

## How to Differentiate Inactive from Active Disease in Patients of Primary Multidrug-resistant Tuberculosis with Persistent Cavity after Anti-tuberculous Therapy

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### ABSTRACT

**Objective:** To determine how to differentiate inactive from active disease in patients with primary multidrug-resistant tuberculosis who have a persistent cavity after completing treatment.

**Methods:** We evaluated computed tomography findings to determine activity of chronic cavitary disease in patients with primary multidrug-resistant tuberculosis after completing treatment. This study evaluated cavity, centrilobular nodules, consolidation, large nodules, calcified nodules, parenchymal calcification, emphysema, bronchovascular distortion, irregular lines, and parenchymal band. The presence of pleural thickening, pleural effusion, and lymphadenopathy was recorded.

**Results:** In univariate analysis, centrilobular nodules and consolidation were significantly less common in the chronic inactive cavitary group. The cavity wall was thinner in the chronic inactive cavitary group than that in the chronic active cavitary group. A multivariate analysis revealed that centrilobular nodules and thickness of the cavity wall were significant computed tomography findings associated with active disease.

**Conclusions:** Centrilobular nodules and thickness of the cavity wall were the most characteristic computed tomography findings to predict active disease in patients with chronic cavitary pulmonary multidrug-resistant tuberculosis at the time of treatment completion. In the proper clinical setting, these computed tomography findings could help decision-making for completing treatment in cases of chronic cavitary multidrug-resistant tuberculosis after anti-tuberculous therapy.

**Key Words:** Lung diseases; Tomography, X-ray computed; Tuberculosis

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## 中文摘要

# 原發性多重耐藥性結核病患者抗結核治療後持續性肺部空洞中活動性與非活動性病變如何鑑別？

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**目的：**確定原發性多重耐藥性結核病患者抗結核治療後持續性肺部空洞中活動性與非活動性病變的鑑別診斷方法。

**方法：**評估抗結核治療後的原發性多重耐藥性結核病患者的電腦斷層掃描（CT）特徵，以確定其慢性肺部空洞性病變的活動性。評估項目包括空洞、小葉中心結節、小葉實變、大結節、鈣化結節、實質鈣化、肺氣腫、支氣管血管扭曲變形、不規則線狀影和肺實質帶。並記錄病人胸膜增厚、胸腔積液和淋巴結腫大的出現。

**結果：**單元分析顯示在慢性非活動性空洞組別中，明顯較少見小葉中心結節和小葉實變；其空洞壁也比活動性空洞組別更薄。多元分析顯示小葉中心結節和空洞壁厚度是與活動性病變顯著相關的CT特徵。

**結論：**原發性多重耐藥性結核病患者抗結核治療後，其小葉中心結節和空洞壁厚度為最具特徵性CT表現，能預測慢性空洞的活動性。在適當的臨床環境中，這些CT特徵有助於抗結核療程終止的決策制定，以防治療後慢性空洞性多重耐藥結核的發生。

## INTRODUCTION

Although the overall prevalence of pulmonary tuberculosis (TB) has decreased, it remains an important cause of morbidity and mortality.<sup>1</sup> Multidrug-resistant TB (MDR TB) has surged as a public health problem worldwide.<sup>2</sup> The major concerns of drug resistance are fear regarding the spread of drug-resistant organisms and the ineffectiveness of anti-microbial treatment in patients infected with these organisms. Lockman et al<sup>3</sup> suggested that human immunodeficiency virus (HIV)-negative patients with primary MDR TB have significantly higher treatment failure rates and higher mortality compared with those with drug-sensitive TB.

Diagnosing pulmonary TB is usually based on detecting acid-fast bacilli in sputum smears or cultures. In addition to the diagnosis of TB, high-resolution computed tomography (CT) is useful for determining disease activity.<sup>4,5</sup> Cavities, the radiological hallmark of reactivated TB, are evident radiographically in 40% to 45% of patients with post-primary TB.<sup>6,7</sup> Multiple cavities are seen more frequently in patients with MDR TB.<sup>8,9</sup> The majority of cavities heal as linear or fibrotic lesions, but some cavities persist after anti-tuberculous therapy. Thus, it can be difficult to determine pulmonary TB activity on imaging studies when cavities persist

after anti-tuberculous therapy. The purpose of this study was to determine how to differentiate inactive from active disease in patients with primary MDR TB who had a persistent cavity after completing treatment.

