Neoplasma 2022; 69(6): 1480–1489

doi:10.4149/neo_2022_220619N649

Clinical characteristics and prognostic value of EGFR mutation in stage I lung adenocarcinoma with spread through air spaces after surgical resection

Mao-Gang GAO, Shi-Ze WANG, Kai-Hong HAN, Shao-Nan XIE*, Qing-Yi LIU*

Department of Medical Thoracic Surgery, The Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei, China

**Correspondence: 5791586@qq.com; zhongmeijian-lqy@163.com*

Received June 19, 2022 / Accepted November 30, 2022

The clinical data of stage I invasive lung adenocarcinoma patients with spread through air spaces (STAS) who underwent lobectomy from January 1, 2013 to January 1, 2016 at the Department of Thoracic Surgery of Hebei Medical University were analyzed retrospectively, and statistical analysis was carried out to explore their clinical features and prognostic value of EGFR mutation. A total of 280 patients were included in the study cohort, and EGFR mutations were detected in 154 patients. EGFR mutations were more common in non-smokers (p=0.045), females (p<0.001), without vascular tumor thrombus (p=0.037), and histological subtype LPA/APA/PPA (p=0.001). Multivariate analysis of the Cox risk regression model showed that EGFR gene mutation (p=0.807) was not an independent influencing factor of recurrence-free survival (RFS), but EGFR mutation was an independent influencing factor of overall survival (OS) (p=0.012), and OS of patients with EGFR mutation was better. The EGFR mutation also significantly increased the progression-free survival (PFS) of relapsed patients (p<0.001), but the PFS of relapsed EGFR mutation patients who received adjuvant chemotherapy after the operation was worse than that of patients who did not receive adjuvant chemotherapy (p=0.029). EGFR gene mutation is not a risk factor for postoperative recurrence in patients with stage I lung adenocarcinoma with STAS but the 5-year survival rate of patients with EGFR gene mutation is better than that of wild-type. Postoperative adjuvant chemotherapy for patients with EGFR mutation should be carefully considered.

Key words: lung adenocarcinoma, spread through air spaces, surgical resection, EGFR mutation

Epidermal growth factor receptor (EGFR) mutation can promote cell proliferation and migration and is one of the most common mutations in the East Asian lung adenocarcinoma population [1]. With the development of next-generation sequencing (NGS) and targeted therapy, lung adenocarcinoma patients with mutations in exon 18–21of tyrosine kinase structural domain have been proven to be more sensitive to tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, ectinib, and oxitinib [2–5]. Therefore, EGFR-TKI has been recommended as the first choice for the first-line treatment of advanced lung adenocarcinoma patients with EGFR mutation [6]. It is reported that compared with patients without EGFR mutation, the OS of patients with EGFR mutation is significantly higher than that of patients without EGFR mutation [3], and the mutation status of EGFR is also considered an effective predictor of EGFR-TKI treatment effect [2].

However, whether EGFR mutation itself has an influence on the prognosis of lung adenocarcinoma patients is still controversial. Previous studies have shown that EGFR mutation status can predict the prognosis of patients with lung adenocarcinoma [7–11]. On the contrary, some studies have claimed that EGFR mutation is not a risk factor for postoperative recurrence of lung adenocarcinoma [12–14]. In addition, most previous studies either did not consider the pathological stage of patients, or did not exclude the influence of histological subtypes, imaging features, EGFR-TKI treatment, and high-risk factors for recurrence [15–17]. According to previous research conclusions, imaging features, histological subtypes, pathological stages, high-risk factors of disease progression, and treatment of EGFR-TKI will affect the prognosis of patients with EGFR mutation.

For stage I lung adenocarcinoma, most studies suggest that EGFR mutation is not a prognostic factor [14–17], and some studies believe that this is related to the low recurrence rate of stage I lung adenocarcinoma [14]. However, spread through air spaces (STAS) is a high-risk factor for a poor prognosis of lung adenocarcinoma patients, and the prognosis of stage I lung adenocarcinoma patients with STAS is significantly poor [18–20]. For stage I lung adenocarcinoma patients with STAS, whether EGFR mutation is a prognostic factor is still blank.

Therefore, we retrospectively analyzed the clinical data of resected stage I lung adenocarcinoma patients with STAS, analyzed the relationship between clinical features and prognosis, and explored the influence of EGFR mutation status on the prognosis of these patients.

Patients and methods

Patient choice. The study (Ethics No. 2021ky103) was approved by the Medical Ethics Committee of the Fourth Hospital of Hebei Medical University, which exempted patients from the need for informed consent. The clinical data of stage I invasive lung adenocarcinoma patients with STAS who underwent lobectomy from January 1, 2013 to January 1, 2016 at the Department of Thoracic Surgery of Hebei Medical University were analyzed retrospectively. All patients received routine preoperative examination before the operation to rule out metastasis. They were excluded from the study cohort if the following conditions were met: 1) Mucinous invasive adenocarcinoma; 2) Receive induction therapy before operation; 3) Multiple primary lesions in the same period; 4) Receive EGFR-TKI adjuvant therapy from postoperative to disease progression; 5) Follow-up was lost within 5 years after operation (Figure 1).

Histopathological evaluation of STAS. All specimens were fixed with formalin immediately after surgical resection and stained with hematoxylin and eosin. The sections were independently evaluated by two experts in the pathology department, and the specimens were classified according to the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) histological classification of lung invasive adenocarcinoma [21]. Lepidic Predominant Adenocarcinoma (LPA), Acinar Predominant Adenocarcinoma (APA), Micropapillary Predominant Adenocarcinoma (MPA), Papillary Predominant Adenocarcinoma (PPA), and Solid Predominant Adenocarcinoma (SPA) were classified according to the growth patterns with the largest proportion (even if < 50%), and LPA was classified as low grade, APA/PPA as middle grade, and MPA/SPA as high grade. STAS lesions are composed of tumor cells, which are morphologically characterized by scattered single cancer cells, micropapillary clusters, and solid nests located in normal alveolar space [22]. In order to avoid artificial cell dissemination during tumor anatomy, each pathologist observed at least three tumor specimen sections separately. Invasive adenocarcinoma dispersed through the alveolar cavity as shown in Figures 2A and 2B. The EGFR gene was sequenced by NGS.

