Lepidic component identifies a subgroup of lung adenocarcinoma with a distinctive prognosis: a multicenter propensity-matched analysis

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Abstract

Background: Our aim was to investigate the prognostic impact of the lepidic component on T stage in patients with lung adenocarcinoma (LUAD).

Methods: A retrospective data set including 863 cases of LUAD with lepidic component and 856 cases without lepidic component was used to identify matched lepidic-positive and lepidic-negative cohorts (n=376 patients per group) using a propensity-score matching. Primary outcome variables included recurrence-free survival (RFS) and overall survival (OS). Prognostic factors were assessed by Cox regression analysis and Kaplan–Meier estimates.

Results: Multivariate analysis revealed that lepidic component presence was an independent prognostic factor for prolonged RFS (p < 0.001) and OS (p < 0.001). Furthermore, lepidic ratio (LR) >25% or ≤25% were confirmed to be independent prolonged survival predictors. No survival differences were observed between patients with LUAD with LR >25% or ≤25% (RFS p = 0.333; OS p = 0.078). The 5-year OS rates of patients with LUAD with a lepidic component were 90% regardless of the T stage, and these survival rates were significantly better than those of patients with LUAD without a lepidic component in the corresponding T stage. Multivariate analysis confirmed that T stage was associated with survival only in patients with LUAD without a lepidic component.

Conclusions: Lepidic component presence identifies a LUAD subgroup with an excellent prognosis independent of the LR, pathological T classification. Considering the lepidic component presence may improve prognostic predictions for patients with LUAD.

Keywords: ground-glass opacity, lepidic component, lung adenocarcinoma, T classification

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Furthermore, Hattori et al. found similar results and proposed that part-solid LUAD should be categorized as clinical ‘T1a’ regardless of invasive size.\textsuperscript{11,12} In contrast, two studies found that part-solid LUAD and pure-solid LUAD within the same T stage had similar survival rates after multivariate adjustment or propensity-score matching.\textsuperscript{13,14} Thus, the influence of GGO on clinical T stage is still unclear.

For pathological staging, invasive size was estimated according to an alternative method proposed by the 2015 World Health Organization classification criteria, which multiplies the percentage of the invasive component by the overall tumor size; in contrast, clinical staging directly measures the maximum diameter. In addition, there are limited studies focusing on the prognostic influence of lepidic components on pathological T stage. Whether a lepidic component has a similar impact on pathological T stage is unknown. To investigate this issue, we aimed to reveal the prognostic value of lepidic components in a Chinese population-based multicenter cohort of patients with LUAD.

\section*{Materials and methods}

\subsection*{Patient cohort}

This retrospective study was approved by the Institutional Review Boards of Shanghai Pulmonary Hospital, Zhejiang Cancer Hospital, Jiangsu Cancer Hospital, Jiangsu Province Hospital, The Second Affiliated Hospital of Zhejiang University School of Medicine, the Affiliated Hospital of Nantong University and The First People’s Hospital of Changzhou on behalf of our collaborative group, the Surgical Thoracic Alliance of Rising Star (STAR). All patients diagnosed with solitary LUAD who had undergone surgical resection at one of the seven institutions included in STAR between January 2009 and December 2012 were reviewed. Patients with surgically resected p-stage T1a–T2a N0M0 LUAD based on the eighth edition of Lung Cancer Stage Classification were included. The T category was determined by invasive size. The exclusion criteria were as follows: (a) receipt of induction therapy; (b) lung cancer within the past 2 years; (c) positive surgical margins; (d) concurrent disease progression; and (e) adenocarcinoma \textit{in situ}, minimally invasive adenocarcinoma; invasive mucinous adenocarcinoma, or colloid-predominant adenocarcinoma. Clinical and follow-up information were obtained by reviewing electronic medical records.

