Minor Components of Micropapillary and Solid Subtypes in Lung Adenocarcinoma are Predictors of Lymph Node Metastasis and Poor Prognosis

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ABSTRACT

Background. Lung adenocarcinoma with micropapillary and solid predominant subtypes was reported to be associated with poor prognosis; however, whether minor components (non-predominant) of micropapillary and solid subtypes predict poor prognosis remains unknown. In this study, we investigated the predictive and prognostic value of lymph node metastasis of minor micropapillary and solid components.

Methods. Specimens of resected tumors of 1244 patients were reclassified to determine the predominant subtype and minor components (>5%, but not predominant). Of these specimens, 105 contained a micropapillary component and 210 contained a solid component. The correlation between each subtype and lymph node metastasis was analyzed, and survival analyses were used to determine the association between each subtype and patient survival.

Results. Adenocarcinomas harboring micropapillary and/or solid components held higher rates of metastatic lymph node stations (25.2% vs. 15.6%, p = 0.002; and 24.0% vs. 14.9%, p < 0.001, respectively) and lymph nodes (17.3% vs. 10.1%, p = 0.004; and 15.5% vs. 9.7%, p = 0.001, respectively). Patients with micropapillary and solid components in their tumors showed a shorter median recurrence-free survival (15.8 vs. 62.8 months, p < 0.001; and 20.8 months vs. not reached, p < 0.001) and overall survival (47.0 months vs. not reached, p < 0.001; and 69.0 months vs. not reached, p < 0.001).

Conclusions. Minor components of micropapillary and/or solid subtypes of lung adenocarcinoma are correlated with lymph node metastasis and poor prognosis. Thus, it is beneficial to focus not only on predominant subtypes but also minor components to predict prognoses and make therapeutic strategies more comprehensively.

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Adenocarcinoma has long been an independent histological class of lung cancer and has been broadly studied for therapeutic efficacy and toxicities.1-5 In 2011, a new classification system of subtypes of lung adenocarcinoma was recommended by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) to further study and advance the field.6 Since then, a number of investigations have provided evidence for the relationship between different subtypes and treatment outcomes.7-11

Several studies have reported that micropapillary- and solid-predominant subtypes of lung adenocarcinoma were
associated with poor prognoses, however, lung adenocarcinomas usually contain complex mixtures of different subtypes. Whether minor components of each subtype are associated with lymph node metastasis and poor prognosis still remains unknown and needs further clarification.

In this study, we comprehensively analyzed 1244 consecutive patients who were diagnosed with stage I–IV invasive lung adenocarcinoma and who underwent surgical resection between August 2006 and May 2013. Our aim was to provide clinical evidence for the predictive and prognostic value of minor components of lung adenocarcinoma.

PATIENTS AND METHODS

Patients and Tissues

Overall, 1244 consecutive patients who were diagnosed with invasive lung adenocarcinoma and who underwent surgical resection between August 2006 and May 2013 were included in this study. R0 resection was achieved in 1240 of the 1244 patients. Patients with no or insufficient archived tumor specimens were excluded, and no patient underwent neoadjuvant therapy. To ensure an accurate assessment, tumors were reclassified by three pathologists (XS, LS, and YL) and categorized into the following subtypes: lepidic (L), acinar (A), papillary (P), micropapillary (M), and solid (S) predominant subtypes, as well as invasive mucinous adenocarcinoma (IMA), according to the newly announced IASLC/ATS/ERS lung adenocarcinoma classification system. Each of the 1244 slides was reviewed by these three pathologists separately. Discordant results were reconsidered together by the three pathologists until a consensus was reached. Specimens that did not belong to any one of these categories were marked as ‘others’. For those specimens that were mixed by more than one subtype, the subtype that occupied most of the tumor (even if <50%) was defined as the predominant subtype, and subtype(s) that occupied no less than 5% but were not predominant were defined as minor components. We put them in a sequence from the largest to the smallest amount.

This study was approved by the Committee for Ethical Review of Research (Fudan University Shanghai Cancer Center IRB# 090977-1).

