Clinicopathologic features and prognostic value of epidermal growth factor receptor mutation in patients with pT1a and pT1b invasive lung adenocarcinoma after surgical resection

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Background: Previous studies have evaluated the prognostic value of epidermal growth factor receptor (EGFR) mutation in different subgroups of lung adenocarcinoma, but there remains controversial on this issue. We conduct this study aimed to reveal the prognostic value of EGFR mutation in patients with pT1a and pT1b invasive lung adenocarcinoma.

Methods: From August 2009 to February 2015, 338 patients with pT1a and pT1b invasive lung adenocarcinoma who underwent EGFR mutation analysis were enrolled into this study. According to clinicopathologic and radiologic characteristics, survival analysis was conducted in different subgroups using Kaplan-Meier methods and Cox regression models.

Results: EGFR mutation was detected in 216 (63.9%) patients. In the entire cohort, EGFR mutation was significantly frequent in female (P=0.011), never smoking (P=0.014) patients, patients with part-solid nodules (P=0.005) and patients with lepidic pattern-predominant adenocarcinoma (LPA)/acinar pattern-predominant adenocarcinoma (APA)/papillary pattern-predominant adenocarcinoma (PPA) (P=0.005). No difference in recurrence-free survival (RFS) was seen between patients harboring EGFR mutation and patients without EGFR mutation in the entire cohort (P=0.664) and the subgroup cohorts. Patients with EGFR mutation had a longer overall survival (OS) compared with patients without EGFR mutation in the entire cohort (P=0.005) and the subgroups of N0 stage cohort (P=0.013), N1–2 stage cohort (P=0.033), APA/PPA/invasive mucinous adenocarcinoma (IMA) cohort (P=0.011) and pT1b cohort (P=0.002). Tyrosine kinase inhibitors (TKIs) could significantly prolong the OS in patients with EGFR mutation after recurrence (P=0.04).

Conclusions: EGFR mutation was not a risk factor for recurrence of patients with pT1a and pT1b invasive lung adenocarcinoma.

Keywords: Small lung adenocarcinoma; epidermal growth factor receptor (EGFR); recurrence-free survival (RFS)

Introduction

Epidermal growth factor receptor (EGFR) mutation, which can promote cell proliferation and migration, is one of the most common oncogene mutations in lung adenocarcinoma of East Asian population (1). With the development of sequencing technology and targeted therapy, mutations in the tyrosine kinase (TK) domain (exons 18-21) of the EGFR in lung adenocarcinoma have been proved to be more sensitive to tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib (2-6). Therefore, TKIs have been recommended as the first-line treatment for advanced lung adenocarcinoma patients with EGFR mutations (7), and the overall survival (OS) of patients with EGFR mutations have been reported to be improved significantly compared to those patients without EGFR mutations in previous studies (6). Additionally, EGFR mutation status is a predictor for the outcome of TKIs therapy (2).

However, whether the EGFR mutation itself has an impact on the prognosis of lung adenocarcinoma patients remains controversial. Several previous studies demonstrated that the status of EGFR mutation could predict the prognosis in lung adenocarcinoma patients (5,8-13). In contrast, some studies revealed that EGFR mutation was not a risk factor for postoperative recurrence of lung adenocarcinoma (3,14-20). Besides, most previous studies either did not consider the pathologic stage and pathologic tumor size, or did not exclude the influence of its histologic subtype, radiologic characteristics and TKIs therapy (21-23). Moreover, the radiologic component, histologic subtype, pathologic stage and TKIs therapy, which may have been related to the EGFR mutation, would significantly influence the prognosis of lung cancer based on previous studies (1,2,5).

Therefore, we retrospectively analyzed the recurrence-free survival (RFS) of the pT1a (pathologic T1a) and pT1b (pathologic T1b) invasive lung adenocarcinoma patients who underwent radical surgery with reference to the status of EGFR mutation along with other clinicopathologic variables aimed to exclude the influence of TKIs therapy and ascertain its impact in small lung adenocarcinoma and analyzed the prognostic factor for OS.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/jtd-21-924).

Methods

Patients

Between August 2009 and February 2015, we retrospectively collected lung adenocarcinoma patients who received radical surgery at the Department of Thoracic Surgery, Fudan University Shanghai Cancer Center (FUSCC). This study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center (No. 090977-1) and was performed in the light of the approved guidelines. Written informed consent was waived since it was a retrospective study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The clinicopathologic data of all patients were recorded in the inpatient system of our hospital. In the current study, patients will be admitted to our study if they met the following criteria: (I) all pathologic slides were histologically confirmed diagnosis of invasive lung adenocarcinoma with pathologic tumor size no more than 2 cm by two experienced pathologist according to the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) classification criteria and were grouped into three grades, lepidic pattern-predominant adenocarcinoma (LPA) as low grade, acinar pattern-predominant adenocarcinoma (APA)/papillary pattern-predominant adenocarcinoma (PPA)/invasive mucinous adenocarcinoma (IMA) as intermediate grade, and micropapillary pattern-predominant adenocarcinoma (MPA)/solid pattern-predominant adenocarcinoma (SPA) as high grade; (II) radiological appearance of all patients were independently reviewed by two radiologists according to the thin-section computed tomography (CT) scan and were divided into three categories: pure ground-glass opacity (GGO), part-solid nodules and solid nodules; (III) EGFR mutations analysis was used sanger sequencing; (IV) follow-up was regular and the data was recorded completely. Finally, 338 patients with pT1a and pT1b invasive lung adenocarcinoma lesions were committed to our study. Demographic and clinicopathologic data such as gender, age, smoking history, histologic subtype, visceral pleural invasion (VPI) and lymphovascular invasion (LVI) of all patients included in the study were obtained from the electronic medical record. TNM classification were assessed according to the UICC 8th TNM classification.

