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Predicting the response to a bronchodilator in patients with airflow obstruction and lung cancer

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ABSTRACT

Background: The aim of the present study was to clarify the predictors of the response of patients with resectable lung cancer and untreated airflow obstruction to tiotropium, an antimuscarinic bronchodilator.

Methods: Tiotropium was administered to 29 preoperative patients with untreated airflow obstruction. The forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were measured before and after the introduction of tiotropium. The response to tiotropium was determined based on the percentage gain in the FEV_1. The volume of the total lung area (TLV) and the low-attenuation area (LAA) was measured by deep inspiratory computed tomography based on the predefined thresholds for attenuation values.

Results: The introduction of tiotropium resulted in a 15% gain in the FEV_1 ($P < 0.001$). A univariate regression analysis revealed that the FVC/TLV was the best predictor of the gain in FEV_1, followed by the FEV_1/FVC. Based on the results of a multiple regression analysis, a regression equation to predict a gain in the FEV_1 was generated using the FVC, TLV, and LAA. A receiver operating characteristic curve analysis revealed that this equation led to the highest area under the curve for predicting a major response to tiotropium, followed by the FVC/TLV and FEV_1/FVC. Postoperatively, six of the 20 minor responders experienced a progression of dyspnea. In contrast, none of the major responders experienced a progression of dyspnea ($P < 0.05$).

Conclusions: We developed an equation for predicting the response to tiotropium using parameters obtained from spirometry and quantitative computed tomography. A large-scale study to validate the usefulness of this equation is warranted.

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Introduction

Tiotropium, a long-acting muscarinic antagonist, is a bronchodilator that is widely used in maintenance therapy for patients with chronic obstructive pulmonary disease (COPD). The administration of tiotropium results in an improvement in both the forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), leading to the improvement in a patient's symptoms and quality of life.[1-3] Because tiotropium is effective for more than 24 h after inhalation, the use of this drug in the perioperative setting is particularly advantageous. The structural abnormalities underlying COPD consist of various degrees of narrowing of the peripheral airways and the enlargement of the alveolar airspace. These pathological conditions led to substantial variations in the degree of airflow obstruction, increased residual volume, and pulmonary hyperinflation. Thus, the phenotypes and severity of COPD should be comprehensively evaluated by an anatomical approach, such as quantitative computed tomography (CT), in combination with pulmonary function tests.[4,5] Quantitative CT is particularly useful for measuring the density and volume of the lung, facilitating the measurement of the lung corporeal size and emphysematous areas. We hypothesized that the response to tiotropium could be accurately predicted using parameters derived from quantitative CT and pulmonary function tests.

Patients and methods

Patients

We prospectively collected the clinical data of 29 consecutive patients with untreated COPD, who were scheduled to undergo anatomical lung resection for primary lung cancer between September 2012 and May 2015. All 29 patients had a history of smoking for at least 10 y and had airflow limitation, which was reflected as a forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) of <70%. Patients with asthma-COPD overlap syndrome were not included in this study. During the perioperative period, the inhaled tiotropium (18 μg, once daily) was routinely administered to the patients of the present study as respiratory rehabilitation (treated group). The median length of preoperative tiotropium administration was 14 d (range: 11-28 d). Tiotropium was continued at least until postoperative day 30. This study was approved by the Institutional Review Board of the Yamaguchi University School of Medicine. The operability was determined based on the existing guidelines for pulmonary resection.[6] The criteria for resection included a partial pressure of arterial carbon dioxide ($PaCO_2$) value of <50 mm Hg and calculated predicted postoperative FEV_1 value of >500 mL. The operation was performed via three ports under thoracoscopy. The following patient data were obtained preoperatively: age, sex, smoking habits, the presence or absence of breathlessness, performance status, arterial blood gases, exercise capacity, extent of resection, spirometric variables, and the extent of the low-attenuation area (LAA) on chest CT.

The preoperative pulmonary assessment

The spirometric variables (FVC and FEV_1) were measured before the introduction of tiotropium. Spirometry was repeated for more than 7 d after the introduction of tiotropium because it takes 7 d after the introduction of tiotropium inhalation for the FVC and FEV_1 to reach a steady state, according to a previous study.[7]

CT scanning and the quantitative analysis

The CT scans were performed using a multidetector row CT scanner (Somatom Definition or Sensation 64; Siemens, Erlangen, Germany) before the introduction of tiotropium. The patient was placed in the supine position, and high-resolution CT images covering the entire lungs were obtained in a 512 × 512 matrix during a deep inspiratory breath-hold, with a scan time of 1.5 s, at 120-140 kVp, 280-320 mA. Transaxial CT images were reconstructed with the lung algorithm. We created volume-rendering three-dimensional density-masked

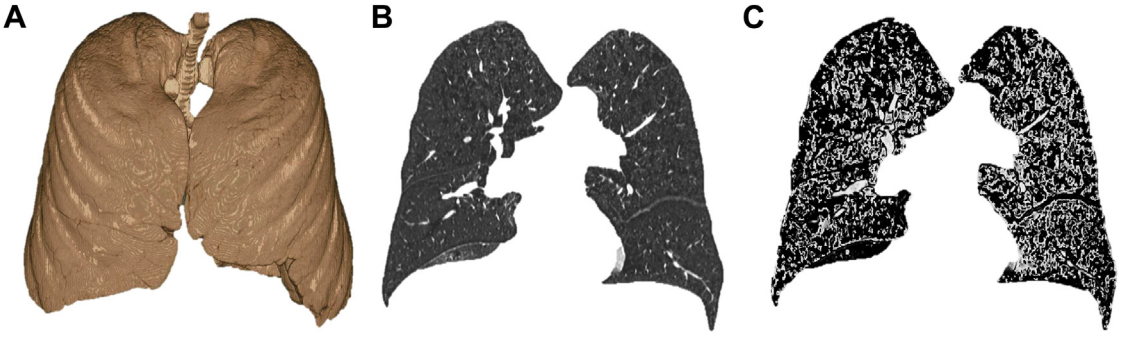

Fig. 1 – Three-dimensional volume-rendering computed tomography images of the lungs (A). Coronal section image of the lung window (B) and the same section image of a lung with normal attenuation (black area) (−600 to −910 Hounsfield units) and a lung with abnormally low attenuation (white area; < −910 Hounsfield units), representing emphysema (C). (Color version of figure is available online.)