Statistical Analysis

Clinical and pathological characteristics, such as sex, age, smoking status, lymphovascular invasion status, tumor location, and nodal status (N0, N1, or N2), together with predominant subtypes and minor components, were analyzed to determine the correlation with lymph node metastasis. \( p \) values, hazard ratios and 95% confidence intervals (CI) were calculated using Pearson’s Chi square test or Fisher’s exact test, and the two-tailed significance level was set at 0.05. Metastatic rates of lymph node stations and lymph nodes of each predominant subtype and minor component were calculated to evaluate the correlation between lymph node metastasis and each subtype. \( p \) values were calculated using Student’s \( t \) test. Moreover, Kaplan–Meier survival curves were used to compare patients’ recurrence-free survival (RFS) and overall survival (OS). Finally, a multivariate Cox model adjusted for sex, age, smoking status, lymphovascular invasion status, tumor location, and nodal status (N0, N1, or N2) was used to determine the odds ratio (OR) and 95% CI for each minor component. All statistical analyses were performed using SPSS version 20.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

For the 1244 patients with pathologically validated lung adenocarcinoma included in this study, a reclassification by three pathologists manifested that there were 158 lepidic-predominant, 598 acinar-predominant, 170 papillary-predominant, 68 micropapillary-predominant, 171 solid-predominant, and 72 invasive mucinous adenocarcinoma. Clinical and pathological characteristics are shown in Table 1. Of the 1244 patients, 109 had a tumor containing a minor component of lepidic subtype, 196 a minor acinar component, 178 a minor papillary component, 105 a minor micropapillary component, 210 a minor solid component, and 62 had a tumor containing a minor invasive mucinous component. Patients were aged 60 years (range 22–110), 560 were males and 684 were females (Table 1). The pathologic stage was 0 in 6 (0.5%) patients, IA in 517 (41.6%) patients, IB in 178 (14.3%) patients, IIA in 120 (9.6%) patients, IIB in 46 (3.7%) patients, IIIA in 338 (27.2%) patients, IIIB in 15 (1.2%) patients, and IV in 24 (1.9%) patients.

The Predictive Value of Lymph Node Metastasis

Of the 1244 patients, 789 (63.4%) had pathologically validated N0 disease and 455 (36.6%) had either pathologically validated N1 or N2 disease (Table 1). Our data showed that lymph node metastasis had a correlation with male sex (\( p < 0.001 \)), younger age at initial diagnosis (\( p = 0.023 \)), ever-smoker (\( p < 0.001 \)), lymphovascular invasion (\( p < 0.001 \)), poor differentiation (\( p < 0.001 \)), and larger tumor size (\( p < 0.001 \)). The micropapillary-
**TABLE 1** Clinicopathological characteristics of different subtypes of lung adenocarcinoma (n = 1244)

