ORIGINAL ARTICLE

Value of adjuvant chemotherapy in patients with resected stage IB solid predominant and solid non-predominant lung adenocarcinoma

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Abstract

Background: The use of adjuvant chemotherapy (ACT) for stage IB lung adenocarcinoma remains controversial. We examined the benefits of ACT in stage IB patients with tumors composed of solid material.

Methods: The records of 309 patients with stage IB lung adenocarcinoma who had undergone complete resection between 2006 and 2015 were reviewed. All pathological slides were evaluated for the composition of solid material.

Results: Our data showed that although disease-free survival (DFS) and overall survival (OS) were not significantly different ($P = 0.306$ and $P = 0.061$, respectively) between patients displaying a solid pattern of tumor growth and treated with or without ACT, patients with a solid predominant pattern of tumor growth treated with ACT had longer DFS (hazard ratio 0.359; $P = 0.033$) and OS (hazard ratio 0.205; $P = 0.003$). In patients with solid non-predominant patterns, treatment with ACT had no effect on DFS ($P = 0.326$) or OS ($P = 0.508$).

Conclusions: Postoperative patients with the solid predominant pattern of stage IB lung adenocarcinoma may benefit from ACT, while those with the solid non-predominant pattern will not.

Introduction

Lung cancer is one of the most threatening diseases in the world.[1] Adenocarcinoma is the most common histological type of lung cancer and incidence continues to increase worldwide. Surgery is recommended by the National Comprehensive Cancer Network (NCCN) for early-stage patients and is an effective treatment in approximately 20% of lung cancer cases. Unfortunately, the long-term survival of patients with early-stage lung cancer is poor. The five-year survival rates of stage I and IB patients who receive surgical treatment alone are 50–70% and 60%, respectively.[2] Postoperative recurrence, the main factor for poor prognosis after surgery, can be controlled by adjuvant chemotherapy (ACT) in patients with resected stage II and IIIA non-small cell lung cancer (NSCLC). However, whether ACT improves prognosis in stage IB patients remains inconclusive.[3–7] The results of the ANITA randomized controlled trial presented no significant survival benefit for stage IB patients.[5] According to CALGB 9633, ACT showed a significant survival

advantage for stage IB patients with tumors ≥ 4 cm.[6] In the JBR-10 trial, stage IB patients with tumors ≥ 4 cm also derived clinical benefit from ACT.[7] The 2017 NCCN guidelines (9th version) recommend ACT for postoperative stage IB patients with risk factors including tumor size > 4 cm, visceral pleural invasion, lymph-vascular invasion, poor tumor differentiation, wedge resection, and incomplete lymph node sampling; however, this proposal lacks high-level evidence and consensus.[8]

Based on the recommendations of the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society (IASLC/ATS/ERS) published in 2011, the World Health Organization (WHO) updated the pathological classification of lung tumors in 2015 and reclassified lung adenocarcinoma, dividing mixed adenocarcinoma into several subtypes including lepidic, papillary, acinar, micropapillary, and solid tumors.[8,9] As several studies have reported, these subtypes show varying degrees of association with recurrence and death, but a number of studies have established that solid growth patterns are associated with poor survival.[10–17]

Therefore, we focused on stage IB patients and examined whether ACT improved prognosis in cases of solid predominant adenocarcinoma (pathologically diagnosed as solid adenocarcinoma) compared to solid non-predominant adenocarcinoma (diagnosed as other histological subtypes but composed of solid material).

Methods

Patients

The Shanghai Chest Hospital institutional review board approved this retrospective study. A total of 309 newly diagnosed, histologically confirmed cases of solid composition adenocarcinoma were enrolled from 1 December 2006 to 31 December 2015 at the Shanghai Chest Hospital (Shanghai, China). Medical data and tissue specimens of all patients were anonymized before analysis. None of the patients had received preoperative chemotherapy or radiotherapy. Patients were personally interviewed to collect demographic data including age, gender, and smoking status. Clinical and follow-up information was obtained from medical records. A non-smoker was defined as a person who had smoked < 100 cigarettes in his or her entire lifetime. Performance status was determined based on the Eastern Cooperative Oncology Group scale prior to treatment. The follow-up date was calculated from the date of surgery. All patients underwent routine preoperative examinations including chest computed tomography (CT), abdominal enhanced CT or abdominal B ultrasound, cranial enhancement magnetic resonance imaging, and bone scan.

