Analysis of MDCT Findings in the Differentiation of Adrenal Masses in Lung Cancer Patients in Siriraj Hospital

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ABSTRACT

Objective: To determine significant multi-detector CT (MDCT) features that may differentiate adrenal metastasis from adrenal adenoma in lung cancer patients.
Methods: We retrospectively analyzed CT images of 52 patients (72 adrenal masses) with history of lung cancer, from January 2005 to September 2010. Two radiologists independently evaluated size, unenhanced and enhanced attenuation, homogeneous or inhomogeneous density, calcification, patterns of involvement, number, unilateral or bilateral sides of the adrenal masses. The nature of these adrenal masses were determined by follow-up CT scans for at least 6 months. Associations between CT characteristics and the nature of these adrenal masses were interpreted.
Results: 22 of these adrenal masses were adenomas and 50 were metastases. CT features that show statistically significant help in differentiating between these two entities were density in non-contrast, post-contrast enhancement, patterns of involvement, and calcification. Differentiations of adenoma from adrenal metastasis by using the unenhanced attenuation criterion (≤ 10 HU), yielded 50% sensitivity, 100% specificity, and 84% accuracy. Patterns of involvements yielded 58% sensitivity and 90.9% specificity.
Conclusion: We found attenuation on unenhanced CT (≤ 10 HU) and the pattern of involvement (diffuse nodular infiltration along body and limbs) of adrenal masses are helpful in differentiating adrenal adenoma and adrenal metastasis in lung cancer patients with high specificity.

Keywords: cutaneous, disseminate, immunodeficiency, tuberculosis

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INTRODUCTION

The chest CT in staging of patients with newly diagnosed lung cancer is routinely scanned to include the adrenal glands in order to exclude metastasis. The adrenal gland is the common site of metastasis of lung cancer and may be the only site in 15% of patients.[1] The frequency of metastases may be as high as 35.6% at autopsy.[2] However, adrenal adenoma which is a benign tumor is common in up to 8.7% of the general population in autopsy series.[3] The previous research showed that it is more likely to be adrenal adenoma than metastasis in patients with lung cancer.[4] Therefore, it is important to distinguish benign from adrenal metastasis in lung cancer patients because diagnosis of distant metastasis precludes surgery.

MDCT is the imaging modality of choice in staging for lung cancer. To avoid more expensive examinations (MRI, positron emission tomography [PET]) or biopsy, it is essential to obtain a conclusive diagnosis of an adrenal mass by CT in as many patients as possible.

Several investigators have tried to identify criteria that would allow the diagnosis of a benign or malignant etiology based on CT. Features that suggest a malignant lesion include a large size (>3 cm), poorly defined margins, adjacent structure invasion, inhomogeneous attenuation, and a thick, irregular enhancing rim. A small ovoid lesion with a thin rim and homogeneous density is more likely to be benign.[5] However, small metastases are often

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homogeneous on contrast-enhanced CT which are indistinguishable from adenomas.[3] One of the features that distinguishes adrenal adenoma from metastasis is that the majority of the adenoma contain abundant cytoplasmic fat, where as metastases do not.[5] Previous published reports found that lipid-rich adenoma has a density ≤10 HU on unenhanced CT and this threshold provides high specificity for diagnosing lipid-rich adenoma.[6,7] For lipid-poor adenomas (>10 HU), there are diagnostic problems to distinguish them from adrenal metastasis. In these groups, previous research used the delayed enhanced CT at 15 minutes and then calculated the relative or absolute percentage wash out which is useful and has high sensitivity and specificity.[7]

The objective of this study was to determine significant CT features in pre-contrast and post-contrast imagings which may provide the differentiation of adrenal adenoma from adrenal metastasis.

