Density Features of Screened Lung Tumors in Low-Dose Computed Tomography

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Rationale and Objectives: Using low-dose computed tomography (LDCT), small and heterogeneous lung tumors are detected in screening. The criteria for assessing detected tumors are crucial for determining follow-up or resection strategies. The purpose of this study was to investigate the capacity of density features in differentiating lung tumors.

Materials and Methods: From July 2008 to December 2011, 48 surgically confirmed tumors (29 malignancies, comprising 17 cases of adenocarcinoma and 12 cases of adenocarcinoma in situ [AdIs], and 19 benignancies, comprising 11 cases of atypical adenomatous hyperplasia [AAH] and eight cases of benign non-AAH) in 38 patients were retrospectively evaluated, indicating that the positive predictive value (PPV) of physicians is 60.4% (29/48). Three types of density features, tumor disappearance rate (TDR), mean, and entropy, were obtained from the CT values of detected tumors.

Results: Entropy is capable of differentiating malignancy from benignancy but is limited in differentiating AdIs from benign non-AAH. The combination of entropy and TDR is effective for predicting malignancy with an accuracy of 87.5% (42/48) and a PPV of 89.7% (26/29), improving the PPV of physicians by 29.3%. The combination of entropy and mean adequately clarifies the four pathology groups with an accuracy of 72.9% (35/48). For tumors with a mean below -400 Hounsfield units, the criterion of an entropy larger than 5.4 might be appropriate for diagnosing malignancy. For others, the pathology is either benign non-AAH or adenocarcinoma; adenocarcinoma has a higher entropy than benign non-AAH, with the exception of tuberculoma.

Conclusions: Combining density features enables differentiating heterogeneous lung tumors in LDCT.

Key Words: Density feature; low-dose computed tomography; lung tumor; computer-aided diagnosis.

The advent of low-dose computed tomography (LDCT) has altered the landscape of lung cancer screening because of its capability of detecting tumors at early stages (1–3). The use of LDCT is particularly necessary for clinical applications in population-based screening and follow-up examinations because the risk of cancer caused by diagnostic X-ray-based examinations can thereby be reduced (4). Thin-section CT is also critical because it depicts realistic tumor characteristics (5), improves the probability of detecting small nodules (6), and identifies true calcification in subcentimeter nodules (7). However, the image quality is determined by the interaction between the radiation dose and slice thickness (8). Thin-section CT has the advantage of depicting realistic characteristics for tumor assessment, but a high radiation exposure is necessary for improving the image quality. The limitation of radiation exposure sacrifices the CT image quality acquired using the low-dose and thin-section protocol (9). Thus, the assessment of aggressive and heterogeneous tumors has become a challenge (10) because interpretation is subjective, resulting in poor interobserver agreement (11,12) regarding LDCT images of inferior quality, low tissue contrast, and high noise ratio.

The tumor disappearance rate (TDR) is a simple method that assesses a lung tumor by comparing tumor sizes in a two-window (lung and mediastinal) setting (13). In each setting, the tumor size is measured according to the maximum diameter or the approximate area, which is the product of the maximum diameter and the perpendicular diameter. The TDR has been reported to correlate with clinical histopathology (14,15) and conveys an independent prognostic factor (16,17). The TDR could also be used to evaluate the presence a high–CT attenuation component in the tumor.

Acad Radiol 2014; 21:41–51

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http://dx.doi.org/10.1016/j.acra.2013.09.021

Based on the presence or absence of high-attenuation components, tumors can be classified into three categories: pure ground-glass opacity (GGO), partial-solid, and solid. In CT screening for lung cancer, the detected nodules are frequently partial-solid or non-solid, which are more likely to be malignant than those that are solid (18).