\subsection*{Histological evaluation}

Standardized training of pathologists from each institution was performed to reduce the interobserver inconsistency before beginning of the study. All available hematoxylin and eosin-stained tumor slides were reviewed by two senior pathologists at each institution who were blinded to the patient’s survival and clinical data. Any discrepancies between the pathologists were resolved \textit{via} consensus by concurrent diagnosis using a multiple-headed microscope. The percentages of lepidic, acinar, papillary, solid and micropapillary patterns were recorded in 5\% increments. Tumors were classified into lepidic-predominant adenocarcinoma, acinar-predominant adenocarcinoma, papillary-predominant adenocarcinoma, micropapillary-predominant adenocarcinoma, and solid-predominant adenocarcinoma according to the 2015 World Health Organization (WHO) classification criteria. LUAD with a lepidic component was defined as non-mucinous lung adenocarcinoma with a lepidic component \(\geq 5\%\). The lepidic ratio (LR) was defined as the proportion of lepidic components.

\subsection*{Pathologic assessment of invasive size}

Invasive size was defined as the size of invasive components, excluding lepidic components. In some cases with a single, invasive focus, invasive size was directly measured with a ruler. However, a large proportion of cases had multiple invasive foci or invasive areas on multiple slides. The 2015 WHO classification system proposed an alternative method to estimate invasive size by multiplying the percentage of invasive component by the overall tumor diameter. Invasive size was estimated using the following equation: invasive size = total size \(\times\) percentage of invasive components/100.\textsuperscript{15}

\subsection*{Follow-up strategy}

Physical examination, internal history review, chest CT scans with or without contrast, ultrasonography of the abdominal/cervical supraclavicular regions, bone scans and magnetic resonance imaging of the brain were performed every 4–6 months for the first 2 years after surgery, every 6–12 months for 2–5 years after surgery, and every 12 months for subsequent years. Overall survival (OS) was defined as the period from the date of surgery to
the date of death or last survival follow up. Recurrence-free survival (RFS) was defined as the period from the date of surgery to the day of first relapse or last follow up.

**Statistical analysis**
A chi-square test was used to compare categorical variables. To investigate the prognostic implication of lepidic component, propensity-score matching was conducted on the basis of inverse probability weighting. Inverse probability weighting was calculated using a logistic regression with age, sex, smoking status, surgical mode, and T category and pathological components as inputs with a 0.001 caliper size. A Cox proportional hazards model was used to identify prognostic factors. The Kaplan–Meier method was used to evaluate OS and RFS. We used the log-rank test to compare the survival of different groups. A two-sided $p$ value less than 0.05 was considered statistically significant. All analyses were conducted with Statistical Package for Social Sciences 23.0 (IBM, Chicago, IL, US), and survival curves were drawn with R software.

**Results**

Clinicopathologic characteristics based on the presence of lepidic components
Patient characteristics before propensity-score matching are summarized in Supplementary Table 1. Of the 1719 patients with T1a–T2aN0M0 LUAD, 863 (50%) had a lepidic component. Nearly half (47%) of the LUAD patients with a lepidic component had an LR $\leq 25\%$. The presence of a lepidic component was associated with female sex ($p < 0.001$), a nonsmoking status ($p < 0.001$), a relatively low T stage ($p < 0.001$), the absence of a solid component ($p < 0.001$) and a micropapillary component ($p < 0.001$). After propensity-score matching, patient age, sex, smoking status, T category and pathological components, and surgical mode were equivalent between the matched groups (Table 1). The median follow-up period was 1820 days for RFS and 1950 days for OS.

Prognostic impact of lepidic components on patients with LUAD
Patients with LUAD with a lepidic component had significantly better survival than those with LUAD without a lepidic component [RFS $p < 0.001$, Figure 1(a); OS $p < 0.001$, Figure 1(b)]. Multivariate analysis confirmed that the presence of a lepidic component was an independent prognostic factor for prolonged RFS [hazard ratio (HR) 0.38; 95% confidence interval (CI) 0.27–0.54; $p < 0.001$] and OS (HR 0.34; 95% CI 0.22–0.51; $p < 0.001$). For the other variables, sex, T stage, and solid and micropapillary components were found to be independent prognostic factors for RFS and OS (Table 2). Results before propensity-score matching is shown in Supplementary Figure 1 and Supplementary Table 2.

