Tumor shrinkage rate as a potential marker for the prediction of long-term outcome in advanced non-small cell lung cancer treated with first-line tyrosine kinase inhibitors

ABSTRACT

Context: Tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptor (EGFR) play an indispensable role in the treatment of non-small cell lung cancer (NSCLC), leading to a survival major breakthrough, but there remains no uniform standard for predicting the efficacy of TKI therapy.

Aims: We retrospectively reviewed the use of EGFR-TKIs for advanced NSCLC between January 2009 and December 2017 in a hospital, which 169 patients who treated with first-line TKIs were enrolled.

Subjects and Methods: Multiple clinical factors, including histology, age, and sex, were analyzed. We calculated the tumor shrinkage rate (TSR) by measuring the longest diameters of the main mass by computed tomography (CT) before TKI therapy and the first CT after TKI therapy. We evaluated overall survival (OS) and progression-free survival (PFS) after first-line TKI therapy, and we assessed factors predicting survival using the Kaplan–Meier method.

Results: Eligible patients were sorted into higher (n = 83) and lower (n = 86) TSR groups according to the mean TSR of 0.49%. The 83 patients with a higher TSR had longer PFS and OS than those in the 86 patients with a lower TSR (14.83 vs. 8.40 months, P < 0.001, and 31.03 vs. 20.10 months, P < 0.001, respectively). Multivariate analyses revealed that TSR was an independent predictor of PFS and OS (PFS hazard ratio [HR]: 0.506, P < 0.001, and OS HR: 0.291, P < 0.001).

Conclusions: These cumulative data support that TSR may be an early predictor of the treatment efficacy in NSCLC with EGFR mutations treated with first-line TKIs.

KEY WORDS: Non-small cell lung cancer, overall survival, progression-free survival, tumor shrinkage rate, tyrosine kinase inhibitor

INTRODUCTION

Lung cancer is a malignant tumor with the highest morbidity worldwide, making it a leading cause of cancer-related deaths. Non-small cell lung cancer (NSCLC) accounts for 80%–85% of all types of lung cancers.[1] Based on its pathology, NSCLC can be subdivided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. While surgery is considered the optimal treatment in theory, about 70% of patients present with locally advanced or metastatic diseases at the time of diagnosis and are not eligible for surgical resection.[2,3] The prognosis for patients with advanced NSCLC is generally poor even after treatment with surgery, radiotherapy, or chemotherapy.[4] In particular, platinum-based chemotherapy, as the standard treatment for advanced or recurrent NSCLC, has reached a bottleneck in efficacy.

Current first-line treatment decisions for advanced NSCLC are based on the presence of genetic aberrations, such as sensitizing mutations of epidermal growth factor receptor (EGFR).[5] EGFR is

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located at the short arm of chromosome 7 (7p11.2) and encodes a 170-kDa Type I transmembrane growth factor receptor with tyrosine kinase (TK) activity. Activating mutations in the TK domain of EGFR drive oncogenic pathways that control cellular proliferation and survival. EGFR is overexpressed in a significant proportion of patients with NSCLC, which leads to the rapid development of inhibitors that target EGFR; also called EGFR TK inhibitors (EGFR-TKIs), such as erlotinib and gefitinib. The advent of EGFR-TKIs has resulted in a significant increase in survival, benefiting a large number of patients with EGFR-activating mutations. Recent Phase III clinical studies of advanced NCSLC have demonstrated that EGFR mutations are the most effective predictors for clinical outcome in response to first-line TKIs. In addition, many prognostic factors used to predict disease control or survival, such as fibrinogen, histology, age, and overexpression of forkhead box M1 (FoxM1), interleukin-6, or lysosomal-associated transmembrane protein 4B, have been investigated in lung cancer. Although there are many well-established prognostic factors, it is still hard to accurately predict the prognosis of individual patients. Thus, clinicians, researchers, and patients urgently need both economical and convenient predictors.

