Clinicopathological variables influencing overall survival, recurrence and post-recurrence survival in resected stage I non-small-cell lung cancer

Chengdi Wang, Yuxuan Wu, Jun Shao, Dan Liu* and Weimin Li*

Abstract

Background: To investigate clinicopathological variables influencing overall survival, overall recurrence, and post-recurrence survival (PRS) in patients who experienced curative-intent surgical resection of stage I non-small-cell lung cancer (NSCLC).

Methods: We investigated a series of 1387 patients with stage I NSCLC who underwent surgical resection from 2008 to 2015. The effect clinicopathological factors on death, recurrence, and PRS were evaluated by Kaplan-Meier estimates and cox regression analysis.

Results: Among the 1387 stage I patients, 301 (21.7%) experienced recurrence. The 5-year cumulative incidence of recurrence (CIR) for all patients was 20.2% and median PRS was 25.5 months. The older age ($P = 0.036$), p-stage IB ($P = 0.001$), sublobar resection ($P < 0.001$), histology subtype ($P < 0.001$), and lymphovascular invasion (LVI) ($P = 0.042$) were significantly associated with worse overall survival. Among 301 recurrent patients, univariable analysis indicated that p-stage IB (versus IA) ($P < 0.001$), LVI ($P < 0.001$) and visceral pleural invasion (VPI) ($P < 0.001$) were remarkably correlated with the higher incidence of recurrence. Taking the effect of clinicopathological variables on PRS into consideration, smoking history ($P = 0.043$), non-adenocarcinoma ($P = 0.013$), high architectural grade of LUAD ($P = 0.019$), EGFR wild status ($P = 0.002$), bone metastasis ($P = 0.040$) and brain metastasis ($P = 0.042$) were substantially related with poorer PRS. Multivariate analysis demonstrated that high architectural grade of LUAD ($P = 0.008$), brain metastasis ($P = 0.010$) and bone metastasis ($P = 0.043$) were independently associated with PRS.

Conclusion: In patients with resected stage I NSCLC, the older age, p-stage IB (versus IA), sublobar resection, histology subtype, and LVI were significantly associated with worse overall survival. P-stage IB (versus IA), LVI, and VPI were significantly correlated with the higher incidence of recurrence. High architectural grade of LUAD, brain metastasis and bone metastasis were independent risk factors with PRS.

Keywords: Non-small-cell lung cancer, Survival, Recurrence, Risk factors, Post-recurrence survival
Background
Lung cancer is so far the leading cause of cancer-related mortality, accounting for an estimate of 690,000 deaths in China and 1,761,000 deaths worldwide in 2018 [1, 2]. The standard of care for patients with early-stage non-small-cell lung cancer (NSCLC) is the curative-intent anatomic surgical resection, whereas tumor metastasis or recurrence leads to the treatment failure and mortality after surgery [3]. Reported locoregional recurrence rates were shown to elevate with advancing pathological stage (5–19%, 11–27%, 24–40% for stage I, II, and IIIA respectively) and to range with various surgical resection modalities (lobectomy, 4.9–7%; segmentectomy, 9.1–16%; and wedge resection, 11–27.8%) [4]. Previous studies have reported that recurrence rates, based on the primary stage and follow-up time, varied between 18.5 and 75% for resected NSCLC patients with stage I to III [5–7]. According to outcomes of the National Lung Screening Trial (NLST) and the Nelson trials for screening computed tomography (CT) scans, the improvements in the early diagnosis and the reduction in the mortality of lung cancer have been greatly anticipated [8, 9]. Appropriate surveillance strategies such as CT scans are therefore of great importance to identify earlier and to screen recurrent patients who have the high probability of mortality. Hence, identification of prognostic variables for recurrence in lung cancer after surgery is of great significance for screening high-risk patients for further and better treatments.