MATERIALS AND METHODS

Patients

A retrospective study was approved by our institutional review board. The study included lung cancer patients who had adrenal masses detected by MDCT at Siriraj Hospital from January 2005 to September 2010. Patients were recruited by computerized search from picture archiving and communication system (PACS) and report systems. Adrenal thickening with preserved gland shape was not included in this study. Patients were identified with the combination of a diagnosis of lung cancer and adrenal mass or adrenal nodule. The patients without adequate follow-up were excluded.

There were 52 patients (28 men and 24 women; age range: 42-86 years; mean age 64 years), with 72 adrenal masses. The diagnosis of the adrenal lesion was established by subsequent CT follow-up (mean 13.5 months). If the size of the lesion was unchanged after a minimum follow-up of 6 months (range 6-46 months, mean 16.3 months), it was considered to be a benign lesion. A mass was considered malignant if the follow-up CT scans showed a rapid change in size. Because of no pathological result to differentiate each kind of benign lesion, we used the basic knowledge that most of benign adrenal lesions are adrenal adenoma. Therefore, we excluded other benign lesions which were benign pheochromocytoma, adrenal cyst, myelolipoma, and infection, by correlation with clinical history, lab profiles, and some CT characteristic features. To exclude benign pheochromocytoma, none of these patients had had history of labile hypertension, sweating, palpitation, headache, flushing, or biochemical evidences that indicated pheochromocytoma. The adrenal cyst was excluded by characteristic CT features, which are adrenal cyst has fluid density, thin imperceptible wall, and sometimes shows peripheral calcifications. Adrenal myelolipoma was excluded by identifying macroscopic fat which is a pathognomonic CT feature. For adrenal infection from tuberculosis, although its CT features are not characteristic enough to differentiate from adenoma, it is usually bilaterally enlarged with rim enhancement, and sometimes contains calcifications. Besides that, none of our patients presented with Addison's disease or adrenal insufficiency which are clinical presentations in tuberculosis. Finally, 22 adenomas and 50 metastases were diagnosed.

CT Technique

All examinations were performed in Siriraj Hospital with 64 slice MDCT (LightSpeed 64 scanner, GE Healthcare) and Dual Energy CT (Somatom Sensation 64 scanner, Siemens Medical Solutions), using the following scanning parameters: tube voltage, 120 kVp; tube current time product, 250-300 mAs; pitch, 0.9; slice collimation, 1.25 mm. All patients were scanned throughout their chest including both adrenal glands on pre-contrast phase and portal venous phase. All patients received intravenous contrast medium administration. CT images were analyzed on a PACS workstation.

Image Analysis

All images were retrospectively reviewed by two abdominal radiologists (NN, KM). Each adrenal mass was evaluated for size, unenhanced and enhanced attenuation, homogeneous or inhomogeneous density, border (well or ill-defined margin), pattern of involvement (focal nodule or diffuse nodular infiltration along limb and body), calcification, number, and unilateral or bilateral sides of lesion. For measurement of the unenhanced and enhanced attenuation, the circular region of interest (ROI) was placed on the adrenal mass, which included at least half of the cross-sectioned area of the lesion and avoided the cystic, necrotic area, or calcification. The ROI for each lesion was carefully placed in the confines of the entire lesion.

Statistical Analysis

All continuous quantitative data, including the patient's age, size, and duration of follow-up study, were reported as the mean and range. The qualitative data of individual CT parameters, included size, unenhanced attenuation, homogeneous or inhomogeneous on non-contrast and post-contrast enhancement, border, pattern of involvement and distribution, presence of calcification, and number of adrenal masses, and were analysed using a Chi-square test. The P-value was considered significant when <0.05. The Kappa statistic was used for inter-observer agreement. The Kappa statistics were defined as follows: Kappa = 0 to 0.20 was indicated as "poor agreement", Kappa = 0.21 to 0.40 as "fair agreement"; Kappa = 0.41 to 0.60 as "moderate agreement"; Kappa = 0.61 to 0.80 as "good agreement"; Kappa = 0.81 to 1.00 as "very good agreement". All the statistical analyses in this study were carried out using SPSS version 13 for windows software (SPSS Inc., Chicago, IL, USA).

