological features for presumed benignancy presents.

**Keywords:** Adrenal adenoma; adrenal gland; CT (Siriraj Med J 2019;71: 14-20)

## INTRODUCTION

The prevalence of an incidental adrenal mass discovered on chest or abdominal contrast-enhanced CT scans is approximately 4% which is mainly a benign adenoma.<sup>1</sup> Using internal attenuation of  $\leq 10$  Hounsfield units (HU) on unenhanced CT images, sensitivity and specificity for the diagnosis of adrenal adenoma were 71% and 98%, respectively.<sup>2,3</sup> Previous study reported

that approximately 30% of non-fat-containing adrenal masses (HU > 10) were lipid-poor adrenal adenomas.<sup>2</sup> Currently, an adrenal gland CT with a 10- or 15-minute delayed protocol is usually performed to evaluate lipid-poor adrenal lesions. A diagnosis of lipid-poor adenoma is established by calculating the absolute contrast washout (ACW) or relative contrast washout (RCW) values. The thresholds for ACW and RCW for 10-minute delayed

Corresponding author: Phakphoom Thiravit

E-mail: art.phak@gmail.com

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ORCID ID: 0000-0001-5058-9624

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protocol were 37% and 53%, respectively - with the sensitivity and specificity of 100% and 98%, respectively.<sup>4,5,6</sup>

Despite the high sensitivity and specificity of specific CT adrenal protocol, this protocol requires another appointment, more expense and exposure to radiation and contrast media.<sup>7</sup> There have been efforts to differentiate benign from malignant adrenal masses by using the morphological features apparent on the first routine CT scan.<sup>7-10</sup> One study found that benign adrenal masses were associated with homogeneous low attenuation, an enlarged gland with the adrenal configuration maintained, a round or oval shape, and a thin or absent rim enhancement, whereas malignant masses were associated with a size exceeding 4 cm, a thick or nodular enhancing rim, and adjacent organ invasion.<sup>9</sup> Another study showed that an irregular margin and a thick rim enhancement were highly associated with malignancy but had low sensitivity.<sup>7</sup> Therefore, the aim of this study was to evaluate the CT imaging features of lipid-poor adrenal lesions on routine contrast-enhanced CTs to differentiate benign from malignant masses.

## MATERIALS AND METHODS

### Subjects

This retrospective study was approved by the Siriraj Institutional Review Board (Si 588/2015). We identified 175 patients with lipid-poor adrenal lesions detected on routine contrast-enhanced CTs of the chest or abdomen at our hospital between January 2013 and March 2014. A lipid-poor adrenal lesion was defined as any adrenal lesion with an HU level > 10 on an unenhanced CT scan. We excluded those patients who had adrenal masses sized smaller than 1 cm or larger than 4 cm, had no accessible pathological reports, or had had no follow-up studies for more than 1 year. Per exclusion criteria, 78 patients with 84 proven lipid-poor adrenal masses (1-4 cm) left for the analysis.

### Adrenal masses

The final diagnosis of adrenal masses was confirmed by histology or imaging studies, as follows:

- A benign mass was considered if it was proven by pathology or imaging studies (in detail, if there was a lesion with calculated ACW and RCW values of > 53% and/or > 37%, respectively, on a 10-minute delayed CT adrenal protocol; or a lesion with calculated ACW and RCW values of > 60% and/or > 40%, respectively, on a 15-minute delayed CT adrenal protocol; or a lesion with a signal drop on opposed phase compared with in-phase chemical shift MR images (CS-MRI); or a lesion with 1-year stability during follow-up.)<sup>4,7</sup>

- A malignant mass was considered if it was proven by pathology or a change of nodule size, or a new lesion developed during chemotherapeutic sessions or imaging follow-up in patients with known malignancy; the changes should be in keeping with primary tumors or the patient's conditions.

### MDCT technique

Routine contrast-enhanced chest and/or abdominal CT examinations were performed by 64-slice scanners. The intravenous low-osmolar contrast medium was administered at the rate of 3 ml/sec, with a dose of 100 ml for standard abdominal CTs or 80 ml for standard chest CTs. The post-contrast images were performed 80 seconds after contrast administration for the abdomen, and 35 seconds after contrast administration for chest studies. The images were reconstructed to 1.25 mm thickness.

### Image interpretation

All lipid-poor adrenal masses on the CT images obtained via the Picture Archiving and Communication System (PACS) system were evaluated by 2 radiologists who had a subspecialty in abdominal imaging and were blinded to the final diagnoses. The imaging features were evaluated according to their shape (round/oval, irregular), margins (smooth/microlobulated, irregular), densities on the unenhanced images (10–20 HU or > 20 HU), and patterns of enhancement (homogeneous, rim/heterogeneous). The location, laterality, and lesion size were also recorded. An adrenal mass was presumed to be benign if a mass had a round or oval shape, a smooth or microlobulated margin, a low density (10–20 HU) on an unenhanced CT image, and a homogeneous enhancement, whereas a malignant mass was presumed to have an irregular shape, an irregular margin, a higher density (> 20 HU) on unenhanced CT images, and a heterogeneous or rim enhancement.