NSCLC accounts for approximately 85% of lung cancer, including the primary subtypes such as lung adenocarcinoma (LUAD), squamous carcinoma (LUSC), and adenosquamous carcinoma (LASC) [10]. LUAD is the most common histologic type of NSCLC, which, based on the predominant subtype, is classified into adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), lepidic-, acinar-, papillary-, micropapillary-, and solid-predominant invasive adenocarcinoma (IA) in accordance with IASLC/ATS/ERS and 2015 WHO classifications [11, 12]. Previous studies have demonstrated that the predominant histologic patterns were strongly associated with recurrence-free survival (RFS) [13, 14]. Up to date, several studies have reported the prognostic value of the new classification to predict mortality and recurrence mainly in LUAD or non-LUAD. Nevertheless, few studies were found to focus on LUSC, LASC or other lung cancer subtypes [15–17]. Among these limited number of studies, even fewer evaluated the predictive value of such classification with regard to recurrence patterns and post-recurrence survival (PRS) in NSCLC, especially LUSC [5, 6, 18–20]. To mend this inadequacy, we set out to investigate the prognostic value of clinicopathologic factors and histologic subtypes on the overall survival, overall recurrence, and PRS. Our study involved a large and homogenous cohort of resected stage-I patients with NSCLC, not limited to lung adenocarcinoma or squamous cell carcinoma. By focusing on recurrent patients following the curative-intent surgery, we could identify the risk factors and explore their effect on the OS, overall recurrence, and PRS in resected stage-I NSCLC patients.

Methods
In this study, we retrospectively reviewed the medical records of all patients who had undergone anatomic resection for pathologically diagnosed stage I NSCLC including LUAD, LUSC, LASC and other histologic subtypes. The medical clinicopathologic data were taken from West China Hospital (WCH), Sichuan University between 2009 through 2015. Lobectomy was deemed to be as the standard surgical modality for early-stage NSCLC patients at WCH. Sublobar resection, including segmentectomy or wedge resection, was regarded as the surgical option for patients with comorbidities, poor pulmonary function, or very small nodules that made lobectomy inappropriate. The clinicopathologic variables were retrieved from our prospectively established Lung Cancer Database of West China Hospital as follows: age (operation age and recurrence age), sex, smoking history, surgery modality, tumor histology, pathologic TNM stage, lymphovascular invasion (LVI), visceral pleural invasion (VPI), EGFR status, adjuvant therapy, PRS. Exclusion criteria were patients who had received preoperative chemotherapy, or and radiation therapy, or had multiple metachronous or metastatic lesions, or had positive surgical margin. A total of 1387 patients who had the complete follow-up were eligible for the study.

Postoperative assessment contained health checkup, serum tumor markers (CEA, CA125, CA199, NSE, CYFRA21-1), chest/upper-abdominal CT scans, and bone scintigraphy. Histologic subtypes of NSCLC were identified according to the IASLC/ATS/ERS and 2015 WHO classifications. LUAD was classified into MIA and IA, the latter of which was subdivided into solid-, micropapillary-, papillary-, acinar-, and lepidic-predominant subtypes [11, 12]. Tumors were divided into 3 groups including high grade group of micropapillary- and solid-predominant IA, intermediate group of acinar- and papillary-predominant IA, low group of MIA and lepidic-predominant IA [13, 21]. Disease stage was determined in accordance with the 8th edition of the American Joint Committee (AJCC) on Cancer Staging Manual [22]. The following factors were also included in this study: pathologic stage, visceral pleural invasion (VPI), lymphovascular invasion (LVI), and EGFR status. Routine follow-up of postoperative lung cancer was carried out on the basis of National Comprehensive Cancer
Network (NCCN) guidelines [23]. Medical examination, blood examination (serum tumor biomarkers), chest or and abdomen CT scans were performed every 6 months for the first 2 years after resection. The clinical follow-up and routine CT scans were carried out annually from the 3rd to 5th year after surgery. Brain magnetic resonance imaging (MRI), abdominal and cervical/supraclavicular ultrasonography, or bone scintigraphy were done if abnormal symptoms were noticed in the corresponding regions. All the data were extracted from the Lung Cancer Database of West China Hospital, which covered the clinicopathological characteristics and complete follow-up information of included patients. The current study was approved by the Institutional Review Board of West China Hospital, Sichuan University, and informed consent was waived by the board because of its retrospective nature.

This study had two main endpoints: (1) recurrence after initial surgery and (2) death with or without recurrence. The identification of recurrence was determined by using the imageological examination such as CT, PET/CT, MRI or obtaining the histological specimen when necessary. Second independent primary lung cancer was distinguished from recurrent or metastatic foci via histologic profile of available biopsy specimen or image omics in accordance with the proposed criteria of the IASLC Lung Cancer Staging Project [24]. Local recurrence was regarded as second loci in the ipsilateral containing the ipsilateral hilus and ipsilateral mediastinum. Distant metastasis or recurrence was deemed as the new lesion in the opposite lung, or elsewhere outside the mediastinum and hemithorax [5].