Studies have reported a correlation between tumor shrinkage rate (TSR) and patient prognosis. Wang et al. assessed the TSR after administration of topotecan plus bispecific 6-Phosphatase mononucleotide peptide in patients with lung cancer who had been treated with radiotherapy. The prognosis of the group with TSR >34% was better than that of the group with TSR <34%. In a previous trial, Professor Ahn et al. reported a significantly better progression-free survival (PFS) for TSR >70% than that for TSR <70% in patients with low rectal cancer after chemotherapy or radiotherapy (P < 0.0001).

We performed a retrospective study of 169 Chinese patients with advanced NSCLC who had received TKI monotherapy in an institution between January 2009 and December 2017. We analyzed the correlations between TSR, prognosis, and other clinical pathologic parameters. Our results may shed light on current endeavors to seek both economical and convenient predictors and provide a theoretical basis for better treatment of NSCLC.

**SUBJECTS AND METHODS**

**Study design**

The present retrospective study screened 568 patients who had received first-line TKIs between January 2009 and December 2017. Information for each patient was obtained from an electronic database and patient medical records. Patients were enrolled in this study according to the following inclusion criteria: (1) pathologically confirmed NSCLC and (2) unresectable Stage III–IV tumors according to criteria from the Union for International Cancer Control. The exclusion criteria were (1) patients with an unmeasurable maximum tumor diameter, (2) patients whose image evaluation was over 6 months before or after treatment, (3) patients treated with chemotherapy during treatment, (4) patients with an operation before treatment, and (5) patients without PFS information (Figure 1).

TKIs were orally administered at a daily dose of 250 mg until disease progression, unacceptable toxicity, or patient withdrawal. The initial variables investigated included age, sex, clinical stage, Eastern Cooperative Oncology Group performance status (ECOG PS) score, tumor histology, smoking history, tumor markers, presence of hypertension or diabetes mellitus, and central nervous system metastasis before treatment. After treatment with first-line TKIs, computed tomography (CT) scans of the chest and upper abdomen were performed at regular intervals to evaluate the status of the primary tumor. Bone scintigraphy and brain CT or magnetic resonance imaging were also used for patients with distant metastases.

**Response assessment**

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 as complete response (CR), partial response (PR), stable disease, or progressive disease. In this study, patients who achieved CR or PR were classified as having a radiologic objective response. Radiology assessments were performed according to the patients’ conditions.

**Statistical analysis**

The differences in categorical variables were compared by Chi-square tests. PFS was defined as the time from the 1st day of TKI treatment to the day of disease progression. Overall survival (OS) was defined as the time from the 1st day of TKI treatment to the day of death or last follow-up. The optimum cutoff points of pretreatment clinical laboratory data were determined according to receiver operating characteristic curves and previous studies. Survival curves and univariate analyses were performed using the Kaplan–Meier method and

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**Figure 1:** Patient selection. EGFR: epidermal growth factor receptor, NSCLC = Non-small cell lung cancer, TSR = Tumor shrinkage rate, PFS = Progression-free survival, TKI = Tyrosine kinase inhibitor
compared using log-rank tests, with \( P < 0.05 \) as the criteria for statistical significance. Multivariate analysis was performed using a Cox proportional-hazards model to identify associations between clinical characteristics and survival, with \( P = 0.10 \) the threshold for adding or removing a covariate to/from the model and \( P < 0.05 \) as the criteria for statistical significance (C-reactive protein [CRP] and cancer antigen-125 [CA-125] were not included in the analysis due to missing data). All statistical analyses were performed with SPSS version 24.0. (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp).

RESULTS

Patient characteristics

The clinicopathological characteristics of the 169 patients are shown in Table 1. All patients were in a good state with ECOG PS scores of 0 or 1. A total of 128 patients carried an EGFR mutation (64 had exon 19 deletions, 56 had exon 21 L858R, and eight had rare or double mutations), and 41 patients were not evaluated. The patients were randomized into two cohorts according to TSR, with 86 patients with TSR <0.49% and 83 with TSR ≥0.49%. There were no significant differences in patient baseline characteristics [Table 2]. The cohort with a high TSR (≥0.49%) had a more favorable clinical response rate than that in the cohort with a low TSR (<0.49%) (\( P < 0.001 \)).