Follow-up and statistical analysis

Follow-up was routinely conducted every 4 months for the first 3 years after surgery, followed by every 6 months for the next 2 years, and at 12-month intervals thereafter. For every follow-up, we routinely checked patients' clinical symptoms, and then perform some necessary clinical examinations, such as chest CT, ultrasound, magnetic resonance imaging (MRI). Recurrence was defined as local recurrence and distant recurrence. RFS was defined as the time between the date of surgery to the date of disease recurrence or the last follow-up. OS time was calculated from the date of surgery to the date of death or the last follow-up.

All statistical analysis was conducted by SPSS 25.0 and GraphPad Prism 8. RFS and OS was estimated by the Kaplan–Meier method. Correlations between two groups were compared with Pearson's chi-square test or Fisher exact test. The log-rank test was used to identify potential prognostic factors such as radiologic component, N stage, EGFR status. Multivariate Cox regression models were used to explore independent prognostic factors. Variables with a P value less than 0.05 in univariate analysis would be included the multivariate survival analysis. The significance level for all statistics was set at P<0.05 with two tail.

Results

Patient characteristics and associations of EGFR mutation status with clinicopathologic features

In this study, 338 patients, who were diagnosed as pT1a (49, 14.5%) and pT1b (289, 85.5%) invasive lung adenocarcinoma from August 2009 to February 2015, were admitted to the analysis cohort. EGFR mutation was found in 216 (63.9%) patients, of whom exon 19 deletions mutation and L858R mutation in exon 21 were the two most frequent mutation, accounted for 44.9% and 47.7% respectively. Other types of EGFR mutations including exon 18, exon 20 were detected in 16 (7.4%) patients. There were 186 (55.0%) females and 152 (45.0%) males, among whom 100 (29.6%) were ever smokers and 238 (70.4%) were never smokers, with the median age of 61 years (range, 24–82 years). According to radiologic component of tumor lesions, all patients were categorized as pure-GGO (13, 3.8%), part-solid nodules (168, 49.7%) and solid nodules (157, 46.4%) respectively. Among the histologic subtype, APA (234, 69.2%) was the most common subtype in our study, followed by LPA (53, 15.7%), PPA (20, 5.9%), SPA (16, 4.7%), MPA (8, 2.4%) and IMA (7, 2.1%). Lymph node metastasis could be found in 56 (16.6%) patients. In the light of 8th Edition of the TNM Classification for Lung Cancer, all patients were divided into pathologic I A1 (47, 13.9%), II A2 (235, 69.5%), II B (15, 4.4%) and III A (41, 12.1%) respectively (Table 1).

This study found that female (P=0.011) and never smoking (P=0.014) patients were more susceptible to EGFR mutation. Moreover, EGFR mutation was more frequent in patients with part-solid nodules (P=0.005) and PPA/APA/LPA (P=0.005; Table 1).

Prognostic value of EGFR mutation status

During follow-up, 52 (15.4%) patients died and 71 (21.0%)

Table 1 Clinicopathologic characteristics of 338 patients with pT1a and pT1b invasive lung adenocarcinoma

Variables	Total (N=338,100%)	Wild-type EGFR (N=122, 36.1%)	Mutated EGFR (N=216, 63.9%)	E19 del-mutation (N=97, 44.9%)	E21 L858R-mutation (N=103, 47.7%)	Other mutations (N=16, 7.4%)	P value
Age (years)							
<60	143 (42.3)	44 (30.8)	99 (69.2)	50 (50.5)	40 (40.4)	9 (9.1)	0.081
≥60	195 (57.7)	78 (40.0)	117 (60.0)	47 (40.2)	63 (53.8)	7 (6.0)	
Gender							
Male	152 (45.0)	66 (43.4)	86 (56.6)	40 (46.5)	39 (45.3)	7 (8.1)	0.011
Female	186 (55.0)	56 (30.1)	130 (69.9)	57 (43.8)	64 (49.2)	9 (6.9)	
Smoking history							
Ever	100 (29.6)	46 (46.0)	54 (54.0)	25 (46.3)	24 (44.4)	5 (9.3)	0.014
Never	238 (70.4)	76 (31.9)	162 (68.1)	72 (44.4)	79 (48.8)	11 (6.8)	