To investigate the prognostic value of clinicopathologic variables in the OS and overall recurrence, we adopted both univariable and multivariable analyses. The length of OS was calculated between the initial operate date and the time of either death or last contact. The length of overall recurrence was measured from the date of resection to the time of initial recurrence. Length of PRS was deemed as the interval between the initial recurrence date and death date or last contact. Patients were censored at the last available follow-up when they had not experienced death or relapse. We performed the Kaplan-Meier approach on the basis of log-rank test to estimate the OS and PRS. Cumulative incidence of recurrence (CIR) was calculated by adopting the probability of recurrence after surgery based on competing risks approaches [25]. We performed the Gray method for univariable nonparametric tests and used Fine-Gray model for multivariable analyses to assess the differences in CIR between groups [26, 27]. SPSS software (version 21.0) and R version 3.6.0 were used to perform the statistical analyses, and two-sided P values < 0.05 were regarded as the statistical significance.

Results
This study cohort consisted of 1387 patients with resected stage I NSCLC, who met the inclusion and exclusion criteria. Among them were 1028 LUAD including 12 MIA, 276 LUSC, 49 LASC, and 34 other tumor histology subtypes (Others). In the current study, no recurrent disease was observed in AIS or in MIA. Of the 1028 LUAD, 447 patients who had the available subtypes were classified as lepidic predominant (n = 183), acinar predominant (n = 178), papillary predominant (n = 48), micropapillary predominant (n = 2), and solid predominant (n = 24). Detailed clinicopathologic characteristics are delineated in Table 1. The median overall survival was more than 60 months and the median follow-up for the identified 1387 patients with NSCLC was 63.6 months (range: 61.6–65.5 months) (Fig. 1a). At the end of the study period, 251 patients had died. The older age (HR: 1.169, 95%CI: 1.010–1.352; P = 0.036), p-stage IB (HR: 1.217, 95%CI: 1.106–1.461; P = 0.001), sublobar resection (HR: 1.548, 95%CI: 1.280–1.871; P<0.001) and histologic subtype (P<0.001), and lymphovascular invasion (LVI) (P = 0.042) were significantly associated with overall survival.

Of the 1387 patients identified, 301 (21.7%) had developed recurrence or relapse. The 5-year overall recurrence for all stage I patients was 20.2% (Fig. 1b). Table 1 presented results of univariate and multivariate analyses of overall survival and overall recurrence according to clinicopathologic characteristics of patients with stage I NSCLC. For univariate analysis, p-stage IB (versus IA) (HR: 2.048, 95%CI: 1.547–2.710; P<0.001), LVI (HR: 3.364, 95%CI: 2.247–5.038; P<0.001), visceral pleural invasion (VPI) (HR: 1.779, 95%CI: 1.408–2.248; P<0.001) were significantly correlated with the higher incidence of lung cancer recurrence.

Of the 301 patients who underwent the recurrence, 230 (76.4%) had distant recurrence, 71 (23.6%) had local recurrence, and 141 died during the at least 5-year follow-up. The most commonly involved organs for distant recurrence were the lung (n = 193), brain (n = 82), bone (n = 85) and liver (n = 30). The majority of recurrences were diagnosed by CT scans. A total of 194 recurrent patients received the post-recurrence therapy (PRT), including chemotherapy for 67 patients, surgery plus chemotherapy or and targeted therapy for 34, targeted therapy alone for 22, surgery alone for 3 (Table 2). Other treatments details are presented in Table 2. On the whole, 1-,2- and 5-year PRS was 75.1%, 55.1, and 16.6% respectively. Median PRS time for the recurrent patients was 25.5 months (range: 22.2–28.9 months) (Fig. 1c). We further explored risk factors associated with post-recurrence survival. Taking the effect of clinicopathological variables on PRS into the account, smoking history (HR:1.266, 95%CI: 1.008–1.589; P = 0.043), non-
Table 1 Patient characteristics and univariable analysis of overall survival and overall recurrence

