The tumour shape of lung adenocarcinoma is related to the postoperative prognosis

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Abstract

We evaluated the tumour shape as a potential prognostic indicator in lung adenocarcinoma patients. Among 994 patients who underwent curative surgery, 78 cases of adenocarcinoma (N0M0) with tumours ≥31 mm in diameter were reviewed. The patients were divided into two groups based on the ratio between the longest and the smallest axis length. The patients who had tumours whose ratios were >0.5 were defined as the globular shape group (GL) and the others, whose ratio was 0.5 or less, were defined as the ellipse shape group (EL). The 78 patients were divided into two subgroups (57 in the GL and 21 in the EL). The tumour shape was related to the prognosis, and the 5-year overall survival (OS) rate in the GL was 51.5%, and that in the EL was 85.5% (P = 0.018). The 5-year disease-free survival rate of the GL was 46.6% and that of the EL patients was 85.0% (P = 0.04). The multivariate analysis showed that the shape of the tumour and the presence of pleural invasion were the independent and significant factors predicting the OS (P = 0.04 and P < 0.01, respectively). In adenocarcinoma patients, the shape of the tumour is related to the postoperative survival.

Keywords: Non-small cell lung cancer • Adenocarcinoma • Tumour shape • Prognosis

INTRODUCTION

Adenocarcinoma is the major histological type of non-small cell lung cancer (NSCLC); however, it has been reported that lung adenocarcinoma is often heterogeneous. It is important for considering the optimal postoperative treatment to determine the accurate prognostic factors in lung adenocarcinoma patients [1–5]; however, it has been still controversial.

In the present study, we reviewed patients with completely resected adenocarcinomas of 31 mm or greater in size, and divided them into two subgroups (the globular form group (GL) and the ellipse form group (EL) based on the ratio of the length of the maximal to the minimal axis). We hypothesized that the ellipsoid tumours would be formed by the inhibition of their growth by vessels, the bronchus, lymphatic tissues or the immune system in the normal lungs, and that the expanding and invasive potential of cancer cells may result in the formation of a globular shape. To examine this hypothesis, we analysed the relationship between the shape of a tumour and the clinical findings.

MATERIALS AND METHODS

Patients

Data were collected from a total of 994 lung cancer patients who underwent surgery at the University of Occupational and Environmental Health, Japan, between January 1996 and December 2008. Seventy-eight of those patients, who had an adenocarcinoma with a diameter of 31 mm or more in the maximal dimension, were reviewed, and patients with the involvement of lymph nodes or any distant metastases were excluded from the analysis. The patients who had received preoperative therapy and died from preoperative complications within 30 days, and those who had multiple lung cancers were also not analysed. In all cases, the measurement of the tumour was performed within 1 h after the lung resection and three axes (the longest axis, the shortest axis and the length of the axis perpendicular to the direction of the plane) were measured by one or two of the surgeons before formalin fixation. In the present study, patients with adenocarcinoma were divided into two subgroups based on the shape of the primary tumour. A patient with a tumour whose ratio of the shortest/longest axes was more than 0.5 was categorized as belonging to the GL group and the others, whose ratio was 0.5 or less, were categorized as part of the EL group. The volume of the tumour was calculated using the formula: \( V = 1.5 \times a \times b \times c \times 3.1 \) (a is the length of the longest axis, b the length of the shortest axis and c the length of the axis perpendicular to the direction of the plane).

All resected specimens underwent a pathological examination, and the pathological T factor was classified according to the 7th edition of the TNM classification described by the IASLC. The patients were followed-up every month during the first postoperative year and at approximately 2–4-month intervals thereafter.
Statistical analysis

The overall survival (OS) time was calculated from the day of the surgery to the known date of death according to the hospital medical records. Disease-free survival (DFS) was defined as the time from the operation to the first event of either recurrence of disease or death. The patient data were censored for DFS on the last date on which the medical records were available if the medical records did not show any evidence of recurrence or death. Survival curves were estimated using the Kaplan–Meier method, and differences among them were evaluated by the log-rank test. The univariate and multivariate analyses of the OS and DFS were performed using the Cox proportional hazard model. Independent t-tests were used for two-group comparisons of continuous variables. The categoric data from the cross-tabulation tables were compared using Fisher’s exact test. A value of \( P < 0.05 \) was considered to be significant. We used the R statistical package (www.r-project.org) for the analyses.

