Thoracic Cancer

Open Access

Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Larger tumors are associated with inferior progression-free survival of first-line EGFR-tyrosine kinase inhibitors and a lower abundance of *EGFR* mutation in patients with advanced non-small cell lung cancer

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Keywords
Adenocarcinoma; efficacy; EGFR-TKIs; tumor size.

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Received: 2 November 2018;
Accepted: 2 January 2019.

doi: 10.1111/1759-7714.12986

Thoracic Cancer **10** (2019) 686–694

Abstract

Background: The impact of primary tumor size on the therapeutic outcomes of EGFR-tyrosine kinase inhibitors (TKIs) in advanced non-small cell lung cancer (NSCLC) with *EGFR* mutation remains unclear.

Methods: A total of 291 consecutive patients with advanced *EGFR*-mutant NSCLC administered first-line EGFR-TKIs were enrolled. Computed tomography was used to assess primary tumor diameter. The amplification refractory mutation system plus was used to quantitatively evaluate the abundance of *EGFR* mutations. Associations between depth of response, abundance of *EGFR* mutations, and tumor size was investigated.

Results: Patients were divided into three groups according to T classification: ≤ 3 cm (n = 109), 3–5 cm (n = 121), and > 5 cm (n = 61). Median progression-free survival (PFS) was significantly longer in the ≤ 3 cm and 3–5 cm groups compared to the > 5 cm group (10.8 vs. 10.5 vs. 7.1 months; $P < 0.001$). Subgroup analysis revealed a consistent result in patients with exon 19 deletion and 21 L858R mutation. Multivariate analysis revealed that tumor size was an independent predictive factor for PFS (hazard ratio 1.528, 95% confidence interval 1.104–2.115; $P = 0.010$). Larger tumors (> 5 cm) were marginally significantly less *EGFR*-mutant abundant than smaller tumors (≤ 5 cm) (mean ± standard deviation 30.5 ± 29.5% vs. 45.8 ± 43.1%; $P = 0.08$).

Conclusion: Larger tumors (> 5 cm) were associated with inferior PFS of first-line EGFR-TKI therapy in advanced NSCLC patients with activating *EGFR* mutations. A potential explaination might be that *EGFR* mutations are less abundant in larger tumors.

Introduction

In patients with *EGFR* sensitizing mutations, EGFR-tyrosine kinase inhibitors (TKIs) significantly improve the objective response rate (ORR) and prolong progression-free survival (PFS) compared to platinum-based chemotherapy.[1–4] However, not all advanced NSCLC patients with *EGFR* mutations respond evenly to EGFR-TKIs. Therefore, it is important to identify the subpopulation that receive an inferior benefit from EGFR-TKIs.

Several studies, including our previous reports, have found that *EGFR* mutation abundance and *BIM* polymorphism could be helpful to predict the efficacy of first-line EGFR-TKI therapy.[5,6] Recently, concurrent genomic mutations, such as *STAT3 and YAP1 or TP53*, were also found to have a detrimental effect on EGFR-TKI efficacy.[7–9] Several other studies also investigated the predictive role of clinicopathological features for EGFR-TKIs and found that squamous cell carcinoma subtype and higher tumor burden were associated

with poor outcomes after EGFR-TKI treatment.[10,11] Tumor size significantly affects survival outcomes in patients with early-stage NSCLC and locally advanced disease.[12] Therefore, the updated 8th edition International Association for the Study of Lung Cancer (IASLC) tumor node metastasis (TNM) classification subcategories, T1 and T2 tumors, have been divided into T1a, T1b, T1c, T2a, and T2b and larger tumors (> 7 cm) have been upgraded to T4.[13] These changes in staging reflect the statistically different prognoses of such cases. However, the impact of these reclassifications on the therapeutic outcomes of EGFR-TKIs in *EGFR*-mutant advanced NSCLC is still not well known.

We conducted this retrospective study of 291 consecutive patients with advanced *EGFR*-mutant NSCLC who received first-line EGFR-TKIs to comprehensively investigate the association of clinicopathological features, especially tumor size, with the efficacy of EGFR-TKIs. We also analyzed the association between clinicopathological features and *EGFR* mutation abundance.