Postoperative follow-up. Follow-up was conducted in the third month after the operation and every six months thereafter. Follow-up data mainly come from patients in our hospital thoracic surgery outpatient reexamination and our hospital follow-up center. For patients who are reexamined in local medical and health institutions, the follow-up data and examination data of patients are collected by e-mail and telephone. Recurrence-free survival is defined as the time from the initial operation to the earliest occurrence of the recurrence certificate, and overall survival (OS) is defined as the time from the operation time to the patient's death or the last follow-up. Progression-free survival (PFS) is defined as the time between the start of a randomized clinical trial and the progression of (any aspect of) tumorigenesis or death from any cause.

Statistical method. SPSS v26.0 (IBM, Armonk, NY, USA) was used for statistical analysis, and Kaplan-Meier was used to evaluate RFS and OS. The correlation between the two groups was compared by the Pearson Chi-square test or Fisher precise test. Cox proportional risk regression model was used to evaluate the independent influencing factors of RFS and OS. All p-values are based on two-tailed statistical analysis, and $p<0.05$ was statistically significant.

Results

A total of 280 patients were included in this study. The median age of onset was 62.0 years (ranging from 28.0 to 79.0 years), including 127 male patients (45.4%) and 153 female patients (54.6%). 100 patients (35.7%) had a smoking history and 180 patients (64.3%) had no smoking history.

All patients were classified according to TNM staging of UICC 8th edition [23], 89 patients were in stage IA (31.8%) and 191 patients were in stage IB (68.2%). APA (170.7%) was the most common histological subtype in our study group, followed by SPA (54, 19.3%), PPA (36, 12.9%), MPA (17,

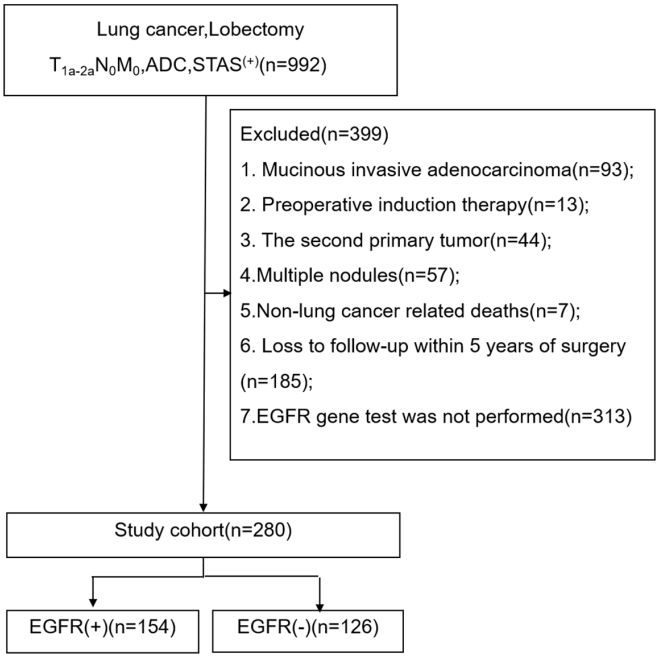

Figure 1. The flow chart. Abbreviation: ADC-adenocarcinoma; STAS-spread through air space; EGFR-epidermal growth factor receptor

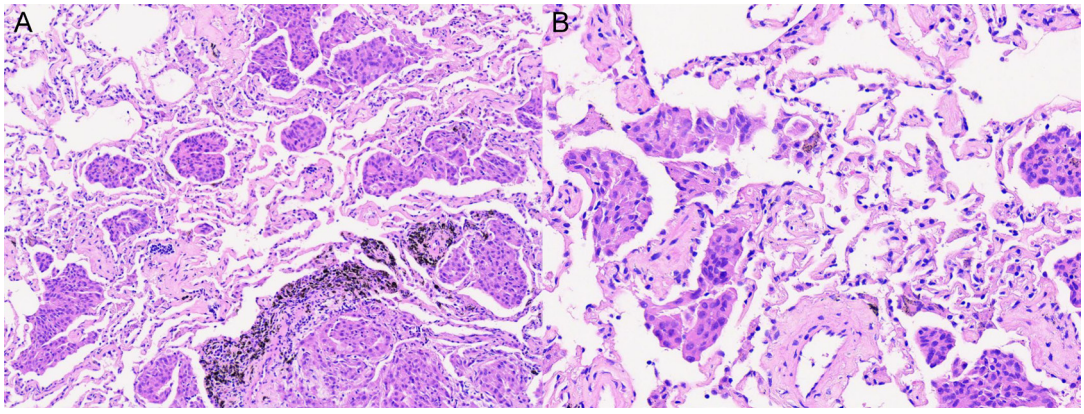

Figure 2. A) Low-power view and B) high-power view of tumor spread through air space in lung adenocarcinoma (original magnification: ×100 in A and ×400 in B).

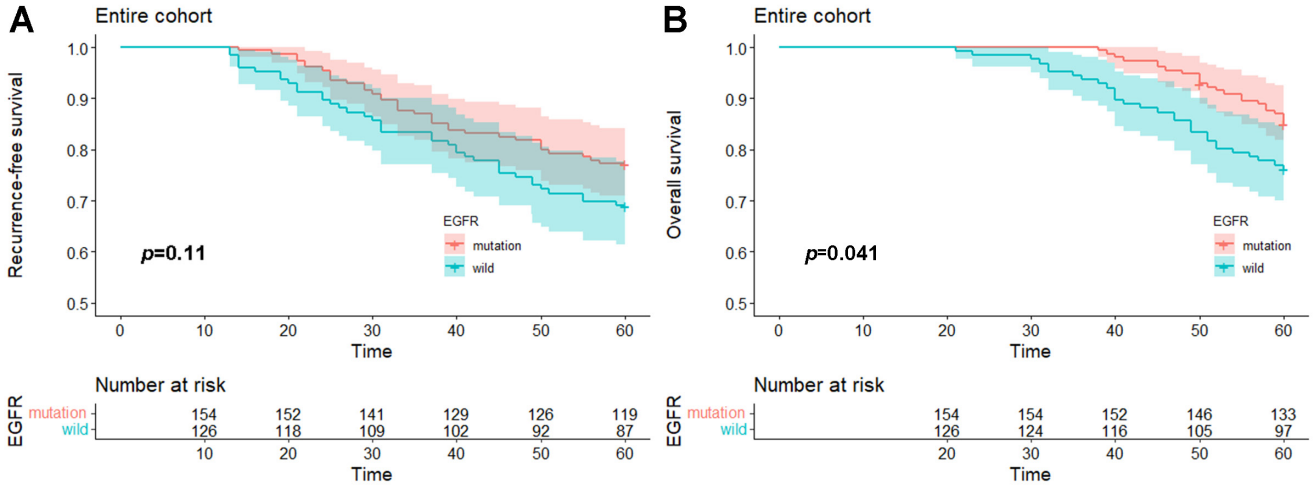

Figure 3. A) 5-year RFS of EGFR mutant and EGFR wild type, B) 5-year OS of EGFR mutant and EGFR wild type. Abbreviation: RFS-recurrence free survival; OS-overall survival; EGFR-epidermal growth factor receptor

