Original Study

Semiquantitative Computed Tomography Characteristics for Lung Adenocarcinoma and Their Association With Lung Cancer Survival

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Abstract

In this study we developed 25 computed tomography descriptors among 117 patients with lung adenocarcinoma to semiquantitatively assess their association with overall survival. Pleural attachment was significantly associated with an increased risk of death and texture was most important for distinguishing histological subtypes. This approach has the potential to support automated analyses and develop decision-support clinical tools.

Background: Computed tomography (CT) characteristics derived from noninvasive images that represent the entire tumor might have diagnostic and prognostic value. The purpose of this study was to assess the association of a standardized set of semiquantitative CT characteristics of lung adenocarcinoma with overall survival. **Patients and Methods:** An initial set of CT descriptors was developed to semiquantitatively assess lung adenocarcinoma in patients (n = 117) who underwent resection. Survival analyses were used to determine the association between each characteristic and overall survival. Principle component analysis (PCA) was used to determine characteristics that might differentiate histological subtypes. **Results:** Characteristics significantly associated with overall survival included pleural attachment ($P < .001$), air bronchogram ($P = .03$), and lymphadenopathy ($P = .02$). Multivariate analyses revealed pleural attachment was significantly associated with an increased risk of death overall (hazard ratio [HR], 3.21; 95% confidence interval [CI], 1.53-6.70) and among patients with lepidic predominant adenocarcinomas (HR, 5.85; 95% CI, 1.75-19.59), and lymphadenopathy was significantly associated with an increased risk of death among patients with adenocarcinomas without a predominant lepidic component (HR, 3.07; 95% CI, 1.09-8.70). A PCA model showed that texture (ground-glass opacity component) was most important for separating the 2 subtypes. **Conclusion:** A subset of the semiquantitative characteristics described herein has prognostic importance and provides the ability to distinguish between different histological subtypes of lung adenocarcinoma.

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Introduction

Adenocarcinoma of the lung is a major cause of cancer-related morbidity and mortality worldwide,[1] and its incidence has been increasing over the past several decades.[2,3] Histological characteristics obtained from relatively small portions of tumor might not be representative of the entire tumor, although histological

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characteristics and staging are commonly used to determine treatment, intratumoral heterogeneity can be a limiting factor to predict prognosis and treatment response. Thus, characteristics derived from analyses of radiological images that represent the entire tumor might have diagnostic and prognostic value. Specifically, imaging features that are associated with the underlying tumor biology could have clinical translational implications. For example, in contrast to solid- or micropapillary-predominant adenocarcinoma, lepidic-predominant adenocarcinoma could eventually be treated with optimized tissue-sparing resection because of the much better outcome and the scarcity of nodal metastases in this subtype.[4]

Medical imaging can provide noninvasive measurements of tumor features. However, current radiological practice is generally qualitative and provides only limited quantitative information such as dimensional measurements of tumor size. Efforts have been made to develop a standardized lexicon for description of lung tumor features and a standard method for conversion of these descriptors into quantitative, mineable data with the intent of discovering their associations with patient survival.[5-7] Computational technical development has permitted a high-throughput process in which a large number of shape, edge, and texture imaging features are extracted.[8,9] However, computerized algorithms are more highly dependent on harmonized acquisition and reconstruction parameters than are human readers. The environment of the tumor, which includes important prognostic information, such as desmoplastic response, vascular supply, or localized infiltration of the tumor cannot be segmented effectively. Therefore, computational analysis is not yet able to replace the trained eyes of a radiologist. Nevertheless, computer-derived features can aid radiological diagnosis with extraction of quantitative and unbiased features. Computationally-derived imaging features have been developed to annotate radiological observations,[10,11] and the expertise of the radiologist can provide guidance for automated approaches to develop the imaging features that have clinical relevance. Thus, we hypothesized that a standardized set of semiquantitative imaging features can predict prognosis of the patients and benefit the development of prognostic-relevant computerized features.

The purpose of this study was to develop and test a standardized set of semiquantitative computed tomography (CT) descriptors of lung adenocarcinoma and assess their association with overall survival. This approach has the potential to support automated analyses by providing guidance and expert evaluation of necessary imaging characteristics, and it can ultimately be used to develop decision-support clinical tools to increase accuracy and efficiency of radiological diagnosis.

Patients and Methods

Study Population

The institutional review board approved this retrospective study and waived the informed consent requirement. Data were collected and handled in accordance with the Health Insurance Portability and Accountability Act. This study included 117 patients diagnosed with histologically confirmed adenocarcinoma of the lung who had surgery for primary lung cancer in our institution between January 2006 and June 2009. The mean age of the patients was 65.1 ± 7.5 years, 93.3% self-reported race as white, 55.2% were female, 90.5% were ever-smokers, and 47% had stage I lung cancer. According to their growth pattern, we classified tumors into 2 subtypes as in previous studies[12-14]: (1) lepidic predominant adenocarcinomas (n = 55); and (2) adenocarcinomas without a predominant lepidic growth (n = 62); among these cases, 11 had a small proportion of a lepidic component. Lepidic growth pattern was defined as involving alveolar septa with a relative lack of acinar filling. In terms of the new multidisciplinary classification of lung adenocarcinoma sponsored by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society in 2011,[15] our subtype of lepidic predominant adenocarcinomas included adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic predominant invasive adenocarcinoma.

Computed Tomography Imaging and Analyses

All CT scans were performed before surgery. Ninety-five patients underwent contrast-enhanced CT scan and 22 patients had nonenhanced CT scan.

A clinical radiologist with 7 years of experience in chest CT diagnosis developed 25 descriptors and subsequently reviewed all of the CT images. The goal was to develop an initial set of descriptors that would cover a broad area of characteristics with as much resolution as possible. As shown in Table 1, these descriptors were classified into 3 categories: (1) measures that describe the tumor (n = 16); (2) measures that describe the surrounding tissue (n = 5); and (3) measures that describe associated findings (n = 4). Among these descriptors, 17 were rated using a 1 to 5 ordinal scale and 8 descriptors were binary categorical variables. Examples of CT images for each scale of characteristics are shown in Supplemental Figure 1 (in the online version).

Our set of descriptors was adapted in part from the Breast Imaging Reporting and Data System (BI-RADS) of the American College of Radiology,[16,17] although differences exist between degree (eg, we used 5 levels compared with 2) and organ-specific descriptions. We also adapted measures from the lexicon of the Fleischner Society[18] that captured lung cancer features. Other descriptors were adapted from the literature.[19,20] In particular, we combined “cavity” and “pseudocavity” used by the Fleischner Society into “air space” as did Matsuki et al[20] because of the difficulty of differentiation of them on CT images. The tumor size was measured in the long axis and then classified according to new 7th lung cancer tumor, node, metastases classification and staging system, which has 5 size-based categories with cutoff points at 2, 3, 5, and 7 cm.[21]

Each tumor was rated by assessing all slices and reporting with a standardized scoring sheet. A second radiologist, with 5 years of experience in chest CT diagnosis, then independently rated the cases using the scoring sheet after training.

Statistical Analyses

The agreement between the 2 readers was measured using Kappa for binary variables or Weighted Kappa index for ordinal variables. The κ value was interpreted as follows: < 0: poor agreement; 0 to 0.2: slight agreement; 0.2 to 0.4: fair agreement; 0.4 to 0.6: moderate agreement; 0.6 to 0.8: substantial agreement; > 0.8: almost perfect agreement.[22]

Kaplan−Meier survival curves with the log-rank test were performed using R version 2.14 (R Project for Statistical Computing;