RESULTS

Fifty-two lung cancer patients (28 male, 24 female) with 72 adrenal masses discovered on MDCT were enrolled. The mean patients' age was 64.3 years (range

TABLE 1. Association between CT characteristics and nature of adrenal masses.

CT parameters	% (Number) Adenoma (n=22)	Metastasis (n=50)	p-value
Size (cm)			
0-3	95.4% (21)	90% (45)	0.660
>3	4.6% (1)	10% (5)	
Attenuation on unenhanced phase			
Homogeneous	86.4% (19)	66% (33)	0.016
Inhomogeneous	13.6% (3)	34% (17)	
Post-contrast enhancement			
Homogeneous	77.3% (17)	70% (35)	<0.001
Inhomogeneous	22.7% (5)	30% (15)	
Border			
Well-defined	86.4% (19)	66% (33)	0.092
Irregular	13.6% (3)	34% (17)	
Involvement pattern			
Focal	90.9% (20)	42% (21)	<0.001
Diffuse nodular	9.1% (2)	58% (29)	
Calcification			
Yes	18.2% (4)	2% (1)	0.028
No	81.8% (18)	98% (49)	
Number of lesion			
Single	75% (12)	63.9% (23)	0.735
Multiple	25% (4)	36.1% (13)	
Side of lesion			
Unilateral	81.3% (13)	72.3% (26)	0.730
Bilateral	18.7% (3)	27.7% (10)	

Significant P value < 0.05

42-86 years). Of 72 lesions, 22 (30.6%) were benign and 50 (69.4%) were metastases.

The diameter of adrenal adenomas ranged from 0.3 to 3.2 cm (mean = 1.54 cm), whereas the size of non-adenomas ranged from 0.4 to 7 cm (mean = 1.94 cm). No statistical significance in differentiating between the two entities was found. Most of the adrenal adenomas (96.9 %, 21 out of 22) were <3 cm in diameter and only 1 adenoma (3.1 %) was >3 cm.

Among the CT parameters, the attenuation on unenhanced phase, post-contrast enhancement, patterns of involvement, and presence of calcification showed statistical significance in differentiating adenoma and metastasis ($p<0.05$). Conversely, the maximum diameter, border, and number of lesions did not show statistical significance ($p>0.05$).

Association between CT characteristics and the nature of adrenal masses have been shown in Table 1. Any discordance in CT findings between two radiologists assessment were resolved by consensus and the Kappa statistic was calculated (Table 2).

TABLE 2. The Kappa value between reviewers in each CT finding.

CT parameters	Kappa
Attenuation on unenhanced phase	0.54
Post-contrast enhancement	0.674
Border	0.567
Pattern of distribution, shape	0.944

Unenhanced attenuation

The mean attenuation of adenoma was 12.23 (range -25 to 33 HU), while the mean attenuation of metastasis was 30.88 HU (range 13 to 61 HU). Significant difference in the unenhanced attenuation between adenoma and metastasis ($P<0.05$) was observed. Different cut off thresholds were used to separate benign form malignant lesions, with the result as shown in Table 3.

Post-contrast medium attenuation

The mean attenuation of adenoma was 86.5 HU (range 18 to 141 HU). For metastasis, the mean attenuation was 76.85 HU (range 24 to 141 HU).

Patterns of involvement

The patterns of involvements were classified as focal nodular or diffuse infiltration along limbs and body

TABLE 3. Different cut off thresholds were used to separate benign form malignant lesions.

Unenhanced attenuation	% (Number) Adenoma (n=22)	Metastasis (n=50)	p- value
HU ≤ 0	22.7% (5)	0% (0)	<0.001
HU > 0	77.3% (17)	100% (50)	
HU ≤ 10	50% (11)	0% (0)	<0.001
HU >10	50% (11)	100% (50)	
HU ≤ 20	63.6% (14)	14% (7)	0.001
HU > 20	36.4% (8)	86% (43)	

Fig 1. A 57-year-old man with lung cancer and adrenal metastasis: (A) Axial unenhanced CT showed a left adrenal mass with attenuation of 26 HU and heterogeneous enhancement on contrast enhanced image (B). Diffuse infiltrative pattern along body, medial and lateral limbs of adrenal gland was noted.

