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

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.

Keywords: Chest CT imaging; lung adenocarcinoma; lung cancer; serum CEA levels; prognosis.

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.

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, 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, 1–1.25mm-thick contiguous transverse sections were reconstructed with a 17.5mm 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 (Figure 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 model, the 5-year probability of recurrence in each patient could

be calculated according to the following exponential function [19]:

$100 - 100 \times \exp(-0.019 \times \exp[0.28 \times \%solid + 0.11 \times postoperative\ CEA\ levels + 0.76 \times Z])$, where Z = 1 if bullae or IP change was adjoining with the tumor, and Z = 0 if bullae or IP change was absent around the tumor.

Subsequently, the AUC of the model was calculated by treating the 5-year probability of recurrence and actual patient status (i.e., recurrence or no recurrence) as the predictive value and reference standard, respectively [18, 19]. The method of DeLong et al. [20] was used to assess whether the AUC of the model was significantly higher than that of %solid alone. The best cut-off values of ROC curves were determined by the Youden's index defined as the point that (sensitivity + specificity – 1) becomes the maximum [21]. The ROC analyses were performed only among patients who completed 5-year follow-up without recurrence or those who developed recurrence within 5-year follow-up. In other words, non-recurrent patients whose follow-up period was <5 years were excluded from the ROC analyses. Using the best cut-off values, survival curves were figured and were compared by the Kaplan-Meier method and the log-rank test, respectively. All statistical analyses were performed with Dr. SPSS II software, version 11.0.1 J (SPSS Japan, Tokyo, Japan) or R Statistical Software, version 3.0.2 for Windows (R Foundation, Vienna, Austria). A P-value of <0.05 was considered

statistically significant. One-sided P-values were used to assess whether the AUC of the model was greater than that of %solid alone, whereas two-sided P-values were used for other statistical analyses.

3. Results

3.1. Patient outcomes

The patients' clinical characteristics and CT findings of tumors are summarized in Table 1. The median follow-up duration was 73.2 months (interquartile range, 38.9–116.1 months). During the follow-up period, 35 (14%) patients developed recurrence of adenocarcinoma, 19 (8%) died from other causes, and the remaining 196 (78%) were alive without recurrence. Of the 35 patients who developed recurrence, 32 had intrathoracic recurrences and 3 had extrathoracic recurrences (bone, liver, and brain). These recurrences were not detected at the time of postoperative CEA level measurement.

3.2. Assessment of disease-free survival by Cox regression analysis

The results of univariate Cox regression analyses are summarized in Table 2. With regard to CT findings, increases in %solid [Hazard ratio (HR), 1.35; 95%

confidence interval (CI), 1.21–1.51; P < 0.001], presence of spiculation (HR, 2.20; 95% CI, 1.11–4.37; P = 0.024), adjacency with bullae or IP change (HR, 4.17; 95% CI, 2.09–8.35; P < 0.001), and presence of notch (HR, 2.68; 95% CI, 1.28–5.58; P = 0.009) were significantly associated with shorter disease-free survival. With regard to clinical factors, male gender (HR, 3.71; 95% CI, 1.68–8.18; P = 0.001), high Brinkman index (HR, 1.07; 95% CI, 1.02–1.12; P = 0.003), high preoperative CEA levels (HR, 1.07; 95% CI, 1.02–1.13; P = 0.006), and high postoperative CEA levels (HR, 1.17; 95% CI, 1.09–1.26; P < 0.001) were significantly associated with shorter disease-free survival. MaxD (P = 0.463), air bronchogram (P = 0.174), pleural indent (P = 0.490), and patient age (P = 0.734) were not significantly associated with disease recurrence. Table 3 provides a summary of the multivariate analysis results, including all variables with P-values of <0.1 in univariate analyses. The best model for predicting disease-free survival was a combination of %solid (HR, 1.32; 95% CI, 1.18–1.48; P < 0.001), adjacency with bullae or IP change (HR, 2.15; 95% CI, 1.04–4.44; P = 0.040), and postoperative CEA levels (HR, 1.12; 95% CI, 1.03–1.22; P = 0.010). Spiculation (P = 0.721), notch (P = 0.268) , preoperative CEA levels (P = 0.191), gender (P = 0.245), and Brinkman index (P = 0.871) were not statistically significant in multivariate analysis.