| Gender       | Total | N0 (n = 789) | N1/N2 (n = 455) | p value | HR (95 % CI) |
|--------------|-------|--------------|-----------------|---------|--------------|
| Male         | 560 (45.0 %) | 327 (41.4 %) | 233 (51.2 %) | 0.001 | 1.282 (1.108–1.483) |
| Female       | 684 (55.0 %) | 462 (58.6 %) | 222 (48.8 %) |         |              |
| Age < Average| 598 (48.1 %) | 360 (45.6 %) | 238 (52.3 %) | 0.023 | 1.185 (1.023–1.372) |
| Age ≥ Average| 646 (51.9 %) | 429 (54.4 %) | 217 (47.7 %) |         |              |
| Smoking status|       |              |                 |         |              |
| Former/current |   |              |                 |         |              |
| Never        | 841 (67.6 %) | 564 (71.5 %) | 277 (60.9 %) |         |              |
| Tumor location a | | | | | |
| LUL | 330 (26.5 %) | 193 (24.5 %) | 137 (30.1 %) | 0.033 | 0.838 (0.717–0.979) |
| LLL | 200 (16.1 %) | 119 (15.1 %) | 81 (17.8 %) | 0.208 | 0.885 (0.734–1.066) |
| RUL | 406 (32.6 %) | 274 (34.7 %) | 132 (29.0 %) | 0.038 | 1.186 (1.006–1.397) |
| RML | 103 (8.3 %) | 64 (8.1 %) | 39 (8.6 %) | 0.777 | 0.963 (0.743–1.248) |
| RLL | 231 (18.6 %) | 150 (19.0 %) | 81 (17.8 %) | 0.597 | 1.053 (0.868–1.277) |
| LVI | Yes | 203 (16.3 %) | 35 (4.4 %) | 168 (36.9 %) | <0.001 | 3.003 (2.674–3.378) |
| No | 1041 (83.7 %) | 754 (95.6 %) | 287 (63.1 %) |         |              |
| Differentiation | | | | | |
| Well | 169 (13.6 %) | 153 (19.4 %) | 16 (3.5 %) | <0.001 | 0.232 (0.145–0.372) |
| Moderate | 714 (57.4 %) | 492 (62.4 %) | 222 (48.8 %) | <0.001 | 0.707 (0.612–0.818) |
| Poor | 361 (29.0 %) | 144 (18.3 %) | 217 (47.7 %) | <0.001 | 2.232 (1.946–2.558) |
| Tumor size (cm) | | | | | |
| < 3 | 756 (60.8 %) | 572 (72.5 %) | 184 (40.4 %) | <0.001 | 2.283 (1.965–2.646) |
| ≥ 3 | 488 (39.2 %) | 217 (27.5 %) | 271 (59.6 %) |         |              |
| Predominant subtype | | | | | |
| L | 158 (12.7 %) | 154 (19.5 %) | 4 (0.9 %) | <0.001 | 0.601 (0.023–0.161) |
| A | 598 (48.1 %) | 211 (46.4 %) | 387 (49.0 %) | 0.363 | 0.935 (0.806–1.082) |
| P | 170 (13.7 %) | 98 (12.4 %) | 72 (15.8 %) | 0.092 | 1.188 (0.979–1.441) |
| M | 68 (5.5 %) | 35 (4.4 %) | 33 (7.3 %) | 0.035 | 1.353 (1.046–1.748) |
| S | 171 (13.7 %) | 62 (7.9 %) | 109 (24.0 %) | <0.001 | 1.976 (1.715–2.278) |
| IMA | 72 (5.8 %) | 48 (6.1 %) | 24 (5.3 %) | 0.556 | 0.907 (0.648–1.267) |
| Minor components | | | | | |
| L | 109 (8.8 %) | 94 (11.9 %) | 15 (3.3 %) | <0.001 | 0.355 (0.221–0.571) |
| A | 196 (15.8 %) | 123 (15.6 %) | 73 (16.0 %) | 0.832 | 1.021 (0.838–1.247) |
| P | 178 (14.3 %) | 97 (12.3 %) | 81 (17.8 %) | 0.008 | 1.297 (1.083–1.553) |
| M | 105 (8.4 %) | 49 (6.2 %) | 56 (12.3 %) | <0.001 | 1.522 (1.252–1.852) |
| S | 210 (16.9 %) | 103 (13.1 %) | 107 (23.5 %) | <0.001 | 1.513 (1.292–1.773) |
| IMA | 62 (5.0 %) | 34 (4.3 %) | 28 (6.2 %) | 0.150 | 1.250 (0.941–1.661) |

*p* value, HR, and 95 % CI were calculated using the Chi square test and Fisher’s exact test

**HR** hazard ratio, **CI** confidence interval, **LUL** left upper lobe, **LLL** left lower lobe, **RUL** right upper lobe, **RML** right middle lobe, **RLL** right lower lobe, **LVI** lymphovascular invasion, **L** lepidic, **A** acinar, **P** papillary, **M** micropapillary, **S** solid, **IMA** invasive mucinous adenocarcinoma

a When adding the percentage of this category together, a number more than 100 % may be obtained as some tumors occurred in more than one lobe

predominant subtype (*p* = 0.035; HR 1.353; 95 % CI 1.046–1.748) and solid-predominant subtype (*p* < 0.001; HR 1.976; 95 % CI 1.715–2.278) were both associated with lymph node metastasis, along with the papillary minor component (*p* = 0.008; HR 1.297; 95 % CI 1.083–1.553), micropapillary minor component (*p* < 0.001; HR 1.522; 95 % CI 1.252–1.852), and solid minor component (*p* < 0.001; HR 1.513; 95 % CI 1.292–1.773). On the other
TABLE 2 Relationship between different subtypes of lung adenocarcinoma and metastatic rate of lymph node station (n = 1244)