| Primary tumor factor                        | Overall Survival (n = 1387) | Overall Recurrence | Univariable Analysis | Multivariate Analysis | Univariable Analysis | Multivariate Analysis |
|--------------------------------------------|----------------------------|--------------------|----------------------|-----------------------|----------------------|-----------------------|
|                                            | N  | HR 95% CI | P value | HR 95% CI | P value | 5-yr CIR | SHR 95% CI | P value | SHR 95% CI | P value |
| Age at surgery, years                      |    |           |         |           |         |          |            |         |            |         |
| ≤ 65                                       | 971| 1         | 1       | 1         | 1       | 19.9%    | 1          |         |            |         |
| >65                                        | 416| 1.169(1.010–1.352) | 0.036 | 1.112(0.898–1.376) | 0.330 | 21.0%    | 1.063(0.826–1.368) | 0.633 |            |         |
| Sex                                         |    |           |         |           |         |          |            |         |            |         |
| Male                                       | 772| 1         | 1       | 1         | 1       | 21.7%    | 1          |         |            |         |
| Female                                     | 615| 0.965(0.930–1.220) | 0.364 | 0.821(0.647–1.041) | 0.104 |          |            |         |            |         |
| Smoking history                            |    |           |         |           |         |          |            |         |            |         |
| Never                                      | 783| 1         | 1       | 1         | 1       | 18.9%    | 1          |         |            |         |
| Ever                                       | 604| 0.875(0.762–1.004) | 0.057 | 1.152(1.026–1.432) | 0.043 | 21.9%    | 1.192(0.944–1.506) | 0.105 |            |         |
| Pathologic stage                           |    |           |         |           |         |          |            |         |            |         |
| IA                                         | 488| 1         | 1       | 1         | 1       | 12.8%    | 1          |         |            |         |
| IB                                         | 899| 1.217(1.106–1.461) | 0.001 | 1.318(1.071–1.621) | 0.010 | 24.2%    | 2.048(1.547–2.710) | <0.001 | 1.123(0.633–1.994) | 0.692 |
| Surgery                                    |    |           |         |           |         |          |            |         |            |         |
| Lobectomy                                  | 1223| 1         | <0.001 | 1         | 1       | 20.6%    | 1          |         |            |         |
| Sublobar                                   | 164| 1.548(1.280–1.871) | <0.001 | 1.196(0.914–1.564) | 0.192 | 20.7%    | 1.053(0.590–1.274) | 0.468 |            |         |
| Tumor histology                            |    |           |         |           |         |          |            |         |            |         |
| LUAD                                       | 1028| 1         |         | 1         | 1       | 19.1%    | 1          |         |            |         |
| LUSC                                       | 276| 0.693(0.576–0.833) | 0.057 | 1.152(0.944–1.506) | 0.104 |          |            |         |            |         |
| LASC                                       | 49 | 0.775(0.520–1.155) | 0.057 | 1.152(0.944–1.506) | 0.104 |          |            |         |            |         |
| Others                                     | 34 | 1.081(0.700–1.669) | 0.001 | 1.196(0.914–1.564) | 0.192 | 20.7%    | 1.053(0.590–1.274) | 0.468 |            |         |
| Carcinoma type                             |    |           |         |           |         |          |            |         |            |         |
| LUAD                                       | 1028| 1         |         | 1         | 1       | 19.1%    | 1          |         |            |         |
| Non-Non-LUAD                               | 359| 0.735(0.623–0.867) | <0.001 | 1.041(0.510–1.733) | 0.029 | 23.3%    | 1.262(0.978–1.629) | 0.074 | 1.987(0.837–2.344) | 0.073 |
| Predominant subtype of LUAD                |    |           |         |           |         |          |            |         |            |         |
| MIA                                        | 12 | 1         |         | 1         | 1       | 8.3%     | 1          |         |            |         |
| Lepidic                                    | 183| 0.580(0.322–0.994) | 0.001 | 1.446(0.587–3.562) | 0.001 | 10.9%    | 1.293(0.174–9.636) | 0.061 | 1.027(0.127–1.261) | 1.261 |
| Acinar                                     | 178| 1.084(0.603–1.950) | 0.001 | 1.119(0.615–2.035) | 0.07 | 20.7%    | 2.603(0.357–8.974) | 1.833 | 2.47(0.247–3.623) | 8.974 |
| Papillary                                  | 48 | 0.877(0.464–1.659) | 0.001 | 1.487(0.574–3.858) | 0.001 | 25.0%    | 3.178(0.413–4.443) | 1.984 | 2.51(0.251–5.702) | 4.443 |
| Micropapillary                             | 2  | 0.478(0.107–2.137) | 0.001 | 0.807(0.800–6.262) | 0.001 | 50.0%    | 10.576(0.661–16.154) | 0.001 | 9.424(0.559–10.928) | 2.137 |
| Solid                                      | 24 | 1.501(0.746–3.023) | <0.001 | 1.611(0.786–3.300) | <0.001 | 33.4%    | 4.911(0.614–9.268) | 0.070 | 2.979(0.368–4.104) | 0.030 |
| EGF status                                 |    |           |         |           |         |          |            |         |            |         |
| Wild-type                                  | 206| 1         |         | 1         | 1       | 33.0%    | 1          |         |            |         |
adenocarcinoma (HR: 1.357, 95%CI: 1.074–1.762; P = 0.013), high architectural grade of LUAD (HR: 2.795, 95%CI: 1.181–6.615; P = 0.019), EGFR wild status (HR: 2.140, 95%CI: 1.307–3.503; P = 0.002), brain metastasis (HR: 1.442, 95%CI: 1.013–2.051; P = 0.042) and bone metastasis (HR: 1.443, 95%CI: 1.017–2.048; P = 0.040) were significantly related with worse PRS (Fig. 2).