3.3. Predictive accuracy for 5-year disease-free survival

Of the 250 patients, 78 patients (including 9 deaths from other cause) did not receive 5-year follow-up, and they also did not develop recurrence during their follow-up period. Therefore, the remaining 172 patients (87 men, 85 women; mean age, 66.8 years) were included to assess the 5-year disease-free survival predictive accuracy. During the 5-year follow-up period, 28 (16%) patients experienced recurrence, whereas 144 (84%) patients were not recurrent. As shown in Figure 2 and Table 4, combined evaluation of %solid, adjacency with bullae or IP change, and postoperative CEA levels provided the highest accuracy (AUC = 0.853; 95% CI, 0.792–0.915), with a sensitivity of 85.7% (24/28) and a specificity of 74.3% (107/144) at the optimal threshold. This level of accuracy was significantly higher than that of %solid alone (AUC = 0.792; 95% CI, 0.693–0.892; P = 0.023). The best cut-off values of %solid and postoperative CEA levels for predicting high-risk patients were 48% [sensitivity = 82.1% (23/28); specificity = 75.0% (108/144)] and 3.7 ng/mL [sensitivity = 53.6% (15/28); specificity = 79.2% (114/144)], respectively.

3.4. Survival curve analysis

Figure 3 shows the Kaplan–Meier survival curves based on (a) %solid and (b)

postoperative CEA levels divided at the best cut-off value, (c) adjacency of bullae or IP around the tumor, and (d) the number of the following risk factors: %solid ≥48%, postoperative CEA levels ≥3.7 ng/mL, and adjacency of bullae or IP around the tumor. All survival curves differed significantly ($P < 0.001$ for each). The probabilities of 5-year disease-free survival in the groups with 0, 1, and 2–3 risk factors were 100%, 83.4%, and 65.4%, respectively. Examples of recurrent cases are shown in Figure 4 and 5.

4. Discussion

The major findings of this study are that high %solid, adjacency of bullae or IP change around the tumor, and high postoperative CEA levels are independently associated with shorter disease-free survival even among patients with same pathological stage. In addition, a combination of these three findings indicates significantly higher accuracy for predicting 5-year disease-free survival than evaluation with %solid alone. The results are considered to be important because serum CEA levels can be easily obtained in clinical practice and CT imaging is widely used for adenocarcinoma management.

The association between high postoperative serum CEA levels and shorter

disease-free survival agrees with the findings of previous reports [2–5]. In this study, the best cut-off value for predicting 5-year disease-free survival was 3.7 ng/mL; this cut-off value was lower than the upper limit (5.0 ng/mL) of the normal CEA range. This result is supported by the findings of Sawabata et al. [5] who demonstrated that even within the normal range of postoperative serum CEA levels, patients with levels of 2.5–5.0 ng/mL exhibited significantly worse survival than those with levels of ≤2.5 ng/mL.

In contrast to postoperative CEA levels, preoperative serum CEA levels were not an independent prognostic factor in multivariate analysis. This finding differs from those of previous studies [12, 13]. For example, Higashi et al. [13] examined 87 resected ≤3-cm lung adenocarcinomas and found that a high ^{18}F-fluorodeoxyglucose uptake and high preoperative serum CEA levels (≥20 ng/mL) were independently associated with shorter disease-free survival in patients with solid tumors on CT. Two possible explanations can account for the discrepancy in the results. First, unlike the present study, the previous studies did not evaluate postoperative CEA levels or detailed CT findings beyond the GGO ratio. Postoperative CEA levels and CT findings such as the adjacency of bullae or IP around the tumor may more accurately reflect prognosis relative to preoperative CEA levels. Second, whereas the present study included only

pathological stage I patients, the previous studies included both stage I patients and those at more advanced pathological stages. However, these staging differences were not statistically adjusted in multivariate analysis of the previous studies. Therefore, patients with high preoperative CEA levels might have involved more advanced pathological stages than those with normal levels.

Considering the multivariate analysis in this study, adjacency of bullae or IP change around tumor has more important prognostic information than other morphologic CT features such as spiculation, air-bronchogram, notch or pleural indent. Although there are limited number of publication that examined the association between bullae or IP change on CT imaging and tumor-recurrence, some previous reports support our finding. For example, Watanabe et al. [22] investigated primary lung cancers with idiopathic pulmonary fibrosis and found that primary tumor recurrences and secondary cancers were very common. Kaneda et al. [23] examined primary lung cancers with adjoining pulmonary bullae on CT imaging and showed that these tumors involved poorly differentiated cancers and indicated a worse prognosis relative to tumors without bullae. However, in contrast to those studies, Hanaoka et al. [24] reported that although lung cancers arising from bullae were associated with poor differentiation, the prognoses did not statistically differ between cancers with and

without bullae. Consequently, it cannot be conclusively stated that adjacency of bullae or IP change around the tumor is an independent indicator of recurrence. Further studies of such tumors will be required.