6.1%), and LPA (3, 1.1%). 154 patients (55.0%) had EGFR gene mutation, 65 patients (42.2%) had exon 21 mutation, 69 patients (44.8%) had exon 19 mutation, 14 patients (9.1%) had a rare mutation in exon 18 or 20, 4 patients had a double mutation in exon 18 (G719X) and exon 20 (S768I), and 2 patients had a double mutation in exon 18 (G719A) and exon 21 (L861Q) (Table 1).

In our study cohort, non-smokers (p=0.045) and women (p<0.001) were more likely to have EGFR gene mutations. It is more common in patients without vascular tumor thrombus (p=0.037) and with histological subtype LPA/APA/PPA (p=0.001) (Table 1).

Clinical features and prognostic value of EGFR mutation. 136 patients received postoperative adjuvant chemotherapy, and the median follow-up time was 72.0 months (21.0–99.0 months). During the follow-up period, 53 patients (39.0%) died and 73 patients (53.7%) relapsed. The main recurrence sites were ipsilateral or contralateral lung metastasis (32/73), mediastinal lymph node metastasis (14/73), pleural metastasis (3/73), distant bone metastasis (8/73), liver metastasis (11/73), adrenal metastasis (3/73), and brain metastasis (2/73).

Univariate analysis of the Cox risk regression model showed that patients with vascular tumor thrombus (p<0.001), without postoperative adjuvant chemotherapy (p=0.030) and visceral pleural invasion (p=0.048) had poor RFS, while multivariate analysis showed that high-risk tissue classification (p=0.047), vascular tumor thrombus (p<0.001) and adjuvant chemotherapy (p=0.022) were independent influencing factors of RFS, while EGFR gene mutation (p=0.807) was not the influencing factor of RFS (Table 2). For OS, univariate analysis showed that patients without EGFR mutation (p=0.042), with vascular tumor thrombus (p<0.001) and high-risk histological components

(p=0.019) had worse OS. Multivariate analysis showed that EGFR mutation (p=0.012), with vascular tumor thrombus (p<0.001) and high-risk histological components (p=0.008) were independent influencing factors of postoperative OS, while postoperative adjuvant chemotherapy was not independent influencing factors of OS (p=0.152) (Table 3). Five-year RFS was 69.0% in EGFR wild type and 77.3% in the EGFR mutant (p=0.11; Figure 3A). The five-year overall survival of the EGFR mutant was 85.1%, which was significantly better than that of the wild type (76.2%, p=0.041; Figure 3B). Patients with vascular tumor thrombus had poor 5-year RFS and 5-year OS (p<0.001, p<0.001; Figures 4A, 4B). Patients with visceral pleural invasion had poor 5-year RFS (p=0.034; Figure 4C), but no difference in 5-year OS (p=0.061; Figure 4D). The 5-year RFS and 5-year OS of the patients who received adjuvant chemotherapy (ACT) were better than those who did not (p=0.038, p=0.017; Figures 4E, 4F).

In subgroup analysis, RFS and OS of EGFR mutant were better than those of wild-type patients in non-smoking patients (p=0.0018, p<0.001; Figures 5A, 5B); RFS of EGFR mutant was better in female patients (p=0.049; Figure 5C), but there was no difference in OS (p=0.065; Figure 5D); Among patients who did not receive adjuvant chemotherapy after surgery, EGFR mutant patients survived better than wild type patients (p=0.027; Figure 5E), but there was no difference among patients who received adjuvant chemotherapy (p=0.45; Figure 5F).

Progression-free survival in EGFR mutant patients was significantly better than that in EGFR wild-type patients after relapse (p=0.0014; Figure 6A), and in EGFR mutant patients, progression-free survival after the first progression in patients receiving adjuvant chemotherapy after surgery was worse than that in patients not receiving chemotherapy (p=0.029; Figure 6B), while no such difference was observed in EGFR wild-type patients (p=0.79; Figure 6C).

Table 1. Patient characteristics.

Variables	EGFR-mutation	EGFR-wild	p-value
Overall patients	154	126	
Age (years)			0.605
≤65	108 (70.1)	84 (66.7)	
>65	46 (29.9)	42 33.3)	
Sex			
Male	52 (33.8)	75 (59.5)	<0.001
Female	102 (66.2)	51 (40.5)	
Smoking History			0.045
Former/current	47 (30.5)	53 (42.1)	
Never	107 (69.5)	73 (57.9)	
Histologic pattern			0.001
Lepidic	1 (0.6)	2 (1.6)	
Acinar	108 (70.1)	62 (49.2)	
Papillary	19 (12.3)	17 (13.5)	
Micropapillary	9 (5.8)	8 (6.3)	
Solid	17 (11.0)	37 (29.4)	
Vascular invasion			0.037
Absent	123 (79.9)	87 (69.0)	
Present	31 (20.1)	39 (31.0)	
Pleural invasion			0.806
Absent	91 (59.1)	77 (61.1)	
Present	63 (40.9)	49 (38.9)	
Lymphatic invasion			0.330
Absent	113 (73.4)	99 (78.6)	
Present	41 (26.6)	27 (21.4)	
Pathologic stage			0.609
Stage IA	51 (33.1)	38 (30.2)	
Stage IB	103 (66.9)	88 (69.8)	
Adjuvant therapy			0.401
Absent	83 (53.9)	61 (48.4)	
Present	71 (46.1)	65 (51.6)	

Discussion

With the wide application of low-dose chest CT in early diagnosis and treatment of lung cancer and health examination, more and more early lung cancer has been detected [24], and lung adenocarcinoma is one of the most common histological subtypes of lung cancer [25]. For these patients with early lung adenocarcinoma, radical surgical resection is the first choice. In addition, due to the populariza-

Table.2 Cox proportional-hazards regression model for DFS with the cohort.

