Clinical predictor of pre- or minimally invasive pulmonary adenocarcinoma: possibility of sub-classification of clinical T1a

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Abstract

OBJECTIVES: A new pathological classification for pre- and minimally invasive adenocarcinoma has been established, with distinction prior to surgery crucial because of the extremely good prognosis.

METHODS: Of 412 patients who underwent surgery for lung cancer from 2008 to 2011, 110 classified as c-stage I had each of the following four parameters assessed for predictive power for pre- or minimally invasive adenocarcinoma and relapse-free survival (RFS): (i) whole tumour size (WS) shown by computed tomography (CT), (ii) size of the solid (SS) component in CT findings, (iii) maximum standard uptake value in fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scan images (SUVmax) and (iv) serum level of carcinoembryonic antigen.

RESULTS: For prediction of pre- or minimally invasive adenocarcinoma, the area under the receiver-operating curve was >0.7 for all the four parameters, while only SS was found to be an independent factor in multivariate logistic regression analysis. In Cox proportional hazard model analysis, SS and SUVmax were statistically significant, and SS was exclusively independent in multivariate analysis. Differences in RFS between T1a and T1b were more pronounced when using SS compared with WS. In the sub-classification of T1a, we used a breakpoint of 1.0 cm in SS (T1a-α and T1a-β), which resulted in a 2-year RFS rate of 1.00 for T1a-α (n = 21), 0.89 for T1a-β (n = 27) and 0.68 for T1b (n = 26) (P = 0.002 between T1a-β and T1b).

CONCLUSIONS: The SS parameter was useful to distinguish pre- and minimally invasive adenocarcinoma from other types of lung cancer, and set a T1a sub-classification.

Keywords: Non-small-cell lung cancer • Computed tomography • Invasive adenocarcinoma • SUVmax • Carcinoembryonic antigen • Surgery

INTRODUCTION

Among patients with lung cancer who undergo surgery, the proportion of those with an adenocarcinoma or small lesions has been increasing, while the prognosis of clinical stage I non-small-cell lung cancer (NSCLC) has improved [1]. The histological classification of pulmonary adenocarcinoma has been revised according to the extent of invasiveness, such as pre-, minimally invasive and invasive [2], and is similar to the method used to calculate tumour size in breast cancer [3]. This is because the prognosis of pulmonary adenocarcinoma is well distinguished by the amount of invasion [2], which dominantly appears as a solid region in computed tomography (CT) findings, contrary to the ground glass opacity (GGO) appearance of a lepidic adenocarcinoma [2, 4]. In addition to CT findings, other clinical parameters including maximum standard uptake value (SUVmax) in fluorodeoxyglucose positron emission tomography (FDG-PET) images [5] and serum carcinoembryonic antigen (CEA) level [6, 7] are used as predictors of aggressiveness and/or prognosis in cases of NSCLC. Therefore, it is crucial to evaluate those clinical parameters prior to surgery in order to distinguish patients with a pre- or minimally invasive adenocarcinoma, because of the extremely good survival [2].