The present study has several limitations. First, positron emission tomography imaging findings and pathological statuses were not included in the prognostic model, because the aim was to investigate the utility of combined evaluation of CT findings and serum CEA levels. Although the prognostic accuracy may improve following the addition of these factors, the results of the current study are important because serum CEA levels can be easily obtained in clinical practice and CT imaging is widely used for adenocarcinoma management. Second, %solid is a 2-dimensional measurement rather than volumetric analysis. Volumetric analysis may be a more accurate prognostic predictor. Third, 78 patients were excluded from the ROC analyses because of their follow-up period of <5 years, which may have influenced the study results. Finally, given the retrospective nature of this study, some population bias may exist.

In conclusion, compared to evaluation of %solid alone, combined evaluation of %solid, adjacency of bullae or IP change around the tumor, and postoperative CEA levels significantly improves recurrence prediction for stage I lung adenocarcinoma. These results would enable improved postoperative patient management.

References

[1] GLOBOCAN. Estimated cancer incidence, mortality and prevalence Worldwide in 2012. Geneva: World Health Organization; 2012. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx (accessed 22. 10. 2014)

[2] Matsuguma H, Nakahara R, Igarashi S, Ishikawa Y, Suzuki H, Miyazawa N, et al. Pathologic stage I non-small cell lung cancer with high levels of preoperative serum carcinoembryonic antigen: clinicopathologic characteristics and prognosis. J Thorac Cardiovasc Surg 2008; 135(1): 44–9.

[3] Okada M, Nishio W, Sakamoto T, Uchino K, Yuki T, Nakagawa A, et al. Prognostic Significance of perioperative serum carcinoembyonic antigen in non-small cell lung cancer: analysis of 1,000 consecutive resections for clinical stage I disease. Ann Thorac Surg 2004; 78(1): 216–21.

[4] Wang CY, Huang MS, Huang MH, Lee HC, Hsu HS. Persistently high serum carcinoembryonic antigen levels after surgery indicate poor prognosis in patients with stage I non-small-cell lung cancer. J Surg Res 2010; 163(2): e45–50.

[5] Sawabata N, Maeda H, Yokota S, Takeda S, Koma M, Tokunaga T, et al. Postoperative serum carcinoembryonic antigen levels in patients with pathologic stage IA nonsmall cell lung carcinoma: subnormal levels as an indicator of

favorable prognosis. Cancer 2004; 15; 101(4): 803–9.

[6] Kondo T, Yamada K, Noda K, Nakayama H, Kameda Y. Radiologic-prognostic correlation in patients with small pulmonary adenocarcinomas. Lung Cancer 2002; 36(1): 49–57.

[7] Shimizu K, Yamada K, Saito H, Noda K, Nakagawa H, Kameda Y, et al. Surgically curable peripheral lung carcinoma: correlation of thin-section CT findings with histologic prognostic factors and survival. Chest 2005; 127(3): 871–8.

[8] Kakinuma R, Kodama K, Yamada K, Yokoyama A, Adachi S, Mori K, et al. Performance evaluation of 4 measuring methods of ground-glass opacities for predicting the 5-year relapse-free survival of patients with peripheral nonsmall cell lung cancer: a multicenter study. J Comput Assist Tomogr 2008; 32(5): 792–8.

[9] Aoki T, Tomoda Y, Watanabe H, Nakata H, Kasai T, Hashimoto H, et al. Peripheral lung adenocarcinoma: correlation of thin-section CT findings with histologic prognostic factors and survival. Radiology 2001; 220(3): 803–9.

[10] Ikehara M, Saito H, Kondo T, Murakami S, Ito H, Tsuboi M, et al. Comparison of thin-section CT and pathological findings in small solid-density type pulmonary adenocarcinoma: prognostic factors from CT findings. Eur J Radiol 2012; 81(1): 189–94.

[11] Takashima S, Maruyama Y, Hasegawa M, Saito A, Haniuda M, Kadoya M. High-resolution CT features: prognostic significance in peripheral lung adenocarcinoma with bronchioloalveolar carcinoma components. Respiration 2003; 70(1):36–42.