Variables		Univariate Analysis			Multivariate Analysis		
		HR	95% CI	p-value	HR	95% CI	p-value
Sex	Male vs. female	1.001	0.631–1.587	0.996	1.010	0.610–1.670	0.971
Smoking history	Current vs. never	1.399	0.854–2.356	0.208	1.373	0.814–2.316	0.245
Age (years)	≤65 vs. >65	0.756	0.470–1.216	0.249	0.766	0.466–1.260	0.295
Histologic pattern	High risk vs. low risk	1.490	0.941–2.360	0.086	1.646	1.006–2.691	0.047
Vascular invasion	Present vs. absent	5.380	3.381–8.562	0.000	5.640	3.491–9.110	0.000
Lymphatic invasion	Present vs. absent	1.499	0.914–2.456	0.108	1.373	0.814–2.316	0.235
Pleural invasion	Present vs. absent	1.583	1.000–2.505	0.048	1.790	0.996–3.214	0.051
Pathologic stage	Stage IB vs. stage IA	1.504	0.083–2.561	0.540	1.298	0.655–2.573	0.455
Adjuvant therapy	Absent vs. present	1.684	1.051–2.700	0.030	1.774	1.086–2.897	0.022
EGFR gene	Mutation vs. wild-type	0.937	0.555–1.580	0.807	1.258	0.702–2.253	0.440

tion and affordability of gene detection technology and the development of targeted therapy, more and more patients choose important lung cancer-driving genes, especially the EGFR gene for sequencing, in order to better understand the disease and guide patients' treatment.

Deng's research shows [11] that EGFR mutation was a strong poor prognostic factor in patients with radiologic solid, historical acinar pattern-predominant adenocarcinoma/papillary pattern-predominant adenocarcinoma/invasive mucous adenocarcinoma, and pathologic stage II

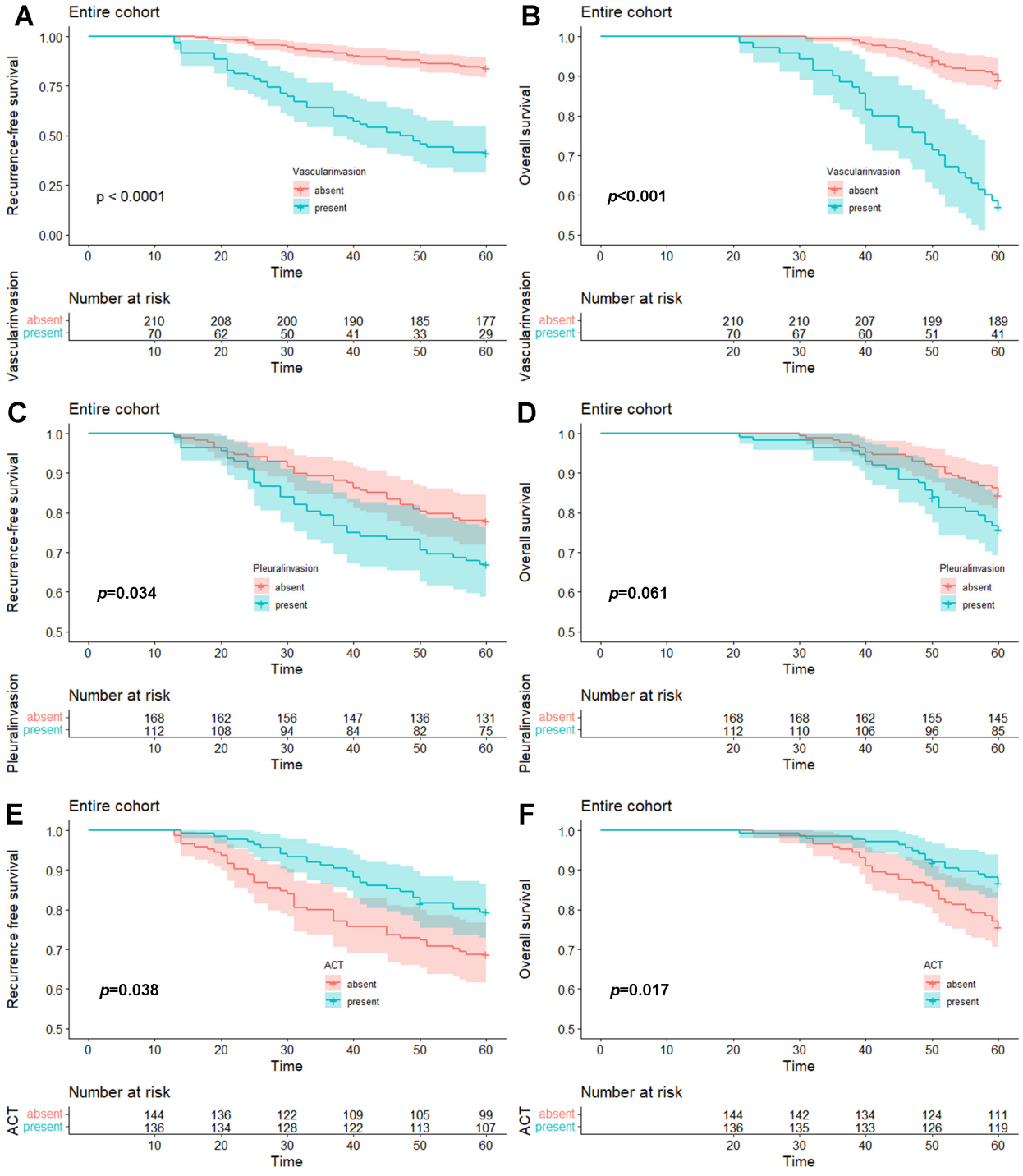

Figure 4. A) 5-year RFS of vascular invasion, B) 5-year OS of vascular invasion, C) 5-year RFS of pleural invasion, D) 5-year OS of pleural invasion, E) 5-year RFS of ACT, F) 5-year OS of ACT. Abbreviation: RFS-recurrence free survival; OS-over survival; ACT-adjuvant chemotherapy

Table 3. Cox proportional-hazards regression model for OS with the cohort.