The CT attenuations within a tumor can be used to define density features (19–22). Compared to measuring the presence of high-attenuation components by using the TDR, the CT values of an entire tumor are regarded as distribution and expressed as density features. Kitami et al. attempted to differentiate atypical adenomatous hyperplasia (AAH), bronchioloalveolar carcinoma (BAC), and invasive carcinoma by using the central tendency of the distribution (19). Similarly, the peak and mean CT values of the distribution were used to distinguish between AAH and BAC (20). The peak and percentile values were used to classify AAH, BAC, and adenocarcinoma (AdCa) (21). However, these density features, including the TDR, were generated from the CT images acquired using a diagnostic radiation dose. In low-dose thin-section CT images, inferior quality, low tissue contrast, and high–noise ratio directly altered the CT values. Thus, the capacity of density features derived from LDCT to differentiate between malignant and benign tumors and to classify pathology types is uncertain. Entropy can also be derived from density distribution and can be used to describe the uncertainty and complexity of a tumor (22). We therefore investigate the effectiveness of the density features, TDR, mean, and entropy, in differential diagnosis of lung tumors in low-dose thin-section CT images. Although the preliminary result was limited by small case numbers and manually assisted tumor segmentation, the density features showed the potential to differentiate the pathology groups detected in the screening (23,24).

The purpose of this study was to investigate the capability of density features detected in low-dose thin-section CT images to diagnose lung tumors in greater detail. To improve the capability, the features were integrated in a computer-aided diagnosis (CAD) system to predict malignancy and distinguish tumor pathology.

MATERIALS AND METHODS

Patients

This study was approved by the Institutional Review Board of China Medical University Hospital. We reviewed the results of LDCT screening as an option for health examination at the Health Examination Centre of China Medical University Hospital. This screening was performed on 2804 people from July 2008 to December 2011. In our screening results, abnormal CT densities were not infrequently detected in most people, which may be accounted by the high sensitivity of CT scanning. An abnormality with a shortest diameter of larger than 4 mm was regarded as clinically significant and requiring further diagnosis. Diagnosis of the suspected abnormality was fully discussed in combined conferences with chest physicians, surgeons, radiologists, and pathologists.

The standard criteria used to diagnose benign abnormality were (1) abnormality being entirely calcified or scar-like, (2) abnormality with satellite densities, particularly in the upper lobe (in which case, tuberculosis was considered first), and (3) abnormality showing popcorn calcifications within a well-circumscribed boundary (in which case, chondroid hamartoma was considered first).

Criteria used for favoring malignant abnormality were (1) sizes between 4 mm and 15 mm with characteristics of internal density other than vascular networks or bronchioles, lobulation, irregularity, and speculation and (2) sizes larger than 15 mm with irregular margin or density other than benign calcification. Abnormalities fitting malignant criteria were recommended for surgery. However, family cancer history, multiple abnormalities, and patient's expectation for excision were also considered, particularly for abnormalities with equivocal characteristics.

A total of 38 patients were recommended to undergo surgical procedures because of uncertain malignancies interpreted in the combined conferences. Their diagnosis was subsequently confirmed through surgical pathology. Furthermore, 14 patients received a positron emission tomography scan before surgery, but none showed lesion uptake on GGO tumors.

Forty-eight surgically confirmed lung nodules with a mean diameter of 10.03 ± 3.37 mm (range, 4.04–17.65 mm) were found in 38 patients (16 men and 22 women) who were enrolled in this study. Most patients had never smoked (n = 28); the number of past and current smokers was three and four, respectively, and the remaining three patients were not recorded. Pulmonary function test was mandatorily performed before surgery, and no patients showed obstructive defects. We also reviewed all the participants' chest X-ray and observed that none met the criteria of emphysema or were compatible with chronic bronchitis. The characteristics of enrolled patients are listed in Table 1. The resected tissues (lobectomy, n = 14; segmental resection, n = 4; and wedge resection, n = 24) were independently interpreted by pathologists, who confirmed diagnoses of malignancy (n = 29) and benignancy (n = 19). The malignancies comprised 17 cases of AdCa tumors (stage I) and 12 cases of adenocarcinoma in situ (AdIs) tumors. The benignancy comprised 11 cases of AAH tumors and eight cases of benign non-AAH tumors. The eight benign non-AAH tumors comprised cryptococcus (n = 3), tuberculosis (n = 2), interstitial fibrosis (n = 1), anthracotic histiocytosis with reactive lymphoid expansion (n = 1), and organizing pneumonia (n = 1). The criteria used for diagnosing AAH, AdIs, and AdCa were in accordance with the World Health Organization pathology classification (25,26).

CT Screening Protocol

Examinations were performed using a 64-row multidetector CT scanner (Light Speed VCT; GE Healthcare, Waukesha,