Prognosis and histologic features of small pulmonary adenocarcinoma based on serum carcinoembryonic antigen level and computed tomographic findings

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Abstract

Objectives: In 2001, we proposed the criteria for combined evaluation of the serum carcinoembryonic antigen (CEA) level and the tumor shadow disappearance rate (TDR) to predict pathologic N0 (pN0) disease in pulmonary adenocarcinomas. The objective of the present study was to determine the prognosis and histologic features in small-sized pulmonary adenocarcinomas according to serum CEA level and TDR.

Methods: We reviewed clinical records of 189 consecutive patients with peripheral pulmonary adenocarcinoma 3.0 cm or smaller who underwent major lung resection and systematic lymph node dissection: 50 patients with TDR ≥ 0.8 and normal CEA level (group I) and 139 patients with TDR < 0.8 and/or elevated CEA level (group II). Among them, we investigated histologic features of 177 adenocarcinomas according to serum CEA level and TDR.

Results: The 5-year survival rates were 95% for group I and 75% for group II (P = 0.002); and for pN0 patients, 97% in group I and 87% in group II (P = 0.04). In univariate analyses, TDR, preoperative serum CEA level, and the maximum tumor dimension on computed tomographic (CT) scan were significantly associated with prognosis. Multivariate analysis showed that only preoperative serum CEA level and TDR were significant independent prognostic factors, and the maximum tumor dimension was not significant. Group I patients developed no local recurrence, including lymph node metastases. In 25 group I adenocarcinomas 2.0 cm or smaller, no lymph node involvement, two lymphatic permeation, two vascular invasion, and one pleural involvement tumors were observed. These signs of local invasiveness were less frequent than the remaining adenocarcinomas. CT findings correlated well with histologic findings in small-sized adenocarcinomas. Conclusions: Combined evaluation of preoperative serum CEA level and TDR may enable us to identify minimally invasive adenocarcinomas with good prognosis. Candidates for limited lung resection without systematic lymph node dissection could be selected based on these findings.

Keywords: Lung cancer; Limited surgery; Carcinoembryonic antigen; Computerized tomography scan; Adenocarcinoma

1. Introduction

Many small-sized lung cancers, especially peripheral adenocarcinomas, have been found as a result of the introduction of computed tomographic (CT) screening for lung cancer [1]. Among them, bronchioloalveolar carcinoma (BAC) with small invasive foci has been found increasingly. Several investigators reported that these BAC type adenocarcinomas are likely to appear as localized ground glass attenuation (GGA) [2–5]. In the latest edition of World Health Organization (WHO) classification of lung tumors [6], BAC is classified as non-invasive carcinoma. If the relationship between GGA and BAC is conclusive, candidates for limited lung resection could be selected based on CT findings.

We previously reported that pathologic N0 (pN0) status in peripheral pulmonary adenocarcinoma was predictable by the combined evaluation of serum carcinoembryonic antigen (CEA) level and a radiological parameter, tumor shadow disappearance rate (TDR) [7]. TDR is the ratio of a maximum tumor area in mediastinal window setting images to that in
pulmonary window setting images on conventional CT scans. We speculated that TDR could be interpreted as the extent of both GGA and BAC. However, we did not show in the previous study the data on the correlation between TDR and histologic features and prognostic implication of TDR.

The objective of the present study was to determine the prognosis and histologic features in small-sized pulmonary adenocarcinomas according to serum CEA level and TDR.

2. Patients and methods

2.1. Patients

From August 1992 to April 1997, 189 consecutive patients with peripheral adenocarcinoma 3.0 cm or smaller who underwent major lung resection and systematic lymph node dissection at the National Cancer Center Hospital East were reviewed. One hundred and eighty-five lobectomies, three lobectomies with bronchoplastic procedures, and one pneumonectomy were carried out. There were 89 men and 100 women. The mean age was 63 years, ranging from 33 to 84 years.