Lepidic component indicated significantly prolonged survival independent of the LR
The log-rank test revealed that the presence of a lepidic component with an LR $> 25\%$ or an LR $\leq 25\%$ was associated with better 5-year RFS [LR $> 25\%$, $p < 0.001$; LR $\leq 25\%$, $p = 0.001$; Figure 1(c)] and OS [LR $> 25\%$, $p < 0.001$; LR $\leq 25\%$, $p = 0.002$; Figure 1(d)] than the absence of lepidic components. No survival difference was observed among patients with LUAD with an LR $> 25\%$ or an LR $\leq 25\%$ [RFS $p = 0.333$, Figure 1(c); OS $p = 0.078$, Figure 1(c)]. Multivariate analysis confirmed that the presence of a lepidic component with an LR $> 25\%$ or an LR $\leq 25\%$ were all independent prognostic factors for prolonged RFS (LR $> 25\%$: HR 0.38; 95% CI 0.19–0.75; $p = 0.006$; LR $\leq 25\%$: HR 0.38; 95% CI 0.26–0.56; $p < 0.001$) and OS (LR $> 25\%$: HR 0.27; 95% CI 0.11–0.67; $p = 0.005$; LR $\leq 25\%$: HR 0.35; 95% CI 0.23–0.55; $p < 0.001$; Table 2). Results before propensity-score matching is shown in Supplementary Figure 2 and Supplementary Table 2.

Prognostic impact of lepidic components on pathological T classification
T classification clearly delineated differences in 5-year RFS (91.4% in T1a, 83.0% in T1b, 75.9% in T1c, and 49.3% in T2a; $p < 0.001$) and OS (95.6% in T1a, 88.1% in T1b, 83.3% in T1c, and 65.2% in T2a; $p < 0.001$). In each T stage except for T1a, the presence of a lepidic component indicated significantly prolonged 5-year RFS [T1a: LR $> 25\%$, $p = 0.894$; LR $\leq 25\%$, $p = 0.283$, Figure 2(a); T1b: LR $> 25\%$, $p = 0.255$; LR $\leq 25\%$, $p = 0.015$, Figure 2(c); T1c: LR $> 25\%$, $p = 0.138$; LR $\leq 25\%$, $p = 0.001$, Figure 2(e); T2a: LR $> 25\%$, $p = 0.002$; LR $\leq 25\%$, $p = 0.006$, Figure 2(g)] and OS [T1a: LR $> 25\%$, $p = 0.682$; LR $\leq 25\%$, $p = 0.702$, Figure 2(b); T1b: LR $> 25\%$, $p = 0.120$;
Table 1. Clinicopathologic characteristics after propensity score matching based on presence of lepidic component.

| Characteristics                  | Lepidic (+) | Lepidic (−) | Adjusted p |
|----------------------------------|-------------|-------------|------------|
|                                  | n = 376     | n = 376     |            |
| Age                              |             |             | 0.952      |
| ≤65                              | 277 [74]    | 278 [74]    |            |
| >65                              | 99 [26]     | 98 [26]     |            |
| Sex                              |             |             | 0.672      |
| Male                             | 159 [42]    | 163 [43]    |            |
| Female                           | 217 [58]    | 213 [57]    |            |
| Smoking                          |             |             | 0.999      |
| Yes                              | 80 [21]     | 80 [21]     |            |
| No                               | 296 [79]    | 296 [79]    |            |
| T stage                          |             |             | 0.852      |
| T1a                              | 39 [10]     | 40 [11]     |            |
| T1b                              | 208 [55]    | 211 [56]    |            |
| T1c                              | 76 [20]     | 69 [18]     |            |
| T2a                              | 53 [14]     | 56 [15]     |            |
| Pathological subtype             |             |             |            |
| Lepidic                          | 33 [9]      | 0 [0]       |            |
| Acinar                           | 204 [55]    | 224 [60]    |            |
| Papillary                        | 121 [32]    | 115 [31]    |            |
| Solid                            | 10 [3]      | 18 [4]      |            |
| Micropapillary                   | 6 [1]       | 19 [5]      |            |
| Lepidic ratio                    |             |             | 0.951      |
| >25%                             | 82 [22]     |             |            |
| ≤25%                             | 294 [78]    |             |            |
| Acinar                           |             |             | 0.951      |
| Present                          | 350 [81]    | 303 [81]    |            |
| Absent                           | 71 [19]     | 94 [19]     |            |
| Papillary                        |             |             | 0.876      |
| Present                          | 247 [66]    | 250 [66]    |            |
| Absent                           | 129 [34]    | 126 [34]    |            |
| Solid                            |             |             | 0.595      |
| Present                          | 32 [9]      | 28 [7]      |            |
| Absent                           | 344 [91]    | 348 [93]    |            |
| Micropapillary                   |             |             | 0.730      |
| Present                          | 153 [41]    | 158 [42]    |            |
| Absent                           | 223 [59]    | 218 [58]    |            |
| Surgery                          |             |             | 0.564      |
| Lobectomy                        | 343 [91]    | 347 [92]    |            |
| Limited resection                | 33 [9]      | 29 [7]      |            |
LR ≤ 25%, \( p = 0.016 \), Figure 2(d); T1c: LR > 25%, \( p = 0.090 \); LR ≤ 25%, \( p = 0.002 \), Figure 2(f); T2a: LR > 25%, \( p = 0.021 \); LR ≤ 25%, \( p = 0.006 \), Figure 2(h)) independent of LR in patients with LUAD. No survival difference was observed between LR > 25% and LR ≤ 25% in each T stage (RFS: T1a, \( p = 0.388 \); T1b, \( p = 0.872 \); T1c, \( p = 0.748 \); T2a, \( p = 0.066 \); and OS: T1a, \( p = 0.947 \); T1b, \( p = 0.713 \); T1c, \( p = 0.756 \); T2a, \( p = 0.336 \)).

