Original Investigation

Assessment of Heterogeneity Difference Between Edge and Core by Using Texture Analysis: Differentiation of Malignant From Inflammatory Pulmonary Nodules and Masses

Shiteng Suo, MS, Jiejun Cheng, MD, Mengqiu Cao, MD, Qing Lu, MD, Yan Yin, MD, Jianrong Xu, MD, PhD, Huawei Wu, MD

Rationale and Objectives: This study aimed to test the hypothesis that the heterogeneity difference between edge and core of lesions by using intensity and entropy features obtained from whole-lesion texture analysis on contrast-enhanced computed tomography (CT) may be useful for differentiation of malignant from inflammatory pulmonary nodules and masses.

Materials and Methods: In all, 48 single pulmonary nodules and masses were retrospectively evaluated. All lesions were histologically or clinically confirmed (malignancy: inflammation = 24:20). We utilized a newly introduced texture analysis method based on contrast-enhanced CT (first described by Grove et al.) that automatically divided the whole lesion volume into two regions: edge and core. Mean attenuation value (AV) and entropy of each region and also the whole lesion were evaluated separately. Each texture metric (absolute value for each region, and difference value defined as difference between edge and core) of malignant and inflammatory lesions were compared using Mann-Whitney *U* test. Individual image parameters were combined by using linear discriminant analysis. Receiver operating characteristic curves were generated to assess each texture metric and their combination for discriminating between the two entities.

Results: Mean AV difference and entropy difference were significantly higher in malignant lesions than in inflammatory lesions (4.71 HU ± 5.06 vs –1.53 HU ± 5.05, $P < .001$; 0.45 ± 0.23 vs 0.18 ± 0.30, $P = .001$). Receiver operating characteristic curves for individual mean AV difference and entropy difference provided relatively high values for the area under the curve (0.836 and 0.795, respectively). The combination of mean AV difference, entropy difference, and lesion volume improved the area under the curve to 0.864.

Conclusion: Heterogeneity difference between edge and core by using whole-lesion texture analysis on contrast-enhanced CT may be a promising tool for estimating the probability of malignancy in pulmonary nodules and masses.

Key Words: Heterogeneity; texture analysis; lung cancer; inflammation; contrast-enhanced CT.

INTRODUCTION

Lung cancer is the leading cause of cancer deaths in both men and women, with a 5-year survival rate of only 18% in the United States (1). Early diagnosis and early surgery are still considered as the most effective methods that may reduce lung cancer mortality. In clinical practice, focal pulmonary lesions are commonly encountered with the wide spread and use of multidetector-row computed tomography (CT) scanners. Typically, focal pulmonary lesions may be classified as nodules (less than 3–4 cm in diameter) or masses (more than 3–4 cm in diameter) (2). Malignancy accounted for

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From the Department of Radiology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, No. 160 Pujian Rd, Shanghai 200127, China. Received November 29, 2015; revised April 12, 2016; accepted April 20, 2016. The first two authors contributed equally to this work. The present research was supported by the National Natural Science Foundation of China (Nos. 81571630, 81501458, 81571670, 81271638, and 81371622). **Address correspondence to:** H.W. e-mail: huaweiwu26@163.com; J.X. e-mail: xujianrong_renji@163.com

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approximately half of nodules, whereas masses tend to be even more likely to be malignant (2). Therefore, it is important to accurately differentiate malignant from benign lesions in the least invasive way to facilitate prompt and effective interventions, as therapeutic approaches are almost completely distinct.

CT imaging has enabled a more detailed characterization of focal pulmonary lesions noninvasively based on imaging features such as internal density, contour shape, margins, and contrast enhancement features. However, among all types of benign focal pulmonary lesions, inflammatory lesions can share not only similar morphologic characteristics, but also comparable contrast enhancement levels with lung cancers (3), making the differential diagnosis even more difficult (4).

