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A combination of preoperative CT findings and postoperative serum CEA levels improves recurrence prediction for stage I lung adenocarcinoma

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ABSTRACT

Objectives: To assess the prognostic value of combined evaluation of preoperative CT findings and pre/postoperative serum carcinoembryonic antigen (CEA) levels for pathological stage I lung adenocarcinoma.
Methods: This retrospective study included 250 consecutive patients who underwent complete resection for ≤3-cm pathological stage I (T1–2aN0M0) adenocarcinomas (132 men, 118 women; mean age, 67.8 years). Radiologists evaluated following CT findings: maximum tumor diameter, percentage of solid component (%solid), air bronchogram, spiculation, adjacency of bullae or interstitial pneumonia (IP) around the tumor, notch, and pleural indent. These CT findings, pre/postoperative CEA levels, age, gender, and Brinkman index were assessed by Cox proportional hazards model to determine the best prognostic model. Prognostic accuracy was examined using the area under the receiver operating characteristic curve (AUC).
Results: Median follow-up period was 73.2 months. In multivariate analysis, high %solid, adjacency of bullae or IP around the tumor, and high postoperative CEA levels comprised the best combination for predicting recurrence ($P < 0.05$). A combination of these three findings had a greater accuracy in predicting 5-year disease-free survival than did %solid alone (AUC = 0.853 versus 0.792; $P = 0.023$), with a sensitivity of 85.7% and a specificity of 74.3% at the optimal threshold. The best cut-off values of %solid and postoperative CEA levels for predicting high-risk patients were ≥48% and ≥3.7 ng/mL, respectively.
Conclusion: Compared to %solid alone, combined evaluation of %solid, adjacency of bullae or IP change around the tumor, and postoperative CEA levels improves recurrence prediction for stage I lung adenocarcinoma.

1. Introduction

Lung cancer is the most common cause of cancer-related death worldwide [1] and to date, various prognostic factors have been reported.

In non-small-cell lung cancer cases, high levels of serum carcinoembryonic antigen (CEA) were found to be associated with invasive tumors and poor survival even at early disease stages [2–5]. Matsuguma et al. [2] investigated pathological stage I non-small-cell lung cancers and found that high preoperative and postoperative CEA levels were associated with shorter survival duration; these associations were independent of pathological prognostic factors such as pleural or vascular invasion. In particular,

Abbreviations: AUC, area under the curve; CEA, carcinoembryonic antigen; CI, confidence interval; GGO, ground-glass opacity; HR, hazard ratio; HU, Hounsfield units; IP, interstitial pneumonia; MaxD, maximum tumor diameter; PerD, the largest diameter perpendicular to the maximum axis; ROC, receiver operating characteristic curve; %solid, percentage of solid component.

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patients with high postoperative CEA levels exhibit exceedingly poor prognoses [2,4], possibly because of the presence of residual tumor or unknown metastasis.

In lung adenocarcinoma cases, CT findings are well-known important prognostic indicators. In particular, the ground-glass opacity (GGO) ratio is strongly associated with survival, such that GGO-dominant tumors have a 5-year survival rate of nearly 100% [6–8]. In addition, spiculation [9], notch [10], and air bronchogram [11] have also been reported to be associated with prognosis.

Both CT findings and serum CEA levels have been associated with prognosis of lung adenocarcinoma; however, only a few studies have assessed the prognostic value of the combined evaluation [12,13]. Although those previous studies concluded that preoperative CEA levels and GGO ratios on CT were independent prognostic factors, they did not evaluate postoperative CEA levels or other CT findings associated with prognosis. Furthermore, although the populations in those studies included various pathological stages, the staging differences were not statistically adjusted in multivariate analysis. Therefore, it remains uncertain whether a combined evaluation of the pre/postoperative serum CEA levels and detailed preoperative CT findings would improve the recurrence prediction even among patients with same pathological stage lung adenocarcinoma. We considered that such a study would be necessary to improve postoperative patient management.

Therefore, this study aimed to assess the prognostic value of combined evaluation of preoperative CT findings and pre/postoperative serum CEA levels for pathological stage I lung adenocarcinoma.

