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Optimal tumor shrinkage predicts long-term outcome in advanced nonsmall cell lung cancer (NSCLC) treated with target therapy

Result from 3 clinical trials of advanced NSCLC by 1 institution

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Abstract

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are used as standard therapies for advanced nonsmall cell lung cancer (NSCLC) patients with EGFR mutation positive. Because these targeted therapies could cause tumor necrosis and shrinkage, the purpose of the study is to search for a value of optimal tumor shrinkage as an appropriate indicator of outcome for advanced NSCLC.

A total of 88 NSCLC enrollees of 3 clinical trials (IRESSA registration clinical trial, TRUST study and ZD6474 study), who received Gefitinib (250 mg, QD), Erlotinib (150 mg, QD), and ZD6474 (100 mg, QD), respectively, during December 2003 and October 2007, were retrospectively analyzed. The response evaluation criteria in solid tumors (RECIST) were used to identify responders, who had complete response (CR) or partial responses (PR) and nonresponders who had stable disease (SD) or progressive disease (PD). Receiver operating characteristics (ROC) analysis was used to find the optimal tumor shrinkage as an indicator for tumor therapeutic outcome. Univariate and multivariate Cox regression analyses were performed to compare the progression-free survival (PFS) and overall survival (OS) between responders and nonresponders stratified based on radiologic criteria.

Among the 88 NSCLC patients, 26 were responders and 62 were nonresponders based on RECIST 1.0. ROC indicated that 8.32% tumor diameter shrinkage in the sum of the longest tumor diameter (SLD) was the cutoff point of tumor shrinkage outcomes, resulting in 46 responders ($\leq$8.32%) and 42 nonresponders ($\geq$8.32%). Univariate and multivariate Cox regression analyses indicated that (1) the responders ($\leq$8.32%) and nonresponders ($\geq -8.32\%$) were significantly different in median PFS (13.40 vs 1.17 months, $P < 0.001$) and OS (19.80 vs 7.90 months, $P < 0.001$) and (2) –8.32% in SLD could be used as the optimal threshold for PFS (hazard ratio [HR], 8.11, 95% CI, 3.75 to 17.51, $P < 0.001$) and OS (HR, 2.36, 95% CI, 1.41 to 3.96, $P = 0.001$).

However, 8.32% tumor diameter shrinkage is validated as a reliable outcome predictor of advanced NSCLC patients receiving EGFR-TKIs therapies and may provide a practical measure to guide therapeutic decisions.

Abbreviations: CR = complete response, EGFR = epidermal growth factor receptor, NSCLC = nonsmall cell lung cancer, PD = progressive disease, PR = partial responses, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease, SLD = the sum of the longest tumor diameter, TKI = tyrosine kinase inhibitors.

Keywords: advanced nonsmall cell lung cancer, EGFR-TKIs, prognostic factor, RECIST, tumor shrinkage

1. Introduction

Lung cancer is a leading factor of cancer-related mortality in human around the world.[1] In 2010, 605,946 new cases (416,333 male and 189,613 female) of lung cancers were diagnosed in China, making up 19.59% of all new cancer cases.[2] Among these lung cancers, nonsmall-cell lung cancer (NSCLC) is the most common type. Majority of the patients with NSCLC are diagnosed with advanced cancer.[3] In the past, palliative chemotherapy based on platinum-based doublets was recommended as the standard therapeutic modality for NSCLC with restraining effectiveness and several serious side effects.[4] Breakthroughs of targeted therapies demonstrated recently have brought new hope to us with alternative therapeutic ways for advanced NSCLC.[5] A primary target therapy using EGFR-tyrosine kinase inhibitors (EGFR-TKIs) such as Gefitinib (Iressa, ZD1839; AstraZeneca, Wilmington, DE) and Erlotinib (Tarceva, OSI-774; OSI Pharmaceuticals) targeting the activating epidermal growth factor receptor (EGFR) gene mutations has been proven to have durable and dramatic clinical benefit.[6,7] NSCLC patients harboring EGFR mutations were more closely related

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with specific characteristics such as East Asian ethnicity, women, no smoking history, and adenocarcinoma histology.[8] Recent randomized phase III trials have uniformly revealed that these EGFR-TKIs were more effective in respect of progression-free survival (PFS), less toxicity, and better tolerance than standard chemotherapy for advanced NSCLC patients harboring an activating EGFR mutation.[9–12] Nowadays, these drugs were approved as the first-line regimen for EGFR-mutant advanced NSCLC.[13] In addition, ZD6474 targeting vascular endothelial growth factor receptor (VEGFR) and EGFR signaling pathways[14] also exerted antitumor activity as a single regimen or in combination therapy in several malignancies including NSCLC and medullary thyroid cancer.[15,16]