(Fig 1-3), with the result as shown in table 1. This characteristic had 58% sensitivity, 90.9% specificity, 68% accuracy, 93.5% positive predictive value, and 48.7% negative predictive value in differentiating adenoma from metastasis.

DISCUSSION

Most patients in this study underwent CT of the upper abdomen in the same setting with CT of the chest, so images of adrenal glands were acquired on the portal venous phase. Therefore, the percentage wash out that is commonly used to differentiate between adrenal adenoma and adrenal metastasis cannot be made at the first time of CT. Most radiologists usually suggest follow up of adrenal CT protocol in every case with undetermined nature of adrenal masses. In our retrospective study, no patient underwent adrenal CT protocol for follow-up, the main reason being that most patients were beyond stage 1 and showed other organ metastases, such as liver or lymph nodes. Besides that, some patients underwent PET scans instead of repeated adrenal CT protocol. Therefore, the purpose of our investigation was to clarify any CT characteristics that are helpful to differentiate between adenoma and metastasis by using only pre-contrast and post-contrast imaging of adrenal glands.

We found only two findings that are suggestive of adrenal adenoma or metastasis:

1) Density on unenhanced image of ≤10 HU is indicative of lipid-rich adenoma.

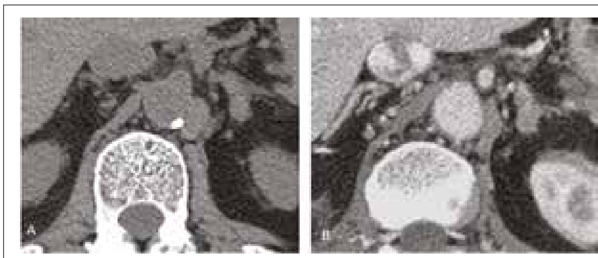

Fig 2. A 59-year-old man with lung cancer and left adrenal metastasis: (A) Axial unenhanced image showed a hypodense mass with attenuation of 39 HU (B) Axial post-contrast CT, this mass showed heterogeneous enhancement and diffuse infiltrative pattern involving medial limb and body of adrenal gland.

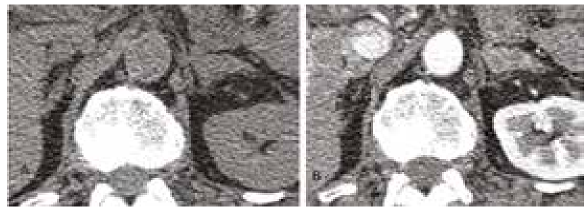

Fig 3. A 72-year-old man with lung cancer and adrenal metastasis: (A) Axial unenhanced image showed a left adrenal mass with attenuation of 39 HU (B) Post-contrast image showed heterogeneous enhancement involving body and lateral limb.

2) Pattern of involvement of adrenal mass (diffuse nodular infiltration along body and limb) is indicative of metastasis.

These entities have statistical significance ($p<0.05$). For the pre-contrast attenuation, we found that when using the unenhanced attenuation value of ≤10 HU, we characterized 11 lipid-rich adenomas out of 22 adenomas, which yielded the highest specificity (100%) and accuracy (84%), although low sensitivity (50%). However, specificity is the most important factor for diagnosis and plan management, so that metastasis is not misdiagnosed as an adenoma. None of adrenal metastases had attenuation ≤10 HU. However, for half of our adrenal adenomas, the attenuation was ≤10 HU which made low sensitivity.

Former research reported that most adenomas had low and homogeneous attenuation on pre-contrast CT and the attenuation of metastasis depended on size.[8] If the size was small, it often showed homogeneous density, but if its size was large, it showed heterogeneous density due to hemorrhage or necrosis. Our study also found the same result.