Table 1 (continued)

Table 1 (*continued*)

Variables	Total (N=338,100%)	Wild-type EGFR (N=122, 36.1%)	Mutated EGFR (N=216, 63.9%)	E19 del-mutation (N=97, 44.9%)	E21 L858R-mutation (N=103, 47.7%)	Other mutations (N=16, 7.4%)	P value
Surgical procedure							
Lobectomy	303 (89.6)	109 (36.0)	194 (64.0)	88 (45.4)	92 (47.4)	14 (7.2)	0.840
Segmentectomy	21 (6.2)	7 (33.3)	14 (66.7)	5 (35.7)	7 (50.0)	2 (14.3)	
Wedge	14 (4.1)	6 (42.9	8 (57.1)	4 (50.0)	4 (50.0)	0	
Radiologic component							
Pure GG0	13 (3.8)	4 (30.8)	9 (69.2)	2 (22.2)	6 (66.7)	1 (11.1)	0.005
Part-Solid	168 (49.7)	47 (28.0)	121 (72.0)	47 (38.8)	65 (53.7)	9 (7.4)	
Solid	157 (46.4)	71 (45.2)	86 (54.8)	48 (55.8)	32 (37.2)	6 (7.0)	
Histologic subtype							
APA	234 (69.2)	77 (32.9)	157 (67.1)	71 (45.2)	73 (46.5)	13 (8.3)	0.005
LPA	53 (15.7)	19 (35.8)	34 (64.2)	10 (29.4)	23 (67.6)	1 (2.9)	
PPA	20 (5.9)	5 (25.0)	15 (75.0)	9 (60.0)	5 (33.3)	1 (6.7)	
MPA	8 (2.4)	5 (62.5)	3 (37.5)	3 (100.0)	0	0	
SPA	16 (4.7)	10 (62.5)	6 (37.5)	4 (66.7)	2 (33.3)	0	
IMA	7 (2.1)	6 (85.7)	1 (14.3)	0	0	1 (100.0)	
Pathological tumor size (mm)							
≤10	49 (14.5)	21 (42.9)	28 (57.1)	6 (21.4)	17 (60.7)	5 (17.9)	0.286
>10, ≤20	289 (85.5)	101 (34.9)	188 (65.1)	91 (48.4)	86 (45.7)	11 (5.9)	
N stage							
N0	282 (83.4)	101 (35.8)	181 (64.2)	73 (40.3)	93 (51.4)	15 (8.3)	0.811
N1–2	56 (16.6)	21 (37.5)	35 (62.5)	24 (68.6)	10 (28.6)	1 (2.9)	
Pathological TNM stage							
IA1	47 (13.9)	21 (44.7)	26 (55.3)	5 (19.2)	16 (61.5)	5 (19.2)	0.565
IA2	235 (69.5)	80 (34.0)	155 (66.0)	68 (43.9)	77 (49.7)	10 (6.5)	
IIB	15 (4.4)	6 (40.0)	9 (60.0)	7 (77.8)	2 (22.2)	0	
IIIA	41 (12.1)	15 (36.6)	26 (63.4)	17 (65.4)	8 (30.8)	1 (3.8)	
VPI							
Present	50 (14.8)	19 (38.0)	31 (62.0)	16 (51.6)	12 (38.7)	3 (9.7)	0.761
Absent	288 (85.2)	103 (35.8)	185 (64.2)	81 (43.8)	91 (49.2)	13 (7.0)	
LVI							
Present	38 (11.2)	13 (34.2)	25 (65.8)	16 (64.0)	8 (32.0)	1 (4.0)	0.797
Absent	300 (88.8)	109 (36.3)	191 (63.7)	81 (42.4)	95 (49.7)	15 (7.9)	

APA, acinar pattern-predominant adenocarcinoma; LPA, lepidic pattern-predominant adenocarcinoma; PPA, papillary pattern-predominant adenocarcinoma; MPA, micropapillary pattern-predominant adenocarcinoma; SPA, solid pattern-predominant adenocarcinoma; IMA, invasive mucinous adenocarcinoma; VPI, visceral pleural invasion; LVI, lymphovascular invasion.