During the period of cytotoxic cancer drugs, reduction of tumor size and a sum of the longest diameters (SLD) for all target lesions as the main indicators of anticancer therapy are considered to be a prerequisite for clinical benefit. Hence, in the clinical study, decreases of tumor size and SLD for all target lesions are listed as the essential criteria among others for assessment of therapeutic effectiveness in the Response Evaluation Criteria in Solid Tumors (RECIST) developed by the World Health Organization (WHO). At present, RECIST criteria are commonly used to assess the outcome of solid tumors treatment in clinical trials including target therapy.[17,18] According to RECIST criteria, a change of at least 30% shrinkage in the SLD of the targeted lesions is considered as objective response. However, RECIST criteria have a key drawback, that is the clinical benefit and the objective response rate of the targeted drugs are not always consistent. Indeed, in several tumors, even if tumor shrank after anticancer treatment, patients' survival time was not extended, whereas in other tumors, although tumor volume did not obviously change after anticancer therapy, patients could still obtain longer survival.[19] The antitumor mechanism of some anticancer agents, especially those used for molecular target therapies, is primarily decelerating or inhibiting the growth rather than markedly shrinking tumor size, which is different from that of traditional chemotherapy. Hence, their effectiveness may not obvious based on tumor size in imaging assessment. Thiam et al[20] showed that 10% tumor shrinkage is validated as a reliable early predictor of outcome in metastatic renal cell carcinoma patients receiving vascular endothelial growth factor-targeted therapies. Recent meta-analyses also demonstrated that colorectal cancer patients with 20% reduction in the SLD of target lesions is associated with a better overall survival (OS) (HR, 0.58; 95% CI, 0.53–0.64; $P < 0.001$) and PFS (HR, 0.57; 95% CI, 0.47–0.69; $P < 0.001$) compared with patients who were nonresponders (<20% reduction in the SLD).[21] Taken all together, their results emphasized the influence of target therapy on long-term outcome and confirmed the potential validity of tumor shrinkage as a worthy indicator of survival to be further explored in clinical trials.

An earlier study put the applicability of RECIST criteria in assessing the efficacy of target therapeutics in question. Changes in tumor sizes might predict survival in advanced NSCLC patients with target treatment and be an alternative endpoint for efficacy in target therapeutics[22] because the aim of advanced cancer therapeutics is to prevent disease progression and prolong survival. Therefore, drugs in target therapies are considered to be promising if patients' survival could benefit from appropriately reduced tumor size and SLD. Thus, the purpose of this research was to explore a more effective and accurate response standard that could distinguish individuals who would likely to have prolong survival in a population of 3 clinical trials.

2. Patients and methods

2.1. Patients

A total of 88 advanced NSCLC patients from 3 clinical trials (TRUST study, IRESSA registration clinical trial and ZD6474 study) with target therapy after failure of chemotherapy from December 2003 to October 2007 in Sun Yat-Sen University Cancer Center (SYSUCC) were included in the study if they met the following inclusion criteria: (1) at least 18 years of age and had performance status between 0 and 2 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale; (2) pathologically confirmed to have advanced NSCLC after the failure of 1 or 2 prior chemotherapy procedures; (3) obligatory to have no less than 1 measurable tumor lesion, (4) with adequate hematologic and biochemical values and at least 3 months of life expectancy, and (5) had not receive any previous systemic therapies including chemotherapy and radiotherapy within 4 weeks and target therapy. All patients signed informed consent forms and the 3 clinical trials were approved by our Institutional Ethical Committee. The process was conducted in accordance with the Declaration of Helsinki and good clinical practice.

2.2. Treatment regimens

Among the 88 enrolled patients, 27 received 250 mg Gefitinib once a day, and 42 received 100 mg Erlotinib per day and 19 received 150 mg ZD6474 per day.

2.3. Evaluation

Target volumes were assessed according to computed tomography or magnetic resonance imaging within 3 weeks before randomization as baseline, every 4 weeks for the first 16 weeks, and every 8 weeks afterwards. The response was assessed by 1 independent radiologist from a third-party radiology department and the attending physicians based on the recorded sum of the longest diameter (SLD) of the targets. The effectiveness was evaluated based on RECIST (version 1.0) criteria and patients were divided into 4 groups of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PR) if they had all target lesions disappeared, the variation of SLD below –30%, between –30% and +20%, and above +20%, respectively.

2.4. Search for Optimal Tumor Shrinkage

Receiver operating characteristic (ROC) curve[23] was constructed similar to that by Krajewski et al[24] with tumor shrinkage as the test variable and survival status as the state variable, and used to determine the factors that could predict the optimal value of tumor shrinkage. The area under the curve (AUC) represents the discriminative power of the test and expected to be between 0.5 (indicating no discriminative ability) and 1.0 (indicating highest detection accuracy). The Confidence Interval for the AUC could be calculated. The highest AUC value of tumor shrinkage was used to predict the responsiveness of patients to the targeted therapy. We search for an optimal tumor shrinkage value to detect prolonged survival and identify patients with clinical benefit.

