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# Adjuvant Chemotherapy Candidates in Stage I Lung Adenocarcinomas Following Complete Lobectomy

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## ABSTRACT

**Background.** This study aimed to explore adjuvant chemotherapy (ACT) candidates based on a recurrence risk-scoring model in completely lobectomized stage I patients with lung adenocarcinoma (LAD).

**Methods.** A retrospective study was performed on 4606 patients (non-ACT group: $n = 3514$; ACT group: $n = 1092$) who underwent complete lobectomy for LAD at Shanghai Chest Hospital from 2008 to 2014. The nomogram predicting recurrence-free survival (RFS) was developed in the non-ACT group using Cox proportional hazards regression. The nomogram-based risk score was calculated in the entire cohort. Differences of RFS between the non-ACT and ACT groups were compared as stratified by the risk score. The score cut-off points were determined using the X-tile software.

**Results.** Six independent predictors, including age, sex, tumor size, pathological subtype, visceral pleural invasion (VPI), and lymphovascular invasion (LVI) were associated with RFS. The nomogram more accurately predicted RFS than the 8th TNM staging {C-index: 0.784 [95% confidence interval (CI) 0.756–0.812] vs. 0.719 (95% CI 0.689–0.749), $p = 0.0017$}. A significant RFS difference was observed among the low-, intermediate- and high-risk groups ($p < 0.0001$), as divided by the optimal cut-points of risk score (203 and 244). ACT did not improve RFS for patients at intermediate-risk, or was even detrimental for low-risk patients; however, improved RFS was observed in ACT receivers at high-risk ($p = 0.0416$). ACT candidates with a risk score $\geq$ 245 constituted 2.6% of stage I patients.

**Conclusions.** The nomogram provided an individual prediction of RFS for stage I LAD following lobectomy. High-risk patients (score $\geq$ 245) may benefit from postoperative ACT.

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Complete surgical resection remains the gold standard in the treatment of early-stage operable non-small cell lung cancer (NSCLC);[1] however, 18–32% of stage I NSCLC patients died within 5 years after resection, mostly due to recurrence.[2–5] Postoperative adjuvant chemotherapy (ACT) improved survival in stages II–IIIA NSCLC, but its efficacy in stage I patients is still inconclusive.[6,7] Previous meta-analyses and a large pooled analysis demonstrated that ACT did not improve, or was even detrimental to, the survival of stage IA patients.[8,9] For stage IB NSCLC, an absolute improvement on overall survival (OS) for ACT was shown in the meta-analyses, whereas discordant results were presented in the randomized controlled studies.[9–11] Moreover, evidences in the context of older TNM staging systems may not be applicable in stage I NSCLC categorized by the 8th TNM staging system since node-negative T2 tumor > 4 cm but $\leq$ 5 cm has been classified as stage

IIA instead of stage IB.[5] Two large studies based on the old TNM staging revealed that ACT only improved survival of stage I NSCLC $\geq$ 4 cm or 3.1–3.9 cm, implying that a redefinition of ACT candidates for stage I patients is necessary.[12,13]

ACT improves survival of postoperative patients by reducing the risk of recurrence and metastasis.[14] A precise identification of patients at high recurrence risk is the prerequisite for optimizing ACT application. High-risk factors in stage IB patients have been defined as poorly differentiated, lymphovascular invasion (LVI), visceral pleural invasion (VPI), incomplete lymph node sampling, or wedge resection in the current National Comprehensive Cancer Network (NCCN) guideline. However, stage I NSCLC was a heterogeneous entity holding various sizes, status of VPI, and multiple clinical, operative and pathological characteristics. Whether the existence of a single or several high-risk factors are sufficient justifications for ACT remains unknown. In addition, other features such as pathological subtype, age, and sex all seemed to affect the prognosis, as proven in previous studies.[4,15,16] An ideal resolution for comprehensively assessing the recurrence risk is to apply a nomogram model with all potential influencing factors transferred into a quantified scoring system. The nomogram has already been proven to create a more precise prediction than the traditional TNM staging.[16]

