Role of CT and PET Imaging in Predicting Tumor Recurrence and Survival in Patients with Lung Adenocarcinoma

A Comparison with the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society Classification of Lung Adenocarcinoma

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Introduction: Recently, a new lung adenocarcinoma classification scheme was published. The prognostic value of this new classification has not been elaborated together with the value of imaging biomarkers including computed tomography (CT) and positron emission tomography (PET).

Methods: We reviewed pathologic specimens and imaging characteristics of primary tumors from 723 consecutive patients who underwent surgical resection for lung adenocarcinoma. On pathology, the predominant histologic subtype and pattern group were quantified. Tumor-shadow disappearance ratio (TDR) on CT and maximum standardized uptake value (SUVmax) on PET were assessed. The relationships between those variables and survival (overall survival [OS] and disease-free survival) were analyzed by using Kaplan–Meier curves and Cox regression analyses.

Results: The median follow-up period was 3.8 years. There were 137 patients (19%) with recurrence and 167 patients (23%) with metastasis after surgical resection. Among 723 patients, 35 patients (4.8%) had adenocarcinoma in situ, 34 patients (4.7%) had minimally invasive adenocarcinoma, 125 patients (17.3%) had lepidic predominant, 314 patients (43.4%) had acinar predominant, 65 patients (9.0%) had papillary predominant, 23 patients (3.2%) had micropapillary predominant, 113 patients (15.6%) had solid predominant, and 14 patients (1.9%) had variant adenocarcinomas. OS and disease-free survival rates were significantly different according to TDR on CT and SUVmax on PET, predominant subtypes, and pattern groups. On multivariate analysis, the SUVmax ($p < 0.001$), TDR ($p = 0.038$), and pattern group ($p = 0.015$) were independent predictors of OS.

Conclusions: TDR on CT, SUVmax on PET, and the new histologic classification schemes appear to be promising parameters for the prognostic stratification of patients with lung adenocarcinomas, allowing for the triage of patients who necessitate further staging workup and adjuvant therapy.

Key words: Lung adenocarcinoma, Survival, Histology, Positron emission tomography, Computed tomography, Ground-glass opacity.

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Lung cancer is the leading cause of cancer death in many countries, and non–small-cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers.[1] Adenocarcinoma is the most common histologic type of NSCLC.[2] Until now, the single most important prognostic factor in patients with NSCLC, including adenocarcinoma, has been tumor stage.[3] However, there is a wide spectrum of tumor behavior that can be predicted by recognizing well-known prognostic factors, such as tumor-node-metastasis (TNM) stage at the time of initial diagnosis.[4] As for early-stage lung adenocarcinomas, surgical resection is the treatment of choice; nevertheless, even after curative surgical resection, the 5-year overall survival (OS) rate in patients with stage 1 lung adenocarcinoma is approximately 60% to 70%, and 30% to 40% of these patients eventually have recurrent disease, which is the most common cause of treatment failure after resection.[5,6] Therefore, we need to identify robust prognostic biomarkers to help predict which patients with operable lung cancer are at the highest

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risk for recurrent disease and, consequently, are candidates for more aggressive surveillance or adjuvant therapy.

Recently, a new lung adenocarcinoma classification scheme was published by the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/and European Respiratory Society (ERS),[7] and the prognostic value of the new classification system with respect to survival and recurrence has been investigated in several studies.[8–14] Meanwhile, there have been many efforts to stratify patients with lung adenocarcinoma using noninvasive surrogate biomarkers, such as imaging tools.[15–20] Although several studies have reported results comparing the prognostication capabilities of computed tomography (CT), positron emission tomography (PET), and histopathologic findings,[20–22] the new classification system for lung adenocarcinomas has not been elaborated together with those prognostic factors. In this article, we focus on the prognostic predictive value of imaging biomarkers such as tumor-shadow disappearance ratio (TDR) on CT and maximum standardized uptake value (SUVmax) on ^{18}F-fluoro-2-deoxyglucose (FDG)-PET/CT in patients with completely resected stages I–III lung adenocarcinomas, and compare this with the prognostic value of the new classification system.