2.2. Outcome and patterns of failure

All clinical records were carefully reviewed to examine patterns of failure and outcome. The median follow-up period for the 189 patients was 57 months. The length of survival was defined as the interval in months between the day of surgical intervention and the date of death due to any cause or the last follow-up. The survival rates were calculated by the Kaplan–Meier method, and the curve differences were tested using the log-rank test. Because the median follow-up time was less than 5 years, we calculated 3- and 5-year survival rates separately.

As in our previous report [7], the following tumor dimensions on conventional CT scan was defined: pDmax, the maximum dimension of a tumor on pulmonary window setting images; pDperp, the largest dimension perpendicular
to the maximum axis on pulmonary window setting images; mDmax, the maximum dimension of a tumor on mediastinal window setting images; and mDperp, the largest dimension perpendicular to the maximum axis on mediastinal window setting images (Fig. 1A and B). TDR was calculated by the following formula as previously described [7]:

\[
TDR = 1 - \frac{(mDmax) \times (mDperp)}{(pDmax) \times (pDperp)}
\]

Univariate and multivariate analyses were performed by means of Cox’s proportional hazards model on Stat View 5.0 (Abecus Concepts, Inc., Berkeley, CA). In multivariate analysis, forward and backward stepwise procedures were used to determine the combination of preoperatively available factors that were essential in predicting prognosis. The present multivariate analysis included five variables: gender, age, TDR, preoperative serum CEA level, and pDmax. In the statistical analyses, we used continuous variables for age, pDmax, and TDR. Because the distribution of serum CEA values was positively skewed, we used the log-transformed values to normalize the distribution.

2.3. Histologic features

Two authors (K.T. and T.Y.) reviewed 177 of 189 pathologic materials of tumors to investigate histologic features. The resected specimens were fixed with 10% formalin or 99.8% methanol injected directly through the bronchial tree or pleura to be fully expanded. Because material fixation was inappropriate for histologic review, 12 cases were excluded. We studied lymphatic permeation, vascular invasion, pleural involvement, and scar grade [8]. Additionally, we measured the following tumor parameters at the maximum tumor dimension on low power view: Tmax, the maximum tumor dimension; Tperp, the largest tumor dimension perpendicular to the maximum axis; non-BACmax, the maximum dimension of a tumor component other than BAC; and non-BACperp, the largest dimension perpendicular to the maximum axis of the non-BAC component (Fig. 1C). The BAC component was defined as a component of lepidic growth patterns of tumor cells. The non-BAC component was composed of papillary, tubular, and/or solid growth pattern components, with or without fibrotic focus, collapse, necrosis, and/or mucus in a tumor. The size of the non-BAC component was evaluated microscopically on elastica van Gieson as well as standard hematoxylin and eosin staining preparations.

In order to examine the correlation between tumor measurements on CT scans and those on pathologic specimens, we calculated Pearson’s correlation coefficient (r). The χ²-test was used to compare several variables between subgroups according to serum CEA level and TDR. In all statistical analyses, differences were considered statistically significant when \( P < 0.05 \).

### Table 1

<table>
<thead>
<tr>
<th>Clinicoradiologic characteristics of patients according to TDR and serum CEA level</th>
<th>TDR ≥ 0.8 and normal CEA level (group I)</th>
<th>TDR &lt; 0.8 and/or elevated CEA level (group II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>50</td>
<td>139</td>
</tr>
<tr>
<td>No. of pN0 patients (%)</td>
<td>49 (98)</td>
<td>93 (67)</td>
</tr>
<tr>
<td>Age (years, mean ± SD)</td>
<td>64 ± 10</td>
<td>62 ± 10</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>14/36</td>
<td>75/64</td>
</tr>
<tr>
<td>CEA (ng/ml) median</td>
<td>2.3</td>
<td>3.8</td>
</tr>
<tr>
<td>(25th, 75th percentile)</td>
<td>(1.8, 3.3)</td>
<td>(2.4, 7.1)</td>
</tr>
<tr>
<td>pDmax, mm (mean ± SD)</td>
<td>19 ± 6</td>
<td>23 ± 5</td>
</tr>
<tr>
<td>pDperp, mm (mean ± SD)</td>
<td>15 ± 5</td>
<td>18 ± 5</td>
</tr>
<tr>
<td>mDmax, mm (mean ± SD)</td>
<td>3 ± 4</td>
<td>16 ± 7</td>
</tr>
<tr>
<td>mDperp, mm (mean ± SD)</td>
<td>2 ± 2</td>
<td>12 ± 6</td>
</tr>
<tr>
<td>TDR (mean ± SD)</td>
<td>0.96 ± 0.05</td>
<td>0.55 ± 0.22</td>
</tr>
</tbody>
</table>