The published nomogram for postoperative stage I patients mostly incorporated ACT as a dependent variable in the survival analysis. In addition, current published nomograms had some limitations, such as without pathological subtype information, based on a relatively small sample size and older TNM staging system. For a better understanding of the impact of ACT in lobectomized stage I lung adenocarcinoma (LAD) in the 8th TNM edition, the current study first developed a nomogram of recurrence-free survival (RFS) probability in naturally progressed non-ACT patients, and then evaluated the differences on RFS between patients with and without ACT as stratified according to the nomogram-based risk scores. We aimed not only to develop a recurrence risk-scoring model but also to explore the high-risk populations that would benefit from ACT.

## PATIENTS AND METHODS

### *Patients and Study Design*

Medical records of patients with lung cancer in the Shanghai Chest Hospital Database were reviewed. Inclusion criteria were a diagnosis between January 2008 and December 2014, primary lung cancer, stage I according to the 8th TNM edition of the American Joint Committee on Cancer (AJCC) cancer staging manual, pathologically confirmed LAD, and underwent complete lobectomy and complete mediastinal lymph node dissection. The extent of mediastinal lymph node dissection was decided according to the guidelines of the European Society of Thoracic Surgeons (ESTS). At least three hilar and interlobar nodes and three mediastinal nodes from three stations were removed, in which the subcarinal station is always included.[17] Exclusion criteria were mixed type or multiple primary LAD, microinvasive adenocarcinoma (MIA), died within 1 month after surgery, and lost to follow-up. Included patients without ACT treatment were classified as the non-ACT group, and those receiving ACT were classified as the ACT group. The patients with high-risk factors such as solid or micropapillary pathological pattern, LVI, and VPI were indicated for ACT at the treating doctor's discretion. Platinum-based doublet chemotherapy was the basic regimen applied. The platinum drugs included cisplatin and carboplatin, and other drugs included pemetrexed, gemcitabine, paclitaxel or vinorelbine. Four cycles of chemotherapy were recommended for all patients and the dosage was administered as recommended in the guidelines, unless severe adverse effects occurred. The study flow chart is shown in electronic supplementary Fig. 1.

The study was approved by the institutional Ethics Committee of the Shanghai Chest Hospital. All patients were anonymized and written signed informed consent was obtained from each participant. The study protocol conformed to the Helsinki Declaration.

### *Clinicopathological Evaluation*

All patients underwent complete lobectomy with a minimally invasive approach, such as video-assisted thoracic surgery or thoracotomy. Histologic classification was established using the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) LAD classification criteria.[18] The tumors were categorized into AIS (adenocarcinoma in situ), MIA, and invasive adenocarcinomas. Invasive adenocarcinomas were subsequently classified as lepidic, acinar, papillary, micropapillary, and solid predominant subtypes, and variants. These histologic subtypes were divided into four groups (low-grade: lepidic predominant; intermediate-grade: acinar/papillary predominant; high-grade: solid/micropapillary predominant; and variant subtype). Pathologic features, such as tumor diameter, site, VPI, and LVI were determined. Whether or not patients received adjuvant therapy was recorded.

### Follow-Up

Patients were followed-up every 3 months for the first 2 years after surgery, and at 6-month intervals thereafter. Physical examination, blood tests, chest computed tomography (CT), abdominal CT, or ultrasound were performed at each scheduled visit. Whole-body bone scans and a cranial CT or magnetic resonance imaging were performed annually. Additional examinations were conducted when patients presented with any symptoms or signs of recurrence during the follow-up period. For patients who did not follow-up in our hospital, a telephone follow-up was performed to record the recurrence and survival status.

### Statistical Analysis

Continuous variables were compared between groups using the *t* test or Mann–Whitney rank-sum test. Categorical variables were analyzed using Pearson's Chi square test or Fisher's exact test.