Variables		Univariate Analysis			Multivariate Analysis		
		HR	95% CI	p-value	HR	95% CI	p-value
Sex	Male vs. female	1.064	0.621–1.825	0.821	0.984	0.552–1.754	0.955
Smoking history	Current vs. never	1.322	0.736–2.377	0.350	1.112	0.582–2.123	0.748
Age (years)	≤65 vs. >65	0.629	0.364–1.086	0.096	0.649	0.367–1.146	0.136
Histologic pattern	High risk vs. low risk	1.971	1.116–3.481	0.019	2.233	1.234–4.039	0.008
Vascular invasion	Present vs. absent	4.910	2.849–8.460	0.000	4.758	2.732–8.287	0.000
Lymphatic invasion	Present vs. absent	1.684	0.954–2.973	0.072	1.786	0.973–3.280	0.061
Pleural invasion	Present vs. absent	1.651	0.963–2.829	0.068	1.921	0.956–3.860	0.067
Pathologic stage	Stage IB vs. stage IA	1.470	0.786–2.748	0.228	1.095	0.484–2.476	0.828
Adjuvant therapy	Absent vs. present	1.440	0.792–2.619	0.231	1.861	0.994–3.485	0.152
EGFR gene	Mutation vs. wild-type	1.756	1.020–3.024	0.042	2.129	1.183–3.830	0.012

and III lung adenocarcinomas. However, the prognostic value of EGFR mutation is still controversial. Although most studies suggest that EGFR mutation is not a prognostic factor [14–17], and some studies believe that it is related to the low recurrence rate of stage I lung adenocarcinoma [14], STAS is a high-risk factor for poor prognosis of lung adenocarcinoma patients, and the prognosis of stage I patients with STAS is significantly worse [18–20]. Therefore, we retrospectively analyzed the clinical data of resected stage I lung adenocarcinoma patients with STAS, analyzed the relationship between clinical features and prognosis, and explored the influence of EGFR mutation status on the prognosis of these patients.

It has been reported that EGFR mutation status is closely related to several clinical case factors of lung adenocarcinoma, including gender, smoking history, tumor size, pathological TNM stage, imaging manifestations, and histological subtypes [26, 27]. Our cohort results are consistent with previous studies suggesting that EGFR mutations in lung adenocarcinoma are most common in women and non-smokers [28]. The study of early lung adenocarcinoma by Saw et al. [29] suggests that EGFR mutation in patients with stage IB lung adenocarcinoma is more than that in patients with stage IA lung adenocarcinoma, but in our study, the probability of EGFR mutation was not different between patients with stage IA and IB (57.3% vs. 53.9% p=0.597).

Matsumura [30] proposed that for patients with early lung adenocarcinoma, excluding the influence of EGFR-TKI treatment, the EGFR mutation status is not an influencing factor of patients' 5-year RFS. On this basis, we further analyzed the patients with stage I lung adenocarcinoma with STAS after surgical resection. Our study found that EGFR mutation status is still not an influencing factor of 5-year RFS in these patients (p=0.086). Although Yotsukura et al. [31] suggested that EGFR gene mutation is not a prognostic factor for patients with stage I lung adenocarcinoma after the operation, in our study, EGFR mutation status is a prognostic factor for patients with stage I lung adenocarcinoma with STAS (p=0.039), and patients with EGFR mutation have longer postoperative survival time, which may be due to the fact that patients with STAS are more likely to relapse, while patients with EGFR-TKI after recurrence in the study cohort have better progression-free survival time than patients without EGFR mutation (p=0. 0014).

Regarding the influence of histological subtypes of invasive lung adenocarcinoma on the prognosis of patients, Yanagawa's study showed that patients with solid/micropapillary lung adenocarcinoma have a poor prognosis, even if they are not the main subtype components. For stage I patients, Tsubokawa's study also believes that patients with solid or micropapillary components have a poor prognosis. In our study, multivariate analysis showed that histological type was an independent determinant of RFS and OS, and patients with solid/micropapillary type as the main component had a worse prognosis. However, we did not analyze the prognosis of patients with high-risk components but not major components.

In recent years, more and more studies have explored the predictive factors of postoperative benefit from adjuvant therapy for patients with stage I lung adenocarcinoma and proposed that postoperative adjuvant chemotherapy can benefit the postoperative survival of patients with stage I lung adenocarcinoma with some high-risk factors [32–34]. In our study cohort, 136 patients received postoperative adjuvant chemotherapy, which was an independent influencing factor for RFS (p=0.022) but not for OS (p=0.152). An interesting finding is that Kaplan-Meier survival analysis shows that among patients who did not receive adjuvant chemotherapy after the operation, EGFR mutant patients have better survival than wild-type patients (p=0.027), but there is no difference in survival among patients who received adjuvant chemotherapy (p=0.45). In order to find out the reasons for this difference, we further studied 74 patients with recurrence and analyzed the subgroup according to the expression status of EGFR in these patients. Among the 74 patients with recurrence, 35 patients with EGFR gene mutation received adjuvant EGFR-TKI after recurrence, and 39 patients without EGFR gene mutation received second-line chemotherapy after recurrence. For patients with EGFR mutations, progression-free survival on EGFR-TKI after relapse was