MATERIALS AND METHODS

Of 412 patients with lung cancer who underwent surgery from 2008 to 2011 at Osaka University Medical Hospital, 110 classified as clinical stage I underwent a segmentectomy or lobectomy (video-assisted thoracic surgery in 72 cases) with removal of lymph nodes, which was greater than the minimal requirement noted in Union for International Cancer Control (UICC) Tumor Node Metastasis (TNM) classification ver. 7, which states the following: ‘Histological examination of hilar and mediastinal lymphadenectomy specimens(s) will ordinarily include 6 or more lymph...
nodes/stations. Three of these nodes/stations should be mediastinal including the subcarinal nodes and 3 from N1 nodes/stations [3]. The number of lymph nodes removed ranged from 6 to 31, with a median of 20. The tumour histology of the p-N2 cases varied (invasive adenocarcinoma \( n = 3 \), squamous cell carcinoma \( n = 1 \) and pleomorphic carcinoma \( n = 1 \)). Cyto-pathological staging of the affected lymph nodes was not performed prior to surgery, and thus clinical staging was accomplished mainly using CT and FDG-PET findings. In these cases, each of the following four parameters was assessed for their predictive power for pre- or minimally invasive adenocarcinoma and relapse-free survival (RFS): (i) WS shown by thin section CT, (ii) size of the solid (SS) component in CT findings, (iii) SUV\(_{max}\) in FDG-PET/CT scan findings (SUV\(_{max}\)) and (iv) CEA (Tables 1 and 2). For the WS parameter, the size (mean ± standard deviation (SD)) according to tumour histology was 2.9 ± 1.0 cm for adenocarcinoma and 3.1 ± 1.3 cm for non-adenocarcinoma. There were no missing data for any of the four parameters. Representative appearances in thin-sliced CT are shown in Fig. 1. The pathological diagnosis of each tumour was defined according to clinical records, except for adenocarcinoma lesions that required rediagnosis according to the new classification [2], which was performed by a pathologist (E.M.). Adjuvant therapy was carried out in 17 cases (oral administration of tegafur-uracil for pathological stage IB in 9, platinum doublet for pathological stage II or III in 8).

The follow-up periods ranged from 12 to 44 months, with a median of 23 months. In the follow-up examinations, all the patients were evaluated at 3-month intervals, which included a physical examination, chest X-ray and blood tests including tumour markers, while additional thoraco-abdominal CT scans were generally performed at 6-month intervals. During the follow-up period, cancer relapse occurred in 19 cases (pathological stage IA in 9 cases, IB in 6, IIA in 2, IIA in 1, and V in 1), which included local recurrence in 8, distant recurrence in 6, local plus distant recurrence in 5 and death in 8 (original lung cancer in 6, heart attack in 1 and suicide in 1).

### Assessment of prediction of pre- or minimally invasive adenocarcinoma

The area under the curve (AUC) of the receiver-operating curve (ROC) was calculated using JMP 9 (SAS Institute Japan, Tokyo, Japan) for WS, SS, SUV\(_{max}\) and CEA. In addition, the relative risk (RR) of the four parameters was calculated by logistic regression analysis, while multivariate analysis was performed using variables that showed statistical significance in the individual analysis using StatView 5.0 (HULINKS, Tokyo, Japan).

### Assessment of survival

RFS was defined as the period from the day of initial surgery to the day of relapse shown in clinical findings (primarily radiography). Survival curves were figured with the Kaplan–Maier method and a log-lank test was used to assess statistical significance. The hazard ratio (HR) was calculated using Cox proportional hazard model analysis and multivariate analysis was performed using variables that showed statistical significance in the individual analysis. These analyses were done using StatView 5.0 (HULINKS, Tokyo, Japan).

### RESULTS

#### RFS curves for pre- or minimally invasive adenocarcinoma

The present pre- and minimally invasive cases had 100% RFS, confirming extremely good prognosis (Fig. 2).
Prediction of pre- or minimally invasive adenocarcinoma

For prediction of pre- or minimally invasive adenocarcinoma, the AUC of the ROC was >0.7 for all the four parameters (0.80 for WS, 0.95 for SS, 0.91 for SUV\(_{\text{max}}\), and 0.70 for CEA) (Fig. 3). In logistic regression analysis, each parameter was statistically significant (Table 3), while SS was exclusively independent in multivariate analysis (Table 4).

RFS based on clinical-T classification using WS or SS

When analysing survival, SS provided a better distinction between T1b and T2a compared with WS. In our assessment of RFS according to clinical T classification based on WS, the 2-year RFS rate was 89% for T1a (n = 26), 79% for T1b (n = 38), 78% for T2a (n = 41) and 80% for T2b (n = 5). There were no statistically significant differences between any neighbouring groups. As for assessment of RFS according to clinical T classification by SS, the 2-year RFS rate was 95% for T1a (n = 48), 68% for T1b (n = 26), 72% for T2a (n = 32) and 75% for T2b (n = 4). There was no statistically significant difference between any neighbouring groups, except between T1a and T1b (P = 0.002).