## METHODS

### Patients and Diagnoses

Our institutional review board approved this retrospective study with a waiver of the requirement for informed patient consent.

A computer-based search was performed to identify patients with pulmonary MDR TB from September 2005 to March 2013. Inclusion criteria for this study were: (1) bacteriologically confirmed TB with positive sputum culture of *Mycobacterium tuberculosis*; and (2) newly diagnosed primary MDR TB (defined as TB resistant to at least isoniazid and rifampicin); the mode of acquisition of drug resistance was defined as 'primary' when it was identified in an individual who had never received anti-tuberculous therapy or who had a therapy history of <1 month; radiological findings might show inadvertently progressed features with an ongoing infection (chronic TB infection) during the development of acquired resistance; thus, we only included patients who had a primary resistant form of MDR TB; (3)

negative for HIV antibody; (4) willingness to complete 24 months of anti-tuberculous therapy based on drug susceptibility testing; and (5) follow-up chest CT scans performed at treatment completion to evaluate the treatment response.

The search identified 31 patients with chronic inactive cavitory MDR TB after anti-tuberculous therapy. We defined chronic inactive cavitory MDR TB as pulmonary MDR TB with a persistent cavity despite a negative sputum culture after anti-tuberculous therapy.

This group was comprised of 17 males and 14 females (mean age, 48 years; range, 16-68 years). A control group of 31 patients with primary MDR TB was formed by random selection. They had a persistent cavity on a follow-up CT scan, and their sputum cultures obtained at treatment completion were positive for acid-fast bacilli. This group was comprised of 22 males and 9 females (mean age, 44 years; range, 22-62 years).

### Image Acquisition and Analysis

All CT examinations were performed using a four-row multidetector CT scanner (Asteion; Toshiba Medical, Tokyo, Japan). None of the patients were administered any intravenous contrast medium. Thin-section CT scans were performed from the lung apices to the lung bases with a 1-mm collimation at 10-mm intervals. The thin-section scanning parameters were 120 kV with a 512 × 512 matrix. Data were reconstructed using a 2.5-mm thickness for transaxial images.

Chest CT scans were reviewed by two radiologists (SHK and JYL) with 4 and 15 years of experience respectively, and both had no knowledge of the patients' clinical information. A final decision regarding the findings was determined by consensus.

The assessed patterns of parenchymal abnormalities included cavity (site, number, size of the largest cavity, and the maximal thickness), centrilobular nodules (including a tree-in-bud pattern), consolidation, large nodules (a well-defined nodule 10-30 mm in

diameter), calcified nodules, parenchymal calcification, paracicatricial emphysema, bronchovascular distortion, irregular lines, and a parenchymal band (a linear opacity that usually extends to the visceral pleura). The laterality (unilateral or bilateral) of cavities was also analysed.

We measured cavity wall thickness at the thickest portion. In addition, the presence of mediastinal or hilar lymph node enlargement and pleural effusion or thickening was recorded. Enlarged lymph nodes were defined as those having a short-axis diameter of >1 cm on CT scan.

### Statistical Analyses

Statistical analyses were performed using the SPSS 19.0 software (SPSS, Inc., Chicago, IL, USA). The mean age and sex ratios of the patients with TB were evaluated using the Mann-Whitney *U* test and the chi-square test, respectively. The CT findings in patients with TB were compared with the chi-square and Fisher's exact tests. The Mann-Whitney *U* test was used to test the number, size, and thickness of cavities. A logistic regression was performed for the multivariate analysis. A *p* value of <0.05 was considered statistically significant.

## RESULTS

The demographic data of the two groups are summarised in Table 1. No significant differences in age or sex were observed between the groups with chronic inactive and active cavitory MDR TB. The CT findings of the two groups are summarised in Table 2. A univariate analysis revealed no significant difference between the two groups in terms of number, size, laterality, or number of involved lobes with a cavity, large nodule, calcified nodule, parenchymal calcification, paracicatricial emphysema, bronchovascular distortion, fibrotic band, lymphadenopathy, pleural effusion, or pleural thickening.

Centrilobular nodules and consolidation were less frequently observed in the chronic inactive cavitory group versus the chronic active cavitory group (Figures 1 and 2; both *p* < 0.001). The cavity wall was thinner

**Table 1.** Comparison of demographic data for inactive and active primary multidrug-resistant tuberculosis with a persistent cavity after anti-tuberculous therapy.