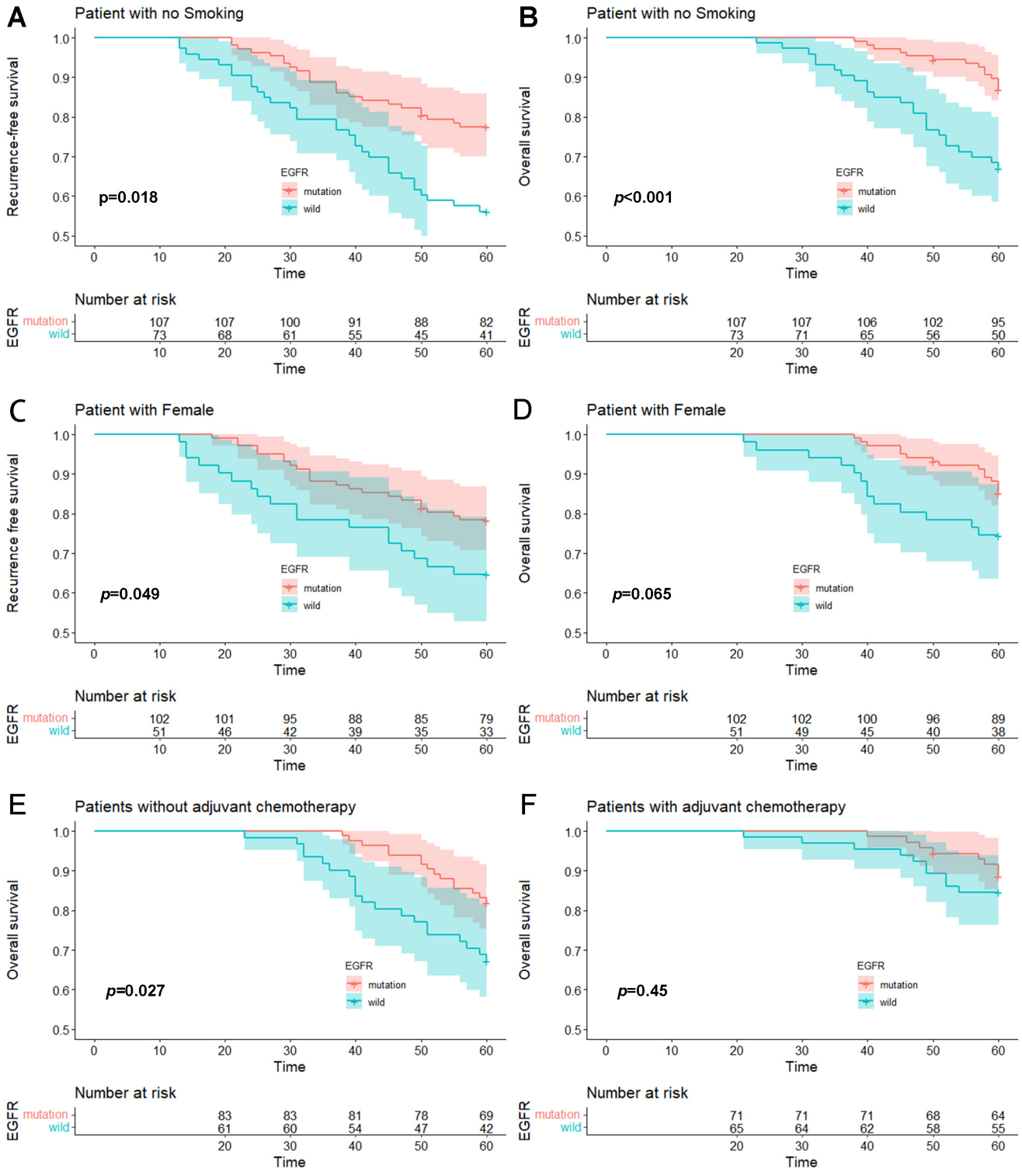

Figure 5. A) 5-year RFS of the patient with no smoking in EGFR mutant and EGFR wild type, B) 5-year OS of the patient with no smoking in EGFR mutant and EGFR wild type, C) 5-year RFS of the patient with female in EGFR mutant and EGFR wild type, D) 5-year OS of the patient with female in EGFR mutant and EGFR wild type, E) 5-year OS of the patient without adjuvant chemotherapy in EGFR mutant and EGFR wild type, F) 5-year OS of the patient with adjuvant chemotherapy in EGFR mutant and EGFR wild type. Abbreviation: OS-over survival; RFS-recurrence free survival; ACT-adjuvant chemotherapy

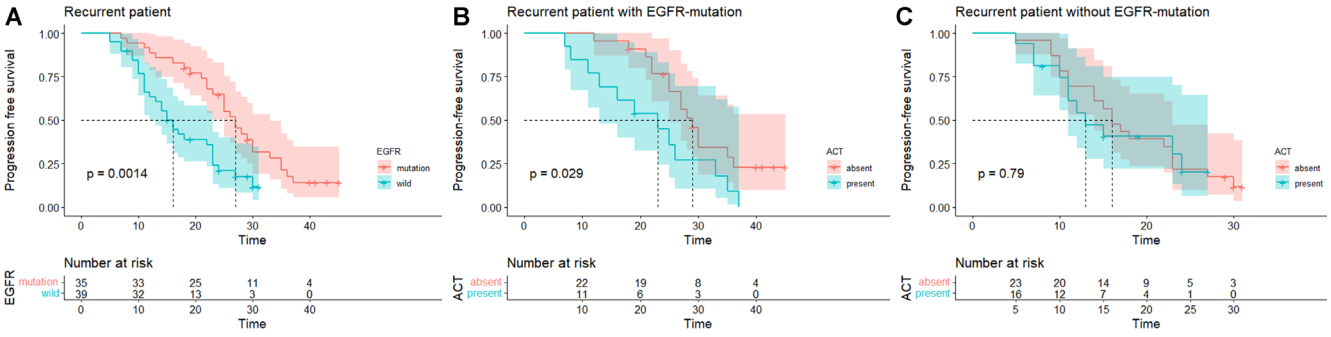

Figure 6. A) PFS of the recurrent patient in EGFR mutant and EGFR wild type, B) PFS of the recurrent patient with EGFR-mutation receiving adjuvant chemotherapy after surgery, C) PFS of the recurrent patient without EGFR-mutation receiving adjuvant chemotherapy after surgery. Abbreviation: OS-over survival; RFS-recurrence free survival; ACT-adjuvant chemotherapy; PFS-progression-free survival

worse in patients receiving adjuvant chemotherapy after surgery than in patients without chemotherapy (p=0.029), while this difference was not observed in patients with EGFR wild type (p=0.79).

Among the recurrent patients with EGFR mutation, 5 patients had RFS less than 5 months after EGFR-TKI, and the disease control was poor. All these 5 patients received adjuvant chemotherapy after the operation. Among 5 patients, because of the poor therapeutic effect of EGFR-TKI, 4 patients were biopsied again and the EGFR gene was detected, and 1 patient could not be biopsied and the gene of blood samples was detected. EGFR mutation was not detected in 3 patients after re-examination. There are many reports that chemotherapy can change the mutation state of driving genes in lung cancer patients [35–37]. Although this situation has also been observed in our research, it is uncertain whether this mutation state change is caused by chemotherapy or tumor heterogeneity, which needs further study.