Recently, texture analysis on CT has emerged as a promising image-processing technique in capturing spatial heterogeneity in various lesions. The underlying hypothesis for the utility of texture analysis is that lesions are heterogeneous both on histopathologic and radiological levels, and texture analysis on radiological data may reflect the cellular and molecular characteristics observed microscopically, which usually cannot be recognized by the naked eye. For example, a previous study showed that CT texture features may reflect the underlying vasculature as defined by CD34 (5). However, as texture analysis is a mathematical method, its biological mechanisms are complex and not completely understood. Nevertheless, texture analysis on radiological data has nowadays become an integral part of an emerging field call *radiomics*, a high-throughput process in which large amounts of advanced quantitative imaging features are extracted and integrated for predictive or prognostic purpose (6–8). Some research groups have developed texture analysis methods to quantify lesion heterogeneity on lung CT (9–11).

Entropy is a representative texture parameter that depicts the lesion heterogeneity. It measures disorder or how much difference there may be in measurements within a given region. Higher entropy indicates increased lesion heterogeneity (12). Several studies have shown that entropy extracted from medical images may add value in assessment of tissue morphologic changes induced by various diseases, including adnexal neoplasms (13,14), liver cirrhosis (15), and lung diseases (10,16). Grove et al. (17) and Gatenby et al. (18) first introduced a new heterogeneity metric by using entropy difference of CT attenuation across the tumor core to boundary regions and found it could predict patient survival in lung adenocarcinoma. Based on previous studies, we hypothesized that measuring entropy would provide meaningful information on the characteristics of pulmonary nodules and masses, and therefore help differentiate between malignant and inflammatory lesions. Because contrast-enhanced computed tomography (CECT) with the use of iodine contrast agent gives insight into lesion heterogeneity related to the presence of areas with different vascularization, it can be hypothesized that hyperintensity on CECT presents high vascularization and hypointensity corresponds to low vascularization (19). Additionally, as described by Grove et al. and Gatenby et al., subdividing the pulmonary lesion into core and edge regions can separately evaluate the spatially explicit biological processes and reveal varying textural behavior across the whole lesion (17,18). Therefore, the purpose of our study was to investigate the value of heterogeneity difference between edge and core by using whole-lesion texture analysis (including intensity and entropy features) on CECT for differentiation of malignant from inflammatory pulmonary nodules and masses.

MATERIALS AND METHODS

Patients

Our institutional review board approved this retrospective study with a waiver of written informed consent from patients. One author (S.S.) searched the clinical and radiological databases of our hospital to identify patients with pathologically or clinically proven pulmonary nodules and masses between August 2010 to May 2013 and who had undergone preoperative chest CECT on the same clinical system (Discovery CT750HD scanner, GE Healthcare, WI). Subjects were excluded for the following reasons: (1) the nodules or masses did not meet research requirement (>8 mm in size, round or oval shaped, solitary, no obvious calcification, necrosis, or cavitation; $n = 21$), (2) patients had ever received treatment for the pulmonary lesion ($n = 9$), and (3) image quality was unsatisfactory caused by severe artifact ($n = 6$). This yielded a final study cohort of 48 patients (mean age, 61.9 years ± 10.3 [standard deviation]; age range 41–80 years). There were 40 men (mean age, 62.3 years ± 9.9; age range 43–80 years) and 8 women (mean age, 59.5 years ± 12.6; age range 41–71 years). Among the 48 patients, 28 patients were diagnosed with primary lung cancer (adenocarcinoma in 14 cases, squamous cell carcinoma in 12 cases, and small cell carcinoma in 2 cases) and 20 patients were diagnosed with inflammatory lesions (focal-organizing pneumonia in 9 cases, granulomatous inflammation in 8 cases, and pulmonary inflammation in 3 cases). In all cases, definitive diagnosis was made at surgical resection, transbronchial lung biopsy, CT-guided percutaneous biopsy or clinical examination and therapy (only for the 3 pulmonary inflammation cases whose results of fiber optic bronchoscopy were negative, but the lesions disappeared or obviously reduced in size on CT after anti-infective therapy as confirmed by one experienced radiologist). Patient characteristics are summarized in Table 1.

CT Examination

All patients underwent contrast-enhanced multidetector CT on the GE Discovery CT750HD scanner in the supine position. Images were acquired 90 seconds after the intravenous injection of 80–100 mL iodinated contrast material (Iopamidol, 370 mg/mL; Shanghai Bracco Sine Phamaceutical Co. Ltd., China) and 50 mL saline chaser at a rate of 4 mL/s via a pump injector, as per the standard practice in our institution. Specific CT protocol parameters were as follows: tube voltage,