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Table 2 Univariate and multivariate RFS and OS analysis of 282 patients in the entire cohort

| Variables	RFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age, years (≥60 vs. <60)	1.195 (0.750–1.905)	0.455			3.266 (1.894–5.631)	<0.001	3.086 (1.585–6.024)	0.001
Gender (male vs. female)	1.079 (0.676–1.723)	0.748			1.604 (0.928–2.774)	0.087		
Smoking history (ever vs. never)	1.145 (0.692–1.894)	0.589			1.736 (0.958–3.147)	0.046	1.767 (1.016–3.077)	0.044
Radiologic component (solid vs. part-solid)	4.871 (3.057–7.759)	<0.001	3.215 (1.678–6.173)	<0.001	5.986 (3.474–10.31)	<0.001	3.759 (1.590–8.850)	0.003
Surgical procedure (LOB vs. SEG/WED)	3.221 (1.401–7.404)	0.08			1.054 (0.389–2.858)	0.92		
Histologic subtype (high vs. intermediate)	1.314 (0.549–3.146)	0.490			2.582 (0.920–7.246)	0.007		0.330
Pathological tumor size (T1b vs. T1a)	1.314 (0.676–2.553)	0.463			1.502 (0.682–3.304)	0.382		
N stage (N1–2 vs. N0)	5.101 (2.602–10.00)	<0.001	3.215 (1.934–5.319)	<0.001	5.110 (2.541–10.28)	<0.001	3.257 (1.799–5.882)	<0.001
VPI (present vs. absent)	1.887 (0.971–3.668)	0.020		0.495	2.047 (0.985–4.256)	0.015		0.566
LVI (present vs. absent)	2.387 (1.103–5.168)	0.002		0.512	3.452 (1.511–7.891)	<0.001		0.401
EGFR mutation (yes vs. no)	0.899 (0.551–1.468)	0.664			0.468 (0.263–0.832)	0.005		0.121

RFS, recurrence-free survival; OS, overall survival; LOB, lobectomy; SEG, segmentectomy; WED, wedge; VPI, visceral pleural invasion; LVI, lymphovascular invasion; EGFR, epidermal growth factor receptor.

patients experienced recurrence. The most common site of recurrence was the local recurrence of lung (32, 45.1%), followed by the distant recurrence of bone (14, 19.7%), lymph node (10, 14.1%), pleura (10, 14.1%), brain (3, 4.2%), liver (1, 1.4%), kidney (1, 1.4%). Among patients with node-positive disease, 44 (78.6%) patients received adjuvant chemotherapy, 5 (8.9%) patients received concurrent adjuvant radiotherapy and chemotherapy, there remained 7 (12.5%) patients did not receive any adjuvant therapy. The median follow-up time was 64 months (interquartile range, 59–73 months) in all patients. In the entire cohort, 56 patients with LPA and pure-GGO nodules had an excellent survival, so we ruled out these patients for the further survival analysis. All patients did not receive EGFR-TKIs therapy before recurrence and 282 patients were admitted to the RFS analysis finally. The 5-year RFS rates were 69% for patients with wild-type EGFR and 72% for patients with mutated EGFR respectively (P=0.664;

Table 2). After recurrence, 27 of 45 patients with EGFR mutation received TKIs therapy. Eighteen of 45 patients with EGFR mutation did not receive TKIs therapy, of whom 9 patients received chemotherapy, 3 patients received radiotherapy and 6 patients did not receive chemotherapy or radiotherapy.

In the entire cohort, EGFR mutation status had no prognostic value for RFS (P=0.664; Table 2, Figure 1). In addition, univariate analysis revealed that EGFR mutation status was significantly associated with the OS of patients with pT1a and pT1b invasive lung adenocarcinoma after excluding LPA and pure GGO (P=0.005; Table 2, Figure 2). However, EGFR mutation status was not an independent prognostic factor for OS in the entire cohort (P=0.121; Table 2).

