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ORIGINAL ARTICLE

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Adjuvant chemotherapy in patients with recurrence after completely resected stage IB lung adenocarcinoma: Propensity-matched analysis in a cohort of 147 recurrences

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Abstract

Background: Adjuvant chemotherapy (ACT) is considered for high-risk patients in stage IB lung adenocarcinoma (LUAD). However, these risk factors are recognized as negative prognostic factors, not as predictors of ACT efficacy. This study aimed to analyze the efficacy of ACT in stage IB patients by retrospectively examining patients who had recurrence.

Methods: We reviewed 1399 patients with stage IB (American Joint Committee on Cancer 7th edition) LUAD from 2012 to 2017 in our institution and found 147 patients with recurrence. The last follow-up date was December 30, 2021. One-to-one propensity-score matching (PSM) was used to reduce the potential selection bias.

Results: Fifty-five (37.4%) patients had received ACT and 92 (62.6%) had not (non-ACT). Patients with ACT were younger ($p < 0.001$), had larger tumors ($p < 0.001$) and more lymphovascular invasion ($p = 0.02$), and seemed to have less distant recurrence ($p = 0.001$). After PSM, 110 patients were matched and baseline characteristics were balanced. ACT was not associated with improved disease-free survival (DFS) after matching (mDFS = 23.5 m for ACT vs. 29.5 m for non-ACT, $p = 0.13$). ACT failed to prolong DFS of patients in the extracranial recurrence subgroup and *EGFR* mutation subgroups, and was even associated with shorter DFS in intracranial relapsed patients (mDFS = 30.3 m vs. 33.5 m, $p = 0.083$) and patients with tumor ≤30 mm (mDFS = 21.9 m vs. 30.8 m, $p = 0.076$).

Conclusion: In patients who were destined to develop recurrence after completely resected stage IB LUAD, ACT might not be associated with improved DFS. Further large multicenter studies are warranted to validate these findings.

KEYWORDS
adjuvant chemotherapy, disease recurrence, lung adenocarcinoma, propensity-score matching

INTRODUCTION

Lung cancer has the highest cancer-related mortality in China and around the world.[1,2] Surgery remains the main treatment for early-stage lung adenocarcinoma (LUAD).[3,4] The overall prognosis for pathologically diagnosed stage IB LUAD is promising, but disease recurrence is still the main cause of treatment failure, causing up to 30% of patients to fail to survive over 5 years after complete resection.[3] In addition, the incidence of newly diagnosed stage IB LUAD has been increasing in developed countries mainly due to improved lung nodules detection and evaluation.[4] Thus, the prevention of disease relapse remains an important and increasingly challenged task for stage IB LUAD patients after curative resection.

Adjuvant chemotherapy (ACT) has been proved to be effective in improving survival among completely resected

patients.[5–8] However, comparing to patients with pathologically positive lymph nodes, stage IB patients seemed to have attenuated benefit from ACT,[9] which still remains controversial.[10–13] Although some subgroup analysis has shown that several high-risk factors (i.e., tumor differentiation) might indicate more benefit from ACT,[10,14–16] the importance of these factors has not been well verified across studies and thus their definitive role in clinical decision is limited. Currently, use of ACT is an option for stage IB patients with negative prognostic factors such as lumphovascular invasion, but there is lack of evidence stating the absolute benefit from ACT.

To answer the question of whether ACT could prolong disease-free survival (DFS) for stage IB patients required a randomized controlled trial (RCT) to be carried out, but because of the relative small probability of recurrence and the lack of explicit risk factors this was difficult. Previous observational studies had enrolled patients who had undergone complete resection and recorded if ACT had impacted their disease recurrence. The analysis method complied with the temporal logic, but because some patients might relapse after the last follow-up date, the results may have shown bias.[17] In addition, the majority of patients who did not relapse might "dilute" the impact of treatment on those who were destined to relapse (patients of interest). We assumed that ACT should benefit those who are destined to relapse if it can prevent relapse in stage IB patients. In this study, we therefore focused on a cohort of patients who had already relapsed after curative resection of pathological stage IB LUAD.

We reviewed the medical records of 1399 patients with pathologically diagnosed stage IB (American Joint Committee on Cancer [AJCC] 7th edition) LUAD from 2012 to 2017 in our institution and found 147 patients with recurrence after curative surgery. Recurrence patterns and patient baseline characteristics were demonstrated. The difference in DFS was compared between patients with and without ACT. Given that physicians' decisions on whether or not to implement chemotherapy treatment might be correlated with some high-risk factors such as age and low tumor differentiation, propensity-score matching (PSM) was used to balance these confounding factors. The purpose of this study was to further demonstrate the role of ACT at the physician's discretion in patients with completely resected stage IB disease by examining 147 relapsed patients.