A three-step analytical approach was performed. First, survival curves were estimated using the Kaplan–Meier method, and the log-rank test was applied to determine the significance between strata. A multivariable Cox proportional hazards model was constructed to analyze the independent factors of RFS in the non-ACT group. Multivariable analyses were conducted in a backward stepwise manner for factors in the univariate analyses with a $p$ value $< 0.10$. Hazard ratios (HR) and 95% confidence intervals (CIs) were reported. The covariates associated with RFS in the non-ACT group were further validated in the entire cohort. Second, the nomogram was established in the non-ACT group to provide the probability of RFS at 2, 3, and 5 years according to the Cox regression analysis. Model performance was assessed by concordance index (C-index) and calibration. The 95% CI was obtained by bootstrapping. The larger the C-index, the more accurate was the prognostic prediction. Calibration of the nomogram for 2-, 3-, and 5-year recurrence was performed by comparing the predicted recurrence with the actual observed recurrence. The difference between the nomogram and the 8th TNM staging system was evaluated using the C-index. Third, the total points for each patient were calculated according to the established nomogram of recurrence. A smooth curve displayed the associations between nomogram-based risk score and recurrence rate. The optimal cut-off value for the nomogram-based risk score was determined using X-tile analysis.[19]

A $p$ value $< 0.05$ was considered statistically significant. All analyses were performed using SPSS software version 22.0 (IBM Corporation, Armonk, NY, USA) and R software version 3.3.1 (http://lib.stat.cmu.edu/R/CRAN/).

## RESULTS

### Clinicopathological Characteristics and Survival Outcomes of the Non-adjuvant Chemotherapy (ACT) and ACT Groups

The median (interquartile) age of the entire cohort was 60 years [interquartile range (IQR) 54–66], and the number of patients in the non-ACT and ACT groups was 3514 (76.3%) and 1092 (23.7%), respectively. Significant differences in the clinicopathological characteristics were observed between the two groups. Patients receiving ACT were more likely to be younger, male, smoker, and with larger tumor size, high-grade pathologic subtype, VPI, and LVI (all $p < 0.001$) (Table 1).

The median (IQR) follow-up was 40.4 months (29.2–57.9). The RFS of the entire cohort at 3 and 5 years was 91.0% (95% CI 90.1–91.9) and 83.6% (95% CI 82.1–85.1), respectively. For the non-ACT group, the corresponding RFS was 93.9% (95% CI 93.0–94.8) and 88.1% (95% CI 86.2–90.0), respectively, and for the ACT group, the 3- and 5-year RFS was 83.0% (95% CI 80.1–85.3) and 72.6% (95% CI 69.5–75.8), respectively.

### Nomogram Development and Predictive Performance Compared with the 8th TNM Staging System

In the non-ACT group, six prognostic factors, including age, sex, tumor size, pathologic subtype, VPI, and LVI were significantly correlated with RFS, as shown in the multivariable Cox regression analysis (Table 2). The covariates associated with RFS were confirmed in the entire cohort (electronic supplementary Table 1).

The nomogram for RFS prediction was established based on the results of the non-ACT group (Fig. 1). In the nomogram, each prognostic factor was given a score (electronic supplementary Table 2). The 2-, 3-, and 5-year probability of recurrence was obtained individually by adding up the scores of each factor. The C-index for prediction of RFS was 0.784 (95% CI 0.756–0.812), which was significantly higher than that of the 8th edition of the TNM staging system (0.719, 95% CI 0.689–0.749, $p = 0.0017$). The calibration curve showed good agreement between prediction and observation in the probability of RFS in the non-ACT group (Fig. 2).