For the pattern of involvement, if the nodules showed diffuse infiltration along the limbs and body of adrenal glands, they were suggestive to be metastases. If adrenal nodules were focal nodular lesions which were confined in only one limb or body, they could not be differentiated between adenomas and metastases. Only 2 out of 50 patients of adenomas showed diffuse nodular infiltrative pattern, so it yielded high specificity (90.9%).

There were other CT findings that showed statistical significance (P value <0.05), which were calcification, homogeneous or inhomogeneous on non-contrast and post-contrast enhancement. For calcification, previous research revealed that calcification is rare in both adenomas and metastases.[3,8] Although calcification has statistical significance, both adenoma and metastasis rarely contain calcification. One case of non-adenoma that contained a small calcification had increased size after follow-up CT 4 months later, so we presumed this lesion was malignant. However, this lesion contained large amounts of cystic portions and some enhancing solid portions, so according to CT features, it could also possibly be malignant pheochromocytoma. For homogeneous or inhomogeneous attenuation on non-contrast study, although they showed statistical significance, it was a non-specific finding. Both adenoma and metastasis could have homogeneous or inhomogeneous density. Post-contrast enhancement also had statistical significance, but raw data showed the same range of attenuation of adenoma and metastasis. Besides that, our research was a retrospective study with no setting scan protocol, so there were different scan times for the post-contrast phase.

Other CT findings which were size, border, number, unilateral or bilateral involvement did not help to differentiate adrenal adenoma or metastasis (P value >0.05). About the size of adrenal mass, no definite size criteria was accurately used to differentiate adenoma from metastasis, although most adenomas are less than 3 cm, but metastasis can be either greater or less than 3 cm.[5] In our study, sizes were greater than 3 cm in only 1 of 22 cases for adenomas, and 5 cases of metastases, so the size criteria did not help for differentiation. Unilateral and bilateral involvement can occur in adrenal adenoma and metastasis. Adrenal metastases are usually unilateral, although bilateral adrenal metastases are seen in 10 % of all lung cancer patients.[9]

The Kappa value for inter-observer agreement for pattern of involvement was 0.94 and for unenhanced attenuation was 0.54, which were a very good and moderate strength of agreement respectively. The Kappa value for unenhanced attenuation was moderately agreement because two radiologists reviewed the CT images independently at different times. Although the same criteria of ROI was used, these two radiologists may have used different placement of the ROI. Other factors which can affect inter-observer agreement were the size of ROI, and different image selection for ROI measurement.

There were some limitations in our study.

First, the retrospective study may cause bias of subject selection, because only patients who had history of lung cancer and adrenal masses with follow-up CT were included.

Second, there was lack of histology results as a gold standard. For the diagnosis of adrenal masses, we used follow-up CT. Although, the mean follow-up period for benign adrenal masses was 16 months, the follow-up was performed only after 6 months in 2 patients. In our study, we defined adrenal lesion as metastasis if rapid growth occurred in less than 6 months. Therefore, slow-growing metastasis may have been falsely classified as adenoma. Besides that, other malignant lesions could not be verified such as in one case that CT features suspected malignant pheochromocytoma.

Third, there were a relatively small number of cases in each group of adenoma and metastasis.

CONCLUSION

A helpful CT characteristic in lung cancer patients found with incidental adrenal masses from CT of the chest and upper abdomen for staging is unenhanced CT attenuation that is ≤10 HU, indicating lipid-rich adenoma, which provides high specificity to exclude metastasis. Another helpful characteristic is the pattern of involvement, if the lesion shows diffuse nodular infiltration along the body and limbs of the adrenal gland, it suggests metastasis. However, there is a limitation of the unenhanced and portal venous phase to diagnose small adrenal lesions, unenhanced attenuation >10 HU, with focal nodular appearance, because it can be either lipid-poor adenoma or small metastasis.

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