Methods

Patient selection

Consecutive patients with advanced *EGFR*-mutant NSCLC who received first-line EGFR-TKI treatment at the Department of Oncology, Shanghai Pulmonary Hospital, China from June 2008 to February 2016 were enrolled. All patients were diagnosed pathologically according to World Health Organization (WHO) pathology classification.[14] The key eligibility criteria included: histologically or cytologically confirmed newly diagnosed stage IIIB or IV or recurrent NSCLC; measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST); Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; harboring *EGFR* sensitizing mutations; and receiving EGFR-TKIs as first-line therapy. Patients administered concurrent thoracic radiotherapy or ablation were excluded from this study. All clinicopathological data were extracted from electronic medical records at Shanghai Pulmonary Hospital. Common *EGFR* mutations were defined as mutations including exon 19 deletion (19del) and Leu858Arg point mutation in exon 21 (L858R). Rare *EGFR* mutations were defined as those in exons 18 and 20 other than 19del and L858R mutations.

This study was approved by the Ethics Committee of Shanghai Pulmonary Hospital. Written informed consent was obtained from each participant before the initiation of the study.

Review of computed tomography images and evaluation of efficacy

Computed tomography (CT) scans were performed on all patients via two CT machines (64 × 1 mm acquisition, slice width 1 mm, Brilliance, Philips Medical Systems Inc, Cleveland, USA; or 128 × 1 mm acquisition, slice width 1 mm, SOMATOM Definition AS, Siemens Aktiengesellschaft, Munich, Germany) before bronchoscopy or a percutaneous CT-guided biopsy.

The largest tumor diameter (cm) was measured according to the baseline CT examination. The CT images were independently evaluated by two investigators. Disagreements were resolved by consensus or by a third reviewer. The response was evaluated according to RECIST version 1.1.[15]

Molecular analyses

All mutational analyses were performed at the Tongji University Thoracic Cancer Institute. Briefly, DNA from tumor tissue was extracted using the DNeasy Blood and Tissue Kit or the QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). *EGFR* mutations (exons 18–21) were detected by amplification refractory mutation system (ARMS, Amoy Diagnostics Co. Ltd., Xiamen, China). The abundance of *EGFR* mutation in tumor tissue samples was quantitatively assessed using ARMS+. The procedure details are described in our previous studies.[5,6,16–19]

Statistical analysis

Categorical variables were compared using Fisher's exact or chi-square tests, and continuous variables were compared using the Mann–Whitney *U* test. PFS was defined as the time from initiation of EGFR-TKI treatment to disease progression or death from any cause, whichever occurred first. Patients not experiencing an event were censored at the last date of follow-up or the last date of disease assessment for PFS. PFS was analyzed by Kaplan–Meier plots and the log-rank test was used to calculate the significance between groups. The predictive factors for PFS were analyzed using univariate and multivariate Cox proportional hazard models. All *P* values are two-sided, confidence intervals (CIs) are at the 95% level, and no adjustments were made for multiple comparisons. The two-sided significance level was set at $P < 0.05$. Data were analyzed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA) and the survival curve was drawn with GraphPad Prism 5.01 (GraphPad Software, San Diego, CA, USA).

Results

Patient characteristics

Overall, a total of 291 patients with *EGFR*-mutant advanced NSCLC who had baseline measurable disease by

Table 1 Clinicopathological characteristics of enrolled patients according to tumor size