Demographics	Inactive TB (n = 31)	Active TB (n = 31)	p Value
Age in years (mean ± standard deviation; range)	48 ± 15; 16-68	44 ± 14; 22-62	0.302
Sex (M:F)	17:14	22:9	0.293

in the chronic inactive cavitory group than that in the active cavitory group (Figure 3). The thickness of the cavity wall was 1.4 to 10.2 mm in the chronic inactive cavitory group (mean, 3.4 mm) and 1.3 to 14.7 mm in the chronic active cavitory group (mean, 6.6 mm;  $p =$

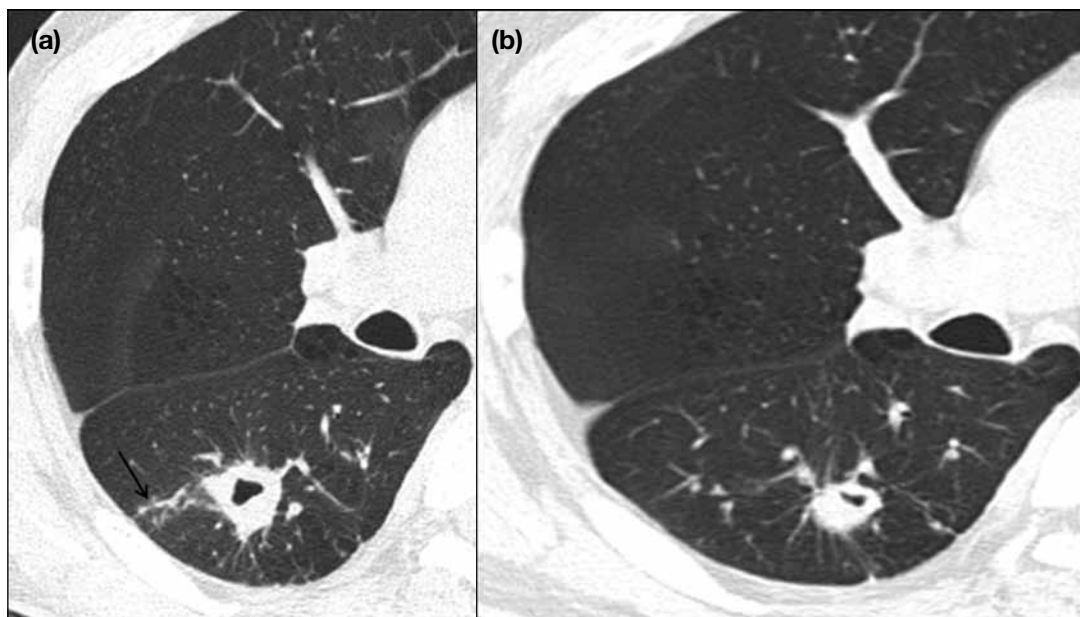
0.002).

A multivariate analysis revealed that centrilobular nodules (odds ratio [OR] = 0.024; 95% confidence interval [CI], 0.03-0.162;  $p < 0.001$ ) and thickness of