### Statistical methods

The features presented in the benign and malignant lesions were compared using a chi-square test, and a P-value of < 0.05 was considered statistically significant. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each morphological feature for presumed benignancy and the combined features were calculated. The corresponding 95% CIs were also reported. The statistical analyses were performed by using SPSS Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

### Patients

There were 50 men and 28 women - with mean age of 60 years (range 18–89). Of them, 56 (66.7%) had a history of malignancy, while 19 (24.4%) had bilateral adrenal masses.

### Overall adrenal lesions

Of the 84 proven, lipid-poor, adrenal masses detected on routine contrast-enhanced CT studies, 46 (55%) were benign, and 38 (45%) were malignant masses. The final diagnosis of benign adrenal masses was pathologically proven for 4 lesions (two adrenal adenomas, 1 bland adrenal cortical tissue, and 1 granulation tissue), and by clinical and/or imaging follow-up for another 42 lesions. Of those 42 lesions, 17 were considered benign adenomas according to the imaging criteria for the 10-minute delayed CT adrenal protocol and/or CS-MRI; a further 4 lesions were considered benign pheochromocytomas by MIBG scans and clinical follow-up; while the remainder (23 masses) were considered benign due to lesion stability during the 1-year follow-up.

Thirty-seven malignant masses were diagnosed as metastases by either tissue diagnosis (n=1) or the imaging criteria (n=36; nodule size changes or new nodules developed after chemotherapeutic session or during imaging follow-up in patients with known malignancy). The other was a pathologically-proven adrenocortical carcinoma.

The mean ages of patients with benign and malignant masses were 59.3 years and 60.2 years, respectively. The average size of all adrenal masses was 2 cm (range 1-4

cm in maximal width). The mean sizes of the benign and malignant masses were 18.2 and 22.0 mm, with an SD of 7.4 and 8.2 mm, respectively ( $P = 0.027$ ). Of the adrenal masses, 59 (70%) were unilateral and 25 (30%) bilateral. Among the 59 unilateral masses, 20 (36%) were benign, and 36 (64%) were malignant. As for the bilateral location, 10 out of the 25 (40%) were benign, and the remaining 15 (60%) were malignant. There were no significant differences between the benign and malignant masses in terms of age, sex, or laterality ( $P > 0.05$ ).

A total of 56 out of the 84 (67%) lesions were found in patients with an underlying extra-adrenal malignancy, while the other were found in patients without one. In the case of the 56 adrenal lesions, the masses were significantly malignant etiologies (n=36, 64%) rather than benign (n=20, 36%;  $P < 0.001$ ).

### CT morphological features of benign and malignant adrenal lesions

A statistically significant difference between benign and malignant lesions is shown in [Table 1](#). Most benign adrenal masses had a round/oval shape (91%), a smooth/microlobulated margin (93%), and a homogenous enhancement (82%); those three features showed a very high sensitivity but rather low specificity to differentiate from malignant lesions. In addition, the density of 10–20 HU on unenhanced CT images showed the highest level of specificity (92%) among other features for presumed benignancy. However, the detection of this feature may be limited due to its low sensitivity (40%; [Table 2](#)).

**TABLE 1.** CT features of 84 lipid-poor adrenal masses.

Variable		Malignant N=38 (%)	Benign N=46 (%)	P-value
Shape	Round/oval	22 (58)	42 (91)	< 0.001
	Irregular	16 (42)	4 (9)	
Margin	Smooth/microlobulated	22 (58)	43 (93)	< 0.001
	Irregular	16 (42)	3 (7)	
Density (HU) on unenhanced CT images	10–20	3 (8)	20 (43)	< 0.001
	> 20	35 (92)	26 (57)	
Pattern of enhancement	Homogeneous	16 (42)	38 (82)	< 0.001
	Rim/heterogeneous	22 (58)	8 (18)	

**TABLE 2.** The sensitivity, specificity, PPV, and NPV of CT features for presumed benignancy in 84 adrenal masses.

Morphology	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV %	NPV %	P-value
Round shape	91.3 (79-98)	42.1 (26-59)	65.6	80	< 0.001
Smooth margin	93.5 (82-99)	42.1 (26-59)	66.1	84.2	< 0.001
Low density (10-20 HU)	43.5 (29-59)	92.1 (79-98)	86.9	57.3	< 0.001
Homogenous enhancement	82.6 (69-92)	57.8 (41-74)	70.4	73.3	< 0.001

**Abbreviations:** PPV, positive predictive value; NPV, negative predictive value

We also specifically analyzed patients with a history of malignancy (n=56), finding that the low density (10-20 HU) showed the highest specificity (91%) in the determination of a benign etiology, and with statistical significance. This result was similar to that for the patients-without-malignancy group. However, the other features for presumed benignancy, including a smooth margin and homogenous enhancement, showed a high sensitivity (75%–85%) but low specificity (42%-56%). A round/oval shape was the only feature that showed no statistical significance to differentiate between benign and malignant diseases in this patient population (P = 0.06; Table 3).

