Original Investigation

Lepidic Predominant Pulmonary Lesions (LPL): CT-based Distinction From More Invasive Adenocarcinomas Using 3D Volumetric Density and First-order CT Texture Analysis

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Rationale and Objectives: This study aimed to differentiate pathologically defined lepidic predominant lesions (LPL) from more invasive adenocarcinomas (INV) using three-dimensional (3D) volumetric density and first-order texture histogram analysis of surgically excised stage 1 lung adenocarcinomas.

Materials and Methods: This retrospective study was institutional review board approved and Health Insurance Portability and Accountability Act compliant. Sixty-four cases of pathologically proven stage 1 lung adenocarcinoma surgically resected between September 2006 and October 2015, including LPL ($n = 43$) and INV ($n = 21$), were evaluated using high-resolution computed tomography. Quantitative measurements included nodule volume, percent solid volume (% solid), and first-order texture histogram analysis including skewness, kurtosis, entropy, and mean nodule attenuation within each histogram quartile. Binomial logistic regression models were used to identify the best set of parameters distinguishing LPL from INV.

Results: Univariate analysis of 3D volumetric density and histogram features was statistically significant between LPL and INV groups ($P < .05$). Accuracy of a binomial logistic model to discriminate LPL from INV based on size and % solid was 85.9%. With optimized probability cutoff, the model achieves 81% sensitivity, 76.7% specificity, and area under the receiver operating characteristic curve of 0.897 (95% confidence interval, 0.821–0.973). An additional model based on size and mean nodule attenuation of the third quartile (Hu_Q3) of the histogram achieved similar accuracy of 81.3% and area under the receiver operating characteristic curve of 0.877 (95% confidence interval, 0.790–0.964).

Conclusions: Both 3D volumetric density and first-order texture analysis of stage 1 lung adenocarcinoma allow differentiation of LPL from more invasive adenocarcinoma with overall accuracy of 85.9%–81.3%, based on multivariate analyses of either size and % solid or size and Hu_Q3, respectively.

Key Words: Lepidic predominant; invasive adenocarcinoma; volumetric density; histogram.

INTRODUCTION

To date, numerous publications have correlated the pathologic spectrum of lung adenocarcinoma with computed tomography (CT) findings (1–7). Although differentiation among these varying CT patterns has important management implications, morphologic distinctions along the spectrum of peripheral adenocarcinomas have shown considerable overlap, including pronounced inter- and intraobserver variability in visual differentiation of nodule features, rendering sole reliance on morphologic characterization problematic (5,7–10). Based on these limitations, recent efforts have moved

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toward quantitative CT methods of differentiating pathologic subtypes, specifically documenting a role for advanced, quantitative assessment of peripheral lung nodules, while taking into account previous evidence that nodule size positively correlates with tumor invasiveness (11,12). Most recently, quantitative CT assessment has included both two-dimensional and three-dimensional (3D) volumetric density and texture or histogram analysis to more precisely characterize these lesions. Encouraging preliminary results were obtained using a 3D volumetric model that emphasizes the proportion of solid component(s) of part-solid lung nodules to differentiate between three specimen groups: a combined group of preinvasive adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), lepidic predominant adenocarcinoma (LPA), and more invasive forms of adenocarcinoma (INV); a statistically significant difference in percentage solid volume (% solid) was found between LPA and INV groups (13).