In the sub-classification T1a, we used 1.0 cm as the breakpoint to provide a suitable sensitivity of 0.91 and specificity of 0.85 for

![Figure 1](image1.png)

**Figure 1:** Representative appearances of pure GGO lesion (A), GGO with solid component lesion (B) and pure solid lesion (C) in thin-sliced CT. Whole size of the lesion is 1.8 cm in (A), 2.8 cm in (B) and 2.8 cm in (C), and size of the solid component is 0 cm in (A), 1.5 cm in (B) and 2.8 cm in (C).

![Figure 2](image2.png)

**Figure 2:** RFS curves according to histology type. Pre: preinvasive adenocarcinoma (n = 8); Min: minimally invasive adenocarcinoma (n = 12), Inv: invasive adenocarcinoma (n = 61); Non-AD: non-adenocarcinoma (n = 29). The 2-year RFS rate (95% CI) was 1.00 (1.00–1.00) for Pre, 1.00 (1.00–1.00) for Min, 0.79 (0.67–0.91) for Inv and 0.74 (0.54–0.94) for Non-AD.
Figure 3: Receiver-operating curves. The AUC was 0.80 for the entire size of the tumour in CT findings (A), 0.95 for the SS (B), 0.91 for SUV\textsubscript{max} in FDG-PET/CT images (C) and 0.70 for serum level of CEA (D).

### Table 3: Results of logistic regression analysis for prediction of pre- or minimally invasive adenocarcinoma

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>WS (n = 110)</td>
<td>0.217</td>
<td>0.095–0.497</td>
</tr>
<tr>
<td>SS (n = 110)</td>
<td>0.051</td>
<td>0.013–0.198</td>
</tr>
<tr>
<td>SUV\textsubscript{max} (n = 110)</td>
<td>0.239</td>
<td>0.108–0.529</td>
</tr>
<tr>
<td>CEA (n = 110)</td>
<td>0.647</td>
<td>0.443–0.957</td>
</tr>
</tbody>
</table>

WS: whole size of the tumour in CT; SS: size of the solid component in CT; SUV\textsubscript{max}: maximum standard uptake value in FDG-PET/CT images; CEA: serum level of carcinoembryonic antigen; CI: confidence interval.

### Table 4: Results of Cox proportional hazards model analysis for disease-free survival

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th>Multivariate</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>WS (n = 110)</td>
<td>1.397</td>
<td>0.889–1.908</td>
</tr>
<tr>
<td>SS (n = 110)</td>
<td>1.574</td>
<td>1.171–2.115</td>
</tr>
<tr>
<td>SUV\textsubscript{max} (n = 110)</td>
<td>1.123</td>
<td>1.035–1.219</td>
</tr>
<tr>
<td>CEA (n = 110)</td>
<td>1.006</td>
<td>0.948–1.066</td>
</tr>
</tbody>
</table>

WS: whole size of the tumour in CT; SS: size of the solid component in CT; SUV\textsubscript{max}: maximum standard uptake value in FDG-PET/CT images; CEA: serum level of carcinoembryonic antigen; HR: hazard ratio; CI: confidence interval.
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ception between T1a-

The 2-year RFS rate (95% CI) was 1.00 (1.00 – 1.00) for T1a-

RFS rate was 1.00 in the T1a-

classi-
cates the SS, was an independent predictor and indicated a sub-

tification of T1a.

DISCUSSION

Pre- and minimally invasive are known to be associated with scant cancer spreading and a very low chance of recurrence following surgery [2], and thus, prediction of such histology type is crucial for important decisions related to surgical treatment. In this investig-

tional of clinical parameters reported to be predictive indicators of cancer spread and recurrence, we found that SS, which indi-

icates the SS, was an independent predictor and indicated a sub-

classification of T1a.