Multivariate analysis revealed that high architectural grade of LUAD (HR: 3.740, 95%CI: 1.405–9.953; P = 0.008), brain metastasis (HR: 3.577, 95%CI: 1.354–9.340; P = 0.010) and bone metastasis (HR: 2.397, 95%CI: 1.026–5.601; P = 0.043) were independently and significantly associated with PRS.

Discussion
Although previous studies have reported molecular and clinicopathologic variables for the recurrence for NSCLC after initial resection especially in LUAD [28, 29], the recurrence pattern of LUSC, LASC or other NSCLC subtypes still needs to be investigated. To our knowledge, this present study is the first to comprehensively explore the influence of clinicopathologic factors on OS, overall recurrence and post-recurrence survival based on a largest cohort of patients with NSCLC having LUAD, LUSC, LASC and other subtypes. The median follow-up period of all resected lung cancer patients was more than 60 months.

The prognostic value of the new IASLC/ATS/ERS classification system in the OS and the overall recurrence has been reported and discussed in several previous studies [15, 16, 21, 30]. Warth et al. reported that solid-, micropapillary-, and papillary-adenocarcinoma patients who underwent the surgery (the frequencies: 37.6, 6.8, and 4.7% respectively), compared to lepidic- and acinar-predominant histologic patterns (the frequencies: 8.1 and 42.5%, respectively), were significantly related with lower disease-free survival (DFS) and poorer OS [15]. Yoshizawa et al. showed that LUAD patients with stage I having...
| Table 2 Patient characteristics and PRS analysis |
|-----------------------------------------------|
| Overall Recurrent Patients | Univariate Analysis | Multivariate Analysis |
| | No. (%) | HR (95% CI) | P value | HR (95% CI) | P value |
| **Primary tumor factor** | | | | | |
| Age at recurrence, years | | | | | |
| ≤ 65 | 195 | 1 | | | |
| >65 | 106 | 1.187(0.936–1.506) | 0.157 | | |
| **Sex** | | | | | |
| Male | 178 | 1 | | | |
| Female | 123 | 0.861(0.683–1.085) | 0.204 | | |
| **Smoking history** | | | | | |
| Never | 163 | 1 | | | |
| Ever | 138 | 1.266(1.008–1.589) | 0.043 | 1.847(0.541–6.313) | 0.328 |
| **Pathologic stage** | | | | | |
| IA | 70 | 1 | | | |
| IB | 231 | 1.113(0.718–1.725) | 0.633 | | |
| **Surgery** | | | | | |
| Lobectomy | 284 | 1 | | | |
| Sublobar resection | 17 | 1.183(0.724–1.933) | 0.502 | | |
| **Tumor histology** | | | | | |
| Adenocarcinoma (LUAD) | 210 | 1 | | | |
| Squamous carcinoma (LUSC) | 65 | 1.344(1.016–1.778) | | | |
| Adenosquamous carcinoma (LASC) | 19 | 1.319(0.823–2.113) | | | |
| Others | 7 | 1.889(0.886–4.025) | 0.068 | | |
| **Carcinoma type** | | | | | |
| Adenocarcinoma (LUAD) | 210 | 1 | | | |
| Non-Adenocarcinoma (Non-LUAD) | 91 | 1.375(1.074–1.762) | 0.013 | 7.421(0.861–8.323) | 0.909 |
| **Architectural grade of LUAD** | | | | | |
| Low/immediate grade | 76 | 1 | | | |
| High grade | 9 | 2.795(1.181–6.615) | 0.019 | 3.740(1.405–9.953) | 0.008 |
| **EGFR status** | | | | | |
| Mutated | 80 | 1 | | | |
| Wild-type | 77 | 2.140(1.307–3.503) | 0.002 | 0.385(0.115–1.284) | 0.120 |
| **Lymphovascular invasion (LVI)** | | | | | |
| Absent | 284 | 1 | | | |
| Present | 17 | 0.749(0.451–1.245) | 0.749 | | |
| **Visceral pleural invasion (VPI)** | | | | | |
| Absent | 115 | 1 | | | |
| Present | 186 | 1.068(0.729–1.566) | 0.735 | | |
| **Type of recurrence** | | | | | |
| Local | 71 | 1 | | | |
| Distant | 230 | 1.009(0.772–1.318) | 0.949 | | |
| **Recurrence pattern** | | | | | |
| Intrathoracic | 62 | 1 | | | |
| Extrathoracic | 87 | 0.756(0.543–1.053) | | | |
| Both | 152 | 0.762(0.566–1.027) | 0.165 | | |
high-grade tumors including solid- and micropapillary-predominant subtypes were significantly associated with worse overall survival and a higher incidence of recurrence [21]. Hung et al. demonstrated that LUAD patients with resected stage I-III owing the high architectural grade including solid- (13.6%) and micropapillary- (19.5%) predominant patterns, compared with papillary- (27.1%), acinar- (33.7%), and lepidic- (6.1%) predominant subtypes, were remarkably associated with worse overall survival, poorer disease-specific survival and higher incidence of recurrence [16, 31]. Our outcomes also demonstrated that the solid-predominant patients of LUAD had the higher possibility of recurrence similarly to the reported results despite the limited number of corresponding patients. According to the regular CT surveillance protocol, we found that most recurrences or disease progression appeared within the first 2 years after the curative-intent surgical section, which indicated that the regular CT surveillance was of great significance for the postoperative lung cancer patients. However, the best interval time for postoperative follow-up is still to be warranted to be investigated and validated in case of excessive or delayed medical treatment due to insufficient diagnosis. In addition, the current study also demonstrated that high architectural grade including solid-predominant LUAD was significantly associated with poor PRS, which highlights the need for medical care for the postoperative clinical contact.