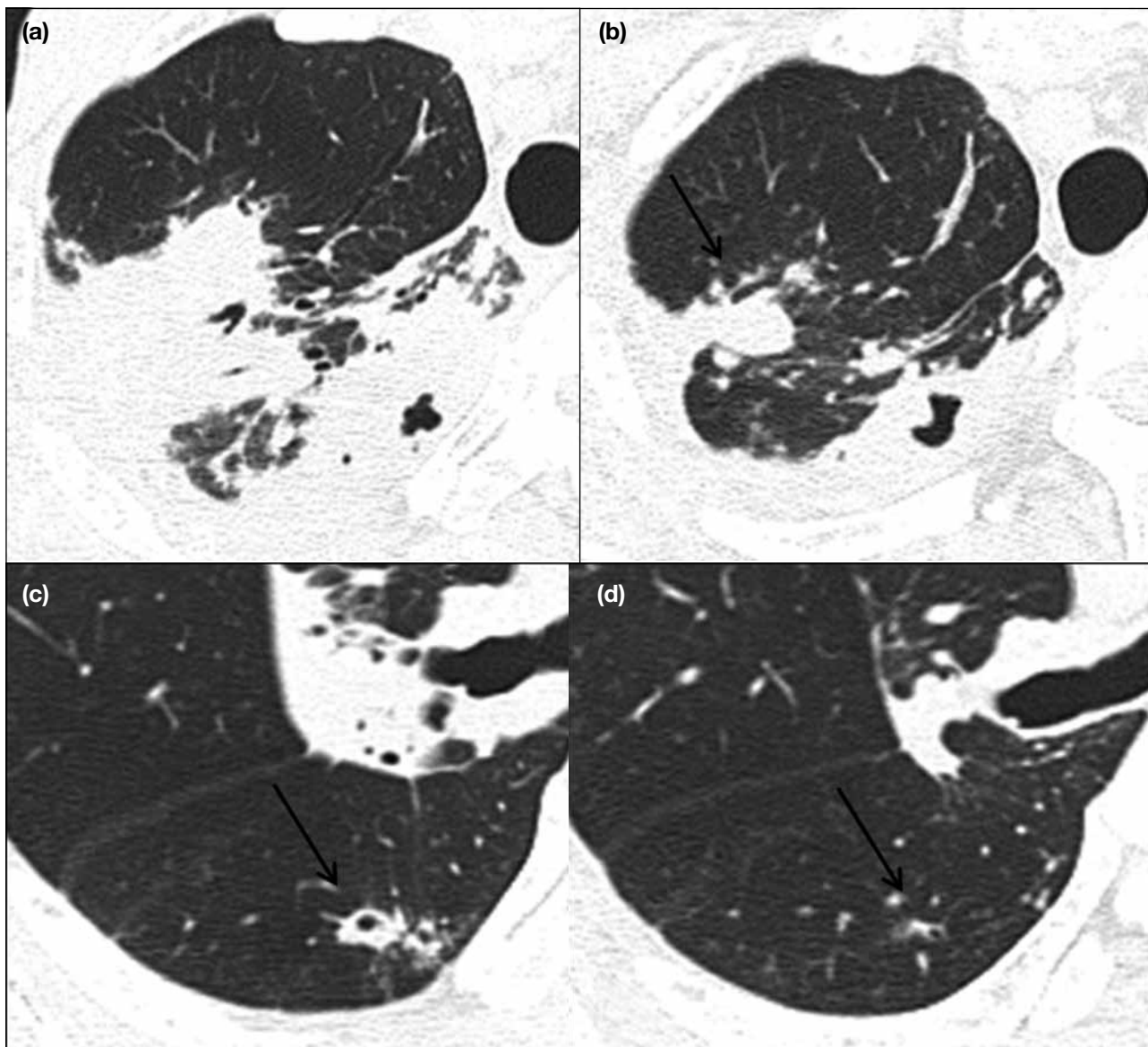
**Table 2.** Comparison of the computed tomography findings for inactive and active primary multidrug-resistant tuberculosis with a persistent cavity after anti-tuberculous therapy.

	Inactive TB (n = 31)	Active TB (n = 31)	p Value
Cavity			
Mean No.*	1.9	1.4	0.108
Mean size (mm)*	32	22	0.227
Mean thickness (mm)*	3.4	6.6	0.002
Laterality			0.068
Unilateral	27 (87%)	21 (68%)	
Bilateral	4 (13%)	10 (32%)	
Centrilobular nodules	4 (13%)	27 (87%)	<0.001
Large nodule	16 (52%)	10 (32%)	0.123
Consolidation	3 (10%)	21 (68%)	<0.001
Calcified nodule	12 (39%)	8 (26%)	0.277
Parenchymal calcification	8 (26%)	4 (13%)	0.199
Paracatricial emphysema	11 (35%)	5 (16%)	0.082
Bronchovascular distortion	28 (90%)	25 (81%)	0.473
Fibrotic band	26 (84%)	20 (65%)	0.082
Lymphadenopathy	6 (19%)	2 (6%)	0.255
Pleural effusion	1 (3%)	4 (13%)	0.354
Pleural thickening	29 (94%)	24 (77%)	0.147

Abbreviation: TB = tuberculosis.



**Figure 1.** Primary multidrug-resistant tuberculosis (MDR TB) in a 58-year-old man with a negative sputum culture for *Mycobacterium tuberculosis* after anti-tuberculous therapy. (a) A transaxial thin-section computed tomography (CT) scan obtained at the level of the bronchus intermedius shows a cavity in the superior segment of the right lower lobe. Note the branching or non-branching centrilobular nodules (arrow) in the superior segment of the right lower lobe. (b) A CT scan shows a persistent cavity with bronchovascular distortion and a fibrotic band after anti-tuberculous therapy, but the centrilobular nodules disappear. No relapse was observed during the follow-up period.



