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.

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 explanation 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. 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. Recently, concurrent genomic mutations, such as STAT3 and YAP1 or TP53, were also found to have a detrimental effect on EGFR-TKI efficacy. 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.\textsuperscript{10,11} Tumor size significantly affects survival outcomes in patients with early-stage NSCLC and locally advanced disease.\textsuperscript{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.\textsuperscript{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.

\section*{Methods}

\subsection*{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.\textsuperscript{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.

\subsection*{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.\textsuperscript{15}

\section*{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.\textsuperscript{5,6,16–19}

\section*{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).

\section*{Results}

\subsection*{Patient characteristics}

Overall, a total of 291 patients with EGFR-mutant advanced NSCLC who had baseline measurable disease by
| Characteristics | All patients | ≤ 3 cm | > 3–5 cm | > 5 cm | P |
|-----------------|-------------|----------|---------|--------|---|
| Age, Median (range), years | 61 (26–86) | 62 (26–81) | 62 (7–86) | 61 (26–85) | 0.472 |
| 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 | 231 (79.4) | 89 (81.7) | 94 (77.7) | 48 (78.7) | 0.751 |
| Non-smoker | 60 (20.6) | 20 (18.3) | 27 (22.3) | 13 (21.3) | | |
| ECOG PS | 270 (92.8) | 103 (94.5) | 110 (91.7) | 56 (91.8) | 0.683 |
| 0 or 1 | 21 (7.2) | 6 (5.5) | 10 (8.3) | 5 (8.2) | | |
| Pathology | 260 (89.7) | 103 (95.4) | 109 (90.1) | 48 (78.7) | 0.003 |
| ADC | 30 (10.3) | 5 (4.6) | 12 (9.9) | 13 (21.3) | | |
| TNM stage | 10 (3.4) | 6 (5.5) | 4 (3.3) | 0 (0.0) | 0.365† |
| Recurrent | 38 (13.1) | 16 (14.7) | 12 (9.9) | 10 (16.4) | | |
| III B | 243 (83.5) | 87 (79.8) | 105 (86.8) | 51 (83.6) | | |
| IV | | | | | |
| T stage | 110 (37.8) | 54 (49.5) | 44 (36.4) | 12 (19.7) | 0.001 |
| T1–2 | 181 (62.2) | 55 (50.5) | 77 (63.6) | 49 (80.3) | | |
| N stage | 69 (23.7) | 31 (28.4) | 27 (22.3) | 11 (18.0) | 0.277 |
| N0–1 | 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 (19.7) | 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 | 54 (18.6) | 20 (18.3) | 25 (20.7) | 9 (14.8) | 0.625 |
| Yes | 237 (81.4) | 90 (81.7) | 96 (79.3) | 52 (85.2) | | |
| Bone radiation | 60 (20.6) | 26 (23.9) | 22 (18.2) | 12 (19.7) | 0.557 |
Table 1 Continued

| Characteristics       | All patients N = 291 (%) | ≤ 3 cm N = 109 (%) | > 3–5 cm N = 121 (%) | > 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)        |    |

1Recurrent/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 | Multivariate analysis |
|------------------------------------|---------------------|-----------------------|
| Tumor size: > 5 cm vs. ≤ 5 cm      | HR (95% CI)         | P                     |
| Female vs. male                    | 1.446 (1.222–1.712) | < 0.001               |
| Age > 65 years vs. ≤ 65 years      | 0.734 (0.554–0.971) | 0.030                 |
| 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                 |
| 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               |
| T3 + 4 stage vs. T1 + 2 stage      | 1.296 (1.129–1.488) | 0.000                 |
| N2 + 3 stage vs. N0 + 1 stage      | 1.234 (1.047–1.454) | 0.012                 |

1Including 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.

**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 mutations.

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 EGFR-TKIs, and EGFR mutation subtypes (Table 2).
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. The median PFS rates in the seven groups were 10.5, 9.6, 10.8, 10.4, 10.1, 6.2, and 5.1 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
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...
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

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**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.
association. Our results reiterate those of two recent studies. 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. 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. 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, 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.

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Disclosure

No authors report any conflict of interest.

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**Supporting Information**

Additional Supporting Information may 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.