As defined by the International Association for the Study of Lung Cancer (IASLC) and the World Health Organization, LPA is a variant of invasive adenocarcinoma in which bland, non-malignant cells predominate, associated with at least one focus of invasion measuring >5 mm in largest dimension, with evidence of tumor necrosis, invasion of lymphatics, blood vessels or pleura, or spread through alveolar spaces (14). In distinction, more invasive subtypes include acinar, papillary, and micropapillary predominant subtypes, as well as the solid tumor subtype. Pathologic subtypes of lepidic predominant and more invasive lesions have shown to have clear prognostic implications (15–19). In a study of 210 postsurgical patients, a combined group of patients with AIS, MIA, and LPA had a 5-year survival of 93%, whereas patients with more invasive subtypes had a worse prognosis, with 71%, 68%, 39%, and 38% 5-year survivals for papillary, acinar, solid, and micropapillary-predominant types, respectively ($P < .0001$) (19). More specifically, patients with AIS and MIA have been reported to have 5-year disease-free survival (DFS) near 100% following surgical resection, with non-mucinous LPA having DFS of 90%–94% (15,19–21). Furthermore, the cumulative incidence of recurrence was zero among patients with AIS and MIA, and disease in patients with LPA was significantly less likely to recur versus more invasive forms of adenocarcinoma (5-year cumulative incidence of recurrence of 8% vs 19%, $P = .003$) (15).

In addition to increasing emphasis on volumetric assessment of peripheral lung nodules, there has also been a corresponding, if less extensive, interest in use of advanced texture analysis as an additional or alternative quantitative measurement tool. This includes quantitative histogram analysis, which uses attenuation values of each voxel and their distribution throughout the lung nodule to provide tissue characterization and lesion differentiation (22–29).

When considering the clinical implications between lepidic predominant lesions (LPL) and INV subtypes, and the current ability to differentiate these subtypes using quantitative imaging features, the aims of the present study include (1) reassessment of prior 3D volumetric density results after inclusion of a larger number of pathologically documented MIA; (2) assessment of the utility of first-order texture histogram measures of nodule attenuation, given that histogram analysis does not entail a fixed density threshold to separate solid from subsolid nodule components; and (3) reinterpretation of these results in light of the original IASLC/American Thoracic Society (ATS)/European Respiratory Society (ERS) classification with a proposal to combine the three lepidic predominant subtypes of peripheral lung adenocarcinoma (AIS, MIA, and LPA) as a single clinical group of LPL, distinct from the remaining INV subtypes. The rationale for such a grouping is the knowledge of much longer DFS in LPL patients (15,17–20).

MATERIALS AND METHODS

Patient and CT Data

This retrospective study was compliant with the Health Insurance Portability and Accountability Act and was approved by the institutional review board; informed consent was waived. Twenty-six surgically resected MIA specimens were added to a previously reported preexisting group of 38 pathologically proven, surgically resected stage 1 lung adenocarcinomas (11). This article differs from the prior effort by reinterpreting a larger data set, with the intention of assessing the ability of advanced CT techniques to differentiate between a group of combined lepidic predominant lesions and a group of more invasive adenocarcinoma subtypes. For this purpose, analysis has been expanded to include first-order texture analysis of lung adenocarcinoma subtypes, in addition to several 3D volumetric density measurements.

All surgically resected pathologically confirmed stage 1 adenocarcinomas in this study were consecutively identified at our institution between September 19, 2006 and October 21, 2015 via search of a thoracic surgical and pathology database. The timing of surgical excision was determined by thoracic surgeons, frequently in consensus in a multidisciplinary group of pulmonary specialists including pulmonologists, oncologists, pathologists, nuclear medicine specialists, and radiologists. MIA specimens were diagnosed in concordance by two pulmonary pathologists at different time points, unaware of CT findings using the IASLC/ATS/ERS international multidisciplinary classification (14).

Only noncontrast CT studies including thin-section (≤1.5 mm) axial images performed within 90 days of surgery were included. Fifty-three potential subjects were excluded because of the presence of IV contrast, the absence of thin-section axial CT images, or a time interval between CT and surgery more than 90 days. However, a total of 64 appropriate cases were obtained from 62 patients (45 women and 17 men, mean age 70.4 years, range 47–84); two patients each had two MIA specimens. Specimens were classified as 31 MIA and 12 LPA, comprising a group of 43 LPL, as well as 21 INV.

All chest CT examinations were performed on multidetector CT scanners with either 64- or 128-detector row configuration