#### **Combined CT morphological features of benign and malignant adrenal lesions**

We combined three morphologies for presumed benignancy (round shape, smooth margin, and homogenous enhancement), for which the sensitivities, specificities, PPVs, and NPVs are presented at Table 4. We also combined all morphological features for presumed

benignancy, including the low density feature; although this increased the specificity to 95%, it decreased the sensitivity to 34.8%.

In predicting malignant adrenal lesions, the combination of the high density (HU > 20) feature and a history of malignancy showed a specificity, sensitivity, PPV, and NPV of 86.8%, 73.9%, 73.3%, and 87.2%, respectively (p < 0.001).

#### **DISCUSSION**

In 2017, the ACR Incidental Findings Committee released an updated version of its White Paper on the management of adrenal incidentalomas. Those lesions are being detected more often than in the past due to the increased use of, as well as improvements to, the spatial resolution of cross-sectional imaging modalities.<sup>11</sup> The guidelines in the White Paper help radiologists and clinicians decide whether an incidentaloma should be further investigated, followed up, or left alone. The guidelines focus mainly on nodules of more than 1 cm

**TABLE 3.** The sensitivity, specificity, PPV, and NPV of CT features for presumed benignancy in 56 adrenal masses in patients with known extra-adrenal malignancy.

Morphology	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV %	NPV %	P-value
Round shape	85.0 (62-97)	38.9 (23-57)	43.6	82.4	0.06
Smooth margin	85.0 (62-97)	41.7 (26-59)	44.8	83.3	0.04
Low density (10-20 HU)	40.0 (19-64)	91.7 (78-98)	72.7	73.3	0.004
Homogenous enhancement	75.0 (51-91)	55.6 (38-72)	48.4	80.0	0.03

**Abbreviations:** PPV, positive predictive value; NPV, negative predictive value

**TABLE 4.** The sensitivity, specificity, PPV, and NPV of combined CT features for presumed benignancy in 84 lipid-poor adrenal masses

Combination	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV %	NPV %	P-value
Benign A	73.9 (59-86)	65.8 (49-80)	72.3	67.6	< 0.001
Benign B	34.8 (21-50)	94.7 (82-99)	88.9	54.6	0.001

Benign A: round shape, smooth margin, and a homogenous enhancement.

Benign B: round shape, smooth margin, a homogenous enhancement, and a low density (10–20 HU).

**Abbreviations:** PPV, positive predictive value; NPV, negative predictive value

in size and on lipid-poor nodules (nodules with an internal density > 10 HU on unenhanced CT scans), both of which are usually troublesome.<sup>11</sup>

A nodule should be evaluated whether its size is more or less than 4 cm because size is an important indicator for malignancy.<sup>10,11</sup> In the evaluation of benign or malignant adrenal nodules, the specific adrenal CT, CS-MRI, PET/CT, or tissue diagnosis can provide the solution.<sup>4,6,11</sup> However, those do not serve as initial tools, which consequently necessitates another appointment, causing additional costs as well as patient worry and inconvenience. In this study, we aimed to evaluate the CT imaging features of lipid-poor adrenal lesions discovered on routine contrast-enhanced CTs as those may help to initially differentiate benign from malignant masses.

Our study showed that there were significant differences in shape, margin, density on unenhanced images and the pattern of enhancement, to determine the nature of lipid-poor adrenal masses. However, three morphological features for presumed benignancy, which were a round/oval shape, a smooth margin, and a homogeneous enhancement, had high sensitivity but relatively low specificity to suggest benignity. That poor specificity implied that recognizing those imaging features on routine CT scans cannot be helpful in differentiating benign from malignant adrenal diseases. The findings were also in concordance with the results in other studies.<sup>7-10,12</sup> For example, a study by Berland et al. reported two features for benign lesions showing 100% PPV but no statistical significance, namely, homogenous attenuation with little punctuate enhancement, and a gland enlargement with the normal configuration maintained.<sup>9</sup> Another interesting finding of a homogenous attenuation lower than that of muscle was reported with a high PPV, but it was not investigated in our study.<sup>9</sup> Homogenous enhancement is considered a feature suggesting benignancy, and it has been reported to be seen in adrenal adenomas rather than

adrenal carcinomas, metastases, and pheochromocytomas by many investigators.<sup>7,10</sup> Nevertheless, a heterogenous enhancement may not be considered an absolute finding for suggesting malignancy since this usually presents in pheochromocytomas.<sup>13</sup>