Characteristics	All patients N = 291 (%)	Tumor size ≤ 3 cm N = 109 (%)	Tumor size > 3–5 cm N = 121 (%)	Tumor size > 5 cm N = 61 (%)	*P*
Age, Median (range), years	61 (26–86)	60 (28–81)	62 (27–86)	61 (26–85)	
≤ 65	185 (63.6)	72 (66.1)	72 (59.5)	41 (67.2)	0.472
> 65	106 (36.4)	37 (33.9)	49 (40.5)	20 (32.8)	
Gender					
Male	108 (37.1)	34 (31.2)	47 (38.8)	27 (44.3)	0.209
Female	182 (62.9)	75 (68.8)	74 (61.2)	34 (55.7)	
Smoking history					
Non-smoker	231 (79.4)	89 (81.7)	94 (77.7)	48 (78.7)	0.751
Former or current smoker	60 (20.6)	20 (18.3)	27 (22.3)	13 (21.3)	
ECOG PS					
0 or 1	270 (92.8)	103 (94.5)	110 (91.7)	56 (91.8)	0.683
> 1	21 (7.2)	6 (5.5)	10 (8.3)	5 (8.2)	
Pathology					
ADC	260 (89.7)	103 (95.4)	109 (90.1)	48 (78.7)	0.003
Non-ADC	30 (10.3)	5 (4.6)	12 (9.9)	13 (21.3)	
TNM stage					
Recurrent	10 (3.4)	6 (5.5)	4 (3.3)	0 (0.0)	0.365†
IIIB	38 (13.1)	16 (14.7)	12 (9.9)	10 (16.4)	
IV	243 (83.5)	87 (79.8)	105 (86.8)	51 (83.6)	
T stage					
T1–2	110 (37.8)	54 (49.5)	44 (36.4)	12 (19.7)	0.001
T3–4	181 (62.2)	55 (50.5)	77 (63.6)	49 (80.3)	
N stage					
N0–1	69 (23.7)	31 (28.4)	27 (22.3)	11 (18.0)	0.277
N2–3	222 (76.3)	78 (71.6)	94 (77.7)	50 (82.0)	
Tumor size (cm), mean ± SD	3.82 ± 1.80	2.16 ± 0.60	3.95 ± 0.58	6.55 ± 1.31	< 0.001
Brain metastasis	75 (26.6)	25 (22.9)	33 (28.7)	17 (29.3)	0.542
Liver metastasis	14 (4.9)	3 (2.8)	4 (3.4)	7 (11.9)	0.021
Bone metastasis	125 (44.0)	42 (38.9)	62 (52.5)	12 (36.2)	0.048
EGFR-TKIs					
Gefitinib	199 (68.4)	77 (70.6)	81 (66.9)	41 (67.2)	0.564‡
Erlotinib	42 (14.4)	12 (11.0)	21 (17.4)	9 (14.8)	
Icotinib	47 (16.2)	18 (16.5)	18 (14.9)	11 (18.0)	
Afatinib/osimertinib	3 (1.0)	2 (1.8)	1 (0.8)	0 (0.0)	
EGFR mutations					
Exon 19 deletion	133 (45.7)	51 (46.8)	52 (43.0)	30 (49.2)	0.934§
Exon 21 L858R	130 (44.7)	48 (44.0)	56 (46.3)	26 (42.6)	
Others¶	18 (9.6)	10 (9.2)	13 (10.7)	5 (8.2)	
Brain radiation					
Yes	54 (18.6)	20 (18.3)	25 (20.7)	9 (14.8)	0.625
No	237 (81.4)	90 (81.7)	96 (79.3)	52 (85.2)	
Bone radiation					
Yes	60 (20.6)	26 (23.9)	22 (18.2)	12 (19.7)	0.557

Table 1 Continued

Characteristics	All patients N = 291 (%)	Tumor size ≤ 3 cm N = 109 (%)	Tumor size > 3–5 cm N = 121 (%)	Tumor size > 5 cm N = 61 (%)	*P*
No	231 (79.4)	83 (76.1)	99 (81.8)	49 (80.3)	
Chest radiation					
Yes	27 (9.3)	12 (11.0)	12 (9.9)	3 (4.9)	0.402
No	264 (90.7)	97 (89.0)	109 (90.1)	58 (95.1)	

†Recurrent/IIIB versus stage IV. ‡Gefitinib versus other EGFR-tyrosine kinase inhibitors (TKIs). §Exon 19 deletion versus others. ¶Including *EGFR* mutations in exons 18 and 20. ADC, adenocarcinoma; ECOG PS, Eastern Corporation Oncology Group performance status; SD, standard deviation; TNM, tumor node metastasis.

Table 2 Univariate and multivariate Cox regression analyses of PFS in patients with *EGFR* mutations

Variable	Univariate analysis HR (95% CI)	*P*	Multivariate analysis HR (95% CI)	*P*
Tumor size: > 5 cm vs. ≤ 5 cm	1.446 (1.222–1.712)	< 0.001	1.528 (1.104–2.115)	0.010
Female vs. male	0.732 (0.559–0.958)	0.023	0.790 (0.601–1.038)	0.091
Age > 65 years vs. ≤ 65 years	0.734 (0.554–0.971)	0.030	0.734 (0.548–0.982)	0.037
ECOG PS > 1 vs. 0 or 1	0.865 (0.660–1.135)	0.297		
Smokers vs. non-smokers	1.193 (0.866–1.643)	0.281		
Non-ADC vs. ADC	1.550 (0.983–2.444)	0.059	1.679 (1.060–2.662)	0.027
TNM stage IV vs. stage III + recurrent	1.262 (0.882–1.806)	0.203		
Liver metastasis: Yes vs. no	1.472 (0.778–2.783)	0.235		
Bone metastasis: Yes vs. no	1.141 (0.875–1.488)	0.331		
Other EGFR-TKIs† vs. gefitinib	0.877 (0.656–1.173)	0.376		
Others vs. exon 19 deletion/L858R mutation‡	0.831 (0.664–1.042)	0.108	0.902 (0.717–1.135)	0.379
T3 + 4 stage vs. T1 + 2 stage	1.296(1.129–1.488)	0.000	1.288 (1.114–1.490)	0.001
N2 + 3 stage vs. N0 + 1 stage	1.234(1.047–1.454)	0.012	1.138 (0.962–1.345)	0.132

†Including erlotinib, icotinib, afatinib (1 patient), AZD9291 (patient). ‡Including *EGFR* mutations in exons 18 and 20. ADC, adenocarcinoma; CI, confidence interval; ECOG PS, Eastern Corporation Oncology Group performance status; HR, hazard ratio; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TNM, tumor node metastasis.