Histopathologic assessment

Surgical specimens were fixed in formalin, dehydrated and embedded in paraffin, sectioned at a thickness of 5 μm, and then stained with hematoxylin and eosin. Histopathological analysis of each specimen was conducted by an experienced lung pathologist and validated by another senior lung pathological diagnostician. Histological growth patterns, including lepidic, acinar, papillary, micropapillary, or solid growth patterns, were identified in 5% increments, and in accordance with the 2015 WHO classification of lung adenocarcinoma. The predominant histological subtype was determined by the pattern with the highest percentage. Patients with a solid component > 5% of the predominant subtype were classified with solid predominant adenocarcinoma, while those with a solid component > 5% without a predominant pattern were classified with solid non-predominant adenocarcinoma. All tumors were confirmed as invasive and the size of the tumors was recorded.

Tumor node metastasis (TNM) staging was performed according to the eighth edition of the American Joint Committee on Cancer/Union for International Cancer Control TNM classification based on surgical resection specimens and pathological findings.[18]

Table 1 Patient characteristics by treatment

Characteristic	Adjuvant chemotherapy (*n* = 193)	Surgical intervention alone (*n* = 116)	*P*
Age			
≥ 60	78 (40.4%)	73 (62.9%)	
< 60	115 (59.5%)	43 (37.1%)	< 0.001
Gender			
Male	127 (65.8%)	72 (62.1%)	
Female	66 (34.2%)	44 (37.9%)	0.507
Smoking history			
Never	111 (57.5%)	80 (69.0%)	
Ever	82 (42.5%)	36 (31.0%)	0.166
Tumor size			
≤ 2	39 (20.2%)	32 (27.6%)	
> 2	154 (79.8%)	84 (72.4%)	0.135
Pleural invasion			
Absent	40 (20.7%)	25 (21.6%)	
Present	153 (79.3%)	91 (78.4%)	0.863
Lymph vascular invasion			
Absent	179 (92.7%)	108 (93.1%)	
Present	14 (7.2%)	8 (6.9%)	0.906
Surgical procedure			
Lobectomy	190 (98.4%)	114 (98.3%)	
Non-lobectomy	3 (1.6%)	2 (1.7%)	0.909
Recurrence			
No	136 (70.5%)	76 (65.5%)	
Yes	57 (29.5%)	40 (34.6%)	0.546

Table 2 Multivariate survival analysis of DFS and OS in the entire patient cohort

	DFS		OS	
Characteristics	HR (95% CI)	*P*	HR (95% CI)	*P*
Age				
≥ 60	1		1	
< 60	0.802 (0.506–1.271)	0.348	1.438(0.793–2.607)	0.180
Gender				
Male	1		1	
Female	0.916 (0.536–1.566)	0.749	1.050 (0.503–2.783)	0.896
Smoking history				
Never	1		1	
Ever	0.724 (0.416–1.292)	0.255	1.210 (0.593–2.471)	0.600
Tumor size				
≤ 2	1		1	
> 2	1.056 (0.564–1.976)	0.865	1.187 (0.482–2.921)	0.709
Pleural invasion				
Absent	1		1	
Present	0.983 (0.581–1.662)	0.948	0.976 (0.496–1.922)	0.945
Lymph vascular invasion				
Absent	1		1	
Present	0.986(0.449–2.167)	0.972	1.121 (0.438–2.896)	0.811
Surgical procedure				
Lobectomy	1		1	
Non-lobectomy	0.766(0.489–1.199)	0.485	1.438(0.793–2.607)	0.296
Adjuvant chemotherapy				
No	1		1	
Yes	0.771(0.469–1.268)	0.306	0.565(0.310–1.207)	0.061

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

Statistical analyses

The primary endpoint, disease-free survival (DFS), was defined as the time from surgery to the first recurrence or metastatic event; the secondary endpoint, overall survival (OS), was defined as the time from surgery to death. OS and DFS were obtained from the patient's clinical medical records or via telephone follow-up.

We used Kaplan–Meier survival curves to estimate DFS in patients who experienced recurrence.[19] The log-rank test (for univariate analysis) and Cox proportional hazards multivariate model (for multivariate analysis) were used to evaluate differences in DFS and OS between the two groups. Hazard ratios (HRs) and 95% confidence interval (CIs) were also calculated. Statistical significance was defined at $P < 0.05$. Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Patient characteristics are listed in Table 1. There were 309 patients in total, 199 men and 110 women. Fifty-one percent of the patients were aged < 60 years, the majority (62%) were non-smokers, 305 patients (99%) underwent lobectomy, and four underwent segmentectomy. Out of 309 patients, 193 (62.4%) received postoperative ACT. In addition to cisplatin/carboplatin, the platinum double-drug chemotherapy programs were: pemetrexed in 31 cases (16.1%), docetaxel in 4 cases (2.0%), vinorelbine in 89 cases (46.1%), gemcitabine in 37 cases (19.2%), and paclitaxel in 3 cases (1.6%) (Table S2). A total of 97 patients (31.3%) relapsed, while 212 patients (68.6%) had no recurrence during follow-up. None of the patients received adjuvant radiotherapy.