At present, the entire tumour size without exclusion of the GGO region in CT findings is employed for detecting the clinical T factor [3]. However, the GGO region corresponds to the lepidic compo-

iment of an adenocarcinoma and possesses a very low level of inva-

siveness, and thus has a very low chance of causing cancer relapse [8]. Okada et al. [9] reported results of a multicentre prospective study and showed that SUVmax, and bronchioloalveolar carcinoma ratio, tumour disappearance rate and GGO ratio mirrored the pathological aggressiveness of tumour malignancy, nodal metastasis, recurrence and prognosis. In addition, Tsutani et al. [10] found that cases with a pure solid adenocarcinoma had inferior prognosis compared with those with a mixed GGO adenocarcinoma, though when SUVmax and solid component size were matched, the differences in pathological prognostic parameters and disease-free survi-

vals between patients with solid and mixed tumours disappeared. Those results led us to consider SS as an effective parameter for tumour invasiveness and prognostic factor, in addition to SUVmax.

Some have reported that SUVmax is a predictive indicator of the aggressiveness of pulmonary carcinoma as well as prognosis [5, 11, 12], even though SUVmax is difficult to calculate with GGO lesions [5] and underestimated in small tumours [13]. The strong clinical implication of SUVmax noted above [9, 10] may be due to use of an absorption revision technique for small lesions. In the present study, SUVmax was shown to be a predictive indicator of pre- and minimally invasive adenocarcinomas as well as poor prognosis, though it was not found to be an independent factor. This may have been because our specimens included a large number of lesions with SS <1 cm and we did not employ an absorption revi-

sion technique. Tsutani et al. [10] reported the clinical usefulness of both SS and SUVmax using an absorption revision technique for patients with a large number of exclusive pulmonary adenocarcinoma tumours. However, that technique is not universally applied.

Tumour markers are also predictive indicators of the aggressiveness of pulmonary carcinoma and patient prognosis [14], with CEA the most frequently employed. Sawabata et al. [15] reported a concept that used a sub-normal level of less than half of the maximum point of normal and showed that a low serum CEA level can be useful clinically to predict prognosis. Their observations may indicate a relationship between serum CEA and adenocarcinoma invasiveness. In the current study, serum CEA level was shown to be a predictive indicator of a pre- or minimally invasive adenocarcinoma, even though serum CEA levels were normal in a large number of our patients.

We performed an intentional segmentectomy procedure in cases with small peripheral GGO dominant lesions and that on an emergency basis in high-risk patients. In all cases, sufficient tumour margin distance and negative margin cytology are mandated based on a concept of previous reports [16–18].

For the present study, we used the clinical parameters: entire size of the tumour in thin section CT findings, SS in CT findings, SUVmax in FDG-PET/CT findings and serum level of CEA, as they have been reported to be predictive factors of tumour aggressiveness and prognosis. Among those, only SS was shown to be an independent predictive factor of pre- or minimally invasive (RR, 0.067; 95% CI, 0.011–0.421 and P-value, 0.004 in multivariate analy-

sis), and chance of recurrence (H.R., 1.434; 95% C.I., 1.006–2.044 and P-value, 0.04 in multivariate analysis).

Since this is a retrospective clinical investigation with a limited number of patients and the observation period was rather short, there are some limitations that must be seriously considered. Above all, care should be taken with assessing prognosis using only RFS. In addition, analysis of RFS using a specific T factor or 1.0 cm as the breakpoint for solid portion size may not show a sig-

ificant distinction between RFS curves. Therefore, additional analy-

sis of a greater number of patients is mandatory prior to establishment of a classification. Although this is a very crucial limitation of this study, we consider that our findings may be helpful for a future prospective investigation.

In summary, in our assessment of surgical patients with clinical stage I NSCLC, the SS showed high potential to distinguish pre- and minimally invasive adenocarcinoma from other types of lung cancer, and may provide important information for a sub-

classification of T1a.

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Conflict of interest: none declared.

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