### Recurrence-Free Survival (RFS) Difference Between the ACT and Non-ACT Patients as Stratified by the Nomogram-Based Risk Score

The nomogram-based risk score was employed in the entire cohort. The non-ACT group had a significantly lower

**TABLE 1** Clinicopathological characteristics of the non-ACT and ACT groups

| Variable | Non-ACT ($n$ = 3514) | ACT ($n$ = 1092) | $p$ Value[a] |
|---|---|---|---|
| Age, years | 60 (54–66) | 59 (53–64) | < 0.001 |
| Sex | | | < 0.001 |
| Male | 1381 (39.3) | 539 (49.4) | |
| Female | 2133 (60.7) | 553 (50.6) | |
| Smoking history | | | < 0.001 |
| Never | 3094 (88.0) | 816 (74.7) | |
| Ever | 420 (12.0) | 276 (25.3) | |
| T size, cm | | | < 0.001 |
| 0–1 | 484 (13.8) | 18 (1.6) | |
| 1–2 | 1775 (50.5) | 216 (19.8) | |
| 2–3 | 1053 (30.0) | 560 (51.3) | |
| 3–4 | 202 (5.7) | 298 (27.3) | |
| Pathological subtype | | | < 0.001 |
| Lepidic | 357 (10.2) | 15 (1.4) | |
| Acinar/papillary | 2938 (83.6) | 933 (85.4) | |
| Solid/micropapillary | 124 (3.5) | 110 (10.1) | |
| Variant | 95 (2.7) | 34 (3.1) | |
| VPI | | | < 0.001 |
| Absent | 3090 (87.9) | 386 (35.3) | |
| Present | 424 (12.1) | 706 (64.7) | |
| LVI | | | < 0.001 |
| Absent | 3429 (97.6) | 982 (89.9) | |
| Present | 85 (2.4) | 110 (10.1) | |
| TNM staging | | | < 0.001 |
| IA | 2957 (84.1) | 235 (21.5) | |
| IB | 557 (15.9) | 857 (78.5) | |

Data are expressed as $n$ (%) or median (interquartile range)

*ACT* adjuvant chemotherapy, *VPI* visceral pleural invasion, *LVI* lymphovascular invasion

[a]Chi square and Mann–Whitney test as appropriate

average score than the ACT group (electronic supplementary Fig. 2).

RFS differences between both groups were compared, as stratified by the TNM staging and the quartiles of the nomogram-based risk score. For stage IA, patients receiving ACT had a significantly worse RFS than those not receiving ACT. For stage IB, no significant improvement after ACT was observed. A significant RFS difference was observed among patients divided by quartiles of the risk scores ($p < 0.0001$). In the lowest and second quartiles, patients in the non-ACT group had a significantly lower RFS than those in the ACT group (both $p < 0.0001$); however, the RFS difference seemed to diminish gradually with the increase in risk score. In the third and highest quartiles, there were no significant differences in RFS between the non-ACT and ACT groups ($p = 0.1764$ and $p = 0.1999$, respectively; electronic supplementary Fig. 3).

The smooth curve showed that the recurrence rate increased with an increase in the risk scores for patients in the non-ACT group. However, compared with the non-ACT group, the recurrence rate of the ACT group was higher in the low-risk zone, similar in the intermediate-risk zone, but lower in the high-risk zone (electronic supplementary Fig. 4). The entire cohort was categorized into low-risk (score ≤ 203), intermediate-risk (score 204–244), and high-risk (score ≥ 245) groups, with cut-off points generated using the X-tile software. ACT was detrimental for low-risk patients. No significant improvement in ACT was observed in patients in the intermediate-risk group; however, ACT did improve RFS and disease-specific survival (DSS) for patients in the high-risk group (Fig. 3).