According to the widely used guidelines for adrenal incidentalomas, a nodule can be considered as benign by measuring the CT density with a threshold less than 10 HU.<sup>11</sup> Despite that, using the higher threshold value (> 10 HU), which has been evaluated in many studies, also demonstrates an impressive performance for lesion characterization.<sup>2,10,12,14</sup> In a meta-analysis study, the reported sensitivity and specificity for adenomas at the cut-off values of 20 HU versus 10 HU were 88% and 84% versus 71% and 98%, respectively.<sup>2</sup> Park et al. also supported the application of a threshold value of 20 HU for characterizing an adrenal adenoma as they reported a sensitivity, specificity, PPV, and NPV of 60%, 100%, 100%, and 67%, respectively.<sup>14</sup> In our study, we showed a specificity and sensitivity of a low-density feature (10-20 HU) on unenhanced CT images of 92% and 44%, respectively. This was the only feature with a high specificity among the other features for presumed benignancy, and we also observed a similar trend in patients either with or without known malignancy. Despite the low sensitivity of this feature, we believe that using a threshold of 20 HU for distinguishing benign and malignant adrenal lesions can be acceptable, subject to the careful consideration of some false negative rates. In the case of patients with a history of cancer, an adrenal nodule may be found on a routine chest or abdominal CT during their metastatic workup. It is therefore important to know whether an adrenal nodule is of a metastatic or benign incidental nature. In our study, a benign-appearing margin, shape, and enhancement pattern were not helpful in predicting benignity except for the low-density feature on unenhanced images, as discussed

earlier. In the study by Song et al., the findings of rim enhancement and an irregular margin were nearly 100% specific to malignant lesions.<sup>7</sup> Our results also revealed that adrenal masses were significantly malignant rather than benign in patients with previously known malignancy. As a history of malignancy is considered significant, diagnosis of a benign or malignant mass using the features on a contrast-enhanced CT alone is usually not reliable in this patient population. Further evaluation such as CT with an adrenal protocol is recommended.<sup>11</sup>

Due to the high sensitivity but low specificity of the individual morphological features for presumed benignancy to indicate a benign mass, we further combined all those features; they included a round/oval shape, a smooth margin, a density at 10–20 HU on unenhanced images, and a homogeneous enhancement. This combination was able to achieve greater percentages for specificity (95%) and PPV (89%). This finding encourages more confidence to diagnose a lipid-poor adrenal mass as being benign if it presents all those features for presumed benignancy within the lesion.

Our study had several limitations. First, it was a retrospective study with a small sample size. The interpretation of the morphological features was also

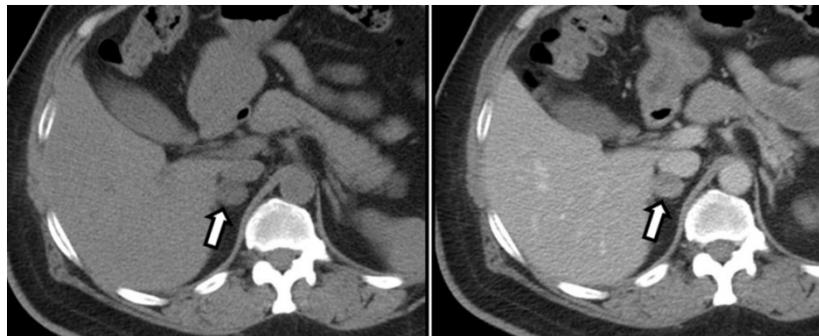
subjective as it depended on the readers' experiences. Still, as this review process was close to daily practice, the results can be applied to real-life situations. In addition, we did not calculate the inter-observer agreement, but instead used a consensus approach to resolve discordant readings. Finally, there were a variety of phases of contrast-enhanced CTs in our study. However, this did not affect our results because different enhancements between phases was not within the scope of our study.

## CONCLUSION

Lipid-poor adrenal masses with a density lower than 20 HU can be considered as benign even in patients with known malignancy. However, the rest of the individual features for presumed benignancy have a poor performance in differentiating benign from malignant adrenal masses.

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**Fig 1.** A 58-year-old man with known rectal cancer was found to have a 19-mm right adrenal mass (arrow) during a metastatic workup. The mass had a density of 14 HU on unenhanced CT images, and had smooth margins, an oval shape, and a homogeneous enhancement. As the mass showed no significant change at the 20-month CT follow-up, it was considered to be benign.



**Fig 2.** A 74-year-old woman with no history of malignancy presented with significant weight loss; bilateral adrenal masses were found on abdominal CT images. The masses showed an oval shape, irregular margins, and an internal density > 20 HU on unenhanced CT images. They were subsequently proven to be malignant by CT-guided core needle biopsy.

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