RESULTS

A total of 78 patients were divided into two subgroups based on the ratio of the length of the tumour axes. Twenty-one cases were defined as EL and another 57 cases were defined as GL. The mean follow-up time was 47.4 months.

The comparisons between the status of the shape of a tumour and the clinical characteristics of the patients are presented in Table 1. The regimens of systemic chemotherapy were concomitant carboplatin and paclitaxel in 11 patients, oral UFT in 3, concomitant carboplatin and gemcitabine in 2 and S-1 in 1, as previously reported [6, 7]. The number of tumours located in the right lung and of younger cases was higher in the EL than the GL group. There were no significant differences in the length of the maximal axis length between the two subgroups (\( P = 0.71 \)); however, the minimal length was lower in the EL patients.

The 5-year OS rate and median survival time after surgery in all cases were 59.2% and 117 months (95% CI, 55.0–not reached), and the DFS was 55.0% and 111 months (95% CI, 33.1–not reached). Fig. 1 shows the survival curves of the OS (Fig. 1A) and DFS (Fig. 1B) between the GL and EL patients. The 5-year OS rate after surgery in the GL patients was 51.5%, and that in EL patients was 85.5%, which was significantly worse in the GL patients (the log-rank test; \( P = 0.018 \)). The 5-year DFS rate of the GL group was 46.6% and that of patients with EL was 85.0%, which was also significantly different (log-rank test; \( P = 0.04 \)).

The univariate survival analysis calculated by the proportional hazard model is shown in Table 2, and it demonstrated that a p1-3 tumour, exceeding 30 mm in the size of the smaller axis, and belonging to the GL group, indicated a significantly poorer prognosis. The joint effects of age, the location of the primary tumour, the presence of pleural invasion, the length of the minimal axis and the shape of the tumour were examined using a Cox regression analysis (Table 3). The length of the maximal axis was eliminated from the multivariate analysis because it was associated with the minimal size of the tumour. In the multivariate analysis, the shape of the tumour and the presence of pleural invasion were identified as the independent and significant factors predicting the OS (hazard ratio, 5.34; \( P = 0.04 \) and hazard ratio, 3.37; \( P < 0.01 \), respectively), and pleural invasion was the independent factor predicting a poor DFS (hazard ratio, 2.74; \( P = 0.01 \)).

DISCUSSION

The prognosis in most NSCLC patients remains poor, and numerous investigators have explored ways to achieve improvements in the clinical outcome. Regarding the pathological aspects of NSCLC, Noguchi et al. [8] reported that the type of pathological findings in the peripheral small-sized adenocarcinomas was related to the patient prognosis. Other reports have demonstrated that CT findings of nodules are associated with pathological bronchioloalveolar carcinoma, and that this is related to the prognosis of patients after surgery [1, 9].

The identification of a biomarker predicting the postoperative prognosis has been also explored, and RAS mutations have been reported to be related to a poor prognosis [6,7,10,11]. ERCC1 expression was demonstrated to be a better prognostic factor
among patients who did not receive adjuvant chemotherapy [11]. We have reported that both the MACC1 overexpression and TS expression in lung adenocarcinoma were related to postoperative recurrence [6, 7] and the expression of cancer/testis antigen negatively affected the survival of patients with NSCLC [3]. We explored the relationship between the tumour shape and several known biomarkers (EGFR mutation, Kras mutation, expression of p53 and the HLA allele); however, we could not detect any associations among them (data not shown). The lack of significance prompted us to explore whether the shape of a tumour is related to the prognosis, and to examine the correlation between the tumour shape and other factors.

In this study, we have explored the relationship between the categorization by tumour shape and the postoperative prognosis. To our knowledge, this is the first report demonstrating that the simple categorization (ellipse vs. globular shape) affects the prognosis of lung adenocarcinoma patients. We analysed only the cases with a tumour size of 31 mm or larger because we wanted to be sure that the tumours were all measurable, and thought it would be difficult to measure and evaluate the size of the minimal axis of a smaller tumour. The estimated 5-year survival rate after surgery in stage IA NSCLC patients was proximately 89% during the past decade [12]; therefore, it was also thought to be difficult to identify prognostic factors in this population because of their highly favourable outcomes; therefore, these patients were also excluded from the present study.