**Table 2** Patient characteristics and PRS analysis (Continued)

| Recurrence Patients | Univariate Analysis | Multivariate Analysis |
|---------------------|---------------------|----------------------|
|                     | No. (%)             | HR (95% CI)          | P value | HR (95% CI) | P value |
| Recurrence pattern  |                     |                      |         |             |         |
| Single site         | 137                 | 1                    | 0.439   |             |         |
| Multiple site       | 164                 | 1.004(0.728–1.148)   |         |             |         |
| Recurrence site     |                     |                      |         |             |         |
| Lung                | 193                 | 1.198(0.837–1.715)   | 0.324   |             |         |
| Brain               | 82                  | 1.442(1.013–2.051)   | 0.042   | 3.557(1.354–9.340) | 0.010 |
| Bone                | 85                  | 1.443(1.017–2.048)   | 0.040   | 2.397(1.026–5.601) | 0.043 |
| Liver               | 30                  | 1.139(0.685–1.893)   | 0.617   |             |         |
| Initial therapy of recurrence |     |                      |         |             |         |
| Single therapy      |                     |                      |         |             |         |
| Surgery             | 3                   | 0.746(0.239–2.331)   | 0.614   |             |         |
| Chemotherapy        | 67                  | 0.896(0.681–1.179)   | 0.432   |             |         |
| Radiation therapy   | 20                  | 1.041(0.660–1.640)   | 0.863   |             |         |
| Targeted therapy    | 22                  | 0.998(0.891–2.380)   | 0.095   |             |         |
| Multimodality       |                     |                      |         |             |         |
| Chemotherapy+ radiation therapy/ targeted therapy | 48 | 0.821(0.602–1.120)   | 0.213   |             |         |
| Surgery + Chemotherapy/radiation therapy/targeted therapy | 34 | 0.758(0.530–0.984)   | 0.046   | 0.663(0.174–2.533) | 0.548 |

Abbreviations: LVI lymphovascular invasion, VPI visceral pleural invasion, LUAD lung adenocarcinoma, LUSC lung squamous carcinoma, LASC lung adenosquamous carcinoma

**Fig. 2** Post-recurrence survival (PRS) curve for recurrent patients with stage I NSCLC by subgroups into brain recurrence status (**a**), bone recurrence status (**b**), architectural grade of LUAD (**c**).
The present study also investigated the clinicopathological factors influencing the PRS of stage I NSCLC patients. Although surgical resection with curative intent is the most effective treatment modality for patients having stage I NSCLC, previous studies have reported an incidence of recurrence in stage I NSCLC ranging from 14 to 36%, with 1- and 2-year PRS rates of 38–88%, and 19–72.3% respectively (Table 3). In this study, overall incidence of recurrence during the postoperative 5 years was 20.2% and median PRS time was 25.5 months. We examined the impact of clinicopathological variables on OS and overall recurrence and identified a number of risk factors that were significantly associated with worse OS including the older age (∼0.036), p-stage IB (∼0.001), sublobar resection(<0.001), histologic subtype (<0.001), and lymphovascular invasion (LVI) (∼0.042). Smoking history (∼0.043), non-adenocarcinoma (∼0.013), high architectural grade of LUAD (∼0.019), EGFR wild status (∼0.002), bone metastasis (∼0.040) and brain metastasis (∼0.042) were marginally correlated with worse PRS. Some risk factors such as sublobar resection and high architectural grade of LUAD were consistent with previous studies.