[12] Takamochi K, Yoshida J, Nishimura M, Yokose T, Sasaki S, Nishiwaki Y, et al. Prognosis and histologic features of small pulmonary adenocarcinoma based on serum carcinoembryonic antigen level and computed tomographic findings. Eur J Cardiothorac Surg 2004; 25(5): 877–83.

[13] Higashi K, Sakuma T, Ito K, Niho S, Ueda Y, Kobayashi T, et al. Combined evaluation of preoperative FDG uptake on PET, ground-glass opacity area on CT, and serum CEA level: identification of both low and high risk of recurrence in patients with resected T1 lung adenocarcinoma. Eur J Nucl Med Mol Imaging 2009; 36(3): 373–81.

[14] Yamazaki M, Ishikawa H, Kunii R, Tasaki A, Sato S, Ikeda Y, et al. Relationship between CT features and high preoperative serum carcinoembryonic antigen levels in early-stage lung adenocarcinoma. Clin Radiol 2014; 69(6): 559–66.

[15] Zwirewich CV, Vedal S, Miller RR, Müller NL. Solitary pulmonary nodule: high-resolution CT and radiologic-pathologic correlation. Radiology 1991; 179(2): 469–76.

[16] Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008; 246(3): 697–722.

[17] Jankowich MD, Rounds SI. Combined pulmonary fibrosis and emphysema syndrome: a review. Chest 2012; 141(1): 222–31.

[18] Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996; 28; 15(4): 361–87.

[19] Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. Stat Med 2004 15; 23(13): 2109–23.

[20] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1998; 44(3): 837–45.

[21] Youden WJ. Index for rating diagnostic tests. Cancer 1950; 3(1): 32–5.

[22] Watanabe A, Higami T, Ohori S, Koyanagi T, Nakashima S, Mawatari T, et al. Is lung cancer resection indicated in patients with idiopathic pulmonary fibrosis? J Thorac Cardiovasc Surg 2008; 136(5): 1357–63.

[23] Kaneda M, Tarukawa T, Watanabe F, Adachi K, Sakai T, Nakabayashi H, et al. Clinical features of primary lung cancer adjoining pulmonary bulla. Interact Cardiovasc Thorac Surg 2010; 10(6): 940–4.

[24] Hanaoka N, Tanaka F, Otake Y, Yanagihara K, Nakagawa T, Kawano Y, et al. Primary lung carcinoma arising from emphysematous bullae. Lung Cancer 2002; 38(2): 185–91.

Table 1 Patients' clinical characteristics and CT findings of tumors

Factor	Number
Age	
Mean (range)	67.8 (39–87)
Gender	
Male	132 (53%)
Female	118 (47%)
Smoking status	
Yes	140 (56%)
No	110 (44%)
Preoperative CEA levels	
≤5.0 ng/mL	173 (69%)
>5.0 ng/mL	77 (31%)
Postoperative CEA levels	
≤5.0 ng/mL	219 (88%)
>5.0 ng/mL	31 (12%)
%solid	
<50%	159 (64%)
≥50%	91 (36%)
MaxD	
Mean (range)	18.6 (6–30)
Air bronchogram	
Yes	170 (68%)
No	80 (32%)
Spiculation	
Yes	59 (24%)
No	191 (76%)
Adjacency with bullae/IP	
Yes	43 (17%)
No	207 (83%)
Notch	
Yes	39 (16%)
No	211 (84%)
Pleural indent	
Yes	147 (59%)
No	103 (41%)

CEA, carcinoembryonic antigen; %solid, percentage of solid component; MaxD, maximum tumor diameter; IP, interstitial pneumonia

Table 2 Univariate Cox regression analysis of disease-free survival

Factor		HR (95% CI)	*P*- value
CT findings			
%solid	Per 10% increase	1.35 (1.21–1.51)	< 0.001
MaxD	Per 1mm increase	1.02 (0.97–1.07)	0.463
Air bronchogram	Yes versus no (reference)	0.63 (0.32–1.23)	0.174
Spiculation	Yes versus no (reference)	2.20 (1.11–4.37)	0.024
Adjacency with bullae/IP	Yes versus no (reference)	4.17 (2.09–8.35)	< 0.001
Notch	Yes versus no (reference)	2.68 (1.28–5.58)	0.009
Pleural indent	Yes versus no (reference)	1.28 (0.64–2.57)	0.490
Clinical factors			
Preoperative CEA levels	Per 1 mg/dL increase	1.07 (1.02–1.13)	0.006
Postoperative CEA levels	Per 1 mg/dL increase	1.17 (1.09–1.26)	< 0.001
Patient Age	Per 1-year increase	1.01 (0.97–1.05)	0.734
Gender	Male versus female (reference)	3.71 (1.68–8.18)	0.001
Brinkman index	Per 100 increase	1.07 (1.02–1.12)	0.003