The responses were first evaluated at the time of the first CT scan after TKI treatment. Each diameter was measured by two board-certified specialists in thoracic radiology using a picture archiving and communication system. The main tumor mass was defined as the lesion with the longest measurable diameter [Figure 2]. TSRs were calculated according to the following formula:

$$\text{TSR} = \frac{\text{longest diameter before treatment} - \text{longest diameter after treatment}}{\text{longest diameter before treatment} \times \text{corresponding time}} \times 100\%$$

The response evaluations according to the modified Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) were available.

Survival according to tumor shrinkage rate

During the follow-up period, disease progression and death occurred in 153 and 100 patients, respectively. Figures 3 and 4 show the Kaplan–Meier survival curves of PFS and OS after first-line TKI therapy according to the TSR.

Table 1: Patient characteristics (\( n=169 \))

| Characteristic                      | \( n \) |
|------------------------------------|--------|
| Median age (range), years          | 67 (40-91) |
| Gender, \( n \)                    |        |
| Male                               | 67     |
| Female                             | 102    |
| Hypertension, \( n \)              |        |
| Yes                                | 70     |
| No                                 | 95     |
| Missing                            | 4      |
| Diabetes mellitus, \( n \)         |        |
| Yes                                | 26     |
| No                                 | 139    |
| Missing                            | 4      |
| Smoking history, \( n \)           |        |
| Current or former smoker           | 37     |
| Never smoker                       | 132    |
| ECOG PS, \( n \)                   |        |
| 0-1                                | 147    |
| ≥2                                 | 15     |
| Missing                            | 7      |
| Pathology, \( n \)                 |        |
| Adenocarcinoma                     | 146    |
| Nonadenocarcinoma                  | 16     |
| Missing                            | 7      |
| CNS metastasis at baseline         | 29     |
| EGFR mutation status, \( n \)      |        |
| 19 Del                             | 64     |
| L858R                              | 56     |
| Others                             | 8      |
| Unknown                            | 41     |
| Type of TKI, \( n \)               |        |
| Gefitinib                          | 71     |
| Icotinib                           | 84     |
| Erlotinib                          | 14     |
| Response to initial TKI (RECIST 1.1), \( n \) |        |
| CR                                 | 0      |
| PR                                 | 74     |
| SD                                 | 89     |
| PD                                 | 6      |
| Median CEA (range), ng/ml          | 16.75 (0.5-5563.1) |
| Median CYFRA 21-1 (range), ng/ml   | 4.5 (1-245.6) |
| Median NSE (range), ng/ml          | 12.7 (7.1-51.5) |
| Median CA12-5 (range), U/ml        | 40.65 (2.5-2134.9) |
| Median hemoglobin (range), g/l     | 128 (64-166) |
| Median CRP (range), ng/ml          | 11.4 (1.15-508) |

ECOG PS=Eastern Cooperative Oncology Group performance status, CNS=Central nervous system, EGFR=Epidermal growth factor receptor, TKI=Tyrosine kinase inhibitor, CEA=Carcinoembryonic antigen, CYFRA=Cytokeratin 19 fragment, NSE=Neuron-specific enolase, CA=Cancer antigen, CRP=C-reactive protein, CR=Complete response, PR=Partial response, SD=Stable disease, PD=Progressive disease, RECIST=Response Evaluation Criteria in Solid Tumors
Patients with a lower TSR had a poorer PFS compared to that in those with a higher TSR (median survival, 8.40 vs. 14.83 months, \( P < 0.001 \)). Moreover, there was a significant difference in OS between the two cohorts (20.10 vs. 31.03 months, \( P < 0.001 \)). A waterfall plot of the response to initial TKIs for individual patients according to the TSRs of the two cohorts showed that patients with a higher TSR had a longer PFS [Figure 5].