Previous research reported that the recurrence sites might be a risk factors for PRS, which was consistent with our findings. Yoshino et al. showed that bone metastasis was reported to be the remarkably significant unfavorable factor for PRS in the NSCLC patients with resected stage I-III [32]. Shimada et al. demonstrated that liver metastasis (∼0.001) and bone metastasis (∼0.001) were independently and significantly correlated with worse PRS [6]. Ujiie et al. showed that solid predominant adenocarcinoma was marginally associated with higher recurrence or metastasis incidence of brain (∼0.007), adrenal gland (∼0.034), and liver (∼0.038) than the non-solid predominant tumors [5]. Hung et al. reported that the higher incidence of distant metastasis occurred in adenocarcinoma and higher probability of local recurrence existed in non-adenocarcinoma [33]. Zhang et al. confirmed that adenocarcinoma histology, compared to squamous cell carcinoma, had the higher incidence of bone or brain recurrence [34]. The present study also indicated that the non-LUAD histology, brain metastasis and bone metastasis were significantly associated with worse PRS.

With the rapid development of management of lung cancer, molecular target therapy of tyrosine kinase inhibitors (TKI) has exerted survival benefit for the NSCLC patients with EGFR mutations [35, 36]. Shimada et al. demonstrated that epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), compared with platinum-based doublet chemotherapy, were significantly

### Table 3 Post-recurrence survival of patients with stage I NSCLC in previous studies

| Series                | Year | No. of patients | Histologic profile | Recurrence | Incidence of Recurrence (%) | PRS, % (y) | Independent factors of poor PRS |
|-----------------------|------|-----------------|--------------------|------------|----------------------------|------------|--------------------------------|
| Current study         | 2019 | 1387            | LUAD: 1028         | LUAD: 210  | 301 (21.7%)                | 75.1% (1-year) | architectural grade              |
|                       |      |                 | LUSC: 276          | LUSC: 65   | Locoregional recurrence: 71 (23.6%); Distant metastasis: 230 (76.4%) | 55.1% (2-year) | (micropapillary and solid predominant); recurrence site of bone or bone |
|                       |      |                 | LASC: 49           | LASC: 19   | Distant metastasis: 129 (69%) | 37.2% (3-year) |                                           |
|                       |      |                 | Others: 34         | Others: 7 | Locoregional recurrence: 59 (31%) | 16.6% (5-year) |                                           |
| Ujiie et al. [5]      | 2014 | 1120            | LUAD: 1120         | LUAD: 188  | 188 (17%)                  | 67% (1-year) | Older age (>65 yr) at the time of recurrence; sublobar resection; solid predominant; distant metastasis; |
|                       |      |                 | LUSC: 1880         | LUSC: 128  | Locoregional recurrence: 59 (31%); Distant metastasis: 129 (69%) | 45% (2-year) |                                           |
|                       |      |                 | Others: 90         | Others: 10 | Locoregional recurrence: 59 (31%); Distant metastasis: 129 (69%) | 36% (3-year) |                                           |
|                       |      |                 | Other: 32          | Other: 2   | Locoregional recurrence: 59 (31%); Distant metastasis: 129 (69%) | 14% (5-year) |                                           |
| Shimada et al. [6]    | 2013 | 919             | LUAD: 919          | LUAD: 46   | 170 (18%)                  | 73% (1-year) | PRT; male sex; poorly differentiated |
|                       |      |                 | Non-LUAD: 46       | Non-LUAD: 46 | Locoregional recurrence: 43 (25%); Distant metastasis: 113 (66%); Locoregional recurrence + Distant metastasis: 14 (9%) | 51% (2-year) |                                           |
| Hung et al. [16]      | 2013 | 283             | LUAD: 283          | LUAD: 283  | 57 (20%)                   | 72.3% (2-year) | Micropapillary and solid predominant |
|                       |      |                 | LUSC: 15           | LUSC: 15   | Locoregional recurrence: 36 (50%); Distant metastasis: 36 (50%) | 31.6% (5-year) |                                           |
| Song et al. [20]      | 2013 | 475             | NSCLC              | NSCLC: 46  | 72 (15%)                   | 88% (1-year) | Bad response for treatment; Recurrence-free interval<12 months |
|                       |      |                 | LUSC: 15           | LUSC: 15   | Locoregional recurrence: 36 (50%); Distant metastasis: 36 (50%) | 53% (3-year) |                                           |
|                       |      |                 | Other: 11          | Other: 11  | Locoregional recurrence: 36 (50%); Distant metastasis: 36 (50%) |                                           |                                           |
| Hung et al. [7]       | 2010 | 933             | NSCLC              | NSCLC: 95  | 166 (17.8%)                | 37.7% (1-year) | Disease-free interval more than 16 months |
|                       |      |                 | LUSC: 46           | LUSC: 46   | Single organ metastasis: 106 | 18.9% (2-year) |                                           |
|                       |      |                 | Other: 25          | Other: 25  | Multiple organ metastasis: 60 |                                           |                                           |
| Hung et al. [19]      | 2009 | 933             | NSCLC              | NSCLC: 45  | 123 (13.2%)                | 48.0% (1-year) | PRT (chemotherapy, surgery, and/or radiotherapy) |
|                       |      |                 | LUSC: 60           | LUSC: 60   | Locoregional recurrence: 74 (13.2%); Distant metastasis: 49 | 18.7% (2-year) |                                           |
|                       |      |                 | Other: 18          | Other: 18  | Locoregional recurrence: 74 (13.2%); Distant metastasis: 49 |                                           |                                           |
| Nakagawa et al. [18]  | 2008 | 397             | LUAD: 300          | LUAD: 87   | 87 (21.9%)                 | 67.7% (1-year) | Symptoms at recurrence: liver or cervico-mediastinum; PRT (non-surgery/surgery) |
|                       |      |                 | LUSC: 89           | LUSC: 89   | Locoregional recurrence: 30 (34.5%); Distant metastasis: 57 (65.6%) | 34.4% (3-year) |                                           |
|                       |      |                 | Other: 8           | Other: 8   | Locoregional recurrence: 30 (34.5%); Distant metastasis: 57 (65.6%) |                                           |                                           |