### *Subgroup Analysis of High-Risk Patients as ACT Candidates*

Among all 120 patients with a risk score ≥ 245, the majority (88.3%) were in stage IB. Accordingly, 7.5% (106 of 1414) of all stage IB patients were categorized into the

**TABLE 2** Univariable and multivariable analysis for RFS using the Cox proportional hazard model in the non-ACT group

| Variable | Univariable analysis *p* value | Multivariable analysis | |
|---|---|---|---|
| | | HR (95% CI) | *p* value |
| Age | 0.000 | 1.030 (1.016–1.045) | 0.000 |
| Sex | | | |
| Female versus male | 0.000 | 0.635 (0.495–0.815) | 0.000 |
| Smoking history | | | |
| Ever versus never | 0.001 | 0.956 (0.675–1.352) | 0.797 |
| Tumor size, cm | | | |
| 0–1 | Reference | Reference | |
| 1–2 | 0.001 | 3.367 (1.365–8.306) | 0.008 |
| 2–3 | 0.000 | 4.745 (1.919–11.735) | 0.001 |
| 3–4 | 0.000 | 7.303 (2.847–18.735) | 0.000 |
| Pathological subtype | | | |
| Lepidic | Reference | Reference | |
| Acinar/papillary | 0.000 | 3.216 (1.313–7.877) | 0.011 |
| Solid/micropapillary | 0.000 | 11.308 (4.375–29.225) | 0.000 |
| Variant | 0.000 | 3.602 (1.226–10.584) | 0.020 |
| VPI | | | |
| Present versus absent | 0.000 | 2.024 (1.545–2.651) | 0.000 |
| LVI | | | |
| Present versus absent | 0.000 | 1.780 (1.107–2.862) | 0.017 |

*RFS* recurrence-free survival, *ACT* adjuvant chemotherapy, *HR* hazard ratio, *CI* confidence interval, *VPI* visceral pleural invasion, *LVI* lymphovascular invasion