**Prognostic indicators for patient survival**

Based on the univariate analysis, the significant predictors for PFS were neuron-specific enolase (NSE), CA-125, cytokeratin 19 fragment (CYFRA 21-1), CRP, and TSR (all \( P < 0.05 \)); the significant predictors for OS were age, histology (WHO), NSE, CA-125, CYFRA 21-1, CRP, and TSR (all \( P < 0.05 \)) with no significant difference observed in carcinoembryonic antigen (CEA) (\( P = 0.069 \)) [Table 3]. The multivariate analysis of PFS showed TSR (hazard ratio [HR] = 0.506, \( P < 0.001 \)) and CYFRA 21-1 (HR = 0.542, \( P = 0.005 \)) to be independent predictors. The multivariate analysis of OS showed TSR (HR = 0.291, \( P < 0.001 \)), age (HR = 0.486, \( P = 0.007 \)), histology (HR = 2.891, \( P = 0.008 \)), CEA (HR = 0.550, \( P = 0.021 \)), and...
and CYFRA 21-1 (HR = 0.377, \(P = 0.001\)) to be independent predictors [Table 4].

**DISCUSSION**

Lung cancer is a leading cause of cancer-related deaths worldwide, with NSCLC accounting for 80%–85% of all types of lung cancers.\(^{20}\) The advent of EGFR-TKI has significantly improved clinical outcomes compared to those for chemotherapy in NSCLC patients with sensitizing EGFR mutations. However, a significant shortcoming of targeted therapy is the lack of effective indicators to predict prognosis. Aiming to identify effective markers to predict the treatment efficacy, the results of this retrospective study revealed shorter PFS and OS in EGFR-TKI-treated patients with a lower TSR than those in patients a higher TSR. In the multivariate analysis of PFS and OS, we concluded that TSR was a significant predictor after first-line TKI therapy according to the categorical classification (HR = 0.506 and 0.291, \(P < 0.001\) and \(P < 0.001\), respectively). Moreover, we also found that the serum levels of NSE, CA12-5, CYFRA 21-1, and CRP differed significantly in predicting TKI efficacy (all \(P < 0.05\)). With the help of these predictors, doctors might be able to determine strategies to shrink tumors at an early stage for better outcomes.

Previous studies reported a correlation between TSR and the prognosis of patients with diseases including renal cell carcinoma, metastatic colorectal cancer, cervical cancer, and NSCLC;\(^{21-25}\) however, studies are relatively sparse for the correlation between TSR and the prognosis of NSCLC.

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**Table 3: Univariate analysis of progression-free survival and overall survival by log-rank test**