Surprisingly, T stage was not associated with survival in patients with LUAD with lepidic component [Figure 3(a–b)]. A further multivariate analysis confirmed the results. T stage was an independent prognostic factor of relatively poor survival only in LUAD without a lepidic component (Table 3). Results before propensity-score matching was shown in Supplementary Table 3. Thus, LUAD with lepidic component was considered as one subgroup in further analysis. LUAD with a lepidic component had comparable or better RFS [T1a without lepidic, \( p = 0.460 \); T1b without lepidic, \( p = 0.021 \); T1c without lepidic, \( p < 0.001 \); T2a without lepidic, \( p < 0.001 \); Figure 3(c)], and OS [T1a without lepidic,
| Variables                  | Recurrence-free survival | Overall survival |
|---------------------------|--------------------------|-----------------|
|                           | Univariate               | Multivariate model 1 | Multivariate model 2 | Univariate               | Multivariate model 1 | Multivariate model 2 |
|                           | p                        | HR (95% CI)      | p                        | HR (95% CI)      | p                        | HR (95% CI)      | p                        |
| Sex (female)              | 0.015                    | 0.70 (0.50–0.98) | 0.039                    | 0.70 (0.50–0.98) | 0.040                    | 0.002             | 0.60 (0.40–0.88) | 0.009                    | 0.59 (0.40–0.88) | 0.008                    |
| Age (> 65)                | 0.239                    | 0.004            | 1.41 (0.95–2.10)         | 0.090            | 1.41 (0.95–2.11)         | 0.089            |
| Smoking (yes)             | 0.935                    | 0.294            |                          |                 |                          |                 |
| T stage                   | <0.001                   | <0.001           | <0.001                   | <0.001           | <0.001                   | <0.001           |
| T1a                       | ref                      | ref              | ref                      | ref              | ref                      | ref              |
| T1b                       | 0.755                    | 1.23 (0.63–2.42) | 0.546                    | 1.23 (0.77–1.87) | 0.550                    | 0.289             | 1.77 (0.70–4.50) | 0.230                    | 1.72 (0.68–4.39) | 0.255                    |
| T1c                       | 0.029                    | 2.56 (1.26–5.24) | 0.010                    | 2.56 (1.25–5.25) | 0.010                    | 0.007             | 4.10 (1.57–10.74) | 0.004                    | 3.99 (1.52–10.51) | 0.005                    |
| T2a                       | 0.001                    | 3.31 (1.65–6.64) | 0.001                    | 3.31 (1.64–6.66) | 0.001                    | 0.001             | 4.47 (1.74–11.51) | 0.002                    | 4.37 (1.69–11.29) | 0.002                    |
| Surgery (lobectomy)       | 0.436                    |                  | 0.764                    |                 |
| Pathological subtype      | 0.059                    |                  | 0.015                    |                  | 0.015                    |                  |
| Lepidic                   | ref                      |                  | ref                      |                  | ref                      |                  |
| Acinar                    | 0.213                    | a                | a                        |                  | a                        |                  |
| Papillary                 | 0.455                    | a                | a                        |                  | a                        |                  |
| Solid                     | 0.023                    | a                | a                        |                  | a                        |                  |
| Micropapillary            | 0.154                    | a                | a                        |                  | a                        |                  |
| Acinar (presence)         | 0.813                    |                  | 0.634                    |                  |
| Papillary (presence)      | 0.018                    | 0.71 (0.50–1.01) | 0.059                    | 0.72 (0.50–1.01) | 0.059                    | 0.027             | 0.71 (0.48–1.05) | 0.086                    | 0.71 (0.48–1.05) | 0.088                    |
| Solid (presence)          | 0.040                    | 1.86 (1.08–3.18) | 0.024                    | 1.86 (1.08–3.19) | 0.025                    | 0.002             | 2.20 (1.25–3.86) | 0.006                    | 2.16 (1.23–3.81) | 0.008                    |
| Micropapillary (presence) | 0.001                    | 2.07 (1.47–2.93) | <0.001                   | 2.07 (1.47–2.93) | <0.001                   | 0.016             | 1.99 (1.35–2.95) | 0.001                    | 1.98 (1.34–2.94) | 0.001                    |
| Lepidic (presence)        | <0.001                   | 0.38 (0.27–0.54) | <0.001                   | 0.38 (0.22–0.51) | <0.001                   | 0.34 (0.22–0.51) | <0.001                   |
| Lepidic ratio             | <0.001                   |                  | <0.001                   |                  | <0.001                   |                  |
| ≤25%                      | ref                      |                  | ref                      |                  | ref                      |                  |
| >25%                      | 0.003                    | 0.38 (0.19–0.75) | 0.006                    | 0.38 (0.23–0.55) | 0.001                    | 0.35 (0.23–0.55) | 0.001                    |