METHODS

Patients enrollment and treatment

The medical records of 1399 patients with pathological stage IB (T2aN0M0) LUAD who underwent complete resection from 2012 to 2017 in our institution were retrospectively reviewed. Pathological staging was based on the AJCC 7th edition staging criteria.[18] Monitoring for recurrence after surgery was a clinical routine in our hospital, where a chest and abdominal computed tomography (CT) scan was performed on patients every 3–6 months within 2 years after surgery and brain imaging was performed every 6–12 months, or when patients developed neurological symptoms or extracranial lesions. The inclusion criteria were patients with recorded recurrence either from documented medical records or routine imaging. The exclusion criteria were indeterminate tumor stage, pathologically mixed adenocarcinoma, inadequate follow-up information, and suspicion of secondary metachronous tumor. The use of ACT was decided in a doctor–patient codetermination way, considering the physician's advice and the patient's wish. Platinum-based doublet chemotherapy was the most common regimen applied in the adjuvant setting.

This study was approved by the Ethics Committee of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College in accordance with the Declaration of Helsinki protocol. Written informed consent was waived because this was a retrospective study and neither the implementation nor the outcome of this study would do harm to the patients involved in it.

Follow-up information

For 147 patients who met the study criteria, the site of initial relapse was recorded. DFS was calculated for each individual as the time between the date of curative resection and the date of disease recurrence. According to the multipeak recurrence pattern revealed by published research,[19] we set the shortest follow-up time after surgery as 4 years. The last follow-up date was December 30, 2021. Clinical and pathological information was also retrospectively collected, including sex, age at surgery, smoking history, histologic subtypes, tumor differentiation, micropapillary status, pleural invasion status, and lymphovascular invasion. *EGFR* and

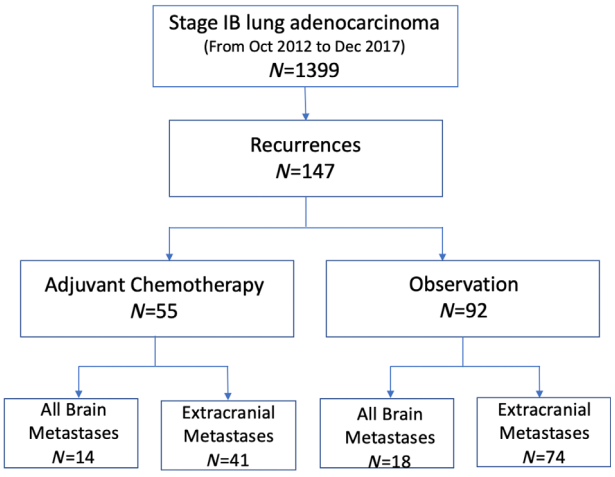

FIGURE 1 Flowchart for this study

KRAS mutations were tested by PCR on tumor tissue, and *ALK* fusions were tested by immunohistochemistry on tumor tissue, which was recorded in the medical records.

Statistical analysis

Patients were divided into two groups: ACT and non-ACT. Baseline characteristics were compared between the groups: Student's *t*-test for continuous variables and Pearson's χ^2 test for categorical variables. The Kaplan–Meier analysis was used to generate the survival curves and the log-rank test was used to compare the differences among the curves. Univariate and multivariate Cox regression models were used to identify independent factors of relapse. PSM was applied to reduce the potential selection bias, with the following covariates used for matching: age, tumor size, differentiation, micropapillary status, visceral pleural invasion, and lymphovascular invasion. The probability of undergoing ACT for each patient was obtained from a logistic regression model. Patients in the ACT group were matched with patients in the non-ACT group using the nearest-neighbor one-to-one matching method from the MatchIt package.[20] A p value <0.05 was considered statistically significant and all statistical tests were two-sided. All statistical analyses were conducted using R software (version 4.0.3 for Mac).