We further evaluated the prognostic value of EGFR mutation status in the subgroups classified by N stage, pT stage, radiologic component and histologic subtype.
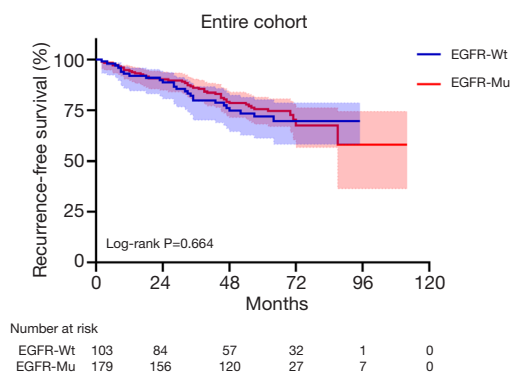
Figure 1 EGFR mutation status could not predict the recurrence-free survival in patients with pT1a and pT1b invasive lung adenocarcinoma after excluding LPA and puro GGO. EGFR, epidermal growth factor receptor; LPA, lepidic pattern-predominant adenocarcinoma; GGO, pure ground-glass opacity.
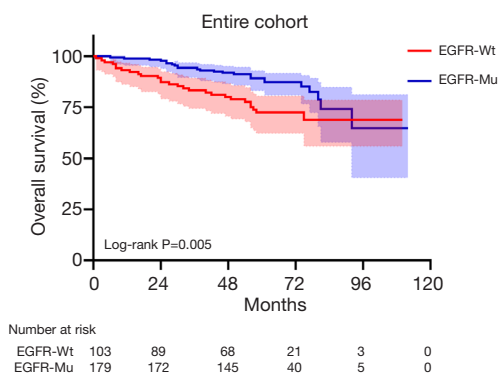
Figure 2 Univariate analysis revealed that EGFR mutation status was significantly associated with the overall survival of patients with pT1a and pT1b invasive lung adenocarcinoma after excluding LPA and puro GGO. EGFR, epidermal growth factor receptor; LPA, lepidic pattern-predominant adenocarcinoma; GGO, pure ground-glass opacity.
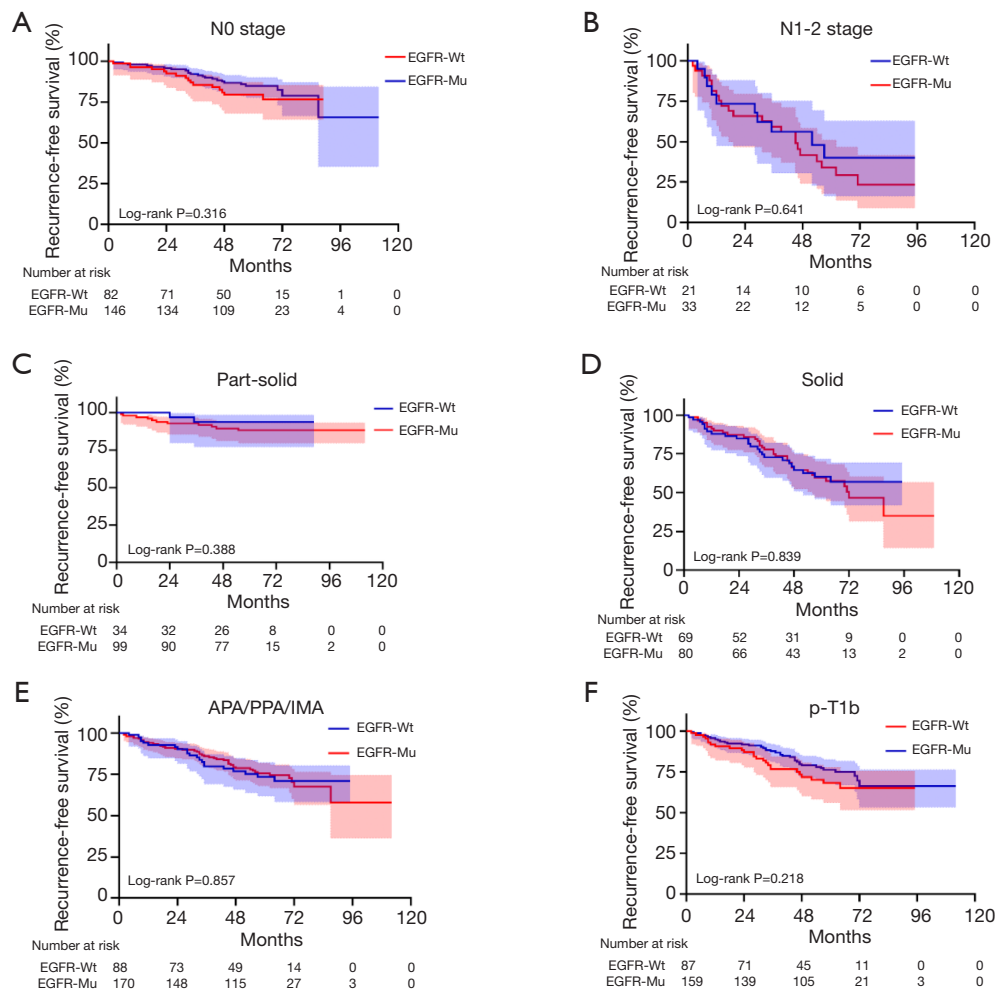
EGFR mutation status could still not predict the RFS time in the subgroup of N0 stage cohort (P=0.316; *Figure 3A*), N1-2 stage cohort (P=0.641; *Figure 3B*), part-solid cohort (P=0.388; *Figure 3C*), solid cohort (P=0.839; *Figure 3D*), APA/PPA/IMA cohort (P=0.857; *Figure 3E*) and pT1b cohort (P=0.218; *Figure 3F*). With regard to OS, EGFR mutation status had the prognostic value for OS in the subgroup of N0 stage cohort (P=0.013; *Figure 4A*), N1-2 stage (P=0.033; *Figure 4B*) cohort, APA/PPA/IMA cohort (P=0.011; *Figure 4C*) and pT1b cohort (P=0.002; *Figure 4D*) in univariate analysis, whereas part-solid cohort

(P=0.679; *Figure 4E*) and solid cohort (P=0.057; *Figure 4F*) did not. EGFR mutations had no independent prognostic significance for OS in the subgroup of N0 stage cohort (P=0.263), APA/PPA/IMA cohort (P=0.107) and pT1b cohort (P=0.056) in multivariate analysis (*Tables 3-5*). pT1a cohort (N=36) and MPA/SPA cohort (N=24) failed to conduct survival analysis due to the smaller number of patients. Similarly, there was no significant difference in RFS between patients with wild type EGFR and patients with the two major mutations (E19del and E21L858R) of EGFR (Figures S1,S2).