2. Materials and methods

2.1. Patients

An institutional review board approved this retrospective study and waived the requirement for informed consent. Between April 2000 and April 2011, 354 patients underwent complete resection for primary lung adenocarcinoma at our institution and were diagnosed with pathological stage I (T1–2aN0M0) disease based on the 7th edition of the TNM classification. Of these, patients with maximum tumor diameters (maxD) of >3 cm ($n = 45$) were excluded because CT imaging evaluations of large tumors are difficult on account of obstructive pneumonia or atelectasis. Patients with any other malignancy ($n = 9$), those who did not undergo preoperative CT examination at our institution ($n = 25$), and those whose preoperative serum CEA levels were not obtained within 3 months before surgery ($n = 1$) or postoperative serum CEA levels were not obtained within 6 months after surgery ($n = 24$) were also excluded. Consequently, this study included 250 consecutive patients (132 men, 118 women) with a mean age of 67.8 years (range, 39–87 years). This patient population is a subset that we previously published [14].

2.2. CT examination

All CT examinations were conducted using a multidetector-row CT scanner (Light Speed Qxi 4-row detector, GE; Somatom Sensation 16-row detector, Siemens; Aquilion 64-row detector, Toshiba; and Somatom Definition Flash, 128 × 2-row detector, Siemens) in the presence or absence of injected contrast agents. From the raw data, 1–1.25 mm-thick contiguous transverse sections were reconstructed with a 17.5 mm field of view and bone algorithm. The resulting images were displayed at a window width of 1600 Hounsfield units (HU) and a level of −600 HU in the lung window and at a window width of 400 HU and a level of 30 HU in the mediastinal window.

2.3. CT image evaluation

All CT images were reviewed retrospectively and independently by three radiologists with 17, 16, and 8 years of experience in chest CT image interpretation, respectively. The radiologists knew that the lung tumors had been pathologically diagnosed as primary adenocarcinoma but were blinded to the patients' prognostic information. First, maxD and the largest diameter perpendicular to the maximum axis (perD) were measured in images from the lung and mediastinal window settings. Subsequently, percentage of solid component (%solid) in each tumor was calculated according to the following formula: %solid = (maxD × perD in the mediastinal window) ÷ (maxD × perD in the lung window) × 100 (Fig. 1 shows a sample measurement). The observers also evaluated the presence or absence of air bronchogram, spiculation, bullae or interstitial pneumonia (IP) coexisting around the tumor, notch, and pleural indent. To determine the most appropriate diagnosis after reviewing the CT findings, the median of the three observers' measurements was selected with regard to the quantitative CT findings (i.e., %solid and maxD), and the majority diagnosis was selected with regard to the remaining qualitative CT findings. Spiculation was defined as the presence of ≥2-mm-thick linear strands that extended from the tumor margin into the lung parenchyma [15]. Pleural indent was defined as the presence of linear structures that originated from the tumor and extended to the pleural surface. Notch was defined as a lobulated tumor margin. The observers considered that bullae or IP was coexisting around the tumor when these lesions were adjoining with the tumor margin. IP imaging findings were defined as reticular opacities or honeycombing with a predominantly peripheral and basal distribution [16]. Prognosis of bullae and IP was not separately assessed because these lesions are sometimes combined in the same patient [17].

2.4. Clinical prognostic factors

Preoperative and postoperative serum CEA levels were measured within 3 months before surgery (median, 16 days before surgery; interquartile range, 9–32 days) and within 6 months after surgery (median, 31 days after surgery; interquartile range, 17–45 days), respectively. All levels were determined at our institution via enzyme immunoassay. Patients' age, gender, and Brinkman index were also recorded as potential prognostic indicators. The Brinkman index was defined as the number of cigarettes smoked per day × the number of smoking years.

2.5. Prognostic assessment

All postoperative patient prognoses were analyzed using the medical records at our institution or those retrieved from other hospitals. Disease-free survival was used as a prognostic indicator and was defined as the time interval from the day of surgery until the recurrence of lung adenocarcinoma. Patients who did not recurrent until final contact or those who died from other cause without recurrence were treated as censored data.

2.6. Statistical analysis

Cox proportional hazards models were used to assess the relationship between each prognostic factor and disease-free survival duration. Factors with P-values of <0.1 in univariate analyses were included in multivariate analysis with a forward selection method to determine the best prognostic model. To evaluate the model's accuracy of predicting 5-year disease-free survival, area under the curve (AUC) of a receiver operating characteristic (ROC) curve was used. From the result of the multivariate Cox proportional hazards