TABLE 1 Characteristics of 147 stage IB recurrence patients

	N	(%)
Age at surgery (years)	61	
Sex		
Male	70	47.6
Female	77	52.4
Smoking history		
Never	91	61.9
Smoker	56	38.1
Location		
Right	79	53.7
Left	68	46.3
Pathology		
Tumor size (mm)	30	
Tumor differentiation		
Low	57	38.8
Medium/high	90	61.2
Subtype		
Acinar	91	61.9
Papillary	25	17.0
Solid	16	10.9
Mucinous	2	1.4
Lepidic	1	0.6
Not assured	12	8.2
Micropapillary	48	32.7
Visceral pleural invasion	132	89.8
Lymphovascular invasion	20	13.6
Driver gene mutation		
EGFR	94	63.9
KRAS	12	8.1
ALK	2	1.4
Uncommon gene	3	2.0
Wild type	18	12.3
Unknown	18	12.3
Adjuvant chemotherapy		
Yes	55	37.4
No	92	62.6

RESULTS

Characteristics of 147 patients with disease recurrence

A total of 147 patients with recurrence were included in this study. Fifty-five (37.4%) patients received ACT and 92 (62.6%) did not (non-ACT group). Thirty-two (21.8%) patients had intracranial recurrence, 14 (25.5%) in the ACT group and 18 (19.6%) in the non-ACT group, while 115 patients only had extracranial metastases. A flowchart of the study is shown in Figure 1. For relapsed patients, baseline clinical and pathological features are illustrated in Table 1. The median age at surgery was 61. There were slightly more females (52.4%) than males. The majority of patients were never-smokers (61.9%). Tumors had slightly higher right-sided location (53.7%). The pathological features are described in Table 1, including tumor size, tumor differentiation, subtype of adenocarcinoma, and the status of the micropapillary, visceral pleural invasion, and lymphovascular invasion. Overall, 63.9% of patients had *EGFR* mutations, while *KRAS* mutations and *ALK* fusions existed in 8.1% and 1.4% of patients.

Recurrence pattern at initial relapse

The pattern of recurrence and initial recurrence sites is shown in Table 2. The pattern of recurrence included local recurrences only in 12 (8.2%) patients, distant recurrences only in 124 (84.3%) patients, and both local and distant recurrences in 11 (7.5%) patients. Most patients with recurrence had distant metastases. The organs most commonly involved at initial relapse were the lungs ($n = 69$, 46.9%), followed by the brain ($n = 32$, 21.8%) and the pleura ($n = 32$, 21.8%). Patients who had undergone ACT seemed to have less distant recurrence (72.7% vs. 91.3%, $p = 0.001$) but more intracranial relapse (25.5% vs. 19.6%, $p = 0.528$).

TABLE 2 Pattern of recurrence and initial recurrence sites in patients with or without adjuvant chemotherapy

	With adjuvant chemotherapy	Without adjuvant chemotherapy	Total	(%)	*p* value
Total number	55	92	147	100	
Pattern of recurrence					0.001[a]
Local-regional	10	2	12	8.2	
Solitary	4	0	4	2.7	
Multiple	6	2	8	5.5	
Distant only	40	84	124	84.3	
Solitary	12	18	30	20.4	
Multiple	28	66	94	63.9	
Both local-regional and distant	3	6	11	7.5	
Initial recurrence site					0.528[b]
CNS	14	18	32	21.8	
Brain only	9	11	20	13.6	
Brain & extracranial	5	7	12	8.2	
CNS-free	41	74	115	78.2	
Lung	21	48	69	46.9	
Lymph node	11	8	19	12.8	
Pleural seeding/effusion	7	25	32	21.8	
Bone	9	16	25	17.0	
Liver	2	4	6	4.1	
Adrenal gland	0	1	1	0.6	

Abbreviation: CNS, central nervous system.
[a]Fisher's exact test was used to compare differences of pattern of recurrence (local-regional, distant only and both local-regional and distant) between groups.
[b]Pearson's chi-squared test was used to compare differences of initial recurrence site (CNS and CNS-free) between groups.

TABLE 3 Univariate and multivariate Cox regression model analysis of recurrence-free survival

	Univariate		Multivariate	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age at surgery (<65 vs. ≥65 years)	0.96 (0.67–1.40)	0.81		
Sex (female vs. male)	0.70 (0.50–0.97)	0.03	0.73 (0.44–1.23)	0.24
Smoking history (ever-smoker vs. never)	1.40 (0.97–1.90)	0.08	1.10 (0.65–1.87)	0.72
Pathology				
Tumor size (mm)	1.00 (0.99–1.00)	0.34		
Differentiation (medium/high vs. low)	0.77 (0.55–1.10)	0.13		
Micropapillary	1.00 (0.71–1.40)	0.96		
Visceral pleural invasion	0.85 (0.50–1.50)	0.55		
Lymphovascular invasion	1.50 (0.93–2.40)	0.10	1.37 (0.83–2.26)	0.22
Adjuvant chemotherapy	1.30 (0.97–1.80)	0.03	1.42 (1.00–2.01)	0.05
Driver gene mutation	1.00 (0.60–1.64)	0.99		
EGFR mutation	1.00 (0.69–1.50)	0.93		

Abbreviation: CI, confidence interval.