Multivariable model 1 includes the lepidic (presence) instead of the lepidic ratio. Multivariable model 2 includes the lepidic ratio instead of the lepidic (presence).

*Pathological subtypes were not included in multivariate analysis because of the association with presence of each component in adenocarcinomas.

Bold numerals indicate statistical significance.

CI, confidence interval; HR, hazard ratio; ref, reference value.
Figure 2. Survival outcomes regarding overall survival and recurrence-free survival based on the presence of lepidic components in each T stage. 
LR, lepidic ratio.
Table 3. Cox regression model in lung adenocarcinoma with or without lepidic component after propensity score matching.

| Variables                  | Recurrence-free survival | Overall survival |
|----------------------------|--------------------------|------------------|
|                            | Univariate | Multivariate | p   | Univariate | Multivariate | p   |
|                            | HR (95% CI) | p           |     | HR (95% CI) | p           |     |
| Lepidic (+)                |             |             |     |             |             |     |
| Sex (female)               | 0.953       |             |     | 0.031       | 0.55 (0.23–1.31) | 0.176 |
| Age (>65)                  | 0.146       |             |     | 0.677       |             |     |
| Smoking (yes)              | 0.893       |             |     | 0.042       | 1.74 (0.71–4.28) | 0.230 |
| T stage                    | 0.503       |             |     | 0.336       |             |     |
| T1a                        | ref         |             |     | ref         |             |     |
| T1b                        | 0.934       |             |     | 0.747       |             |     |
| T1c                        | 0.648       |             |     | 0.288       |             |     |
| T2a                        | 0.375       |             |     | 0.272       |             |     |
| Surgery (lobectomy)        | 0.469       |             |     | 0.992       |             |     |
| Pathological subtype       | 0.931       |             |     | 0.985       |             |     |
| Lepidic                    | ref         |             |     | ref         |             |     |
| Acinar                     | 0.726       |             |     | 0.732       |             |     |
| Papillary                  | 0.826       |             |     | 0.981       |             |     |
| Solid                      | 0.977       |             |     | 0.982       |             |     |
| Micropapillary             | 0.982       |             |     | 0.983       |             |     |
| Acinar (presence)          | 0.382       |             |     | 0.394       |             |     |
| Papillary (presence)       | 0.218       |             |     | 0.285       |             |     |
| Solid (presence)           | 0.295       |             |     | 0.126       |             |     |
| Micropapillary (presence)  | **0.001**   |             |     | **0.070**   | 2.06 (0.99–4.27) | 0.052 |
| Lepidic ratio (>25%)       | 0.780       |             |     | 0.337       |             |     |
| Lepidic (−)                |             |             |     |             |             |     |
| Sex (female)               | **0.005**   | 0.63 (0.42–0.95) | **0.026** | 0.021       | 0.67 (0.42–1.06) | 0.090 |
| Age (>65)                  | **0.013**   | 1.41 (0.92–2.15) | 0.116 | <**0.001** | 1.83 (1.16–2.90) | **0.010** |
| Smoking (yes)              | 0.772       |             |     | 0.912       |             |     |
| T stage                    | <**0.001**  | <**0.001**  |     | <**0.001**  | <**0.001**  |     |
| T1a                        | ref         |             |     | ref         |             |     |
| T1b                        | 0.634       | 1.36 (0.57–3.24) | 0.490 | 0.289       | 2.00 (0.61–6.61) | 0.256 |
| T1c                        | **0.017**   | 3.15 (1.27–7.79) | **0.013** | 0.011       | 5.03 (1.48–17.09) | **0.010** |
| T2a                        | **0.001**   | 4.15 (1.72–10.00) | **0.002** | 0.002       | 5.71 (1.72–19.03) | **0.005** |