HR, hazard ratio; CI, confidence interval; %solid, percentage of solid component; MaxD, maximum tumor diameter; IP, interstitial pneumonia; CEA, carcinoembryonic antigen

Table 3 Multivariate Cox model for predicting disease-free survival

Factor		HR (95% CI)	*P*-value
%solid	Per 10% increase	1.32 (1.18–1.48)	< 0.001
Adjacency with bullae/IP	Yes versus no (reference)	2.15 (1.04–4.44)	0.040
Postoperative CEA levels	Per 1 mg/dL increase	1.12 (1.03–1.22)	0.010

Spiculation (P = 0.721), notch (P = 0.268), preoperative CEA levels (P = 0.191), gender (P = 0.245), and Brinkman index (P = 0.871) were not statistically significant.

HR, hazard ratio; CI, confidence interval; %solid, percentage of solid component; IP, interstitial pneumonia; CEA, carcinoembryonic antigen

Table 4 Summary of the 5-year disease-free survival predictive accuracy

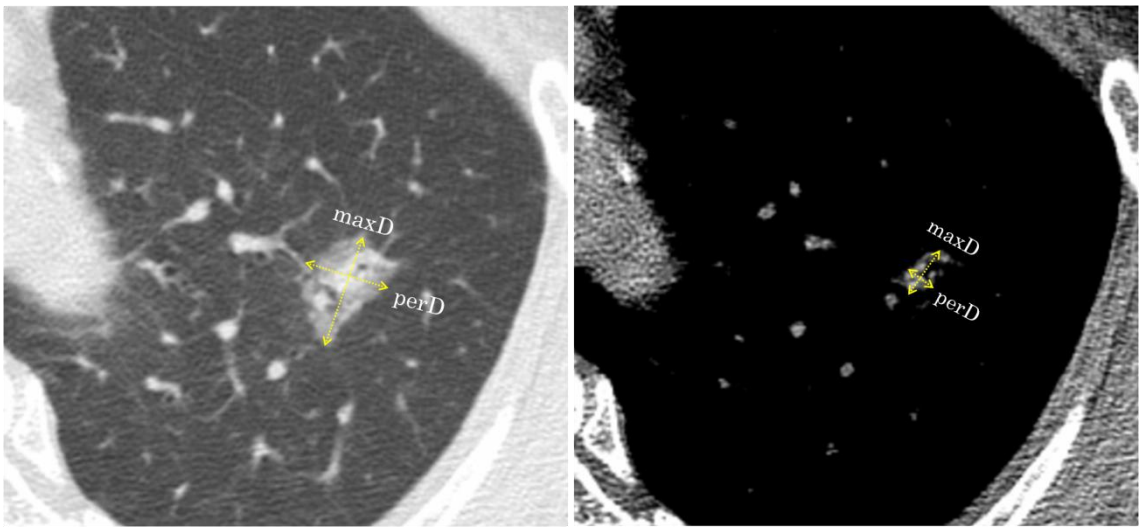
Predictive factor	Best cut-off	Sensitivity*	Specificity*	AUC (95% CI)
%solid + bullae/IP + postoperative CEA levels	11.0% †	85.7% (24/28)	74.3% (107/144)	0.853 (0.792–0.915)
%solid alone	48%	82.1% (23/28)	75.0% (108/144)	0.792 (0.693–0.892)
Postoperative CEA levels alone	3.7 ng/mL	53.6% (15/28)	79.2% (114/144)	0.692 (0.593–0.792)

* The Sensitivity and the specificity are percentages at the best cut-off level.

† The percentage is a 5-year probability of recurrence calculated by the following formula: $100 - 100 \times \exp(-0.019 \times \exp[0.28 \times \%\text{solid} + 0.11 \times \text{postoperative CEA levels} + 0.76 \times Z])$, where Z = 1 if bullae or IP change was adjoining with tumor and Z = 0 if bullae or IP change was absent around tumor.