2.5. Statistics analysis

Progression-free survival (PFS) was defined from the time of taking target therapies to the earliest occurrence of disease

progression or death for any reasons. Overall survival (OS) was calculated as the duration from the time of taking target therapies to the time of death for any reason. Patients who had not progressed or died at the time of last follow-up were investigated at the time of statistical analysis. The distributions of the postrandomization prognostic factors in the 2 groups based on the cutoff value of tumor shrinkage were compared using the chi-square test for heterogeneity or the Kruskal–Wallis test. Survival curves were constructed using the log-rank test and compared using either univariate or multivariate Cox regression analyses. All statistical analyses were performed using Empower (R) (www.empowerstats.com, X&Y solutions, Inc., Boston, MA) and R (http://www.R-project.org) and Statistical Package for Social Sciences (SPSS) 21.0 software (IBM, Armonk, NY), with a 2-sided significant level setting at $P < 0.05$.

3. Results

3.1. Threshold evaluation by ROC analysis

For tumor shrinkage threshold assessment, ROC curve analysis yielded –8.32% in SLD as the optimal threshold for responsiveness/nonresponsiveness with respect to OS (Supplementary Figure S1, http://links.lww.com/MD/B164) and the AUC area under the ROC curve was 0.714 (95% confidence interval [95% CI]: 0.574–0.849, $P = 0.002$). Using –8.32% as the optimal cutoff value for tumor shrinkage score, the specificity and sensitivity were 87.5% and 55.6%, respectively, and all patients were divided into 2 groups: the responders with SLD of target lesions decreased by ≥8.32% and the nonresponders with the SLD of target lesions shrunk by <8.32%.

3.2. Patients

A total of 88 patients were included in the retrospective analysis. Their median follow-up time was 12 months. Table 1 lists the baseline characteristics of all patients. Their median age was 55 years (range: 26–74 years). Among these patients, 37 patients (42.0%) were female and 46 (52.3%) were nonsmokers. In total, 73 patients (82.9%) were in Stage IV. Evaluation of all 88 patients by RECIST 1.0 and using 8.32% tumor diameter shrinkage as thresholds indicated that (1) the objective response rate (CR+PR) was 29.5%, (2) 46 (52.3%) patients were considered as responders (Fig. 1) whereas 42 (47.7%) were deemed as nonresponders. Changes of SLD of target lesions by referencing to baseline in all patients were in the range of 100% decrease to 110% increase in the SLD (Fig. 2). Table 2 shows the characteristics of patients in each subgroup.

3.3. Association between tumor changes and PFS

The median PFS of all patients was only 5 months, but that for patients with CR+PR was 11.10 months, significantly higher than that of 3.07 months for patients with SD + PD ($P = 0.002$, Fig. 3A). The linear regression analysis of PFS and tumor shrinkage rate indicated that longer PFS was positively correlated with higher tumor shrinkage rate ($P < 0.001$) (Supplementary Figure S2, http://links.lww.com/MD/B164). Kaplan–Meier survival analysis and log-rank test also revealed that the median PFS for responders who had ≥8.23% tumor shrinkage in SLD was significantly longer than that of 1.17 months for nonresponders who had <8.23% tumor shrinkage in SLD ($P < 0.001$, Fig. 3B), suggesting that 8.23% tumor shrinkage could well set the responders apart from the nonresponders in terms of PFS.

Table 1

Baseline characteristics of all patients.

Characteristics	Cases (n = 88)	Percentage (%)
Age, y		
Mean	54.1	
Median	55	
Range	26 to 74	
Gender		
Female	37	42.0
Male	51	58.0
Smoking status		
Never-smoking	46	52.3
Current or ever Smoking	42	47.7
Histology		
Adenocarcinoma	64	72.7
Nonadenocarcinoma	24	27.3
Clinical stage		
IIIB	15	17.1
IV	73	82.9
Previous chemotherapy		
1–2 regimen	49	55.7
≥3 regimens	39	44.3
Target therapy		
Gefitinib	27	30.7
Erlotinib	42	47.7
ZD6474	19	21.6
ECOG PS		
0	17	19.3
1	64	72.7
2	7	8.0
CT size change from baseline to last follow-up CT (%)		
Median	−10	
Range	−100 to 110	
RECIST Response		
CR	1	1.1
PR	25	28.4
SD	40	45.5
PD	22	25.0
Tumor shrinkage threshold		
Responder patients	46	52.3
Non-responder patients	42	47.7

Responder patients: <8.32% decreased in the sum of the longest diameter of the target lesions; nonresponder patients: ≥8.32% decreased in the sum of the longest diameter of the target lesions. CR = complete response, ECOG = Eastern Cooperative Oncology Group, PD = progressive disease, PR = partial response, PS = performance status, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease.

3.4. Association between tumor changes and OS

The median OS was 13.43 months of all patients, 16.77 months for patients with CR + PR, and 11 months for patients with SD + PD. There was no significant difference in median OS between patients with CR + PR and patients with SD + PD ($P = 0.105$, Fig. 4A). The curve of linear regression analysis of OS and tumor shrinkage rate indirectly showed that OS was positively correlated with tumor shrinkage ($P = 0.071$) (Supplementary Figure S3, http://links.lww.com/MD/B164). Kaplan–Meier survival analysis and log-rank test demonstrated that 8.23% decrease in SLD could be used as a significant predictor of OS and distinguish responders, who had median OS of 19.80 months, from nonresponders, who had median of 7.90 months ($P < 0.001$, Fig. 4B).