Survival analyses

The results of the univariable and multivariable Cox regression models for patients are summarized in Table 3. In multivariable analysis, ACT was the only independent prognostic factor for DFS. Patients who had undergone ACT had shorter DFS (HR = 1.42 [95% CI 1.00–2.01], $p = 0.05$). Before PSM, patients treated with ACT had shorter DFS than those in the non-ACT group (mDFS = 23.5 m vs. 30.3 m, $p = 0.032$) (Figure 2a).

PSM was applied to balance confounding covariates between the two groups. Detailed distribution of patients in

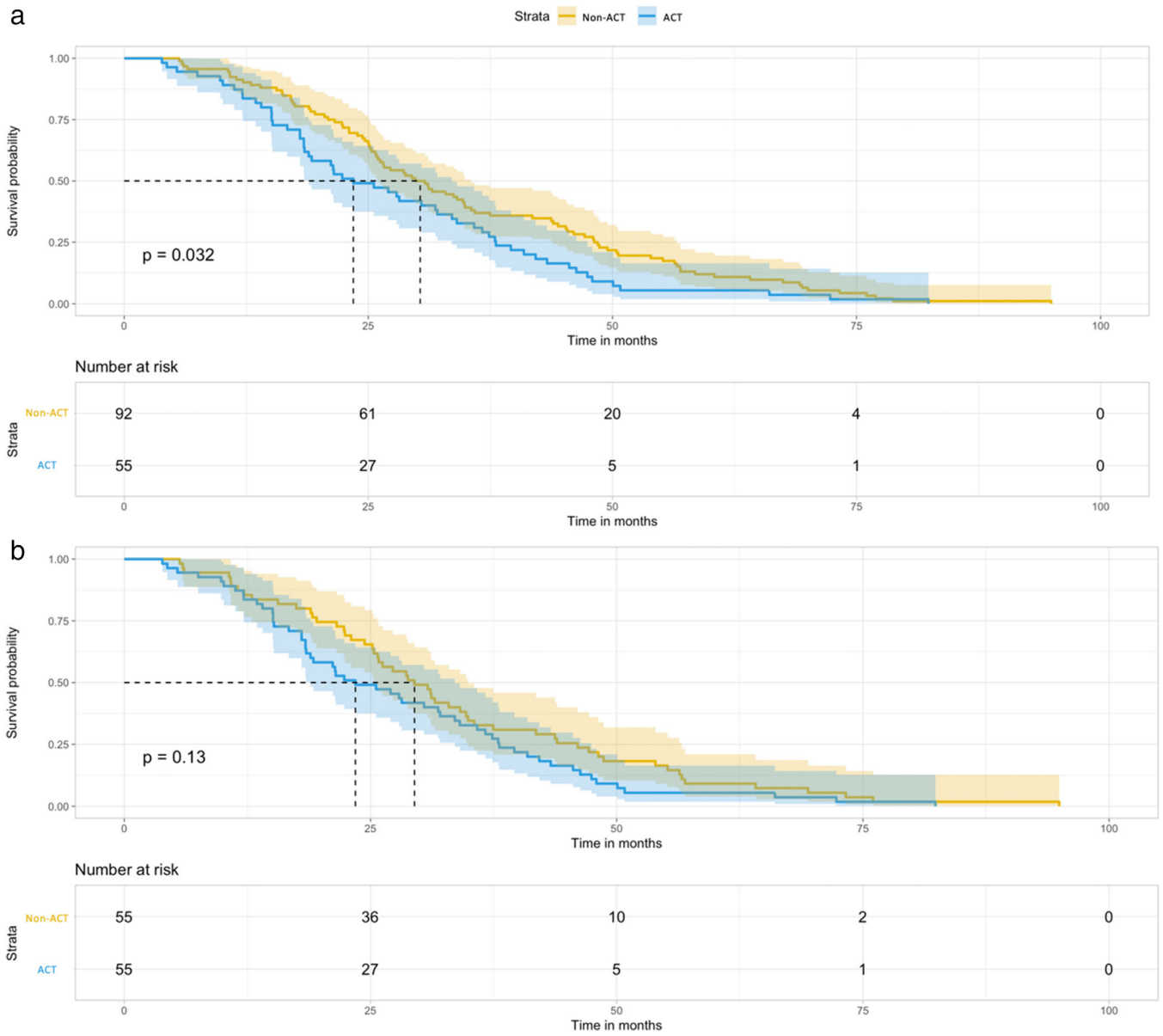

FIGURE 2 The Kaplan–Meier survival curves of disease-free survival for patients with adjuvant chemotherapy (ACT) or not (non-ACT) before (a) and after (b) propensity-score matching