Discussion

With the widespread application of thin-CT in the disease screening and physical examination, the number of small lung nodules are increasingly detected (24), and lung adenocarcinoma is one of the most common histologic subtypes of lung cancer (25). In addition, more and more patients choose important oncogene especially EGFR for sequencing due to the affordability of gene sequencing and the development of targeted therapy in order to better understand the disease and instruct the future treatment. Our previous study has revealed that EGFR mutation was a poor prognostic factor in specific subgroup including radiologic solid, histologic APA/PPA/IMA, and pathologic stage II and III lung adenocarcinomas (13). But there remains controversial in the prognostic value of EGFR mutation. Therefore, we conduct this study aimed to investigate the prognostic value of EGFR mutation in patients with small (pT≤2 cm) invasive lung adenocarcinoma.

EGFR mutation status has been reported to be closely correlated with several clinicopathologic factors in lung adenocarcinoma including gender, smoking history, tumor size, pathologic TNM stage, radiologic component and histologic subtype in multiple previous studies (3,14,15,26,27). Several previous studies showed that the presence of EGFR mutation was significantly frequent in female and never smokers, which was consistent with our present study (13). Besides, Lin *et al.* (14), whose study also focused on the small lung adenocarcinoma, recognized that EGFR mutation rate was significantly higher in patients with pT1b. However, our study found that the rate of EGFR mutation was similar in pT1a and pT1b (57.1% *vs.* 65.1%, P=0.286), it might be explained that our study excluded adenocarcinoma *in situ* (AIS) and microinvasive adenocarcinoma (MIA) patients, which trend to be have a

Figure 3 EGFR mutation status could not predict the recurrence-free survival in patients with different subgroups classified by N stage, radiologic component, histologic subtype and pathologic tumor size after excluding LPA and puro GGO. EGFR, epidermal growth factor receptor; LPA, lepidic pattern-predominant adenocarcinoma; GGO, pure ground-glass opacity.

smaller tumor size, whereas they did not. According to the radiologic component and histologic subtype, our study demonstrated that part-solid nodules and intermediate-grade lung adenocarcinoma exist more mutated EGFR, which was in line with previous studies (13,15,26,27).

EGFR mutation status has been reported to be a prognostic factor in several studies; some studies believed that EGFR mutation was a good prognostic factor for lung adenocarcinoma (5,8,10,28), while others believed that it was a poor prognostic factor including our previous study (12,13). To sum up, there remains controversial in the prognostic value of EGFR mutation. In our study, we choose RFS as a study endpoint in order to exclude the influence of TKIs therapy. In addition, we excluded patients

with pure GGO and LPA in the survival analysis aimed to eliminate the bias caused by the excellent prognosis of patients with pure GGO and LPA. Our present study showed that EGFR mutation was not correlated with RFS in the entire cohort and the subgroups classified by clinicopathologic characteristics and radiologic component, which was similar to the research results of Matsumura *et al.* (17) and Lin *et al.* (14), whose studies also focused on the small lung adenocarcinoma and excluded the influence of TKI therapy. In addition, Ohba *et al.* (18) and colleagues found that EGFR mutation was not a prognostic factor in resected stage I lung adenocarcinoma. Moreover, our study revealed that RFS was also not significantly different between patients with wild type EGFR, E19del mutation
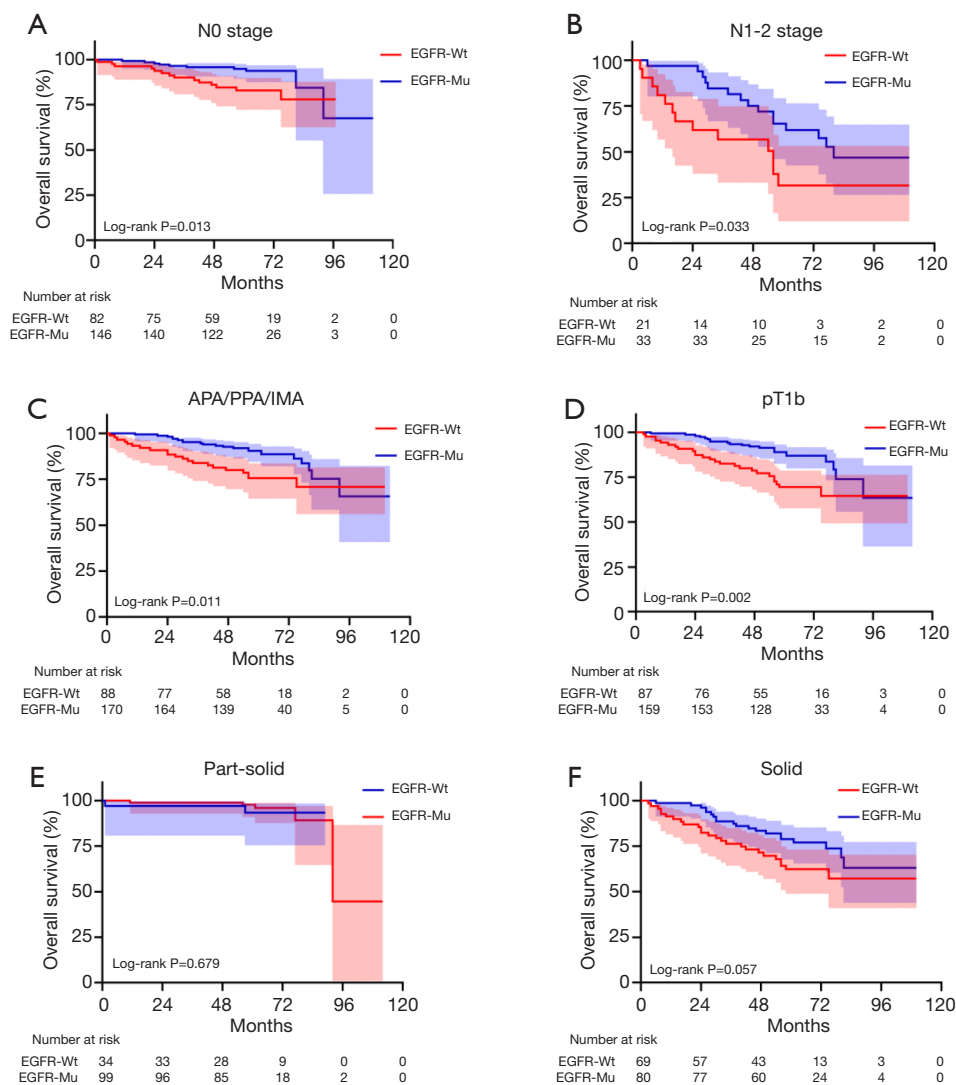
Figure 4 The prognostic value of EGFR mutation status in the subgroups of patients with pT1a and pT1b invasive lung adenocarcinoma after excluding LPA and puro GGO. EGFR, epidermal growth factor receptor; LPA, lepidic pattern-predominant adenocarcinoma; GGO, pure ground-glass opacity.