Table 2: The results of the univariate survival analyses in patients with adenocarcinoma ≥30 mm in size

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<tr>
<th></th>
<th>Overall survival</th>
<th>Disease-free survival</th>
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<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age, ≥75 years/younger than 75 years</td>
<td>1.42 (0.64–3.14)</td>
<td>0.38; NS</td>
</tr>
<tr>
<td>Location of tumour, right/left</td>
<td>1.19 (0.57–2.57)</td>
<td>0.68; NS</td>
</tr>
<tr>
<td>Pathological p factor, p 1–3/p 0</td>
<td>2.44 (1.12–5.29)</td>
<td>0.02</td>
</tr>
<tr>
<td>Length of maximal axis, more than 50 mm/50 mm or less</td>
<td>2.41 (0.96–6.08)</td>
<td>0.06; NS</td>
</tr>
<tr>
<td>Length of minimal axis, more than 30 mm/30 mm or less</td>
<td>4.06 (1.60–10.3)</td>
<td>&lt;0.01</td>
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<tr>
<td>Volume of tumour1, small2/large3</td>
<td>1.40 (0.65–2.99)</td>
<td>0.39; NS</td>
</tr>
<tr>
<td>Shape of tumour, globular shape/ellipse shape</td>
<td>4.81 (1.14–20.3)</td>
<td>0.03</td>
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The volume of the tumour1 was calculated using the formula: v = 1.5 × a × b × c × 3.1 (a is the length of the longest axis, b the length of the shortest axis and c the length of the axis perpendicular to the direction of the plane).
Small2 means the calculated tumour volume is smaller than 127231 mm3 (1.5 × 30 mm × 30 mm × 30 mm × 3.1).
Large3 means the calculated tumour volume is larger than 127231 mm3.
NS: not significant.

Table 3: The results of the multivariate analyses in patients with adenocarcinoma ≥30 mm in size

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<th>Overall survival</th>
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<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age, ≥75 years/younger than 75 years</td>
<td>1.18 (0.51–2.71)</td>
<td>0.70; NS</td>
</tr>
<tr>
<td>Location of tumour, right/left</td>
<td>0.97 (0.35–2.71)</td>
<td>0.95; NS</td>
</tr>
<tr>
<td>Pathological p factor, p 1–3/p 0</td>
<td>3.02 (1.33–6.87)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Length of minimal axis, more than 30 mm/30 mm or less</td>
<td>2.85 (0.88–9.30)</td>
<td>0.08; NS</td>
</tr>
<tr>
<td>Shape of tumour, globular shape/ellipse shape</td>
<td>5.34 (1.69–26.1)</td>
<td>0.04</td>
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</table>
We measured the tumour size before formalin fixation, because Hsu et al. [13] reported that the formalin fixation may cause tumour shrinkage, and that the measurement after formalin fixation resulted in the underestimation of tumour size.

There is some limitation in our analysis as follow: (i) the sample size was limited, so the prognostic significance for the DFS could not be confirmed by the multivariate analysis. Regarding the duration between the operation and the recurrence, the mean duration in EL was 11.4 months and it was shorter than GL (24.4 months). It might be the one reason we could not statistically prove the tumour shape as a prognostic factor in DFS. (ii) We could not demonstrate any reason why the tumour shape resulted in the survival difference; however, the tumour volume was not related to the prognosis in our analysis. Then, the tumour shape was more closely related to survival in comparison with both the maximal and minimal tumour size. The survival difference could not be detected between the GL and EL groups if the threshold of the ratio was defined as 0.6–0.9 (data not shown), suggesting that the shape of the tumour might be more important for the prognostic prediction than the length of the smallest axis.

In the present study, we demonstrated that the simple categorization of lung adenocarcinoma patients based on the tumour shape was closely associated with the prognosis after surgery. Our findings indicate that the categorization may be a useful tool to determine the prognostic value of a lung adenocarcinoma, and that it can contribute to the adequate selection of an optimal therapeutic strategy for individual patients.

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Conflict of interest: none declared.

REFERENCES