| Subtype | Negative (%)a | Minor component (%) | p value | Predominant (%) | p value |
|---------|---------------|---------------------|---------|-----------------|---------|
| L       | 17.5          | 5.2                 | <0.001  | 8.2             | <0.001  |
| A       | 16.6          | 15.6                | 0.650   | 15.5            | 0.233   |
| P       | 15.9          | 19.5                | 0.106   | 20.1            | 0.081   |
| M       | 15.6          | 25.2                | 0.002   | 23.8            | 0.066   |
| S       | 14.9          | 24.0                | <0.001  | 28.7            | <0.001  |
| IMA     | 16.2          | 21.4                | 0.138   | 14.7            | 0.580   |

Metastatic rate of lymph node station = (number of metastatic lymph node stations/number of totally resected lymph node stations) × 100 %

L lepidic, A acinar, P papillary, M micropapillary, S solid, IMA invasive mucinous adenocarcinoma

a Percentage of patients with subtype of interest not observed or less than 5 %

hand, tumors presenting as well-differentiated (p < 0.001) or moderately differentiated (p < 0.001), lepidic-predominant subtype (p < 0.001), and lepidic minor component (p < 0.001) showed lower probabilities of having lymph node metastasis (Table 1).

To further investigate the correlation between different subtypes and lymph node metastasis, we also recorded the number of metastatic lymph node stations/lymph nodes and resected lymph node stations/lymph nodes, and made a calculation of metastatic rates (Tables 2, 3). Regional lymph node stations were defined as per the recommendations made by Mountain and Dresler in 1997. According to our data, tumors harboring the micropapillary minor component and solid minor component had higher metastatic rates of lymph node station (25.2 vs. 15.6 %, p = 0.002; and 24.0 vs. 14.9 %, p < 0.001, respectively) and lymph node (17.3 vs. 10.1 %, p = 0.004; and 15.5 vs. 9.7 %, p = 0.001, respectively). A similar trend was observed in tumors with micropapillary-predominant and solid-predominant subtypes (Tables 2, 3). Additionally, we found that patients with lepidic-predominant or minor component tumors had a lower probability of experiencing lymph node metastasis (also shown in Tables 2, 3). Furthermore, we also analyzed the relationship between the second predominant subtype and lymph node metastasis. All 606 patients with two or more presenting subtypes were included (see electronic supplementary Table 1), and this analysis showed a similar result as previous ones (see electronic supplementary Tables 2 and 3).

Does Each Subtype Predict a Different Prognosis?

Of the 1244 patients, 288 lacked sufficient follow-up data; therefore, we included the remaining 956 patients in subsequent survival analysis. Seventy-eight of the 956 patients had a tumor containing a minor micropapillary component, and 124 had a tumor containing a minor solid component, along with 19 micropapillary-predominant subtypes and 161 solid-predominant subtypes (Fig. 1).

TABLE 3 Relationship between different subtypes of lung adenocarcinoma and metastatic rate of lymph node station (n = 1244)

| Subtype | Negative (%)a | Minor component (%) | p value | Predominant (%) | p value |
|---------|---------------|---------------------|---------|-----------------|---------|
| L       | 11.4          | 3.1                 | <0.001  | 6.3             | <0.001  |
| A       | 10.8          | 10.1                | 0.663   | 9.8             | 0.176   |
| P       | 10.5          | 11.9                | 0.397   | 13.5            | 0.081   |
| M       | 10.1          | 17.3                | 0.004   | 17.5            | 0.056   |
| S       | 9.7           | 15.5                | 0.001   | 18.0            | <0.001  |
| IMA     | 10.6          | 12.7                | 0.441   | 9.7             | 0.687   |

Metastatic rate of lymph node station = (number of metastatic lymph nodes/number of totally resected lymph nodes) × 100 %