both groups before PSM and after PSM were demonstrated in Table 4. After matching, ACT still showed no improvement of DFS compared to non-ACT (mDFS = 23.5 m vs. 29.5 m, $p = 0.13$) (Figure 2b). Subgroup analysis concerning driver mutation status and recurrence site was also done in the matched population (Figure 3). ACT did not prolong the DFS in patients with or without EGFR mutations (mDFS, 23.5 m vs. 30.1 m, $p = 0.32$ and 32.7 m vs. 24.9 m, $p = 0.37$, respectively), or in patients with extracranial recurrence (mDFS = 22.3 m vs. 26.2 m, $p = 0.54$). For patients with intracranial recurrence, ACT was associated with worse DFS (mDFS = 30.3 m vs. 33.5 m, $p = 0.083$). Since tumors smaller than 30 mm are classified as stage IB only when visceral pleural invasion exists, subgroup analysis of chemotherapy was also done on tumor size. For tumors ≤30 mm, ACT was associated with shorter DFS (mDFS = 21.9 m vs. 30.8 m, $p = 0.076$), and for tumors >30 mm, ACT showed no improvement of DFS (mDFS = 27.0 m vs. 29.1 m, $p = 0.63$).

DISCUSSION

This study reviewed a cohort of 147 stage IB LUAD patients with recurrence after curative surgery with the intention of answering the question of whether ACT could prolong DFS for patients. First, we determined the characteristics and recurrence patterns of the relapsed patients. In this cohort, 21.8% of patients had intracranial metastases, 63.9% had *EGFR* mutations, and 37.4% had received ACT. The

TABLE 4 Characteristics of patients receiving adjuvant chemotherapy or not before and after PSM

Characteristic	Before PSM			After PSM		
	With adjuvant chemotherapy ($N = 55$)	Without adjuvant chemotherapy ($N = 92$)	p value	With adjuvant chemotherapy ($N = 55$)	Without adjuvant chemotherapy ($N = 55$)	p value
Age (years)	56.0 ± 9.3	61.4 ± 8.3	**<0.001***	56.0 ± 9.3	58.8 ± 8.3	0.10
Sex			0.45			0.44
Male	24 (43.6)	46 (50.0)		24 (43.6)	28 (50.9)	
Female	31 (56.4)	46 (50.0)		31 (56.4)	27 (49.1)	
Tumor size (mm)	32.1 ± 9.7	26.5 ± 9.2	**<0.001***	32.1 ± 9.7	30.2 ± 8.3	0.26
Differentiation			0.10			0.34
Low	26 (47.3)	31 (33.7)		26 (47.3)	21 (38.2)	
Medium/high	29 (52.7)	61 (66.3)		29 (52.7)	34 (61.8)	
Micropapillary			0.71			0.54
No	36 (65.5)	63 (68.5)		36 (65.5)	39 (70.9)	
Yes	19 (34.5)	29 (31.5)		19 (34.5)	16 (29.1)	
Visceral pleural Invasion			0.83			0.40
No	6 (10.9)	9 (9.8)		6 (10.9)	9 (16.4)	
Yes	49 (89.1)	83 (90.2)		49 (89.1)	46 (83.6)	
Lymphovascular Invasion			**0.02***			0.12
No	43 (78.2)	84 (91.3)		43 (78.2)	49 (89.1)	
Yes	12 (21.8)	8 (8.7)		12 (21.8)	6 (10.9)	
EGFR status			0.53			0.20
Wild type	14 (30.4)	21 (25.3)		14 (30.4)	10 (18.2)	
Mutated	32 (69.6)	62 (74.7)		32 (69.6)	42 (81.8)	

Note: Continuous variables are reported as mean ± standard deviation. Dichotomous variables are reported as number (%). Bold indicates significant values ($p < 0.05$).
Abbreviation: PSM, propensity-score matching.

majority of patients developed distant metastases and 8.2% had local recurrences only. The organs most commonly involved at initial relapse were the lungs, followed by the brain and the pleura. We then explored the role of ACT at the physician's discretion in patients. Since the physician's decision on ACT might be affected by high-risk factors, PSM was used to balance these confounding factors when comparing DFS between the ACT and non-ACT groups. After matching, we found ACT did not result in an improvement in DFS in this cohort. Subgroup analysis also showed that the ACT group had worse DFS for brain metastases patients and for tumor smaller than 30 mm, while ACT did not improve DFS in extracranial metastases patients, in patients with or without *EGFR* sensitive mutations, and in patients with tumors larger than 30 mm.