**Figure 2.** Primary multidrug-resistant tuberculosis (MDR TB) in a 64-year-old man with a positive sputum culture for *Mycobacterium tuberculosis* after anti-tuberculous therapy. (a) A transaxial computed tomography (CT) scan obtained at the level of the great vessels in the thoracic inlet shows segmental air-space consolidation with air-bronchogram and cavity in the right upper lobe. (b) A thick-walled cavity remains after anti-tuberculous therapy. Note nodular consolidation, multiple centrilobular nodules, and pleural thickening in the right upper lobe (arrow). (c) A CT scan obtained at the level of the right bronchus demonstrates small cavity and satellite centrilobular nodules in the right lower lobe (arrow). (d) The cavity disappears almost completely (arrow) from the right lower lobe after anti-tuberculous therapy. Additionally, the satellite centrilobular nodules disappear. This case illustrates both responding and non-responding areas of MDR TB in the same patient. We believe that the non-responding area is more important for detecting pulmonary MDR TB activity than the responding area.

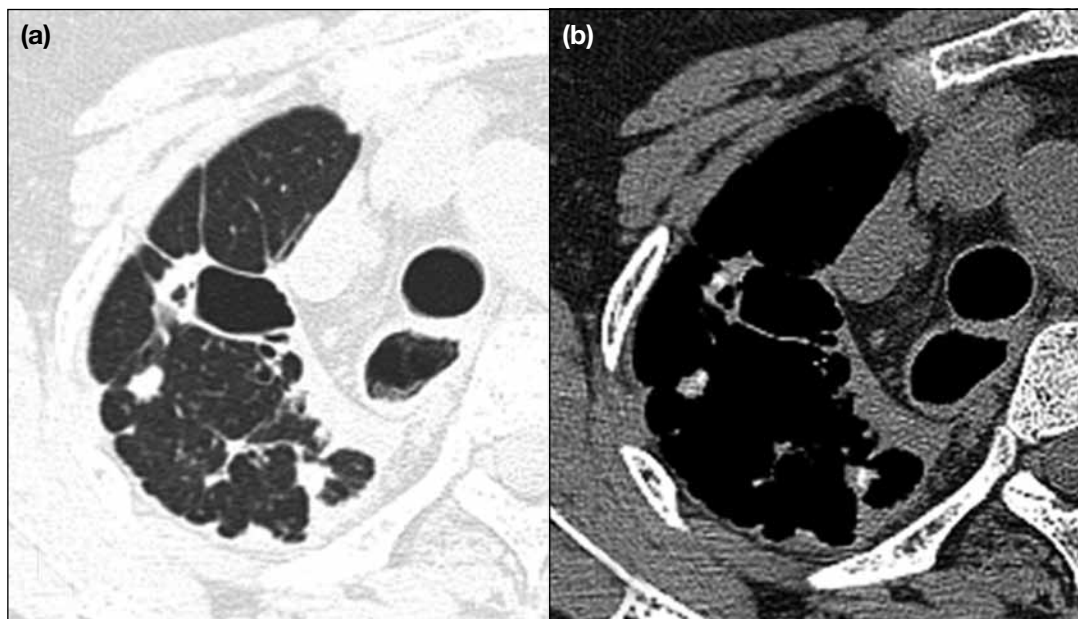
the cavity wall (OR = 0.701; 95% CI, 0.503-0.988; p = 0.042) were significant CT findings in the chronic inactive cavitory group.

## DISCUSSION

It is often necessary to determine pulmonary TB disease activity at treatment completion before the results of

TB cultures are available. The decision must be based on clinical and radiological evidence. In this situation, a persistent cavity on imaging studies may cause confusion regarding treatment completion.