RECIST criteria were identified. The patient characteristics are presented in Table 1. The majority of patients (89.7%) had histology of adenocarcinoma and the median age was 61 (range: 26–86) years. Briefly, 62.9% of patients were female; 92.8% had ECOG PS 0 or 1; 79.4% were never-smokers; 37.8% had T1–2 stage, 23.7% had N0–1 stage; 45.7% had 19del; 26.6% had baseline brain metastasis, 4.9% had liver metastasis, and 44.0% had bone metastasis; and 68.4% of patients received first-line gefitinib, 14.4% received first-line erlotinib, and 16.2% received first-line icotinib.

Patients were divided into three groups according to baseline primary tumor size: ≤ 3 cm (37.5%, 109/291); 3–5 cm (41.6%, 121/291); and > 5 cm (20.9%, 61/291). The mean tumor sizes in these groups were 2.16 cm, 3.95 cm, and 6.55 cm, respectively ($P < 0.001$). Patients with larger tumors (> 5 cm) were more likely to have later T stage, histology of non-adenocarcinoma (21.3%), and liver metastasis (11.9%). There was no significant difference between the three groups with respect to age, gender, ECOG PS, smoking status, TNM stage, the incidence of baseline brain and bone metastases, and the types of EGFK-TKIs, and *EGFR* mutation subtypes (Table 2).

Efficacy of EGFR-tyrosine kinase inhibitors (TKI) according to tumor size

The median PFS rates in ≤ 3 cm, 3–5 cm, and > 5 cm groups were 10.8 (95% CI 8.5–13.1), 10.5 (95% CI, 9.7–11.3), and 7.1 (95% CI 5.5–8.7) months, respectively ($P < 0.001$). Of note, the difference was statistically significant between the ≤ 5 cm and > 5 cm groups, but was not significant between the ≤ 3 cm and 3–5 cm groups ($P = 0.335$) (Figs 1–2). The results were consistent in in patients with 19del or L858R mutations.

The ORRs of the ≤ 3 cm, 3–5 cm, and > 5 cm groups were 60.6%, 59.5%, and 54.1%, respectively ($P = 0.405$), and the disease control rates (DCRs) were 93.6% versus 91.7% versus 91.8%, respectively ($P = 0.832$) (Fig 3a,b). Therefore, the ORR and DCR were not statistically different between the three groups (Table S1). Furthermore, the results remained the same in patients with 19del or L858R