L lepidic, A acinar, P papillary, M micropapillary, S solid, IMA invasive mucinous adenocarcinoma

a Percentage of patients with subtype of interest not observed or less than 5 %

In univariate analysis, patients with tumors containing a minor component of micropapillary subtype had a significantly shorter RFS (p < 0.001) and OS (p < 0.001). A similar observation was made among patients with tumors containing a minor component of solid subtype, which also showed a significantly shorter RFS (p < 0.001) and OS (p < 0.001). Meanwhile, patients with tumors of micropapillary- or solid-predominant subtype also had significantly worse RFS (p = 0.006 and p < 0.001, respectively) and OS (p = 0.007 and p < 0.001, respectively).

In a multivariate analysis using the Cox model adjusted for sex, age, smoking status, lymphovascular invasion status, tumor location, and nodal status (N0, N1, or N2), we found that tumors with a minor component of micropapillary subtype were correlated with shorter RFS (p < 0.001; OR 0.524; 95 % CI 0.388–0.708) and OS (p = 0.012; OR 0.585; 95 % CI 0.385–0.890) (Table 4). Tumors with a minor component of solid subtype were also related to a worse RFS (p = 0.014; OR 0.728; 95 % CI 0.567–0.936) and OS (p = 0.039; OR 0.690; 95 % CI
No significant difference was observed between other minor components and patient survival.

**DISCUSSION**

Lymph node metastasis is a major way for cancer cells to migrate from the primary tumor to distant organs, which promises a poor prognosis for lung cancer patients. With the classification of subtyping lung adenocarcinoma by the IASLC/ATS/ERS, several studies have reported that micropapillary- and solid-predominant subtypes were related to poor prognoses; however, lung adenocarcinomas usually contain a mixture of different subtypes. Thus, it is necessary for clinicians and researchers to understand whether minor components influence patients’ prognoses to help predict their prognoses and make therapeutic strategies. Yeh et al. pointed out that the presence of micropapillary or solid patterns were of predictive value with increased risk of occult lymph node metastasis; studies focusing on minor components are limited. In this study, our aim was to determine whether there was a correlation between minor components of lung adenocarcinoma and lymph node metastasis. According to our study of 1244 patients with pathologically proven lung adenocarcinoma that was initially diagnosed between August 2006 and May 2013, we found that patients with lung adenocarcinoma of lepidic

![Graphs showing Kaplan-Meier survival curves](image-url)
Overall survival

| Subtype                        | OR    | 95 % CI   | p value |
|-------------------------------|-------|-----------|---------|
| Lepidic                       | 1.730 | 0.878–3.413 | 0.113   |
| Acinar                        | 1.122 | 0.754–1.669 | 0.571   |
| Papillary                     | 1.284 | 0.861–1.912 | 0.220   |
| Micropapillary                | 0.585 | 0.385–0.890 | 0.012   |
| Solid                         | 0.690 | 0.484–0.982 | 0.039   |
| Invasive mucinous carcinoma   | 0.870 | 0.519–1.456 | 0.594   |

Multivariate Cox model was adjusted for sex, age, smoking status, lymphovascular invasion or no lymphovascular invasion, tumor location, and nodal status (N0, N1, or N2). A two-tailed p < 0.05 was regarded as statistically different

OR odds ratio, CI confidence interval

Minor components, as well as predominant subtypes of micropapillary and solid subtypes of lung adenocarcinoma, are independent poor indicators of lymph node metastasis and prognosis. Our study concentrates not only on the predominant subtype but also on minor components of lung adenocarcinoma. It is believed that more data are needed to better clarify this issue, and we hope that minor components of lung adenocarcinoma are taken into consideration by clinicians when predicting patients’ prognosis and designing comprehensive therapeutic strategies in order to benefit more patients.

CONCLUSIONS

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DISCLOSURE

This study was approved by the Committee for Ethical Review of Research (Fudan University Shanghai Cancer Center IRB# 090977-1). It identifies that not only micropapillary- and solid-predominant subtypes but also minor micropapillary and solid components of lung adenocarcinoma are poor predictors for lymph node metastasis and poor prognosis.

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