(Continued)
In 2011, the Japanese Clinical Oncology Group recommended the CTR as an important radiological indicator to guide surgical treatment. Tumors with a total size $\leq 2$ cm and a CTR $\leq 0.25$ were considered radiologically noninvasive LUAD. The CTR was associated with the prognosis of patients with LUAD. However, a study performed by Hattori et al. suggested that the CTR was not associated with 5-year OS in patients with part-solid lung cancer ($0 < \text{CTR} < 0.5$: 98.4%; $0.5 < \text{CTR} < 1.0$: 95.0%; $p = 0.125$). Ye et al. also found that the CTR with a cut-off value of 0.5 or 0.8 was not a prognostic factor for part-solid LUAD. Theoretically, the prognostic influence of a lepidic component is equivalent to that of a GGO component. Our study revealed that the LR was not associated with the prognosis of LUAD with a lepidic component. No survival difference was observed between the groups with and without a lepidic component.

Results before propensity-score matching is shown in Supplementary Figures 3 and 4.

Discussion

The presence of GGO on CT images always indicates a long natural history and favorable oncologic outcome for early-stage LUAD. Many studies have indicated that the prognostic significance of GGO is associated with the consolidation/tumor ratio (CTR). The 5-year OS of LUAD with a CTR $< 0.5$ is higher than that of LUAD with a CTR $>0.5$. Whether a small amount of GGO predicts prolonged survival still needs to be investigated. Correspondingly, limited studies have focused on the prognostic impact of a small lepidic component. In our study, the presence of a lepidic component proportion $\leq 25\%$ was an independent prognostic factor for prolonged RFS (HR, 0.51; $p < 0.001$) and OS (HR, 0.36; $p < 0.001$), which was confirmed by multivariate Cox analysis. This result indicated that LUAD patients with even a small lepidic component have better survival than patients with LUAD without a lepidic component. The prognostic significance of the lepidic component was also proven in each T stage and pathological subtype. The lepidic component was a strong indicator of a relatively good prognosis, more than a noninvasive component of LUAD.

Table 3. (Continued)

| Variables                      | Recurrence-free survival | Overall survival |
|--------------------------------|--------------------------|------------------|
|                                | Univariate | Multivariate | Univariate | Multivariate |
|                                | $p$ | HR (95% CI) | $p$ | HR (95% CI) |
| Surgery (lobectomy)            | 0.793 | 0.531 |
| Pathological subtype           | 0.040 | 0.013 |
| Acinar                         | ref | ref |
| Papillary                      | 0.475 | 0.687 |
| Solid                          | 0.011 | 0.008 |
| Micropapillary (presence)      | 0.541 | 0.077 |
| Acinar (presence)              | 0.759 | 0.279 |
| Papillary (presence)           | 0.035 | 0.040 |
| Solid (presence)               | 0.047 | 0.006 |
| Micropapillary (presence)      | 0.089 | 0.073 |