Tuberculous cavitation usually indicates a high likelihood of activity.<sup>10</sup> However, disease activity



**Figure 3.** Primary multidrug-resistant tuberculosis (MDR TB) in a 56-year-old woman with a negative sputum culture for *Mycobacterium tuberculosis* after anti-tuberculous therapy. (a and b) Transaxial computed tomography (CT) scans obtained at the level of the great vessels in the thoracic inlet show a cavity remaining in the right upper lobe. Fibrotic bands, bronchovascular distortion, pleural thickening, and calcified nodules (b, mediastinal window) suggesting fibrotic changes are also observed in the right upper lobe. The cavity is thin and no small centrilobular nodules are found on CT that suggests active disease.

cannot be determined based on a cavity alone. Zierski<sup>11</sup> reported no bacteriological relapse for up to 5 years after anti-tuberculous therapy was stopped in patients who had a persistent cavity and a negative sputum culture, if adequate therapy was administered for a long period of time.

In this study, we evaluated CT findings to determine the activity of chronic cavitory disease in patients with primary MDR TB at the time of treatment completion. The most common CT findings of active pulmonary TB are centrilobular small nodules, branching linear and nodular opacities (tree-in-bud sign), patchy or lobular areas of consolidation and cavitation.<sup>12</sup> In our study, centrilobular nodules were significant CT findings associated with active disease in the multivariate analysis. Im et al<sup>13</sup> showed that small airway changes are the most characteristic findings of tuberculous infection. Small centrilobular nodules and the tree-in-bud sign reflect the presence of endobronchial spread and are due to the presence of caseous necrosis or granulomatous inflammation filling the surrounding terminal and respiratory bronchioles and alveolar ducts.<sup>10</sup> This appearance of the centrilobular nodules is highly suggestive of active TB but not pathognomonic for active TB. In the proper clinical setting, the centrilobular

nodules are thought to be a reliable criterion for active disease. Coalescence of centrilobular opacity occurs with more extensive disease, resulting in focal areas of bronchopneumonia. In our study, consolidation was also less frequently observed in the chronic inactive cavitory group in the univariate analysis.

In our study, the cavity wall was thinner in the chronic inactive cavitory group than that in the chronic active cavitory group. Lee et al<sup>14</sup> reported that cavities could be a good diagnostic sign, but they found no specific correlation between the CT appearance of cavities and disease. However, active-disease cavities typically have thick, irregular walls that become smooth and thin with treatment.<sup>15</sup> Therefore, thickness of the cavity wall seems to be important for evaluating disease activity after completion of anti-tuberculous therapy.

No significant differences were observed between the two groups with respect to the presence of calcified nodules, parenchymal calcification, paracatricial emphysema, bronchovascular distortion, fibrotic band, or pleural thickening. These findings may be due to the presence of residual fibrotic changes. Some patients in the sputum-positive group also showed these fibrotic changes. Im et al<sup>13</sup> showed that cavitory lesions cause

more cicatricial changes than other areas without cavitation following treatment, and that the prevalence of distortion of bronchovascular structures, emphysema, fibrotic bands, or bronchiectasis tend to increase on follow-up CT scans. Thus, fibrotic changes on CT may not be useful to differentiate between a chronic cavity and ongoing disease after anti-tuberculous therapy.

This study had some limitations. First, some selection bias may have occurred because not all patients with pulmonary TB underwent a CT scan. The evaluation of pulmonary TB involved sputum smear examination, sputum culture, and chest radiographs due to ease of performance, widespread availability, low cost, and a considerable diagnostic yield. CT scans were usually performed in patients with more grave symptoms and signs. Moreover, a chest CT scan was often performed in patients with cavitory TB for possible surgical treatment.<sup>16</sup> Therefore, this study was probably biased towards patients who were surgical candidates or had somewhat atypical clinical manifestations of TB. Second, the population studied was small and patients were recruited from only one hospital. As a result, this study population may not be representative of the general population. Additional investigations with larger populations are necessary. Third, we classified patients with MDR TB based on findings of sputum culture alone. Therefore, the 'chronic inactive cavitory MDR TB' group may have been wrongly classified, based upon a negative sputum culture, and no further testing, such as bronchoalveolar lavage, was used. In practice, as bronchoscopy examination is very painful, many patients refuse this examination. In our study, the chronic inactive cavitory MDR TB group was followed up for at least 1 year after treatment. No relapses were observed during this period.

## CONCLUSION

Centrilobular nodules and thickness of the cavity wall were the most characteristic CT findings to predict active disease in patients with chronic cavitory pulmonary MDR TB at the time of treatment completion. In the proper clinical setting, these CT findings could help decision-making for completing treatment in cases of chronic cavitory MDR TB after

anti-tuberculous therapy.

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