3.5. Univariate and multivariate Cox regression analyses

Univariate Cox regression analyses of PFS demonstrated that PFS had statistically significant correlations with 8.23% tumor

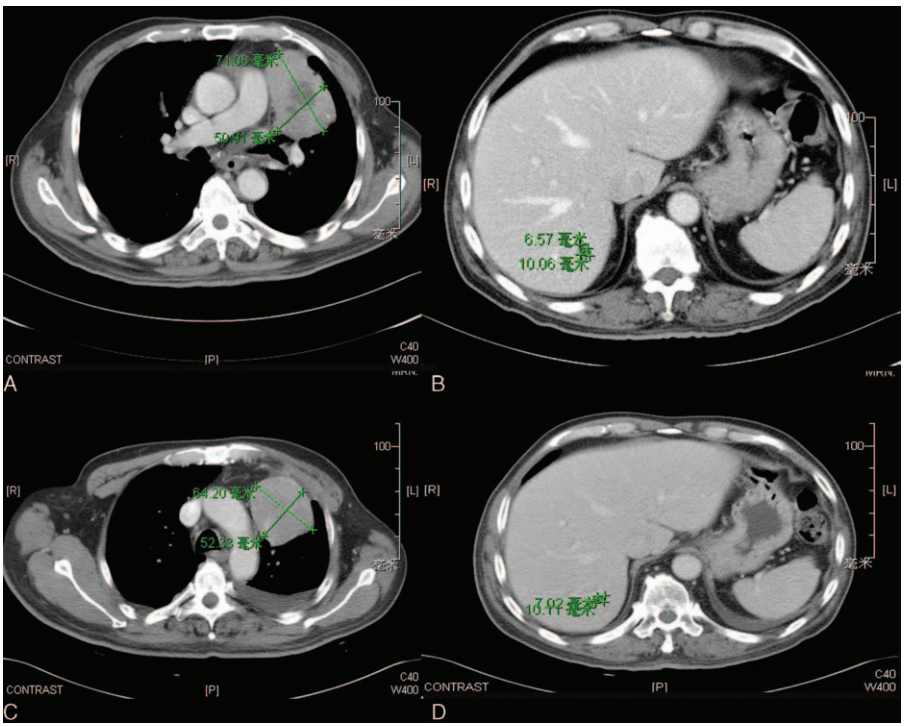

Figure 1. Baseline and first follow-up computed tomography (CT) images of a 60-year-old man with metastatic lung adenocarcinoma treated with EGFR-TKIs. Axial CT images at baseline (A and B) demonstrate the target left lung and liver metastases (green measurement lines), measuring 71.06 mm and 10.06 mm in long axis, respectively. Axial contrast-enhanced CT at first follow-up after treatment initiation (C and D) demonstrated ~9% decrease in the sum of the longest diameter of the targets (green measurement lines), measuring 64.20 mm and 10.11 mm, respectively. CT = computed tomography, EGFR = epidermal growth factor receptor, TKI = tyrosine kinase inhibitors.

shrinkage ($P < 0.001$), age ($P = 0.027$), and RECIST response ($P = 0.003$) (Table 3) and multivariate analyses further revealed that tumor shrinkage was an independent prognostic factor of PFS (HR, 8.11, 95% CI, 3.75 to 17.51, $P < 0.001$) and age was also a valid prognostic factor of PFS (HR, 0.97, 95% CI, 0.95–1.00, $P = 0.027$) (Table 4). Similarly, univariate Cox regression analyses of OS also found that 8.23% tumor shrinkage ($P < 0.001$), the SLD at baseline ($P = 0.013$), and smoking status ($P = 0.005$) were independent factors (Table 5) and multivariate analyses also proved 8.23% tumor shrinkage as a valid prognostic factor of OS (HR, 2.36, 95% CI, 1.41–3.96, $P = 0.001$). In addition, the multivariate analysis also showed that the SLD at baseline was an independent prognostic factor for OS (HR, 1.10, 95% CI, 1.02–1.18, $P = 0.007$). (Table 6).

Furthermore, the univariate Cox analyses were performed for PFS and OS with the different subgroups of receiving target therapy. Responder patients who received Gefitinib or Erlotinib had a better outcome in comparison to nonresponder patients for PFS and OS (Supplementary Tables 1 and 2, http://links.lww.com/MD/B164).