3. Results

3.1. Patients

The clinical characteristics of the patients are presented in Table 1. There were 49 (98%) pN0 cases and one pathologic N1 (pN1) case in the 50 peripheral adenocarcinoma patients with TDR 0.8 or more and normal preoperative serum CEA level (group I). There were 93 (67%) pN0 cases in the 139 peripheral adenocarcinoma patients with TDR <0.8 and/or elevated preoperative serum CEA level (group II).
The relationship between tumor histologic characteristics and TDR and serum CEA level combined according to tumor size (2.0 cm or smaller versus 2.1–3.0 cm) is shown in Table 4. No lymph node involvement was found in group I tumors 2.0 cm or smaller. Although there was one pN1, no pathologic N2 cases were found in group I tumors 2.1–3.0 cm in size. There were significantly more pN0 tumors in group I than in group II. Group I tumors were more frequently negative for lymphatic permeation and vascular invasion, and there were more lower scar grade tumors (grade 1/2 versus grade 3/4) than group II tumors. Pleural involvement tended to be negative in group I tumors 2.0 cm or smaller (P = 0.06) and was significantly more frequently negative in group I tumors 2.1–3.0 cm in size (P = 0.005) compared with group II.

Statistical correlation was shown between pDmax and Tmax (r = 0.63, P < 0.0001), pDperp and Tperp (r = 0.61, P < 0.0001), mDmax and non-BACmax (r = 0.56, P < 0.0001), mDperp and non-BACperp (r = 0.60, P < 0.0001), pDmax x pDperp and Tmax x Tperp (r = 0.62, P < 0.0001), mDmax x mDperp and non-BACmax x non-BACperp (r = 0.58, P < 0.0001; Fig. 4). These findings suggested that the measurements of non-BAC component in pathologic specimens correlated well with those of tumor opacity on mediastinal window setting images.

3.3. Histologic features

The relationship between tumor histologic characteristics and TDR and serum CEA level combined according to tumor size (2.0 cm or smaller versus 2.1–3.0 cm) is shown in Table 4. No lymph node involvement was found in group I tumors 2.0 cm or smaller. Although there was one pN1, no pathologic N2 cases were found in group I tumors 2.1–3.0 cm in size. There were significantly more pN0 tumors in group I than in group II. Group I tumors were more frequently negative for lymphatic permeation and vascular invasion, and there were more lower scar grade tumors (grade 1/2 versus grade 3/4) than group II tumors. Pleural involvement tended to be negative in group I tumors 2.0 cm or smaller (P = 0.06) and was significantly more frequently negative in group I tumors 2.1–3.0 cm in size (P = 0.005) compared with group II.

Statistical correlation was shown between pDmax and Tmax (r = 0.63, P < 0.0001), pDperp and Tmax (r = 0.61, P < 0.0001), mDmax and non-BACmax (r = 0.56, P < 0.0001), mDperp and non-BACperp (r = 0.60, P < 0.0001), pDmax x pDperp and Tmax x Tperp (r = 0.62, P < 0.0001), mDmax x mDperp and non-BACmax x non-BACperp (r = 0.58, P < 0.0001; Fig. 4). These findings suggested that the measurements of non-BAC component in pathologic specimens correlated well with those of tumor opacity on mediastinal window setting images.