The relapsed patients might have unique tumor biology different from those without relapse, according to our previous findings.[21,22] Based on their distinct tumor biology, we supposed that the destined-to-relapse patients should be the population whose benefit from adjuvant therapy should be investigated. However, the negative role of ACT in our study suggested that ACT might not prolong and may even reduce DFS among stage IB patients who were destined to have disease recurrence. This has also been seen in early-stage breast cancer,[23] where high-risk factors such as HER2 overexpression did not predict benefit from ACT. One presumed mechanism was that relapsed stage IB patients might have initiated metastases cascade relatively early, before the cancer cells evade into lymph nodes. This could happen in 10–15% of cases.[24] Compared to tumor cells evading into lymph nodes, those circulating in the peripheral blood might encounter a more challenging microenvironment[25] and undergo transition into dormancy,[26] which would explain the insensitivity of ACT in this scenario.

The lack of effectiveness of ACT for completely resected stage IB LUAD patients was also revealed by previous studies.[9,27] This study contributes another perspective, that is, when examining stage IB patients who were destined to relapse, ACT at physician's discretion might not result in survival benefit for these population. Our study therefore has two clinical implications. On the one hand, it is suggested that up-to-date minimal residual disease (MRD) monitoring by circulating tumor DNA (ctDNA) technology should be used for stage IB patients to facilitate clinical decisions on ACT.[28] Bench-to-bedside research remains to be conducted on investigating distinct biological markers and