Among the 309 patients, 193 underwent ACT, while 116 received surgical intervention alone (Table S1). Table 1 shows that age was significantly associated with the administration of ACT ($P < 0.001$); while gender ($P = 0.507$), smoking history ($P = 0.166$), pleural invasion ($P = 0.863$), lymph vascular invasion ($P = 0.906$), and surgical procedure ($P = 0.909$) were not significantly associated with ACT.

Survival analysis

The patients had a median follow-up time of 41 months (7–98 months). Relapse occurred in 97 patients: within 12 months in 34 patients (35.1%), between 12 and
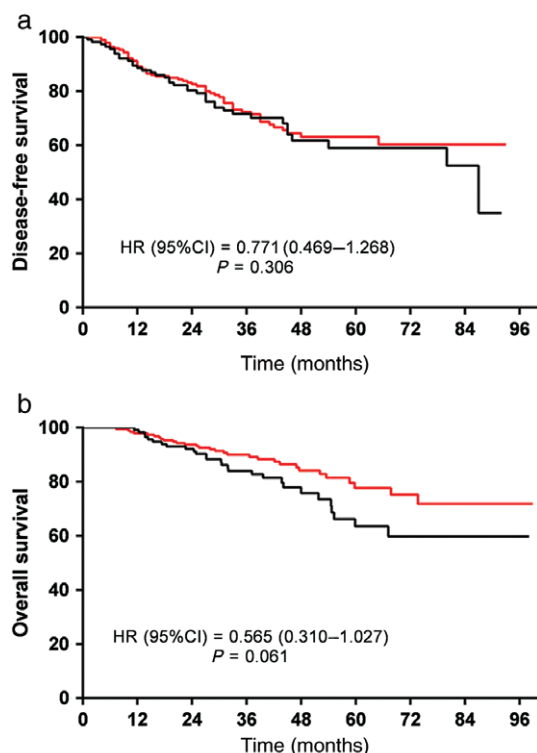
Figure 1 Survival curves of (**a**) disease-free and (**b**) overall survival of all 309 patients with or without adjuvant chemotherapy (ACT). (——) ACT (*n* = 193) and (——) without ACT (*n* = 116). CI, confidence interval; HR, hazard ratio.

Figure 2 Survival curves of (**a**) disease-free and (**b**) overall survival of solid predominant and solid non-predominant groups. (——) solid predominant (*n* = 125) and (——) solid non-predominant (*n* = 184). CI, confidence interval; HR, hazard ratio.

24 months in 23 patients (23.7%), and after 24 months in 40 patients (41.2%). The relapse locations were: the lungs in 26 patients (26.8%), the brain in 20 (20.6%), and bone in 13 patients (13.4%).

According to multivariate survival analysis, among all patients, age, gender, smoking history, tumor size, pleural invasion, lymph vascular invasion, and survival procedures had little influence on prognosis. Furthermore, there was no significant difference in DFS (*P* = 0.306) and OS (*P* = 0.661 between patients who received ACT and those who did not for stage IB lung adenocarcinoma (Table 2; Fig 1). There was no significant difference in DFS (*P* = 0.383) and OS (*P* = 0.147) between patients with the solid predominant pattern versus the non-predominant pattern (Fig 2).