AUC, area under the curve; CI, confidence interval; %solid, percentage of solid component; IP, interstitial pneumonia; CEA, carcinoembryonic antigen

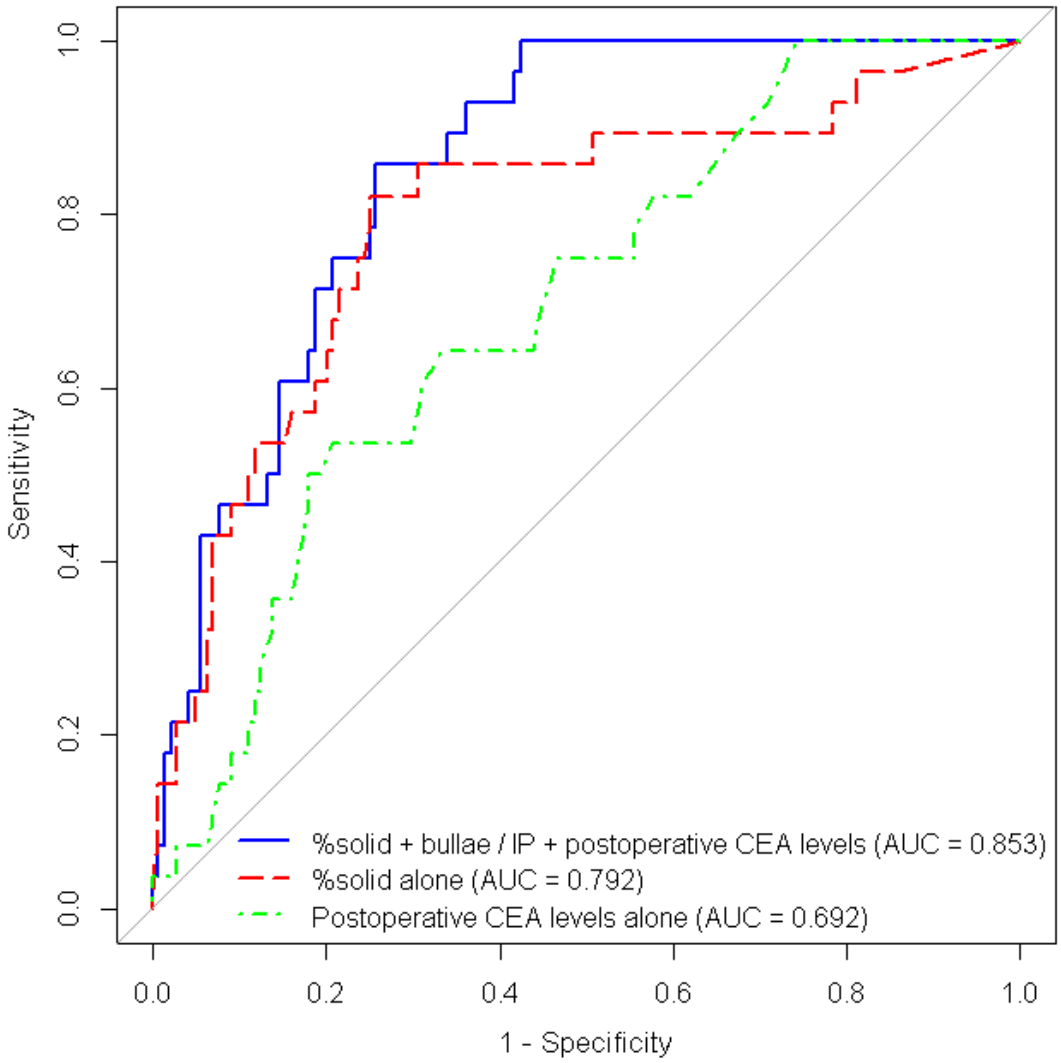
Figure 1: Sample measurement of %solid



The maxD and perD are 18 mm and 11 mm, respectively, in the lung window and 7 mm and 4 mm, respectively, in the mediastinal window. %solid of the tumor is calculated as follows: %solid = (7 × 4) ÷ (18 × 11) × 100 = 14%.