PATIENTS AND METHODS

Patients

This single institution retrospective study was approved by our institutional review board with a waiver of informed consent. Between September 2003 and August 2011, we identified 859 consecutive patients who underwent complete resection of adenocarcinoma with mediastinal lymph node dissection at Samsung Medical Center (Seoul, Korea). All patients were treated with surgery alone or surgery plus postsurgical adjuvant therapy. Sixty-eight patients were excluded because of the following prognosis-related factor: the presence of micrometastasis at the time of surgery (n = 25) and the presence of another cancer (n = 43). Another 68 patients were excluded because of radiologically or pathologically related factors such as insufficient pathologic slides for the evaluation of the whole tumor (n = 39), poor CT image quality (n = 23), and limited tumor evaluation due to the presence of concurrent extensive inflammation or lung infarction (n = 6). Thus, 723 patients (372 males, 351 females; median age, 60 years) were included in the present analysis. All cases were reviewed according to the International Multidisciplinary Lung Adenocarcinoma Classification criteria[7] and were staged according to the 7th edition of the TNM classification for lung cancer.[21,22]

Imaging and Analysis

Imaging characteristics of each primary lung tumor were evaluated using chest CT and the PET component of PET/CT. PET/CT and chest CT were obtained within 1 month (mean: 17.5 days; median: 13.5 days) of each study. FDG PET/CT images were acquired using a PET/CT device (Discovery LS; GE Healthcare, Milwaukee, WI), which consisted of a PET scanner (Advance NXi; GE Healthcare, Milwaukee, WI) and an eight-section CT scanner (Light-Speed Plus; GE Healthcare). The imaging methods used are described in detail in a previous report.[20]

Dedicated chest CT images were obtained with an 8- (LightSpeed Ultra, GE Healthcare) or 16-detector row (LightSpeed16, GE Healthcare) CT scanner. CT images were obtained using the following parameters: detector collimation, 0.625 mm; field of view, 34.5 cm; beam pitch, 1.35 or 1.375; gantry speed, 0.6 seconds per rotation; 120 kVp; 150 to 200 mA; and section thickness, 1.25 mm for transverse images. All imaging data were reconstructed using soft tissue algorithms.

A nuclear medicine physician with 11 years of experience in PET/CT interpretation and who was unaware of clinical and pathologic data evaluated all PET images. For semiquantitative analysis of FDG uptake, regions of interest (ROIs) were placed over the most intense area of FDG accumulation. When nodular FDG uptake could not be assessed on PET component images of PET/CT, an ROI was drawn in a presumed nodular location by taking into consideration CT component images of PET/CT. FDG uptake within the ROIs was calculated as SUVmax.

Chest CT data were interfaced directly to a picture archiving and communication system (Path-Speed or Centricity 2.0; GE Healthcare, Mt. Prospect, IL), which displayed all image data on two monitors (1536×2048 matrix, 8-bit viewable grayscale, 60-foot-lambert luminescence). The monitors were adapted to view both mediastinal (width, 400 HU; level, 20 HU) and lung (width, 1500 HU; level, −700 HU) window images. Two chest radiologists with 7 and 2 years of experience in thoracic CT interpretation, respectively, who were unaware of the clinical data, PET findings, and histologic diagnoses retrospectively evaluated the CT scans for nodule size and TDR. Nodule size and TDR were assessed by independent observers, and discrepancies in evaluation among them were resolved by averaging their determined values. For nodule size, the longest tumor diameters were measured on lung window images. On transverse images, tumor diameters were measured manually on picture archiving and communication system monitors using electronic measurement tools. In all cases, observers measured the maximum dimension of the tumors (max$D$) and the largest dimension perpendicular (per$D$) to the maximum diameter (max$D$) using both the lung and mediastinal windows. Two methods were adopted for simplified application of TDR and its quantification.[20] First, TDR-4 was defined to divide the TDR extent into four categories: 100% (pure ground-glass opacity [GGO]), greater than or equal to 50%, greater than or equal to 25%, and less than 25%. Second, TDR-2 was defined to divide the TDR extent into two categories: greater than or equal to 15% and less than 15%. The optimal cut-off value for TDR extent was calculated using receiver operating characteristic (ROC) curve analysis. The optimal cut-off value was determined as the point closest to the upper left corner of the ROC curve. Interobserver agreement for TDR at CT was calculated by means of intraclass correlation coefficient (ICC) on a small group of randomly extracted patients. The 95% CIs for the ICC were also estimated.

Pathologic Evaluation

Whole tumor tissue sections were obtained, and each section was placed on a slide. Comprehensive histologic