Univariate analysis was performed to assess the effect of adjuvant treatment on DFS and OS in the solid predominant and solid non-predominant groups. Among all stage IB postoperative patients with solid predominant tumors, DFS (*P* = 0.033) and OS (*P* = 0.003) were significantly longer in the ACT group than in the group who received surgical intervention alone. However, analysis of the solid non-predominant pattern showed no significant difference in DFS (*P* = 0.326) or OS (*P* = 0.508) (Fig 3).
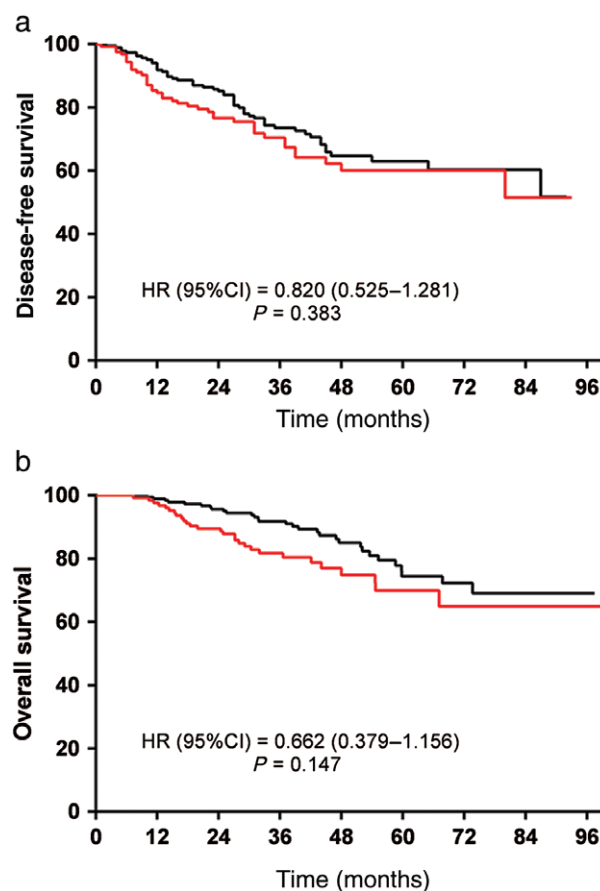
Finally, multivariate survival analysis indicated that patients with solid predominant tumors administered ACT had longer DFS (HR 0.359 [95% CI 0.159–0.809]; *P* = 0.013) and OS (HR 0.205 [95% CI 0.071–0.579]; *P* = 0.003) (Fig 3) than those who were not administered ACT.

Discussion

This study followed a cohort of 309 patients to investigate the benefit of ACT in completely resected stage IB lung adenocarcinoma with a solid growth pattern. Patients with the solid predominant subtype had longer survival after ACT. However, ACT did not predict a better outcome in patients with solid non-predominant lung adenocarcinoma.

Although ACT is the standard therapy for NSCLC in stage II–IIIA, the effect of ACT in stage IB NSCLC has not
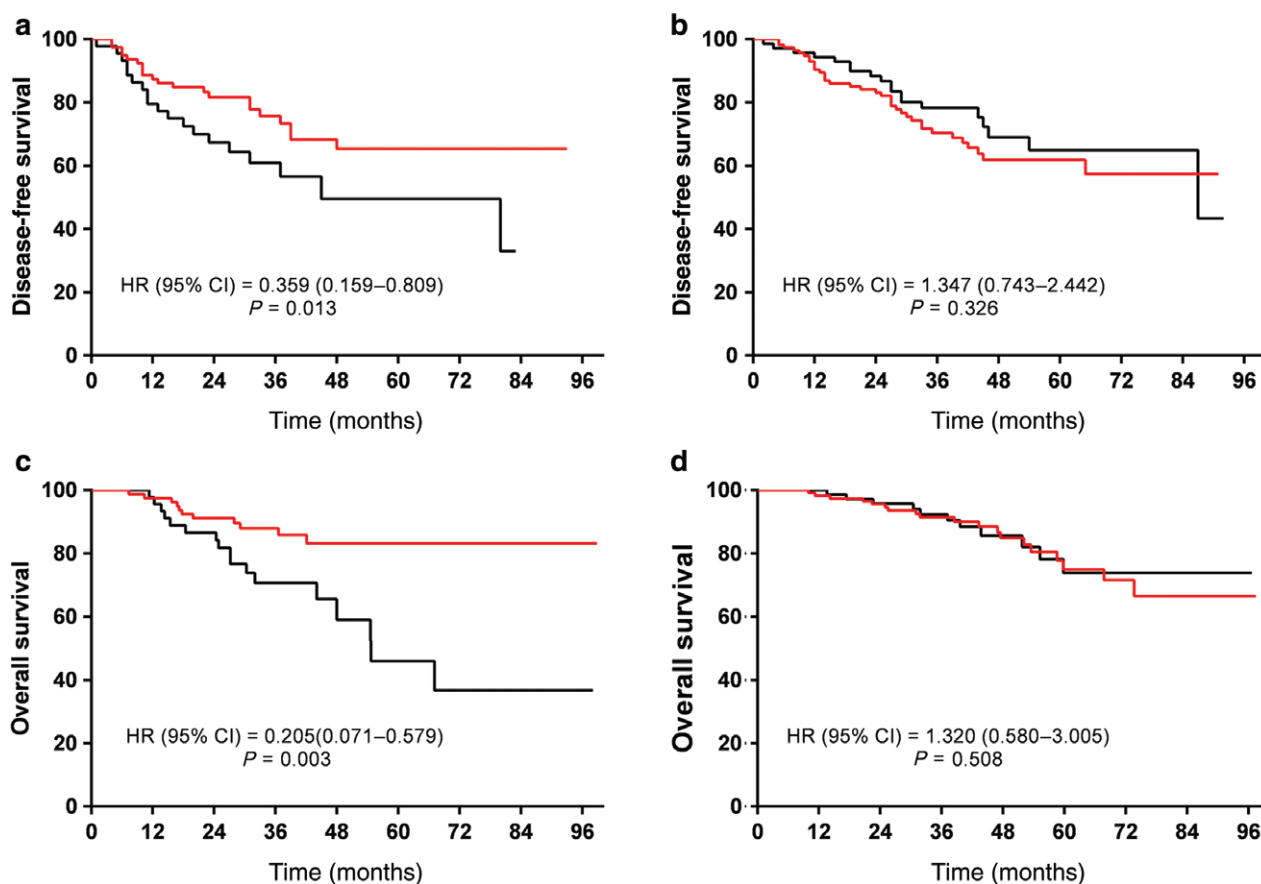
Figure 3 Survival curves of (**a**) disease-free and (**b**) overall survival of the solid predominant group and (**c**) disease-free and (**d**) overall survival of the solid non-predominant group, with or without adjuvant chemotherapy (ACT), respectively. Predominant: (——) ACT (*n* = 79) and (——) without ACT (*n* = 46); non-predominant group: (——) ACT (*n* = 114) and (——) without ACT (*n* = 70). CI, confidence interval; HR, hazard ratio.