and E21L858R mutation. The similar results were found in the studies of Takamochi *et al.* (10) and Kosaka *et al.* (9), but they found that patients with EGFR mutations survived for a longer period than those without mutations. Angelo demonstrated that patients with EGFR mutation had a lower risk of death compared with patients without EGFR mutation, which might be accounted by the treatment of EGFR-TKIs. In our study, relapses were found in 45 patients with EGFR mutation, and the 5-year OS rate was higher in patients treated with TKIs than in those not treated with TKIs, which reveals that EGFR mutation

is a predictor for EGFR TKIs response. Overall, our results suggested that EGFR mutation itself had no value in predicting the relapse in patients with pT1a and pT1b invasive lung adenocarcinoma, but it could predict the response of TKIs in patients with EGFR mutation after recurrence.

To the best of our knowledge, this is the largest study to compare the clinicopathologic characteristics and survival in relation to the status of EGFR mutation in patients with pT1a and pT1b invasive lung adenocarcinoma. However, there are some limitations. Firstly, although our study had

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Table 3 Univariate and multivariate RFS and OS analysis of 228 patients with N0 stage

Variables	RFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age, years (≥60 vs. <60)	1.068 (0.570–2.001)	0.837			6.144 (2.755–13.70)	<0.001	5.988 (1.757–20.41)	0.004
Gender (male vs. female)	1.038 (0.553–1.950)	0.907			1.726 (0.772–3.858)	0.181		
Smoking history (ever vs. never)	1.419 (0.718–2.804)	0.285			1.959 (0.819–4.683)	0.094		
Radiologic component (solid vs. part-solid)	4.915 (2.593–9.318)	<0.001	3.096 (1.590–6.024)	0.001	4.734 (2.117–10.59)	<0.001	4.926 (1.821–13.33)	0.002
Surgical procedure (LOB vs. SEG/WED)	3.937 (1.342–11.55)	0.143			0.500 (0.124–2.011)	0.195		
Histologic subtype (high vs. intermediate)	1.636 (0.459–5.827)	0.345			2.581 (0.549–12.14)	0.071		
Pathological tumor size (T1b vs. T1a)	1.099 (0.473–2.552)	0.830			1.339 (0.451–3.982)	0.633		
VPI (present vs. absent)	1.334 (0.508–3.506)	0.508			3.190 (0.991–10.27)	0.004		0.109
LVI (present vs. absent)	1.874 (0.396–8.868)	0.285			5.369 (0.807–35.74)	<0.001	3.257 (1.179–9.009)	0.023
EGFR mutation (yes vs. no)	0.724 (0.372–1.407)	0.316			0.375 (0.162–0.871)	0.013		0.263

RFS, recurrence-free survival; OS, overall survival; LOB, lobectomy; SEG, segmentectomy; WED, wedge; VPI, visceral pleural invasion; LVI, lymphovascular invasion; EGFR, epidermal growth factor receptor.