In conclusion, EGFR gene mutation is not a risk factor for postoperative recurrence in patients with stage I lung adenocarcinoma with STAS, but the 5-year survival rate of patients with EGFR gene mutation is better than that of wild type. Postoperative adjuvant chemotherapy for patients with EGFR mutation should be carefully considered.

Acknowledgments: We thank American Journal Experts for language editorial assistance, Yueping Liu M.D. and Yan Ding for pathological examination. This study was supported by the Medical Science Research Project of Hebei province (Grant No.20201076) and the program of Government Funding Clinical Excellence of Hebei province (2019 Grant No.139).

References

[1] SUDA K, TOMIZAWA K, MITSUDOMI T. Biological and clinical significance of KRAS mutations in lung cancer: an oncogenic driver that contrasts with EGFR mutation. Cancer Metastasis Rev 2010; 29: 49–60. https://doi.org/10.1007/s10555-010-9209-4

[2] LYNCH TJ, BELL DW, SORDELL AR, GURUBHAGAVATULA S, OKIMOTO RA et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004; 350: 2129–2139. https://doi.org/10.1056/NEJMoa040938

[3] RAMALINGAM SS, VANSTEENKISTE J, PLANCHARD D, CHO BC, GRAY JE et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med 2020; 382: 41–50. https://doi.org/10.1056/NEJMoa1913662

[4] SHI Y, ZHANG L, LIU X, ZHOU C, ZHANG L et al. Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): a randomised, double-blind phase 3 non-inferiority trial. Lancet Oncol 2013; 14: 953–961. https://doi.org/10.1016/S1470-2045(13)70355-3

[5] CATALDO VD, GIBBONS DL, PÉREZ-SOLER R, QUINTÁS-CARDAMA A. Treatment of non-small-cell lung cancer with erlotinib or gefitinib. N Engl J Med 2011; 364: 947–955. https://doi.org/10.1056/NEJMct0807960

[6] ETTINGER DS, WOOD DE, AISNER DL, AKERLEY W, BAUMAN JR et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2.2021. J Natl Compr Canc Netw 2021; 19: 254–266. https://doi.org/10.6004/jnccn.2021.0013

[7] D'ANGELO SP, JANJIGIAN YY, AHYE N, RIELY GJ, CHAFT JE et al. Distinct clinical course of EGFR-mutant resected lung cancers: results of testing of 1118 surgical specimens and effects of adjuvant gefitinib and erlotinib. J Thorac Oncol 2012; 7: 1815–1822. https://doi.org/10.1097/JTO.0b013e31826bb7b2

[8] ITO M, MIYATA Y, TSUTANI Y, ITO H, NAKAYAMA H. Positive EGFR mutation status is a risk of recurrence in pN0-1 lung adenocarcinoma when combined with pathological stage and histological subtype: A retrospective multicenter analysis. Lung Cancer 2020;141: 107–113. https://doi.org/10.1016/j.lungcan.2020.01.018

[9] ITO M, MIYATA Y, KUSHITANI K, YOSHIYA T, KAI Y. Increased risk of recurrence in resected EGFR-positive pN0M0 invasive lung adenocarcinoma. Thorac Cancer 2018; 9: 1594–1602. https://doi.org/10.1111/1759-7714.12866

[10] KISHI N, ITO M, MIYATA Y, KANAI A, HANDA Y. Intense Expression of EGFR L858R Characterizes the Micropapillary Component and L858R Is Associated with the Risk of Recurrence in pN0M0 Lung Adenocarcinoma with the Micropapillary Component. Ann Surg Oncol 2020; 27: 945–955. https://doi.org/10.1245/s10434-019-07854-2

[11] DENG C, ZHANG Y, MA Z, FU F, DENG L. Prognostic value of epidermal growth factor receptor gene mutation in resected lung adenocarcinoma. J Thorac Cardiovasc Surg 2021; 162: 664–674.e667. https://doi.org/10.1016/j.jtcvs.2020.05.099

[12] SHEPHERD FA, LACAS B, LE TEUFF G, HAINAUT P, JÄNNE PA et al. Pooled Analysis of the Prognostic and Predictive Effects of TP53 Comutation Status Combined With KRAS or EGFR Mutation in Early-Stage Resected Non-Small-Cell Lung Cancer in Four Trials of Adjuvant Chemotherapy. J Clin Oncol 2017; 35: 2018–2027. https://doi.org/10.1200/JCO.2016.71.2893

[13] LIN MW, WU CT, SHIH JY, CHANG YL, YANG PC. Clinicopathologic characteristics and prognostic significance of EGFR and p53 mutations in surgically resected lung adenocarcinomas ≤2 cm in maximal dimension. J Surg Oncol 2014; 110: 99–106. https://doi.org/10.1002/jso.23628

[14] CHEN S, YANG S, ZHANG Y, XIANG J, ZHANG Y et al. Clinicopathologic features and prognostic value of epidermal growth factor receptor mutation in patients with pT1a and pT1b invasive lung adenocarcinoma after surgical resection. J Thorac Dis 2021; 13: 5496–5507. https://doi.org/10.21037/jtd-21-924

[15] HAN X, FAN J, LI Y, CAO Y, GU J et al. Value of CT features for predicting EGFR mutations and ALK positivity in patients with lung adenocarcinoma. Sci Rep 2021; 11: 5679. https://doi.org/10.1038/s41598-021-83646-7

[16] YIN J, XI J, LIANG J, ZHAN C, JIANG W et al. Solid Components in the Mediastinal Window of Computed Tomography Define a Distinct Subtype of Subsolid Nodules in Clinical Stage I Lung Cancers. Clin Lung Cancer 2021;22: 324–331. https://doi.org/10.1016/j.cllc.2021.02.015

[17] HATTORI A, MATSUNAGA T, FUKUI M, TAKAMOCHI K, SUZUKI K. Prognosis of epidermal growth factor receptor-mutated stage I lung adenocarcinoma with radiologically solid features. Eur J Cardiothorac Surg 2022; 61: 769–777. https://doi.org/10.1093/ejcts/ezab481