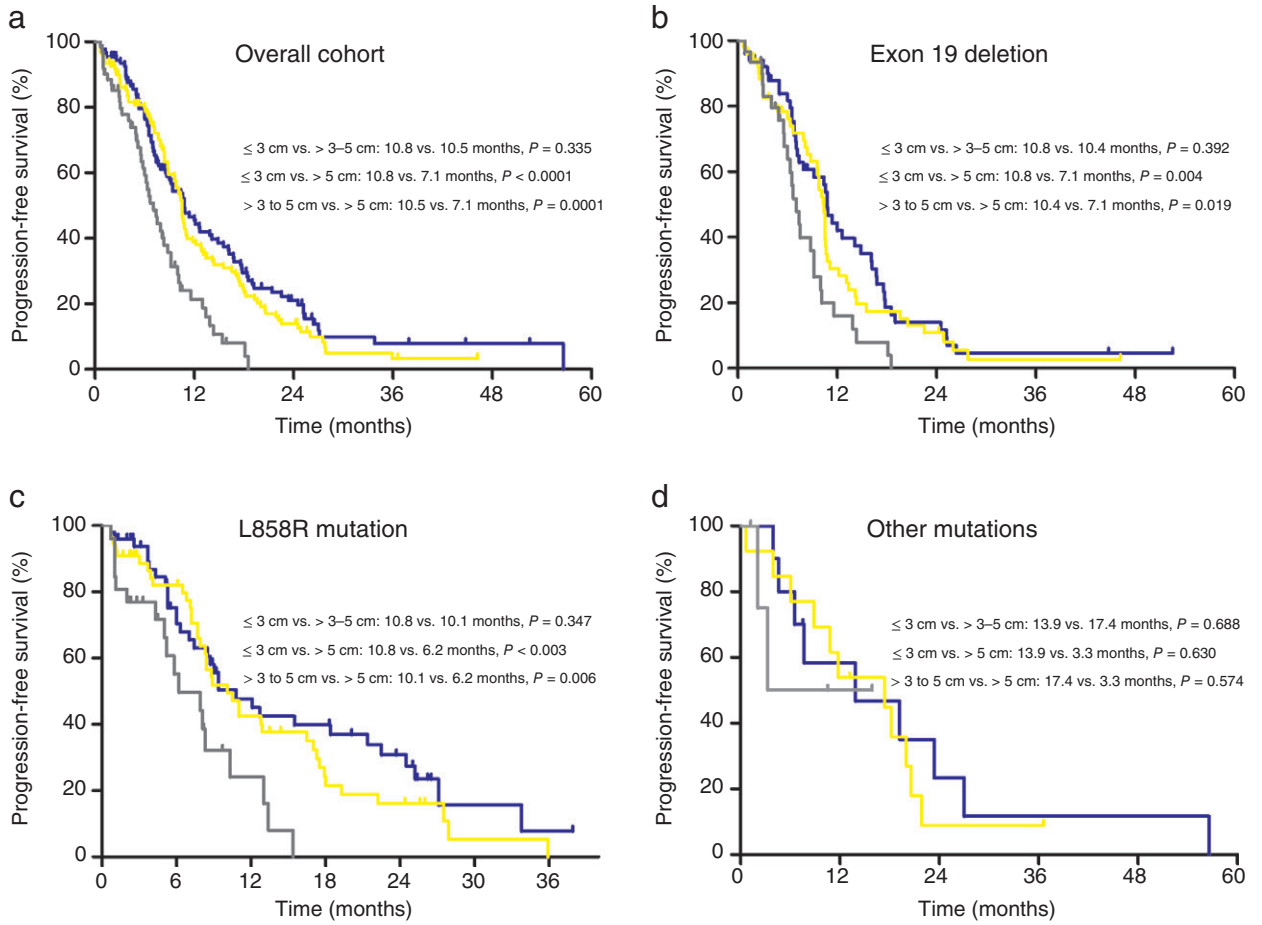

Figure 1 Progression-free survival of *EGFR*-mutant patients treated with first-line EGFR-tyrosine kinase inhibitors according to baseline tumor size (≤ 3 cm vs. > 3–5 cm vs. > 5 cm) in: (**a**) the overall cohort, (**b**) patients with *EGFR* exon 19 deletion, (**c**) patients with L858R mutation, and (**d**) patients with other mutations. (——) ≤ 3 cm, (——) > 3–5 cm, and (——) > 5 cm.

mutations (Table S1). We further clarified the association between depth of response and tumor size. As shown in Figure 3c, a waterfall plot revealed that the depth of response among the three groups was similar.

Patients were divided by tumor shrinkage according to the depth of response: shrinkage > 60%, 51–60%, 37–50%, 26–36%, 13–25%, 1–12%, and no tumor shrinkage.[20] The median PFS rates in the seven groups were 10.5, 9.6, 10.8, 10.4, 12.8, 8.4, and 1.9 months ($P < 0.001$), respectively, indicating no significant association between tumor shrinkage and median PFS (Fig 4c).

Efficacy of EGFR-TKIs according to *EGFR* mutation abundance

As our previous study identified an association between the abundance of *EGFR* activating mutation by ARMS+ and therapeutic response to EGFR-TKIs,[5] we further investigated whether the baseline primary tumor size was associated with the abundance of *EGFR* activating mutations. The mean abundance of *EGFR* mutations was 45.8% in the ≤ 3 cm group, 45.6% in the 3–5 cm group, and 32.2% in the > 5 cm group ($P = 0.125$) (Fig 4a). Interestingly, larger tumors (> 5 cm) had numerically lower *EGFR*-mutant abundance than smaller tumors (≤ 5 cm) (mean ± standard deviation 32.2 ± 29.4% vs. 45.8 ± 43.1%; $P = 0.08$) (Fig 4b). These results suggest that *EGFR*-mutant abundance may be higher in smaller tumors, which may contribute to better PFS. Furthermore, *EGFR* mutation abundance was similar among the different tumor shrinkage groups, which could partially explain why tumor shrinkage was not associated with PFS outcomes (Fig 4d).