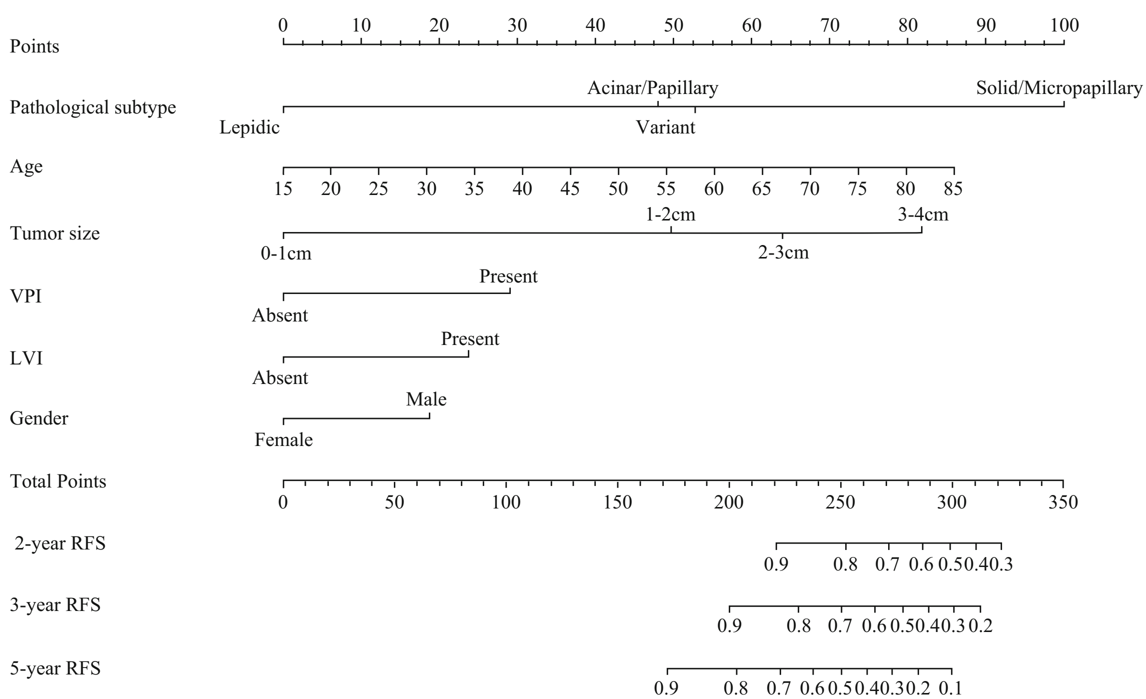



**FIG. 1** The established nomogram model for predicting 2-, 3-, and 5-year RFS in stage I LAD patients undergoing complete lobectomy. *RFS* recurrence-free survival, *LAD* lung adenocarcinoma, *VPI* visceral pleural invasion, *LVI* lymphovascular invasion, *RFS* recurrence-free survival

high-risk group. When looking specifically into stage IB subgroups, high-risk patients accounted for 62.8, 27.6, and 13.0% in the solid/micropapillary subtype, LVI, and tumor size 3–4 cm subgroups, respectively.

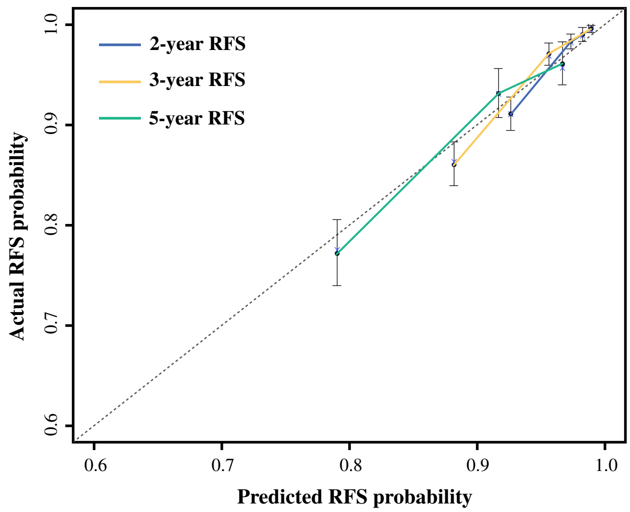



**FIG. 2** Calibration curves of the nomogram showed good agreement between predicted and observed RFS. *RFS* recurrence-free survival

## DISCUSSION

The established nomogram incorporating six independent recurrent factors, namely age, sex, tumor size, histologic subtype, and presence of LVI or VPI, showed a superior predictive value of RFS than the 8th edition of TNM staging in completely lobectomized stage I LAD. We found that ACT contributed to the improved survival for high-risk patients only, defined as having a risk score $\geq$ 245. In all lobectomized stage I LAD patients, those with predominant solid or micropapillary subtype may benefit the most from ACT.