| Covariate                        | \(n\) | PFS Median (months) | \(P\) | OS Median (months) | \(P\) |
|----------------------------------|-------|---------------------|------|-------------------|------|
| Age (years)                      |       |                     |      |                   |      |
| \(\geq 65\)                      | 100   | 10.430              | 0.394| 22.830            | 0.015|
| \(< 65\)                         | 69    | 12.830              |      | 30.370            |      |
| Gender                           |       |                     |      |                   |      |
| Male                             | 59    | 11.600              | 0.358| 30.100            | 0.358|
| Female                           | 94    | 11.130              |      | 25.600            |      |
| Histology (WHO)                  |       |                     |      |                   |      |
| Adenocarcinoma                   | 146   | 11.600              | 0.227| 27.830            | 0.022|
| Nonadenocarcinoma                | 16    | 8.200               |      | 23.200            |      |
| Smoking status                   |       |                     |      |                   |      |
| Ever                             | 37    | 10.030              | 0.937| 30.370            | 0.346|
| Never                            | 128   | 11.600              |      | 25.870            |      |
| T                                |       |                     |      |                   |      |
| T1-T2                            | 131   | 11.870              | 0.439| 26.170            | 0.434|
| T3-T4                            | 29    | 10.030              |      | 26.930            |      |
| CEA, ng/ml                       |       |                     |      |                   |      |
| \(\geq 32.3\)                    | 64    | 10.600              | 0.265| 24.670            | 0.069|
| \(< 32.3\)                       | 96    | 11.430              |      | 27.870            |      |
| NSE, ng/ml                       |       |                     |      |                   |      |
| \(\geq 13.75\)                   | 61    | 9.770               | 0.047| 22.600            | 0.023|
| \(< 13.75\)                      | 88    | 11.900              |      | 30.100            |      |
| CA12-5, U/ml                     |       |                     |      |                   |      |
| \(\geq 35\)                      | 47    | 9.730               | 0.028| 22.770            | 0.006|
| \(< 35\)                         | 39    | 12.230              |      | 48.730            |      |
| CYFRA 21-1, ng/ml                |       |                     |      |                   |      |
| \(\geq 2.95\)                    | 100   | 10.030              | 0.012| 25.600            | 0.025|
| \(< 2.95\)                       | 44    | 15.830              |      | 40.470            |      |
| Hemoglobin, g/l                  |       |                     |      |                   |      |
| \(\geq 127\)                     | 83    | 11.930              | 0.288| 27.830            | 0.166|
| \(< 127\)                        | 72    | 10.030              |      | 24.400            |      |
| CRP, mg                          |       |                     |      |                   |      |
| \(\geq 14\)                      | 46    | 8.400               | 0.004*| 20.430           | 0.005*|
| \(< 14\)                         | 53    | 14.870              |      | 31.030            |      |
| EGFR mutation point              |       |                     |      |                   |      |
| 19Del                            | 64    | 11.900              | 0.595| 26.930            | 0.967|
| L858R                            | 56    | 11.400              |      | 27.870            |      |
| Others                           | 8     | 6.530               |      | 24.270            |      |
| First-line treatment             |       |                     |      |                   |      |
| Gefitinib                        | 71    | 11.870              | 0.638| 26.470            | 0.601|
| Icotinib                         | 84    | 11.030              |      | 27.830            |      |
| Erlotinib                        | 14    | 7.230               |      | 25.870            |      |
| Tumor shrinkage rate (%)         |       |                     |      |                   |      |
| \(\geq 0.49\)                    | 83    | 14.830              | <0.001| 31.030           | <0.001|
| \(< 0.49\)                       | 86    | 8.400               |      | 20.100            |      |

*\(P < 0.05\). PFS=Progression-free survival, OS=Overall survival, NSE=Neuron-specific enolase, CEA=Carcinoembryonic antigen, CYFRA=Cytokeratin 19 fragment, CA=Cancer antigen, CRP=C-reactive protein, EGFR=Epidermal growth factor receptor*
Compared to these studies, the patients screened in our study and finally included in the analysis were all patients receiving first-line TKI targeted therapies, which was relatively univocal in reflecting the therapeutic effect of TKIs due to the absence of other therapies. Moreover, we included the length of time in the TSR formula considering the differences in the time periods for each patient assessed. Therefore, the TSR in our study is the true “average” TSR, which is the most significant aspect that differentiates it from other studies. Intratumoral heterogeneity of clones sensitive to EGFR-TKI might determine the TSR,\[^{26}\] which is why we deemed that the average TSR may be a better way to assess the tumor status. Moreover, we found that PFS cannot be easily or accurately predicted during treatment in clinical practice according to nonregular image reexaminations, leading to slight deviations in prognosis. The findings of previous reports indicated that subsequent treatment after disease progression following early-line treatments may significantly affect OS and that postprogression survival was more strongly correlated with OS than PFS, which reflected the drawbacks of PFS and OS as two common endpoints of cancer trials.\[^{27,28}\] These findings suggest that TSR may represent a useful surrogate marker for OS and PFS after first-line TKI therapy; in other words, TSR may help us to predict OS. As shown in our study, a high TSR may be a positive predictor for PFS and OS in NSCLC patients with advanced EGFR mutations. However, larger studies are needed for the validation of these findings.