Univariate and multivariate analysis of progression-free survival

Univariate analysis identified female gender, age < 65 years, and tumor size ≤ 5 cm as being significantly associated with

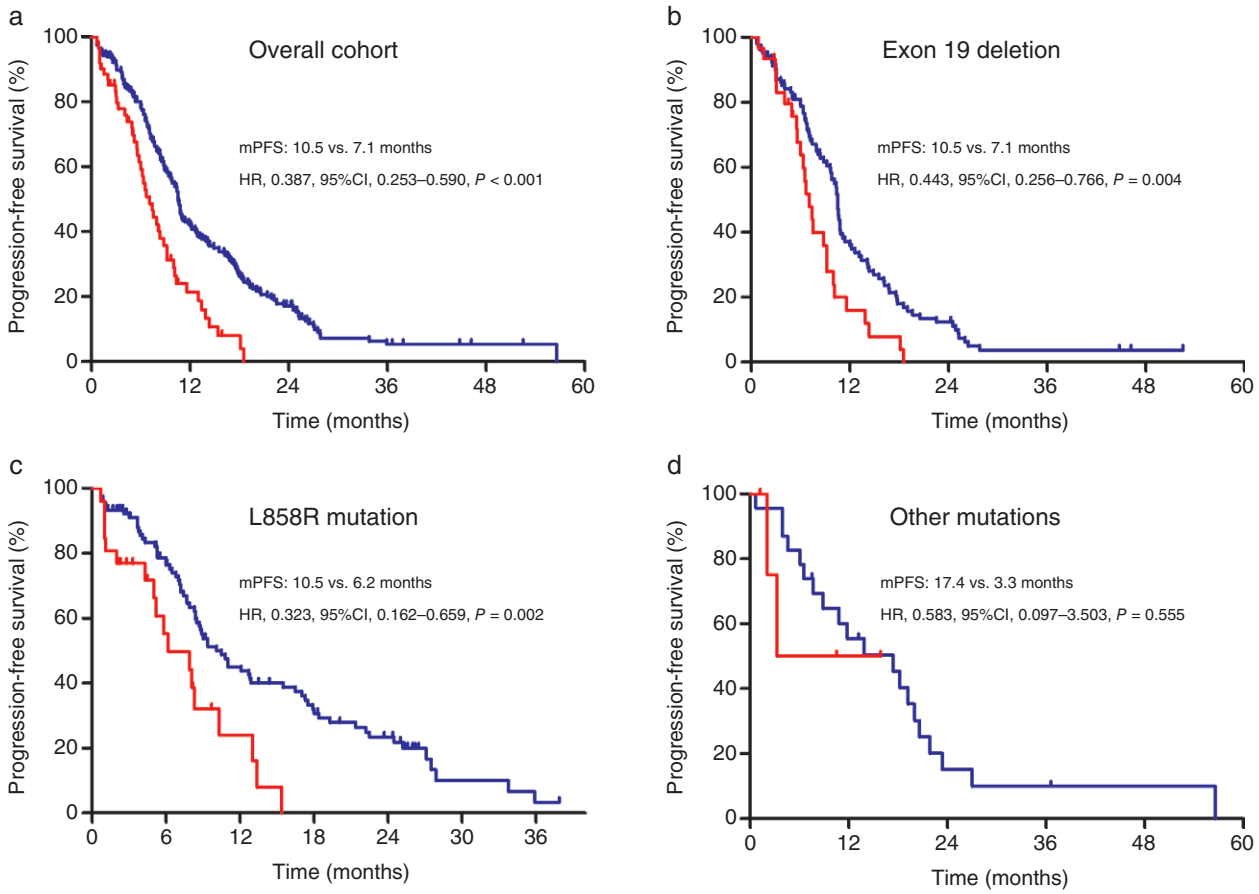

Figure 2 Progression-free survival (PFS) of *EGFR*-mutant patients treated with first-line EGFR-tyrosine kinase inhibitors according to baseline tumor size (≤ 5 cm vs. > 5 cm) in: (**a**) the overall cohort, (**b**) patients with *EGFR* exon 19 deletion, (**c**) patients with L858R mutation, and (**d**) patients with other mutations. (——) ≤ 5 cm and (——) > 5 cm. CI, confidence interval; HR, hazard ratio; mPFS, median PFS.