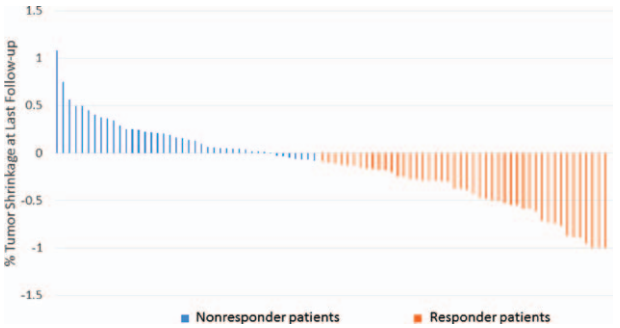

Figure 2. Waterfall plot—change of baseline in percentage with best overall response' follow-up evaluation. Changes in the sum of long axis diameter (SLD) of target lesions were recorded. Patients with measurable changes had a range of tumor changes from complete disappearance to a 110% increase in SLD. Responder patients with 8.32% tumor shrinkage at the time of the best overall response' follow-up (red bars) had median progression-free survival (PFS) and overall survival (OS) of 13.40 and 19.80 months, respectively. Whereas nonresponder patients who did not achieve at least 8.32% tumor shrinkage (blue bars) had median PFS and OS of 1.17 and 7.90 months. OS = overall survival, PFS = progression-free survival, SLD = the sum of the longest tumor diameter.

4. Discussions

It is well known that target therapy is beneficial to advanced NSCLC patients. However, how to best evaluate this benefit is still under debate. In our study, a total of 88 advanced NSCLC patients were enrolled in 3 clinical trials and treated with EGFR-TKIs. If based on the RECIST criteria, only 26 patients (29.5%) achieved the objective response, which is much fewer than the actual patients (n = 40, 45.5%) who was evaluated as SD in our cohort. Thus, whether RECIST is the best criteria for evaluation of target therapy remains unclear. In this study, we first attempted to assess the concept of tumor shrinkage after target therapy using 2 main steps. First, we calculated the optimal cutoff value of the tumor shrinkage using the analysis of ROC curve. Second, we analyzed the correlation between survival time (PFS and OS) and

Table 2

Clinical manifestations according to 8.32% tumor diameter shrinkage on the evaluation of best overall response.

Characteristics	Responder patients Number of patients (%) N = 46	Nonresponder patients Number of patients (%) N = 42	P
Age, y			0.933*
Mean	54.6	53.5	
Median	56	55	
Range	38–73	26–74	
Gender			0.014†
Female	25 (54.3)	12 (28.6)	
Male	21 (45.7)	30 (71.4)	
Smoking history			0.034†
Never-smoking	29 (63.0)	17 (40.5)	
Current or ever Smoking	17 (37.0)	25 (39.5)	
Histology			0.223†
Adenocarcinoma	36 (78.3)	28 (66.7)	
Nonadenocarcinoma	10 (21.7)	14 (33.3)	
Clinical stage			0.511†
IIIB	9 (19.6)	6 (14.3)	
IV	37 (80.4)	36 (85.7)	
Previous chemotherapy			0.146†
1–2 regimen	29 (63.0)	20 (47.6)	
≥3 regimens	17 (37.0)	22 (52.4)	
Target therapy			0.256†
Gefitinib	14 (30.4)	13 (31.0)	
Erlotinib	19 (41.3)	23 (54.8)	
ZD6474	13 (28.3)	6 (14.3)	
ECOG PS			0.140†
0	9 (19.6)	8 (19.0)	
1	32 (69.6)	32 (76.2)	
2	5 (10.9)	2 (4.8)	

Responder patients: <8.32% decreased in the sum of the longest diameter of the target lesions; nonresponder patients: ≥8.32% decreased in the sum of the longest diameter of the target lesions. ECOG = Eastern Cooperative Oncology Group, PS = performance status.

* Kruskal–Wallis test

† Chi-square test

different evaluation criteria, respectively. Based on the ROC curve, the threshold was set as 8.23% shrinkage in SLD of the target lesions and used to identify responders and nonresponders to EGFR-TKIs therapy. Based on this criterion, the median PFS and OS were 13.40 months and 19.80 months, respectively, for responders, which were significantly longer than those of 1.17 months and 7.90 months, respectively, for nonresponders ($P < 0.001$ for both). Furthermore, the number of responders defined by 8.32% tumor diameter shrinkage were higher than that of individuals with objective response based on the RECIST criteria, demonstrating that half (n = 20) of patients with stable disease (n = 40) could benefit from EGFR-TKIs treatment. It should be noted that patients enrolled in our study was homogeneous, ensuring truthful size analysis. In addition, using 8.32% tumor diameter shrinkage for patients' allocation had the advantage over the RECIST criteria: the former divided individuals into only 2 settings whereas the latter into 4 groups (complete response, partial response, stable disease, and progressive disease). In the second step, univariate and multivariate Cox regression analyses were performed to explore the relationship of survival time (PFS and OS) with different evaluation criteria. Univariate Cox analyses indicated that the 8.32% tumor diameter shrinkage was an independent factor for both PFS ($P < 0.001$) and OS ($P < 0.001$). Multivariate Cox regression analyses further demonstrated that 8.32% tumor diameter shrinkage was a valid prognostic factors for PFS ($P < 0.001$) and OS ($P = 0.001$). We further performed the analyses of subgroups according to the 3 target therapy for PFS and OS, respectively. The responder patients who received Gefitinib or Erlotinib had statistically significant. Although the responder patients who received ZD6474 had no statistically significant, the results of the univariate analyses indicated that the nonresponder patients had higher hazard of progression or death from the target therapy (Supplementary Tables 1 and 2, http://links.lww.com/MD/B164). These results affirmed us that 8.32% tumor diameter shrinkage was a better evaluation criterion than RECIST criteria. In the future clinical practice, according to the 8.32% tumor diameter shrinkage, we might be clear to judge whether or not the patients received the current target therapeutic regimen.