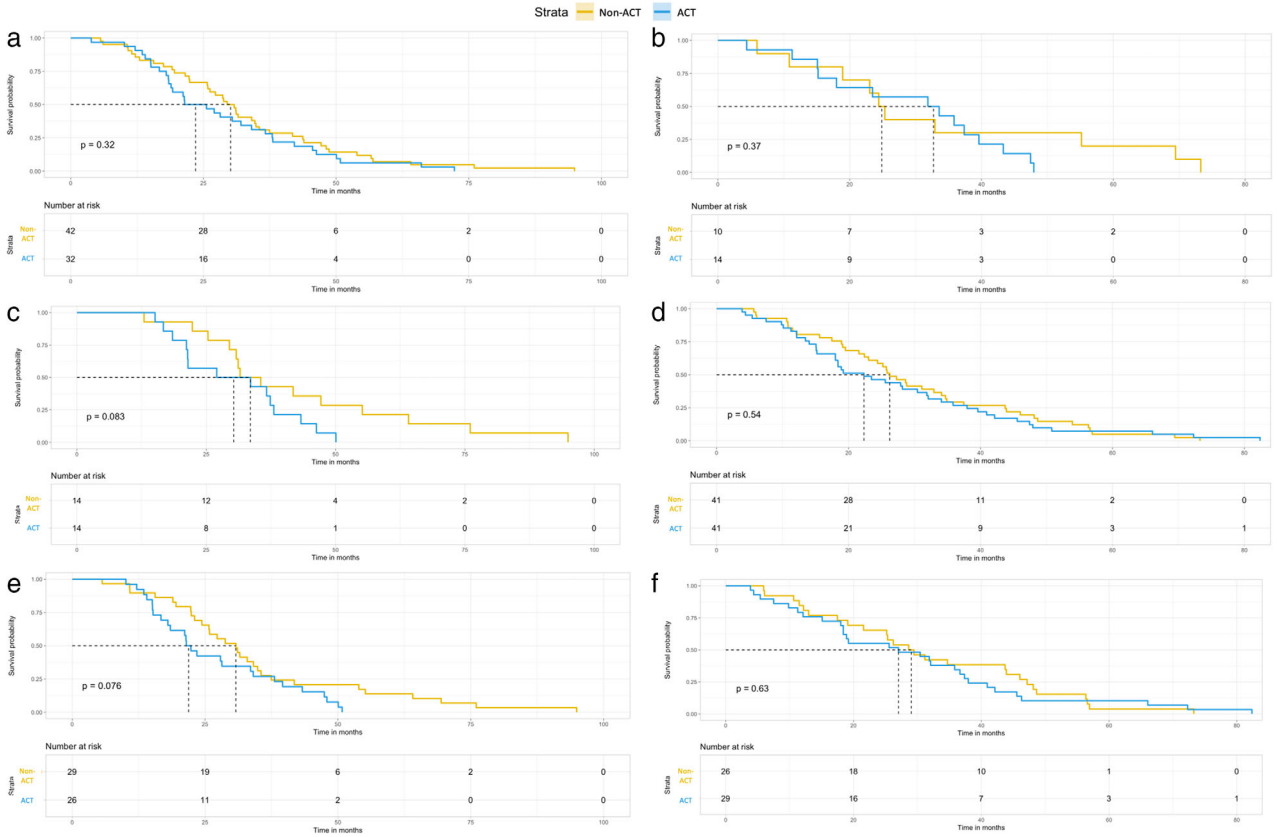

FIGURE 3 Subgroup analysis in matched patients: Kaplan–Meier survival curves of disease-free survival for ACT and non-ACT patients with (a) or without (b) *EGFR* mutations, with intracranial recurrence (c) or extracranial recurrence (d), and with tumors ≤30 mm (e) and >30 mm (f)

mechanisms behind the relapsed early-stage lung cancer population. On the other hand, adjuvant targeted therapy[29] and immunotherapy[30] have been investigated for stage IB-IIIA patients, but whether or not to use ACT was not clarified. However, a recent editorial article argued that the ACT might not be used for *EGFR*-mutated patients if 3-year osimertinib is adopted as the adjuvant regimen,[31] based on a follow-up report on chemotherapy use in the ADAURA trial.[32] In that study, the 2-year DFS rate was lower in patients receiving ACT in both the osimertinib group (81% vs. 90%) and the placebo group (66% vs. 74%). Our study endorses this opinion, that ACT might not bring benefit for stage IB patients, in a cohort of deemed-to-relapse patients after curative surgery. However, prospective clinical trials are warranted to draw the final conclusion.

There are limitations to this study. First, there could be selective bias because this study was a retrospective study and some relapsed patients might not be treated at our hospital. Second, the number of patients included in the PSM was relatively small, so there is a possibility that the matched population did not represent the whole cohort. The strength of this study was that we analyzed a cohort of 147 recurrences in completely resected stage IB LUAD, which has not previously been investigated. We hope this result will add to the knowledge of this area.

CONCLUSION

In patients who were destined to relapse after completely resected stage IB LUAD, ACT might not be associated with improved DFS. Further large multicenter studies are warranted to confirm this.

FUNDING STATEMENT
None.

AUTHOR CONTRIBUTIONS
F.X. drafted the manuscript and carried out acquisition and analysis of data. H.C., H.X., J.L., X.H., and P.X. carried out acquisition and interpretation of data. Y.W. and Y.J.M. designed the study and Y.W. revised it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Not applicable.

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data, models, or code generated or used during the study are available from the corresponding author on reasonable request.

ETHICS APPROVAL

This study was approved by the Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College in accordance to the Declaration of Helsinki protocol. Written informed consent was waived because this was a retrospective study and neither the implementation nor the outcome of this study would do harm to the patients involved in it.