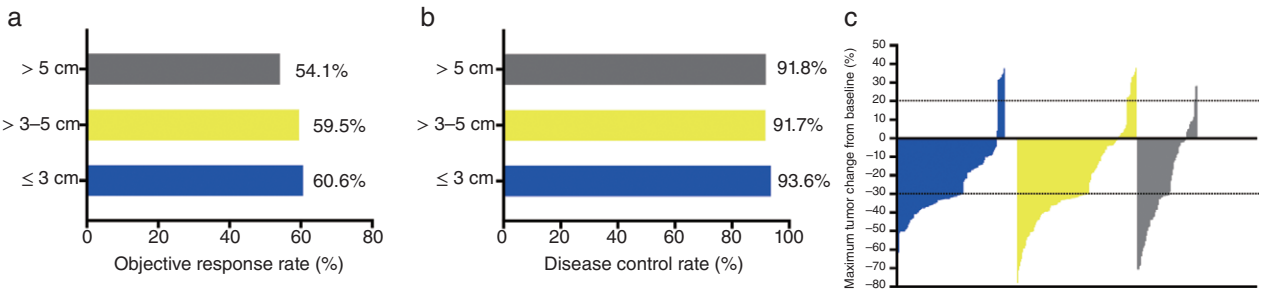

Figure 3 Responses to EGFR-tyrosine kinase inhibitor treatment (TKI) in patients with *EGFR* mutations according to tumor size: (**a**) objective response rate, (**b**) disease control rate, and (**c**) depth of response to EGFR-TKIs according to tumor size (——) ≤ 3 cm, (——) 3–5 cm, and (——) > 5 cm.

better PFS. Multivariate analysis revealed tumor size as an independent predictive factor for PFS (hazard ratio [HR] 1.528, 95% CI 1.104–2.115; $P = 0.010$), as well as age (HR 0.734, 95% CI 0.548–0.982; $P = 0.037$), histologic subtype (HR 1.679, 95% CI 1.060–2.662; $P = 0.027$), and T stage (HR 1.288, 95% CI 1.114–1.490; $P = 0.001$).

Discussion

To our knowledge, the present study is the first to investigate the association between clinicopathological features and therapeutic outcomes of first-line EGFR-TKI treatment in patients with *EGFR* sensitizing mutations. We found

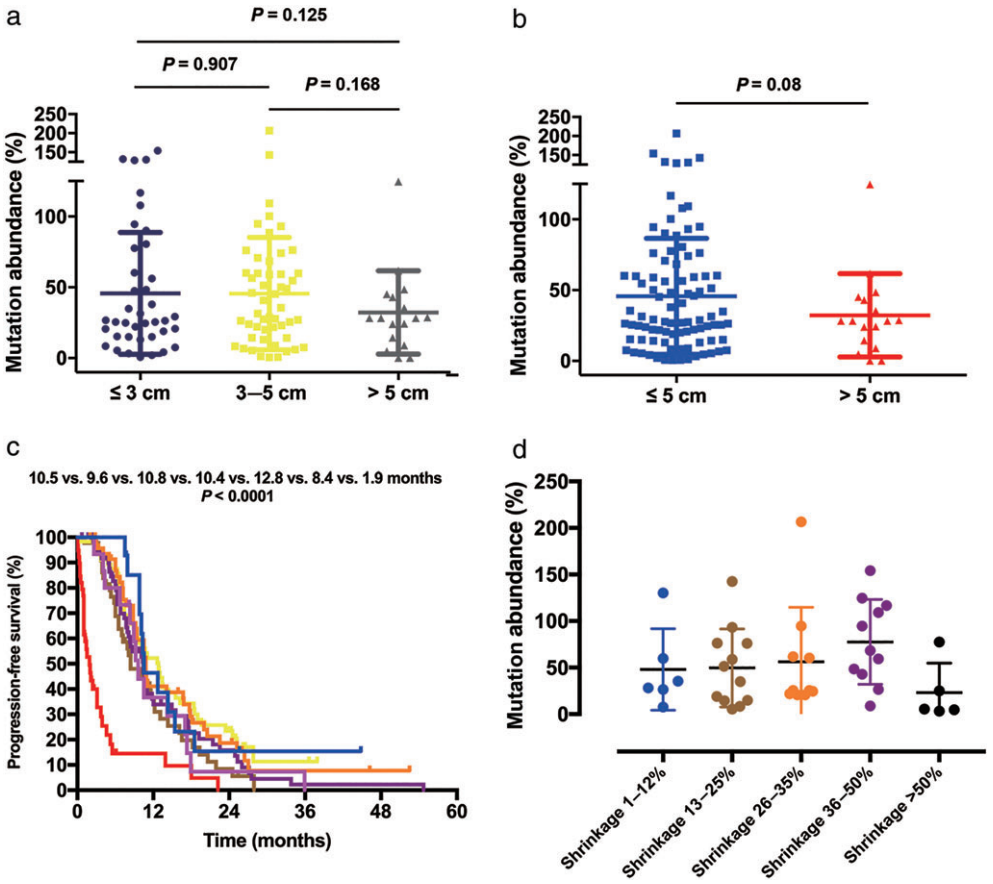

Figure 4 The association between tumor size, tumor shrinkage, and *EGFR*-mutant abundance. The relationship between tumor size and *EGFR*-mutant abundance in: (**a**) ≤3 cm vs. > 3 to 5 cm vs. > 5 cm and (**b**) ≤ 5 cm vs. > 5 cm. (**c**) Progression-free survival according to tumor shrinkage magnitude (—) > 60%, (—) 51–60%, (—) 37–50%, (—) 26–36%, (—) 13–25%, (—) 1–12%, and (—) no tumor shrinkage. (**d**) The relationship between tumor shrinkage magnitude and *EGFR* mutation abundance.

that median PFS was significantly shorter in patients with large tumors (> 5 cm) than in those with smaller ones (≤ 5 cm); however, *EGFR* mutation was less abundant in larger tumors. Tumor size was not associated with radiographic response, including response rate and depth of response.