In addition, we also adopted the RECIST criteria to evaluate all the patients. Excepted for the objective responders who achieved the benefit, the criteria failed to distinguish patients in the SD group who would have prolonged PFS or OS by target therapeutics from those who would not, consequently supplying no information on the treatment efficacy. By contrast, using the optimal tumor shrinkage value could better predict the outcome, suggesting it is a

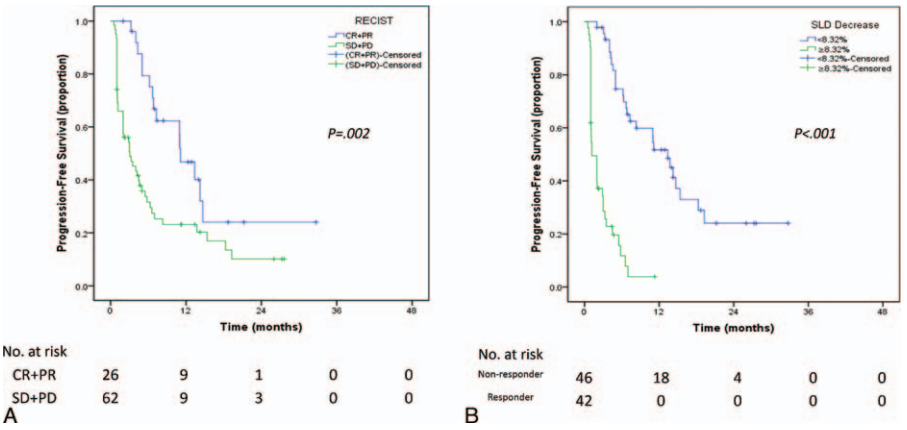

Figure 3. Progression-free survival (PFS) curves for all patients by RECIST response and according to −8.32% thresholds after target therapy (A) PFS stratified by RECIST response (CR + PR) versus no response (SD + PD). (B) PFS stratified by −8.32% threshold-defining responder patients (<−8.32% SLD) versus nonresponder patients (≥−8.32% SLD). CR = complete response, PD = progressive disease, PFS = progression-free survival, PR = partial responses, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease, SLD = the sum of the longest tumor diameter.

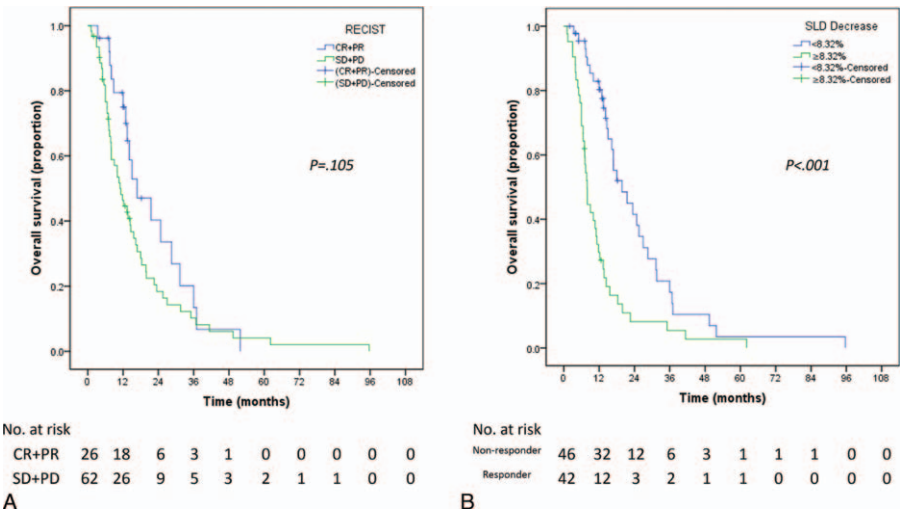

Figure 4. Overall survival (OS) curves for all patients by RECIST response and according to −8.32% thresholds after target therapy (A) OS stratified by RECIST response (CR+PR) versus no response (SD+PD). (B) OS stratified by −8.32% threshold-defining responder patients (<−8.32% SLD) versus nonresponder patients (≥−8.32% SLD). CR = complete response, OS = overall survival, PD = progressive disease, PR = partial responses, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease, SLD = the sum of the longest tumor diameter.

Table 3

Correlation of basic characteristics in all patients to the PFS by univariate analyses.