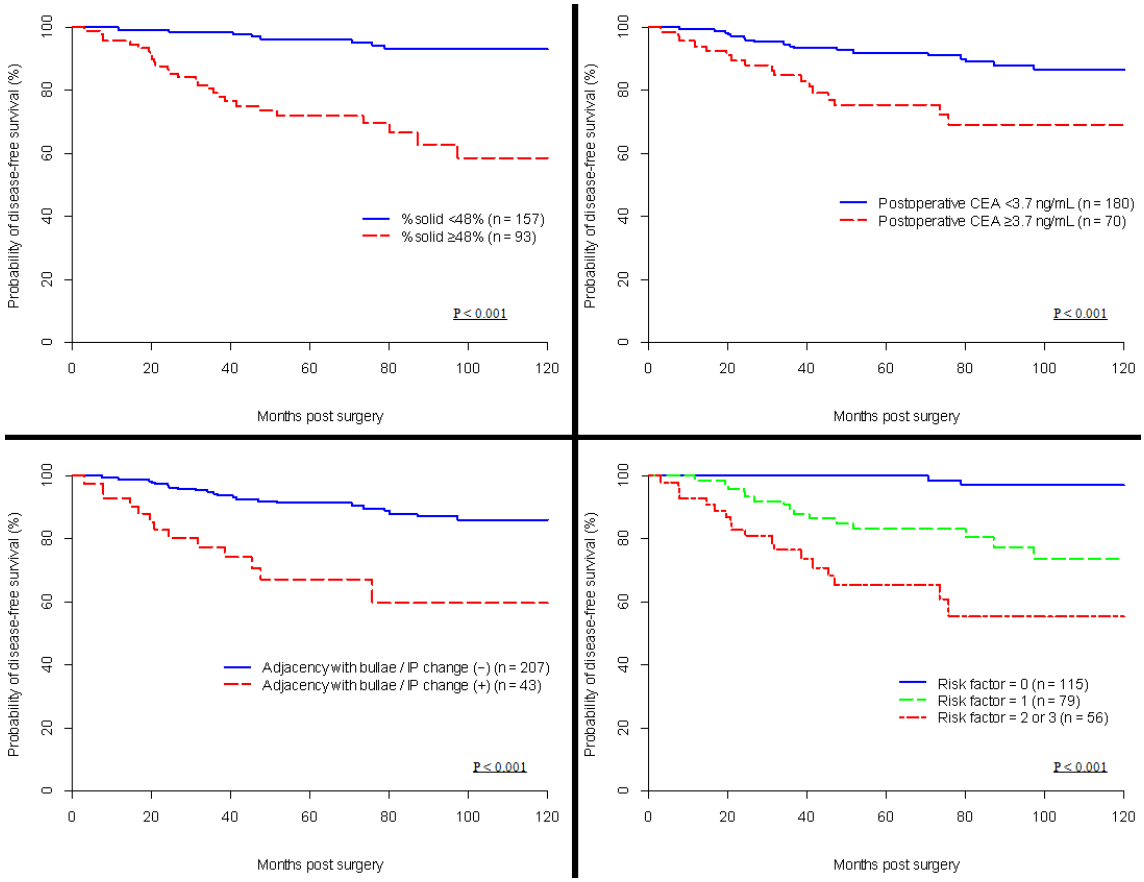
%solid, percentage of solid component; maxD, maximum tumor diameter; perD, largest diameter perpendicular to the maximum axis

Figure 2: ROC curves showing the predictive accuracy (AUC) for 5-year disease-free survival.



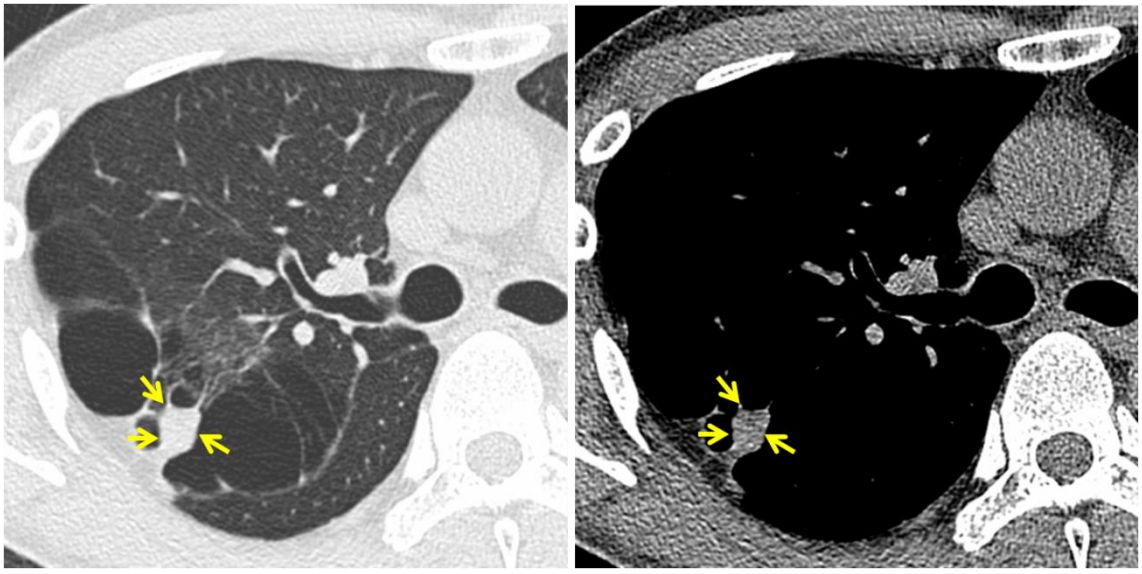
ROC, receiver operating characteristic curve; AUC, area under the curve; %solid, percentage of solid component; IP, interstitial pneumonia; CEA, carcinoembryonic antigen