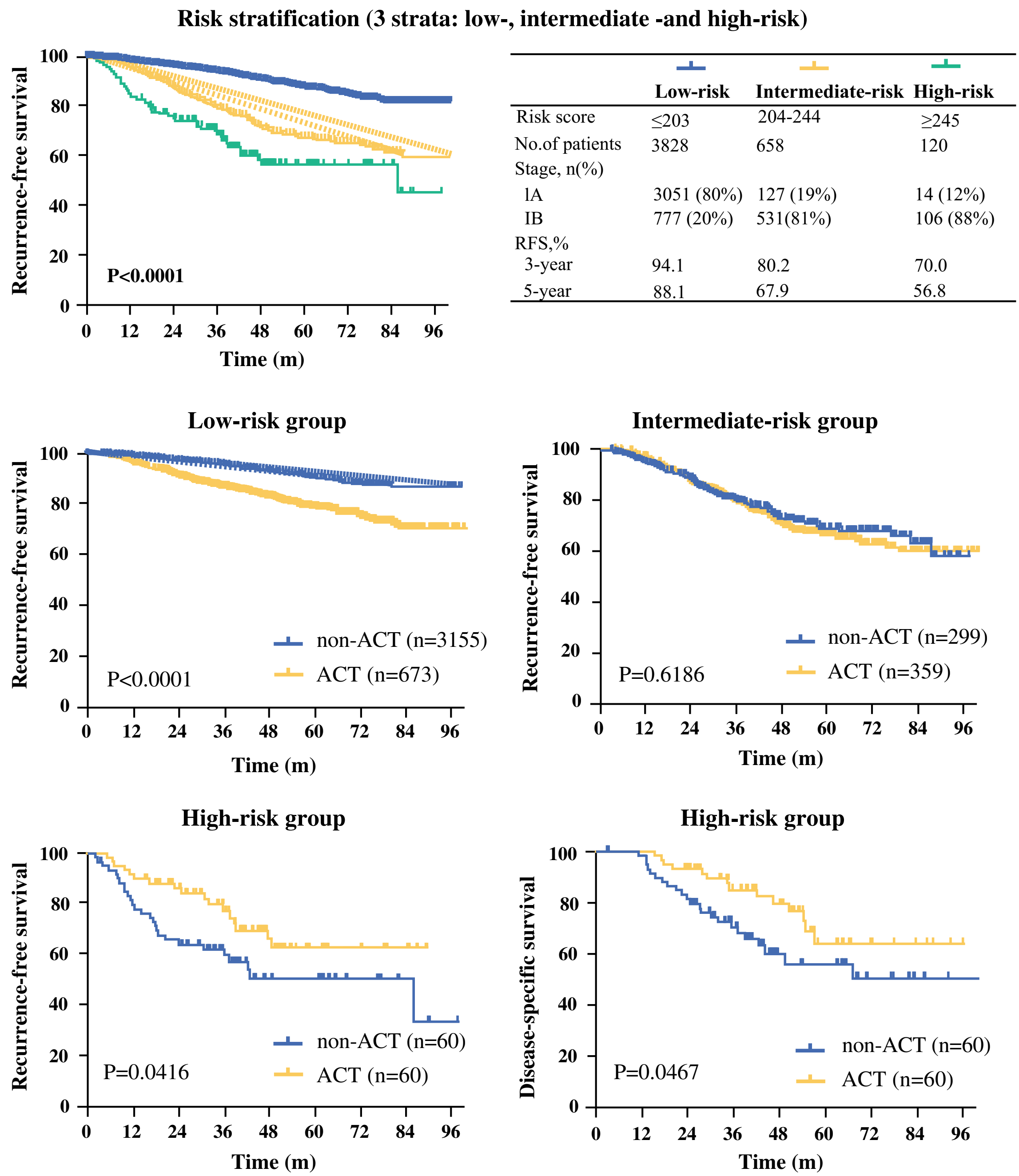
Survival of postoperative stage I LAD is largely affected by baseline clinical and pathological factors. Our results revealed that the benefit of ACT increased along with the elevated recurrence probabilities, as reflected by a factor-incorporated total score. In patients with a low-risk of recurrence, ACT exhibited a negative effect on RFS. The result was in accordance with previous findings that ACT was detrimental for stage IA patients as stage IA constituted the majority (80%) of the low-risk group.[8] No significant improvement in RFS was observed in the ACT group until the risk score ascended to 245. Since the majority of stage IB patients receiving ACT were in the intermediate-risk group, this result may partly explain why previous large-scale pooled analyses and RCT trials based on overall stage IB NSCLC did not prove the benefit from ACT.[8,10,11,13]

ACT improved prognosis for only a small portion of stage I patients in the 8th TNM staging system. As shown in the current study, the number of ACT candidates constituted 2.6% of the overall stage I population and 7.5% of the stage IB population. It is noteworthy that the observed 5-year OS rate of these high-risk patients without ACT was 53%, approaching the survival of stage IIA in the 7th TNM staging, and IIB in the 8th TNM staging.[5] The fact that ACT was recommended in stage II patients provided additional rationale for ACT application in patients at high risk.