**Abbreviations:** LASC lung adenosquamous carcinoma, LUAD lung adenocarcinoma, LUSC lung squamous carcinoma, PRT post-recurrence therapy
associated with favorable PRS (HR = 0.460, 95%CI 0.245–0.862, \( P = 0.015 \)), which improved the quality of life and survival benefit [6]. The current study also suggested that NSCLC patients with EGFR mutations, having received the EGFR-TKIs, obtained a favorable PRS. However, since no EGFR mutations accounts for the majority of the lung cancer, the most appropriate treatment modality for resected lung cancer with no mutations is needed to be investigated. Nonetheless, the present study had some limitations. First, the retrospective nature hinders us to assess the influence of clinicopathological factors on the post-recurrence survival. Prospective randomized controlled trials (RCTs) are more appropriate in this regard. Second, our sample may not be largely representative because all patients involved in the study were Chinese. A multi-center investigating targeting non-Asian populations will certainly validate the results. Finally, not all LUADs had the predominant histologic subtypes due to insufficient records data. Despite these limitations, this current study is, to our knowledge, the first to investigate comprehensively the impact of clinicopathologic factors on post-recurrence survival based on the largest cohort of patients diagnosed with NSCLC with a median follow up of more than 5 years.

Conclusion
In conclusion, the clinicopathological variables have significant prognostic and predictive value for the OS, overall recurrence, and PRS, which will likely affect the clinical decision making in the near future. This study also provides new insight to help clinicians to identify high-risk patients, make personalized postoperative follow-up strategies and conduct the appropriate post-recurrence therapies.

Abbreviations
AIS: Adenocarcinoma in situ; CIR: Cumulative incidence of recurrence; LASC: Lung adenosquamous carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous carcinoma; LVI: Lymphovascular invasion; MIA: Minimally invasive adenocarcinoma; NSCLC: Non-small cell lung cancer; PRT: Post-recurrence therapy; RCTs: Randomized controlled trials; VPI: Visceral pleural invasion

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Authors’ contributions
WL and DL contributed to conceptualization and supervision. CW, YW performed data acquisition and statistical analysis. CW and JS wrote and reviewed the manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials
The original data that support the results of this study are available from the corresponding authors upon reasonable request.

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of West China Hospital, Sichuan University* that approved the retrospective study in which informed consent was waived, but patient confidentiality was protected.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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