Figure 3:



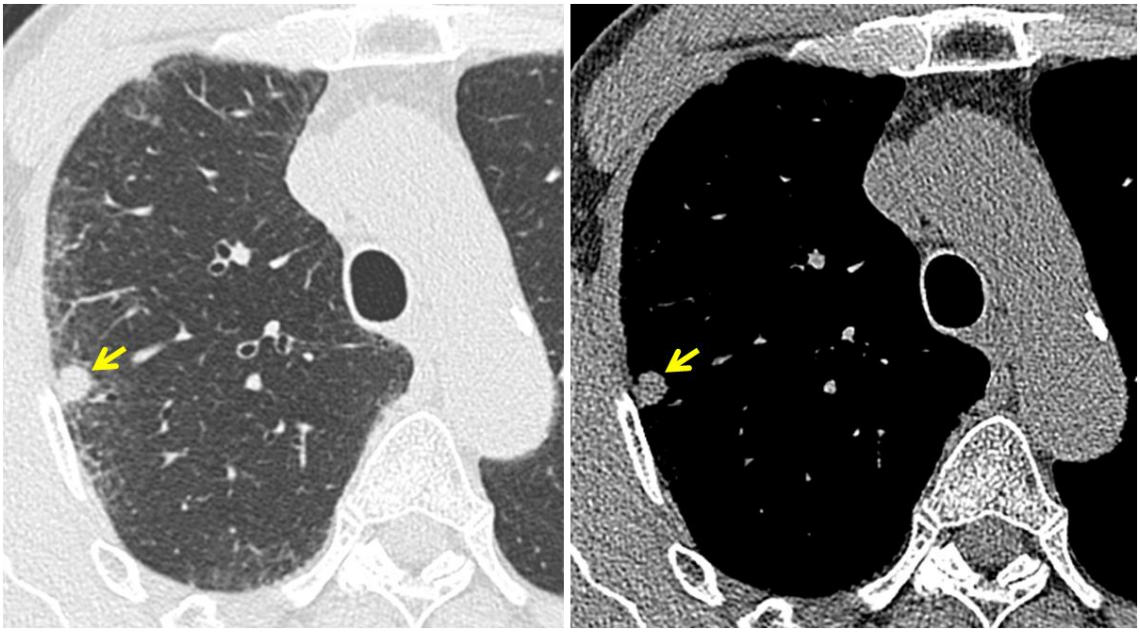
Line graphs display the Kaplan–Meier survival curves based on (a) %solid and (b) postoperative CEA levels divided at the best cut-off value, (c) adjacency of bullae or IP change around the tumor, and (d) the number of the following risk factors: %solid ≥48%, postoperative CEA levels ≥3.7 ng/mL, and adjacency of bullae or IP change. %solid, percentage of solid component; CEA, carcinoembryonic antigen; IP, interstitial pneumonia

Figure 4: A 39-year-old male patient.



Preoperative CT images reveal a solid tumor without ground-glass opacity in the right upper lobe. The tumor is surrounded by multiple large bullae. Preoperative serum CEA levels were high (8.2 ng/mL) and remained high (5.6 ng/mL) even after surgery (risk factors = 3). Mediastinal lymph node swelling subsequently appeared and was pathologically confirmed to be adenocarcinoma.

Figure 5: A 64-year-old male patient.



Preoperative CT images show a solid tumor without ground-glass opacity in the subpleural region of the right upper lobe. Reticular opacity with a peripheral distribution, which is considered as IP change, can be observed around the tumor. Preoperative serum CEA levels were high (7.4 ng/mL) and remained high (5.8 ng/mL) even after surgery (risk factors = 3). A local recurrence subsequently appeared.