As discussed above, we identified significant prognostic indicators to monitor TKI response and predict survival, including CYFRA 21-1, CA125, and CRP. In addition, serum CA199, CEA, TPS, and NSE were significant predictors for survival in advanced NSCLC.\[^{39-42}\] Therefore, we might be able to accurately predict the prognosis of patients with advanced NSCLC by computer modeling using these prognostic indicators. Thus, clinicians might be able to carry out reasonable treatment strategies under the guidance of the predicted results of the model, which may conserve medical resources and benefit patients.\[^{33}\] The use of artificial intelligence to predict prognosis is common. For example, Yu et al.\[^{34}\] reported the prediction of NSCLC prognosis based on pathological microscopic image features.

Our study has several limitations. First, it is a retrospective single-center study based on a small sample size, resulting in potential biases in the survival analysis. Therefore, a prospective multicenter study with a larger sample size is needed to confirm our results. Second, some patient data were missing. For example, CA125 and CRP levels were not included in the multivariate analysis due to data missing in these indicators for many patients (n = 83 and 99, respectively). Moreover, EGFR mutation status was unknown in 41 patients. However, given the favorable prognoses for most patients with unknown EGFR status, we also included these patients in the study.

In summary, the results of our study demonstrated that TSR is an independent predictor for PFS and OS among advanced patients with NSCLC with EGFR mutations who had been treated and showed a response to first-line TKIs. A higher TSR indicates superior survival after first-line TKI therapy compared to a lower TSR. Moreover, the serum levels of NSE, CA12-5, CYFRA 21-1, and CRP showed statistically significant differences in predicting the efficacy of TKIs. A computer model based on these indicators may assist in clinical decision-making and patient survival prediction during treatment.

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**Table 4: Multivariate analysis of progression-free survival and overall survival**

| Covariate                                | PFS (years) | HR (95% CI) | P       | OS (years) | HR (95% CI) | P       |
|------------------------------------------|-------------|-------------|---------|------------|-------------|---------|
| Age (years)                              |             |             |         |            |             |         |
| ≥65                                      | 0.836 (0.573-1.219) | 0.352 |         | 0.486 (0.288-0.820) | 0.007 |
| <65                                      |             |             |         |            |             |         |
| Histology (WHO)                          |             |             |         |            |             |         |
| Adenocarcinoma                           | 1 (reference) |   |         | 1 (reference) |   |         |
| Nonadenocarcinoma                        | 1.702 (0.902-3.212) | 0.101 |         | 2.891 (1.323-6.320) | 0.008 |
| NSE, ng/ml                               |             |             |         |            |             |         |
| ≥13.75                                   | 0.999 (0.673-1.483) | 0.994 |         | 1.109 (0.662-1.857) | 0.694 |
| <13.75                                   |             |             |         |            |             |         |
| CEA, U/ml                                |             |             |         |            |             |         |
| ≥32.3                                    | 0.842 (0.575-1.231) | 0.374 |         | 0.550 (0.331-0.914) | 0.021 |
| <32.3                                    |             |             |         |            |             |         |
| CYFRA 21-1, ng/ml                        |             |             |         |            |             |         |
| ≥2.95                                    | 0.542 (0.354-0.829) | 0.005 |         | 0.377 (0.208-0.683) | 0.001 |
| <2.95                                    |             |             |         |            |             |         |
| Tumor shrinkage rate (%)                 |             |             |         |            |             |         |
| <0.49                                    | 0.506 (0.345-0.742) | <0.001 |         | 0.291 (0.171-0.493) | <0.001 |
| ≥0.49                                    |             |             |         |            |             |         |

PFS=Progression-free survival, OS=Overall survival, HR=Hazard ratio, CI=Confidence interval, NSE=Neuron-specific enolase, CEA=Carcinoembryonic antigen, CYFRA=Cytokeratin 19 fragment
Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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