*Pathological subtypes were not included in multivariate analysis because of the association with presence of each components in adenocarcinoma. Bold numerals indicate statistical significance. CI, confidence interval; HR, hazard ratio; lepidic (+), lung adenocarcinoma with lepidic component; lepidic (−), lung adenocarcinoma without lepidic component; ref, reference value.
among LUAD patients with different LRs. The 5-year OS rate of patients with LUAD with a lepidic component was 95.2%. When there was no lepidic component in LUAD, the 5-year OS rate decreased significantly to 75.2%. The presence of a lepidic component, not a specific LR, predicted significantly prolonged survival in LUAD. Our study also supported the conclusion that the CTR may not be a good prognostic marker in part-solid LUAD from the standpoint of pathology.

In 2017, the eighth edition of Lung Cancer Stage Classification recommended invasive size instead of total tumor size be used as a T descriptor. The GGO component is not taken into consideration in T classification. Part-solid LUAD and pure-solid LUAD with the same solid component size are classified within the same clinical T category. Yamanashi et al. found that the prognoses of part-solid and pure-solid LUAD in clinical T1a–c were similar after propensity-score matching. T stage determined by solid component size could stratify the prognosis of part-solid tumors.13 However, many studies have indicated that the T stage of part-solid LUAD may not be simply determined by the solid component size. Hattori et al. revealed that survival was excellent at 90%
Despite the revised T categories (5-year OS: T1a, 98.9%; T1b, 90.2%; T1c, 90.8%; T2, 90.0%) for part-solid LUAD. Similarly, Ye et al. found that solid component size was not associated with the prognosis of patients with part-solid LUAD. For pathological staging, our study suggested that patients with LUAD with a lepidic component had significantly better 5-year OS than patients with LUAD without a lepidic component after stratification by T classification (T1b: 94.9% versus 83.5%, p < 0.001; T1c: 93.8% versus 72.8%, p < 0.001; T2a: 93.0% versus 57.6%, p < 0.001). LUAD with a lepidic component staged in T1a–T2a had survival comparable with that of LUAD without a lepidic component staged in T1a. Furthermore, LUAD with a lepidic component staged in T1a–T2a had better survival than LUAD without a lepidic component staged in T1b, T1c, or T2a. Our study supported the conclusion of the study described above, specifically that part-solid LUAD and pure-solid LUAD with equal solid component sizes may not be classified into the same T stage from the standpoint of pathology.

GGO or the lepidic component may be a potential T stage migration factor. Recognition of the presence of a lepidic component would be simpler and more reproducible than measurement of the percentage of the lepidic component. Frozen-section diagnosis of lepidic components to guide surgical strategies seems possible because of the high specificity. However, there are still insufficient data to utilize either GGO or the lepidic component as a T factor in clinical practice. First, there is still no globally accepted standard for GGO. Measurements of part-solid LUAD with the presence of scattered consolidations cannot be made uniform. The interobserver consistency for diagnosing the lepidic component is unsatisfying, as the kappa value is only 0.55 in typical cases and 0.08 in difficult cases. Second, evaluation of a particular T factor must be subjected to confirmation in multiple patient subgroups, institutions, and regions, as was done for the stage classification system. All above conclusions need further prospective multicenter validation.

In conclusion, the lepidic component identifies a subgroup of LUAD with a favorable prognosis regardless of the LR and T stage. Considering the presence of the lepidic component may improve prognostic predictions for patients with LUAD. Although our results need further validation, the forthcoming tumor-node-metastases staging system may take these findings into consideration.

**Author contributions**
Erjia Zhu conceived the idea; Erjia Zhu and Chenyang Dai conceived and designed the experiments; Erjia Zhu wrote the paper; Huikang Xie, Hang Su, Xuefei Hu, Ming Li, Junqiang Fan, Jinshi Liu, Quan Zhu, Honggang Ke, Lei Zhang, and Chang Chen provided all the data from seven institutions of our collaboration group. All authors approved the final version.

**Conflict of interest statement**
The authors declare that there is no conflict of interest.

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**Ethics approval and consent to participate**
This study has been authorized by ethic committee of seven institution from our collaboration.
group, Surgical Thoracic Alliance of Rising Star. The study was performed in accordance with the Declaration of Helsinki.

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Supplemental material
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