[18] TOYOKAWA G, YAMADA Y, TAGAWA T, KOZUMA Y, MATSUBARA T et al. Significance of Spread Through Air Spaces in Resected Pathological Stage I Lung Adenocarcinoma. Ann Thorac Surg 2018; 105: 1655–1663. https://doi.org/10.1016/j.athoracsur.2018.01.037

[19] LIU H, YIN Q, YANG G, QIE P. Prognostic Impact of Tumor Spread Through Air Spaces in Non-small Cell Lung Cancers: a Meta-Analysis Including 3564 Patients. Pathol Oncol Res 2019; 25: 1303–1310. https://doi.org/10.1007/s12253-019-00616-1

[20] Yi E, Lee JH, Jung Y, Chung JH, Lee Y et al. Clinical implication of tumour spread through air spaces in pathological stage I lung adenocarcinoma treated with lobectomy. Interact Cardiovasc Thorac Surg 2021; 32: 64–72. https://doi.org/10.1093/icvts/ivaa227

[21] TRAVIS WD, BRAMBILLA E, NOGUCHI M, NICHOLSON AG, GEISINGER KR et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011; 6: 244–285. https://doi.org/10.1097/JTO.0b013e318206a221

[22] DAI C, XIE H, SU H, SHE Y, ZHU E et al. Tumor Spread through Air Spaces Affects the Recurrence and Overall Survival in Patients with Lung Adenocarcinoma >2 to 3 cm. J Thorac Oncol 2017; 12: 1052–1060. https://doi.org/10.1016/j.jtho.2017.03.020

[23] CHANSKY K, DETTERBECK FC, NICHOLSON AG, RUSCH VW, VALLIÈRES E et al. The IASLC Lung Cancer Staging Project: External Validation of the Revision of the TNM Stage Groupings in the Eighth Edition of the TNM Classification of Lung Cancer. J Thorac Oncol 2017; 12: 1109–1121. https://doi.org/10.1016/j.jtho.2017.04.011

[24] ZHANG Y, JHEON S, LI H, ZHANG H, XIE Y et al. Results of low-dose computed tomography as a regular health examination among Chinese hospital employees. J Thorac Cardiovasc Surg 2020; 160: 824–831.e824. https://doi.org/10.1016/j.jtcvs.2019.10.145

[25] SUN D, CAO M, LI H, HE S, CHEN W. Cancer burden and trends in China: A review and comparison with Japan and South Korea. Chin J Cancer Res 2020; 32: 129–139. https://doi.org/10.21147/j.issn.1000-9604.2020.02.01

[26] SHIGEMATSU H, LIN L, TAKAHASHI T, NOMURA M, SUZUKI M et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst 2005; 97: 339–346. https://doi.org/10.1093/jnci/dji055

[27] KASEDA K, ASAKURA K, KAZAMA A, OZAWA Y. Clinicopathological and prognostic features of surgically resected pathological stage I lung adenocarcinoma harboring epidermal growth factor receptor and K-ras mutation. Thorac Cancer 2017; 8: 229–237. https://doi.org/10.1111/1759-7714.12428

[28] SINGAL G, MILLER PG, AGARWALA V, LI G, KAUSHIK G et al. Association of Patient Characteristics and Tumor Genomics With Clinical Outcomes Among Patients With Non-Small Cell Lung Cancer Using a Clinicogenomic Database. Jama 2019; 321: 1391–1399. https://doi.org/10.1001/jama.2019.3241

[29] SAW SPL, ZHOU S, CHEN J, LAI G, ANG MK et al. Association of Clinicopathologic and Molecular Tumor Features With Recurrence in Resected Early-Stage Epidermal Growth Factor Receptor-Positive Non-Small Cell Lung Cancer. JAMA Netw Open 2021; 4: e2131892. https://doi.org/10.1001/jamanetworkopen.2021.31892

[30] MATSUMURA Y, SUZUKI H, OHIRA T, SHIONO S, ABE J et al. Matched-pair analysis of a multi-institutional cohort reveals that epidermal growth factor receptor mutation is not a risk factor for postoperative recurrence of lung adenocarcinoma. Lung Cancer 2017; 114: 23–30. https://doi.org/10.1016/j.lungcan.2017.09.003

[31] YOTSUKURA M, YASUDA H, SHIGENOBU T, KASEDA K, MASAI K et al. Clinical and pathological characteristics of EGFR mutation in operable early-stage lung adenocarcinoma. Lung Cancer 2017; 109: 45–51. https://doi.org/10.1016/j.lungcan.2017.04.014

[32] TSUTANI Y, IMAI K, ITO H, MIYATA Y, IKEDA N et al. Adjuvant Chemotherapy for High-risk Pathologic Stage I Non-Small Cell Lung Cancer. Ann Thorac Surg 2022; 113: 1608–1616. https://doi.org/10.1016/j.athoracsur.2021.04.108

[33] YOH K, TAKAMOCHI K, SHUKUYA T, HISHIDA T, TSUBOI M et al. Pattern of care in adjuvant therapy for resected Stage I non-small cell lung cancer: real-world data from Japan. Jpn J Clin Oncol 2019; 49: 63–68. https://doi.org/10.1093/jjco/hyy165

[34] QIAN J, XU J, WANG S, QIAN F, YANG W et al. Adjuvant Chemotherapy Candidates in Stage I Lung Adenocarcinomas Following Complete Lobectomy. Ann Surg Oncol 2019; 26: 2392–2400. https://doi.org/10.1245/s10434-019-07366-z

[35] LUO YH, CHEN YM. Influence of chemotherapy on EGFR mutation status. Transl Lung Cancer Res 2013; 2: 442–444. https://doi.org/10.3978/j.issn.2218-6751.2013.10.12

[36] DEAN L, KANE M, PRATT VM, SCOTT SA, PIRMOHAMED M et al. (Eds.) Cetuximab Therapy and RAS and BRAF Genotype. In: Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012.

[37] BAI H, WANG Z, CHEN K, ZHAO J, LEE JJ et al. Influence of chemotherapy on EGFR mutation status among patients with non-small-cell lung cancer. J Clin Oncol 2012; 30: 3077–3083. https://doi.org/10.1200/JCO.2011.39.3744