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REFERENCES

1. Zhang S, Sun K, Zheng R, et al. Cancer incidence and mortality in China. J Natl Cancer Center. 2021;1(1):2–11.
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49.
3. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WEE, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. J Thorac Oncol. 2016;11:39–51.
4. Ganti AK, Klein AB, Cotarla I, Seal B, Chou E. Update of incidence, prevalence, survival, and initial treatment in patients with non-small cell lung cancer in the US. JAMA Oncol. 2021;7:1824–32.
5. Arriagada R, Bergman B, Dunant A, le Chevalier T, Pignon JP, Vansteenkiste J, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med. 2004;350:351–60.
6. Waller D, Peake MD, Stephens RJ, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the big lung trial. Eur J Cardiothorac Surg. 2004;26:173–82.
7. Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med. 2005;352:2589–97.
8. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol. 2006;7:719–27.
9. Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the cancer and leukemia group B, radiation therapy oncology group, and north central cancer treatment group study groups. J Clin Oncol. 2008;26:5043–51.
10. Park SY, Lee JG, Kim J, Byun GE, Bae MK, Lee CY, et al. Efficacy of platinum-based adjuvant chemotherapy in T2aN0 stage IB non-small cell lung cancer. J Cardiothorac Surg. 2013;8:151.
11. Morgensztern D, Du L, Waqar SN, et al. Adjuvant chemotherapy for patients with T2N0M0 NSCLC. J Thorac Oncol. 2016;11:1729–35.
12. Arora RK, Gibson AW, Bebb DG, Cheung WY. The population-based impact of adjuvant chemotherapy on outcomes in T2N0M0 non-small cell lung cancer. Am J Clin Oncol. 2020;43:496–503.
13. Xu Y, Wan B, Zhu S, Zhang T, Xie J, Liu H, et al. Effect of adjuvant chemotherapy on survival of patients with 8th edition stage IB non-small cell lung cancer. Front Oncol. 2021;11:784289.
14. Pathak R, Goldberg SB, Canavan M, Herrin J, Hoag JR, Salazar MC, et al. Association of survival with adjuvant chemotherapy among patients with early-stage non-small cell lung cancer with vs without high-risk clinicopathologic features. JAMA Oncol. 2020;6:1741–50.
15. Vaidya P, Bera K, Gupta A, Wang X, Corredor G, Fu P, et al. CT derived radiomic score for predicting the added benefit of adjuvant chemotherapy following surgery in stage I, II resectable non-small cell lung cancer: a retrospective multicohort study for outcome prediction. Lancet Digit Health. 2020;2:e116–e28.
16. Zhang Z, Xie S, Cai W, Hong ZN, Yang C, Lin Y, et al. A nomogram to predict the recurrence-free survival and analyze the utility of chemotherapy in stage IB non-small cell lung cancer. Transl Lung Cancer Res. 2022;11:75–86.
17. Othus M, Bansal A, Erba H, Ramsey S. Bias in mean survival from fitting cure models with limited follow-up. Value Health. 2020;23:1034–9.
18. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol. 2007;2:706–14.
19. Demicheli R, Fornili M, Ambrogi F, Higgins K, Boyd JA, Biganzoli E, et al. Recurrence dynamics for non-small-cell lung cancer: effect of surgery on the development of metastases. J Thorac Oncol. 2012;7:723–30.
20. Ho D, Imai K, King G, et al. MatchIt: nonparametric preprocessing for parametric causal inference. J Stat Softw. 2011;42:1–28.
21. Yang L, Zhang J, Yang G, Xu H, Lin J, Shao L, et al. The prognostic value of a methylome-based malignancy density scoring system to predict recurrence risk in early-stage lung adenocarcinoma. Theranostics. 2020;10:7635–44.
22. Yang L, Zhang J, Song Y, Yang G, Xu H, Li J, et al. Genomic profile and immune microenvironment in patients with relapsed stage IA lung adenocarcinoma. Transl Oncol. 2021;14:100942.
23. Cao L, Towe CW, Shenk R, Stabellini N, Amin AL, Montero AJ. A comparison of local therapy alone with local plus systemic therapy for stage I pT1aN0M0 HER2+ breast cancer: a National Cancer Database analysis. Cancer. 2022;128:2433–40.
24. Leong SP, Tseng WW. Micrometastatic cancer cells in lymph nodes, bone marrow, and blood: clinical significance and biologic implications. CA Cancer J Clin. 2014;64:195–206.
25. Ubellacker JM, Tasdogan A, Ramesh V, Shen B, Mitchell EC, Martin-Sandoval MS, et al. Lymph protects metastasizing melanoma cells from ferroptosis. Nature. 2020;585:113–8.
26. Baumann Z, Auf der Maur P, Bentires-Alj M. Feed-forward loops between metastatic cancer cells and their microenvironment-the stage of escalation. EMBO Mol Med. 2022;14:e14283.
27. Li X, Zhang C, Sun Z, Yang F, Xiao R, Sui X, et al. Propensity-matched analysis of adjuvant chemotherapy for completely resected stage IB non-small-cell lung cancer patients. Lung Cancer. 2019;133:75–82.
28. Zhang JT, Liu SY, Gao W, Liu SYM, Yan HH, Ji L, et al. Longitudinal undetectable molecular residual disease defines potentially cured population in localized non-small cell lung cancer. Cancer Discovery. 2022;12:1690–701.
29. Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med. 2020;383:1711–23.
30. Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer

(IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet. 2021;398:1344–57.

31. Zhang SS, Ou SI. Deconstructing ADAURA: it is time to forgo adjuvant platinum-based chemotherapy in resected IB-IIIA EGFR+ NSCLC (except with RB alterations?) when adopting adjuvant Osimertinib. Lung Cancer. 2022;13:23–31.
32. Wu YL, John T, Grohe C, Majem M, Goldman JW, Kim SW, et al. Postoperative chemotherapy use and outcomes from ADAURA: Osimertinib as adjuvant therapy for resected EGFR-mutated NSCLC. J Thorac Oncol. 2022;17:423–33.

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