Our findings confirmed the concept that pathological subtype is an important prognostic factor in stage I LAD. Patients with predominant solid/micropapillary subtype may benefit the most from ACT because of their higher recurrence risk compared with other subtypes. Previous studies indicated that patients with solid and micropapillary pattern had a more aggressive malignant potential and were more likely to recur than those without such subtypes, without exceptions for postoperative early-stage adenocarcinomas.[4,20–24] The present study demonstrated that solid/micropapillary subtypes were associated with a more than 11-fold increased risk of recurrence compared with the lepidic subtype. What is more crucial is that pathological subtype accounted for the first-weighed influencing factor of recurrence. In addition, recurrence of the LAD variant subtype is rarely separately studied and remains controversial, partly due to the limited sample size. In the current study, approximately 3% of LADs were of the variant subtype, mostly classified as invasive mucinous adenocarcinoma (IMA). In contrast to previous studies that categorized the variant subtype into the high-grade group,[25] we found that the recurrence risk of the variant subtype was similar to that of the acinar or papillary subtype. Our results were consistent with previous reports that the disease-free survival of IMA was between that of low-grade LAD and intermediate-grade LAD.[26,27]

The 8th edition of the TNM staging updated T descriptors in stage I NSCLC for better stratification. However, heterogeneous prognosis has been disclosed in stage I NSCLC, especially for stage IB. With the exception of tumor size, VPI and the abovementioned histologic subtypes, advanced age, sex, and LVI were also reported to be significant factors affecting survival.[15,16,28,29] By incorporating all influencing risk factors of recurrence, our established nomogram showed a better prognostic value than the 8th edition of the TNM staging. Individual prognostic estimation is feasible in the nomogram. More importantly, the ACT candidates who might be excluded from the conventional analyses were selected from the overall population.

Our study presents several potential limitations. First, this was a retrospective study performed at a single institution and follow-up periods were variable; however, we tried to collect a sufficient sample size to minimize selection bias. Second, additional studies are warranted in order to clarify the recurrence of stage I LAD through external validation. Third, genetic information was not included because gene detection was not a routine practice for




| | Low-risk | Intermediate-risk | High-risk |
|---|---|---|---|
| Risk score | ≤203 | 204-244 | ≥245 |
| No.of patients | 3828 | 658 | 120 |
| Stage, n(%) | | | |
| IA | 3051 (80%) | 127 (19%) | 14 (12%) |
| IB | 777 (20%) | 531(81%) | 106 (88%) |
| RFS,% | | | |
| 3-year | 94.1 | 80.2 | 70.0 |
| 5-year | 88.1 | 67.9 | 56.8 |

**FIG. 3** Comparison of RFS according to the X-tile generated risk group stratification. *RFS* recurrence free survival, *ACT* adjuvant chemotherapy

postoperative early-stage patients in the early years. In addition, recent studies have revealed that the presence of mutations in the epidermal growth factor receptor gene might not be a prognostic factor of long-term outcome in resected NSCLC.[30] Fourth, the toxicity of ACT was not completely assessed in this study. The most frequent toxicity was fatigue and bone marrow suppression such as neutropenia. Our results also showed that stage IA patients receiving ACT had a worse prognosis than those not receiving ACT. Furthermore, patients in the ACT groups all had risk factors and were more prone to recurrence than non-ACT patients. The possibly that chemotherapy itself had a detrimental effect on survival could not be excluded since chemotherapy could contribute to relapse by damaging DNA, generating new mutations, and allowing tumor cells to evolve.[31] Finally, we only included stage I patients with complete lobectomy. The nomogram was therefore not applicable for patients undergoing other surgical procedures.

## CONCLUSIONS

We established a nomogram to precisely predict the probability of recurrence in stage I LAD after complete lobectomy. The subsequent analysis based on the nomogram confirmed that patients at high-risk, as defined by a score of $\geq$ 245, were potential candidates for ACT. The established nomogram is able to guide the decision regarding whether or not chemotherapy should be performed in postoperative stage I patients.

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