Characteristics	HR	95% CI	*P*
Age, y	0.97	0.95–1.00	0.027*
Gender			
Female	1.00 (ref.)		
Male	1.31	0.79–2.16	0.299*
Smoking history			
Never-smoking	1.00 (ref.)		
Current or ever Smoking	1.49	0.89–2.50	0.128*
Histology			
Nonadenocarcinoma	1.00 (ref.)		
Adenocarcinoma	0.97	0.55–1.72	0.924*
Clinical stage			
IIIB	1.00 (ref.)		
IV	0.93	0.50–1.76	0.833*
Previous chemotherapy			
1–2 regimen	1.00 (ref.)		
≥3 regimens	1.09	0.66–1.80	0.735*
Target therapy			
Gefitinib	1.00 (ref.)		
Erlotinib	0.94	0.54–1.63	0.823*
ZD6474	0.67	0.32–1.44	0.309*
ECOG performance status			
0	1.00 (ref.)		
1	0.58	0.31–1.07	0.082*
2	0.44	0.14–1.33	0.145*
The SLD at baseline	1.02	0.94–1.10	0.591*
RECIST response			
CR+PR	1.00 (ref.)		
SD+PD	2.41	1.34–4.34	0.003*
Tumor shrinkage threshold			
Responder patients	1.00 (ref.)		
Nonresponder patients	7.06	3.87–12.90	<0.001*

Responder patients: <8.32% decreased in the sum of the longest diameter of the target lesions; nonresponder patients: ≥8.32% decreased in the sum of the longest diameter of the target lesions. CI = confidence interval, CR = complete response, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, PD = progressive disease, PR = partial response, PS = performance status, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease. SLD = sum of the longest diameter.

* Univariate Cox regression analyses.

better predictor. In most literature, RECIST criteria were used to evaluate large clinical trials to assess the response to target therapies and evaluate the efficacy of chemotherapy on solid tumors. However, previous studies proposed a dispute that whether RECIST criteria were appropriate standard to assess the changes of tumor size after target therapies, such as antiangiogenic drugs[20] and EGFR-TKIs.[22] Tumor burden is a vital character of the clinical assessment of anticancer therapeutics. Changes in both tumor size and the time to the disease progression are main endpoints in cancer clinical trials.[25] The revised RECIST 1.1 added the numbers of lesions, pathological lymph nodes, and so on, as new criteria to the previous RECIST 1.0. Nevertheless, objective response still holds a –30% threshold-defining response. The low rate of tumor shrinkage always was a crucial problem in particular to target therapeutics such as EGFR-TKIs. We tried to search for optimal tumor shrinkage and believed that the value of optimal tumor shrinkage after target therapeutic treatments must be addressed specifically.

For new anticancer treatment, newer agents are expected to differ from the "classical" cytotoxic agents. They are expected to have lower toxicities and longer duration of administration.[26,27]

Table 4

Multivariate analysis for PFS.

Variable	HR	95% CI	*P*
Age	0.97	0.95–1.00	0.027*
RECIST response			
CR+PR	1.00 (ref.)		
SD+PD	0.85	0.39–1.85	0.683*
Tumor shrinkage threshold			
Responder patients	1.00 (ref.)		
Nonresponder patients	8.11	3.75–17.51	<0.001*

Responder patients: <8.32% decreased in the sum of the longest diameter of the target lesions; nonresponder patients: ≥8.32% decreased in the sum of the longest diameter of the target lesions. CI = confidence interval, CR = complete response, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, PD = progressive disease, PFS = progression-free survival, PR = partial response, PS = performance status, SD = stable disease.

* multivariate cox regression analyses.

Table 5

Correlation of basic characteristics in all patients to the OS by univariate analyses.

Characteristics	HR	95% CI	P
Age, y	0.99	0.97–1.01	0.346*
Gender			
Female	1.00 (ref.)		
Male	1.34	0.83–2.15	0.227*
Smoking history			
Never-smoking	1.00 (ref.)		
Current or ever Smoking	2.01	1.23–3.29	0.005*
Histology			
Nonadenocarcinoma	1.00 (ref.)		
Adenocarcinoma	0.72	0.42–1.22	0.218*
Clinical stage			
IIIB	1.00 (ref.)		
IV	1.72	0.88–3.37	0.115
Previous chemotherapy			
1–2 regimen	1.00 (ref.)		
≥3 regimens	0.93	0.58–1.49	0.761*
Target therapy			
Gefitinib	1.00 (ref.)		
Erlotinib	0.81	0.47–1.38	0.438*
ZD6474	1.30	0.60–2.81	0.510*
ECOG performance status			
0	1.00 (ref.)		
1	0.69	0.37–1.28	0.237*
2	1.43	0.54–3.75	0.470*
The SLD at baseline	1.10	1.02–1.18	0.013*
RECIST response			
CR + PR	1.00 (ref.)		
SD + PD	1.55	0.91–2.66	0.108*
Tumor shrinkage threshold			
Responder patients	1.00 (ref.)		
Nonresponder patients	2.63	1.63–4.24	<0.001*

Responder patients: <8.32% decreased in the sum of the longest diameter of the target lesions; nonresponder patients: ≥8.32% decreased in the sum of the longest diameter of the target lesions. CI = confidence interval, CR = complete response, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, PD = progressive disease, PR = partial response, PS = performance status, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease, SLD = sum of the longest diameter.