4. Discussion

Adenocarcinoma is the most common histologic type of lung cancer, and its incidence has been increasing [9]. Many small peripheral adenocarcinomas with BAC component have, in particular, been found since helical CT scanning was introduced for lung cancer screening [1]. In the latest edition of WHO classification [6], BAC is clearly defined as an adenocarcinoma with a pure bronchioloalveolar growth pattern and no evidence of stromal, vascular or pleural invasion. Noguchi et al. [10] classified small peripheral adenocarcinomas into six subtypes (types A–F). Type A
localized BAC) and type B (localized BAC with a focus of collapsed alveolar structure) showed no lymph node metastasis, rare vascular invasion and excellent prognosis of 100% 5-year survival rate. BAC and Noguchi’s types A/B could be regarded as minimally invasive, possibly in situ, adenocarcinomas.

Recently, several investigators reported that GGA on high-resolution computed tomography (HRCT) corresponded to lepidic tumor growth in the BAC component [2–5]. A greater extent of GGA in a tumor opacity on HRCT scans correlated with histopathologic lower invasiveness and better outcomes [2,11–13]. Others reported better outcomes in adenocarcinoma with a greater extent of BAC components in pathologic specimens [14,15]. Suzuki et al. [16] reported that in peripheral pulmonary adenocarcinomas 3.0 cm or smaller, a good correlation was demonstrated between the size of central fibrosis in pathologic specimens and outcome. The central fibrosis or non-BAC component in a tumor would appear as consolidation on HRCT scans [3,5].

Based on these previous findings, we can assume that histopathologically minimally invasive adenocarcinomas, possible candidates for limited surgical resection, are predictable based on CT findings: greater extent of GGA or minimal consolidation in a tumor opacity. However, no quantitative analyses comparing the size of GGA or consolidation in tumor opacities on CT scans, with the sizes of BAC or non-BAC components in pathologic specimens have been reported previously. In this study, we showed that the size of non-BAC component

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### Table 4

The relationship between tumor histologic characteristics and TDR and serum CEA level combined according to tumor size

<table>
<thead>
<tr>
<th>pDmax 0–20 mm (n = 69)</th>
<th>pDmax 21–30 mm (n = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of tumors</strong></td>
<td>25</td>
</tr>
<tr>
<td><strong>Lymph node status</strong></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>25 (100)</td>
</tr>
<tr>
<td>N1</td>
<td>0 (0)</td>
</tr>
<tr>
<td>N2</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Lymphatic permeation</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>23 (92)</td>
</tr>
<tr>
<td>Positive</td>
<td>2 (8)</td>
</tr>
<tr>
<td><strong>Vascular invasion</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>23 (92)</td>
</tr>
<tr>
<td>Positive</td>
<td>2 (8)</td>
</tr>
<tr>
<td><strong>Pleural involvement</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>24 (96)</td>
</tr>
<tr>
<td>Positive</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>Scar grade</strong></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>16 (64)</td>
</tr>
<tr>
<td>3 or 4</td>
<td>9 (36)</td>
</tr>
</tbody>
</table>

\( P \text{-value in } \chi^2\text{-test.} \)

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![Fig. 4](image-url) Statistical correlation was shown between pDmax × pDperp and Tmax × Tperp \((r = 0.62, P < 0.0001)\), mDmax × mDperp and non-BACmax × non-BACperp \((r = 0.58, P < 0.0001)\).
correlated well with that of tumor opacity in mediastinal window setting images on conventional CT scans.