been determined.[3–7,20–23] The Cancer and Leukemia Group B 9633 trial is the only randomized clinical trial to investigate ACT in resected stage IB patients, and the results demonstrated no survival benefit in the ACT group.[6] From earlier research, we hypothesized that patients with high risk factors might benefit from ACT. Furthermore, the NCCN guidelines have been updated for patients with high risk factors in stage IB adenocarcinoma, such as tumor size > 4 cm, visceral pleural invasion, lymph-vascular invasion, poorly differentiated tumors, wedge resection, or incomplete lymph node sampling.[8] After publication of the IASLC/ATS/ERS classification, the relationship between pathological subtypes and the prognosis of recurrence has drawn considerable attention.[24–28] In an American cohort of 240 subjects, Solis *et al.* found that the presence of solid material predicted a worse outcome than non-solid material, with lower recurrence-free survival and a shorter OS rate in stage I/II patients with solid histological-composed tumors.[14] However, this research did not consider whether solid material was predominant or non-predominant, which may have led to a different conclusion. According to

Makinen *et al.*, no statistically significant prognostic value was associated with non-predominant solid tumors.[29] Therefore, we hypothesized that tumors with a non-predominant solid growth pattern might have a different prognosis from the predominant solid growth pattern. Our results show that patients with tumors with the predominant solid growth pattern tend to have poorer outcomes than those with other pathological types with non-predominant solid composition, although the difference was not statistically significant (Fig 2). Nonetheless, the DFS curves comparing patterns between the solid predominant and solid non-predominant groups were clearly different; the limited sample size and short follow-up time may explain the failure to find a statistically significant difference.

The results of the current study demonstrate that in the solid predominant patient population, ACT can provide significant survival benefits for patients in stage IB. This finding is consistent with previous reports.[20] In contrast, in the solid non-predominant population, there was no significant difference in DFS with or without ACT. According to

Barletta *et al.*, the percentage of solid pattern was significantly associated with outcome, and a lower composition of solid pattern (< 90%) had better OS than a higher composition (≥ 90%). Therefore, ACT may not show an apparent survival benefit because of the lower relapse rates in the non-predominant population.[10]

Although several previous studies have reported poor prognosis of solid tumors in stage IB postoperative recovery and suggested ACT for this population, direct evidence regarding the prognosis of solid predominant versus solid non-predominant tumor types is limited, and no direct proof regarding the effect of ACT in these two groups has been found.[10–14,16,17,25,29–32] Therefore, we believe our results provide important novel insights into the clinical relevance of this treatment. There are, however, some limitations that should be considered when evaluating our research, including the retrospective nature of the study, patient selection bias, the choice of ACT, and non-randomized regimens. Furthermore, there were some differences in gender that may have affected results. A larger sample size and randomized trials would be helpful to verify our results.

In summary, our study has shown that ACT may improve the DFS and OS of completely resected patients with a solid predominant tumor pattern in stage IB adenocarcinoma, but likely has no benefit for patients with the solid non-predominant pattern.

Acknowledgments

Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Table S1. Characteristics of solid predominant and solid non-predominant types in adjuvant chemotherapy and surgical intervention alone groups.

Table S2. Adjuvant chemotherapy regiments.