* Univariate Cox regression analyses.

Studies in murine models indicated that they often demonstrate growth inhibition rather than tumor regression. Michaelis and Ratain[28] also have summarized that both WHO and RECIST standards were insufficient for evaluating the benefit from clinical treatment, and the potential optimal endpoint for such clinical trials would depend on more aspects including whether or not the trial is blinded, response rate, and the time to progression or clinical symptoms. Recently, a variation of −10% in the sum of longest diameters were demonstrated to best reflect the outcome of metastatic renal cell carcinoma patients treated with sunitinib[20] and achieving an early tumor shrinkage ≥ or < 20% is likely able to predict different outcome in metastatic colorectal cancer patients treated with first-line chemotherapy plus bevacizumab.[29] In addition, a systematic review and pooled-analysis revealed that a decrease of at least 20% in tumor size at first re-evaluation was associated with a better OS (HR, 0.58; 95% CI, 0.53–0.64; $P < 0.001$) and PFS (HR, 0.57; 95% CI, 0.47–0.69; $P < 0.001$) compared with patients who were not achieving the reduction of 20% in the tumor size in colorectal cancer.[21] Facing the challenges from the new evaluation, for advanced NSCLC patients treated with EGFR-TKIs, we believed the 8.32% tumor diameter shrinkage is an optimal indicator for the patients during the target therapy.

Table 6

Multivariate analysis for OS.

Variable	HR	95% CI	P
Smoking history			
Never-smoking	1.00 (ref.)		
Current or ever smoking	1.51	0. 89–2.56	0.119*
The SLD at baseline	1.10	1.02–1.18	0.007*
Tumor shrinkage threshold			
Responder patients	1.00 (ref.)		
Nonresponder patients	2.36	1.41–3.96	0.001*

Responder patients: <8.32% decreased in the sum of the longest diameter of the target lesions; nonresponder patients: ≥8.32% decreased in the sum of the longest diameter of the target lesions. CI = confidence interval, CR = complete response, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, PD = progressive disease, PR = partial response, PS = performance status, SD = stable disease, SLD = sum of the longest diameter.

* Multivariate Cox regression analyses.

However, several limitations are existing in our study. First, a recent study showed that intra- and inter-observer reproducibility was a focus in tumor size assessment in NSCLC.[30] In our study, the imaging review were manually processed rather than electronic caliper. Nevertheless, our data were derived from 3 clinical trials, ensuring specifications of surveys. Second, some patients only had 1 target measurable lesion, so that accurate measurement of 8.32% reduction in SLD is almost impossible. To overcome the shortage, we use the RECIST standard, in which > 5 mm changes is defined as significant, to evaluate such small changes and avoid inappropriate conclusion. It is essential to select more target lesions whenever possible. Third, our study is not a multicenter study, because all patients were from 3 trials of 1 center, and the number of patient size was small. Finally, in the 3 clinical trials, the Chinese patients were enrolled from 2003 to 2007 during which the EGFR mutation testing was not widely used in clinic and it is hard to do retrospective EGFR mutation testing now because of no enough tumor sample left for the kind of testing. Therefore, it is unknown how many of them had EGFR mutation.

It is controversial whether high percentage of tumor shrinkage stands for a favorable treatment effect and how we identify progress in the domain of advanced NSCLC. The time of target therapeutics has carried a new level of efficacy to the domain of advanced NSCLC, because the objective response crowed depending on RECST standard is not enough to contain most or all individuals achieving clinical benefit from targeted agents. Nevertheless, RECST standard remains the main status in future clinical advancement and is still suitable for patients as a whole. It becomes evident that the variation of tumor shrinkage after targeted therapies in addition to increases in efficacy or prognosis should be afford to subgroups, which brings an argument about end points and selection criteria for clinical trials. For the field of immunotherapies or targeted therapies, that one size fits all approaches has been deserted instead of the aim to achieve durable remissions. Moreover, our research contributes to improve RECIST criteria and even create new targeted therapeutic evaluation criteria. Above all, new targeted therapeutic advancement is valuable and the goal may turn out to be more apparent in the near future.

5. Conclusions

The 8.32% tumor diameter shrinkage threshold was predictive of survival in this validated cohort of advanced NSCLC patients

treated with single target therapeutic agent. Univariate and multivariate Cox regression analyses further confirmed that a reduction 8.32% in the SLD of targets is validated as a reliable, proper predictor for PFS and OS in these settings. As mentioned above, first, based on the specificity of targeted therapy, we should further add new evaluation, which is more accurate to evaluate whether patients really benefit from the treatment, to clinical standards, especially RECST standard. Second, inappropriate evaluation may not reveal whether a new drug has enough clinical activity to warrant larger scale assessment. In a clinical trial, the tumor threshold is only 1 statistical way to prove targeted therapeutic efficacy. In a clinical decision, there is no absolute truth for the threshold but only acting as suggestions for reference for the clinician.

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