The most common definition of GGA is “a hazy increased attenuation of lung, but with preservation of bronchial and vascular structure” [17]. However, it is sometimes difficult to accurately define the edges of GGA when measuring its size. GGA area usually disappears in mediastinal window setting images. Measuring the size of tumor opacity in a mediastinal window-setting image is an easy and reproducible way to evaluate the size of a non-GGA area. Calculating TDR is more objective than quantifying GGA by visual estimation in a pulmonary window setting image as in previous studies [3,11,12]. However, the reproducibility and inter-observer variations in calculating TDR need to be verified in a larger prospective study. Since HRCT should yield more accurate measurements than conventional CT scans, especially in small-sized tumors, we are planning a similar study using HRCT data.

Kondo et al. [13] classified surgically resected pulmonary adenocarcinomas 2.0 cm or smaller into two types: ‘air-containing type’ and ‘solid density type’. The air-containing type was defined as a tumor in which the tumor opacity area on a mediastinal window setting image was half or less of that on a pulmonary window setting image by visual estimation on HRCT. The solid density type, on the other hand, was defined as a tumor in which the tumor opacity area on mediastinal window setting images was more than half of that on a pulmonary window-setting image. Among 66 air-containing type adenocarcinomas, no lymph node involvement, one lymphatic permeation, one vascular invasion, and one pleural involvement tumors were observed histopathologically. The air-containing type adenocarcinoma could be considered minimally invasive. All patients with air-containing type adenocarcinomas were alive and relapse-free after a mean observation period of 851 days following resection. These results were consistent with ours. In our study, no lymph node involvement, two lymphatic permeation, two vascular invasion, and one pleural involvement tumors were observed in 25 adenocarcinomas 2.0 cm or smaller in patients with TDR 0.8 or more and normal preoperative serum CEA level. Shimosato et al. [8] initially reported prognostic impact of fibrotic focus (scar) in patients with adenocarcinomas 3.0 cm or smaller. They proposed scar grade, which correlated well with tumor invasiveness such as lymph node involvement, vascular invasion, and pleural involvement. They suggested that a small peripheral adenocarcinoma <3.0 cm with no or little collagenization (grade 1 or 2) could be considered to be in an ‘early stage’ of development and could be surgically curable. There were more grade 1/2 tumors in group I patients than in group II in our series. If limited lung resection is curative enough for small-sized adenocarcinomas with no or minimal invasiveness, preoperative combined evaluation of serum CEA level and TDR is useful in selecting candidates for limited lung resection.

Although a number of prognostic factors have been reported for patients with surgically resected non-small cell lung cancer, tumor size and lymph node status are considered to be the most significant prognostic factors. We showed that the outcome of group I patients was excellent (5-year survival rate: 95%) and significantly better than group II patients with completely resected adenocarcinomas 3.0 cm or smaller. Even when the prognostic impact of pathologic lymph node status was excluded, the same result was demonstrated. Multivariate analysis showed that both preoperative serum CEA level and TDR were significant independent prognostic factors. Maximum tumor dimension on CT scan was significant in univariate analysis, but not significant in multivariate analysis. These results indicate that tumor size does not have independently significant impact on prognosis in adenocarcinomas 3.0 cm or smaller.

Patients with an adenocarcinoma 2.0 cm or smaller, if preoperative serum CEA level was normal and TDR was 0.8 or more, showed no lymph node involvement (pN0) and developed no local recurrence including lymph nodes. The results suggest that limited lung resection without systematic mediastinal lymph node dissection might be acceptable for these patients. Because these factors are available preoperatively, they are useful not only to predict outcome but also to determine the extent of resection.

In summary, peripheral small-sized pulmonary adenocarcinomas predicted as pN0 by combining serum CEA level and TDR showed no mediastinal lymph node involvement and resulted in excellent outcomes without local recurrence. CT findings correlated well with histologic findings in small-sized adenocarcinomas. Signs of local invasiveness such as lymphatic permeation, vascular invasion, and pleural involvement, were rare in small-sized adenocarcinomas with normal preoperative serum CEA level and a TDR of 0.8 or more. Combined evaluation of preoperative serum CEA level and TDR may enable us to identify minimally invasive adenocarcinomas with good prognosis.

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References