Tumor size can significantly predict the prognosis of patients with NSCLC.[12] Therefore, more detailed T classification according to primary tumor size was adopted in the updated 8th edition TNM classification system.[13] However, the impact of the classification changes on the therapeutic response in NSCLC is still largely unknown. In post-hoc analysis of the E4599 clinical trial, the median PFS was 5.1 months in patients with a baseline sum longest diameter (BSLD) > 7.5 cm, which was marginally statistically significantly shorter than 5.3 months in those with BSLD ≤ 7.5 cm (HR, 1.14; $P = 0.08$).[21] Consistent with this result, we also found that larger tumors were associated with inferior PFS of first-line EGFR-TKI therapy (> 5 cm vs. ≤ 5 cm: 7.1 vs. 10.5 months; $P < 0.0001$). Previous studies have shown that larger tumors may have relatively poor blood supply and elevated interstitial pressure and hypoxia as tumors grow, which may contribute to tumor cell resistance to EGFR-TKIs.[22–24] Another possible explanation is intra-tumoral heterogeneity in larger tumors. During the process of tumor clonal evolution, large tumors might theoretically be more heterogeneous than smaller ones because of growth pressure. Our findings that the abundance of *EGFR* activating mutations is marginally statistically significantly lower in larger tumors ($P = 0.08$) indirectly supports this hypothesis.

We also investigated the association between radiographic tumor size and response rate and found a similar ORR in these two groups. Consistently, similar results were found between BSLD and response rates in patients treated with chemotherapy or chemotherapy plus bevacizumab.[21] We further analyzed the depth of response to first-line EGFR-TKIs and median PFS and found no significant

association. Our results reiterate those of two recent studies.[20,25] In a study by Wu *et al.,* although patients who achieved a partial response had significantly longer PFS and overall survival at 16.5 and 56 weeks, respectively, higher tumor shrinkage was not related to better PFS or overall survival.[20] In another study including 1081 patients from five randomized-controlled trials, the depth of response at 6 or 12 weeks was not associated with PFS.[25] Our results show that the abundance of *EGFR* mutations is similar among different tumor shrinkage subgroups, which could partially explain this result.

Our study results have several implications for clinical decision-making. Firstly, as shown in NEJ009,[26] prolongation of PFS1 is critical for *EGFR*-mutant patients. Patients with larger tumors usually have significant symptoms. Once diseases progress, patients may not be eligible for subsequent treatment because of deteriorative ECOG PS. Therefore, EGFR-TKIs in combination with chemotherapy may have significant clinical value in patients with larger tumors. Secondly, as the depth of response was not correlated with survival outcomes, tumor shrinkage should not be used as a surrogate for benefit in routine clinical decision-making.

The current study also has several limitations. Firstly, it was affected by the limitations inherent to studies with a retrospective design. In addition, we enrolled a relatively limited sample from a single-center and concomitant mutations were not available. Thirdly, the abundance of *EGFR* mutations may not precisely reflect the "true" intratumoral heterogeneity status of primary tumors, as a few of the tumor tissue samples were obtained from metastatic sites rather than primary tumors. Finally, the abundance of *EGFR* activating mutations was only marginally statistically significantly lower in larger tumors ($P = 0.08$). It is possible that this result is a chance finding or a result of the limited number of patients enrolled in this study. Therefore, further study is required to validate our findings.

In conclusion, smaller tumors were associated with superior PFS of first-line EGFR-TKI therapy in patients with advanced NSCLC harboring *EGFR* sensitizing mutations. A possible explanation might be that patients with smaller tumors are more likely to have *EGFR* mutations.

Acknowledgments

This study was partly supported by the Shanghai Sailing Program (16YF1409600), the Shanghai Municipal Commission of Health and Family Planning (No. 20144Y0190), and the National Natural Science Foundation of China (81703020).

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. A brief summary of responses to EGFR-tyrosine kinase inhibitor (TKI) treatment according to tumor size in patients with *EGFR* mutations.