Table 4 Univariate and multivariate RFS and OS analysis of 258 patients with APA/PPA/IMA

Variables	RFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age, years (≥60 vs. <60)	1.174 (0.719–1.917)	0.522			3.467 (1.906–6.307)	<0.001	3.268 (1.565–6.849)	0.002
Gender (male vs. female)	1.016 (0.620–1.666)	0.948			1.519 (0.831–2.777)	0.167		
Smoking history (ever vs. never)	1.154 (0.675–1.973)	0.589			1.791 (0.925–3.469)	0.055		
Radiologic component (solid vs. part-solid)	4.834 (2.954–7.912)	<0.001	3.096 (1.590–6.024)	0.001	6.279 (3.453–11.42)	<0.001	4.184 (1.650–10.64)	0.003
Surgical procedure (LOB vs. SEG/WED)	2.612 (1.046–6.523)	0.164			0.795 (0.256–2.466)	0.659		
Pathological tumor size (T1b vs. T1a)	1.186 (0.591–2.379)	0.649			1.235 (0.523–2.924)	0.656		
N-stage (N1–2 vs. N0)	5.632 (2.707–11.72)	<0.001	3.509 (2.049–6.024)	<0.001	5.060 (2.344–10.92)	<0.001	2.985 (1.553–5.747)	0.001
VPI (present vs. absent)	1.963 (0.958–4.023)	0.019		0.452	1.961 (0.876–4.388)	0.039		0.894
LVI (present vs. absent)	2.261 (0.971–5.264)	0.009		0.304	2.806 (1.123–7.012)	0.001		0.674
EGFR mutation (yes vs. no)	0.953 (0.563–1.613)	0.857			0.470 (0.246–0.897)	0.011		0.107

RFS, recurrence-free survival; OS, overall survival; APA, acinar pattern-predominant adenocarcinoma; PPA, papillary pattern-predominant adenocarcinoma; IMA, invasive mucinous adenocarcinoma; LOB, lobectomy; SEG, segmentectomy; WED, wedge; VPI, visceral pleural invasion; LVI, lymphovascular invasion; EGFR, epidermal growth factor receptor.

Table 5 Univariate and multivariate RFS analysis of 246 patients with pT1b

Variables	RFS Univariate analysis HR (95% CI)	P value	RFS Multivariate analysis HR (95% CI)	P value	OS Univariate analysis HR (95% CI)	P value	OS Multivariate analysis HR (95% CI)	P value
Age, years (≥60 vs. <60)	1.121 (0.683–1.840)	0.653			3.151 (1.776–5.593)	<0.001	2.976 (1.477–5.988)	0.002
Gender (male vs. female)	1.052 (0.639–1.732)	0.842			1.561 (0.875–2.786)	0.123		
Smoking history (ever vs. never)	1.077 (0.624–1.860)	0.786			1.696 (0.889–3.234)	0.073		
Radiologic component (solid vs. part-solid)	5.610 (3.423–9.195)	<0.001	3.745 (1.808–7.752)	<0.001	7.621 (4.299–13.51)	<0.001	5.076 (1.905–13.51)	0.001
Surgical procedure (LOB vs. SEG/WED)	3.129 (1.337–7.321)	0.093			1.411 (0.514–3.876)	0.560		
Histologic subtype (high vs. intermediate)	1.468 (0.586–3.678)	0.333			2.857 (0.975–8.371)	0.003		0.107
N-stage (N1–2 vs. N0)	4.890 (2.479–9.644)	<0.001	2.933 (1.721–5.000)	<0.001	4.715 (2.331–9.537)	<0.001	2.770 (1.497–5.128)	0.001
VPI (present vs. absent)	1.893 (0.932–3.843)	0.028		0.508	1.882 (0.877–4.037)	0.045		0.807
LVI (present vs. absent)	2.355 (1.093–5.077)	0.003		0.585	3.420 (1.508–7.755)	<0.001		0.418
EGFR mutation (yes vs. no)	0.730 (0.431–1.237)	0.218			0.413 (0.224–0.763)	0.002		0.056

RFS, recurrence-free survival; LOB, lobectomy; SEG, segmentectomy; WED, wedge; VPI, visceral pleural invasion; LVI, lymphovascular invasion; EGFR, epidermal growth factor receptor.

a larger population than the study of LIN, whose study also focused on the small lung adenocarcinoma, the bias of patients' selection and follow-up procedure were inevitable. Additionally, the occurrence and development of lung cancer is a complex process of multi-gene mutations, such as mutations in the driver gene EGFR and mutations in tumor suppressor gene TP53. Therefore, a single gene mutation may not be sufficient to explain the prognosis, further analysis of other genes mutation is needed.

Conclusions

EGFR mutation was not a risk factor for recurrence of patients with pT1a and pT1b invasive lung adenocarcinoma.

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Footnote

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in the light of the approved guidelines. Written informed consent was waived since it was a retrospective study.

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