Volumetric Tumor Response and Progression in *EGFR*-mutant NSCLC Patients Treated with Erlotinib or Gefitinib

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Rationale and Objectives: The aims of this study were to investigate the association between 8-week tumor volume decrease and survival in an independent cohort of *epidermal growth factor receptor* (*EGFR*)-mutant advanced non-small cell lung cancer (NSCLC) patients treated with first-line erlotinib or gefitinib, and to assess the rate of their volumetric tumor growth after the volume nadir.

Materials and Methods: In patients with advanced NSCLC harboring sensitizing *EGFR* mutations treated with first-line erlotinib or gefitinib, computed tomography (CT) tumor volumes of dominant lung lesions were analyzed for (1) the association with survival, and (2) the volumetric tumor growth rate after the volume nadir.

Results: In 44 patients with the 8-week follow-up CT, the 8-week tumor volume decrease (%) was significantly associated with longer overall survival when fitted as a continuous variable in a Cox model ($P = 0.01$). The growth rate of the logarithm of tumor volume ($\log_e V$), obtained using a linear mixed-effects model adjusting for time since baseline, was 0.096/month (SE: 0.013/month; 95% confidence interval [CI]: 0.071–0.12/month), which was similar to the rate of 0.12/month (SE: 0.015/month; 95%CI: 0.090–0.15/month) observed in the previous report.

Conclusions: The 8-week tumor volume decrease was validated as a marker for longer survival in the independent cohort of *EGFR*-mutant NSCLC patients treated with first-line erlotinib or gefitinib. The volumetric tumor growth rate after the nadir in this cohort was similar to that of the previous cohort, indicating the reproducibility of the observation among different patient cohorts.

Key Words: Lung cancer; non-small cell; *EGFR* mutations; tyrosine kinase inhibitors; tumor volume.

INTRODUCTION

The discoveries of genomic abnormalities in the tumors from patients with lung cancer and the effective treatment with targeted agents have ushered in a new era of therapeutic approaches to lung cancer (1,2). Epidermal growth factor receptor (*EGFR*) mutations in non-small cell lung cancer (NSCLC) have been studied as one of the major therapeutic targets since their discovery in 2004 (3–5). Patients with NSCLC harboring sensitizing *EGFR* mutations have initial dramatic responses to the *EGFR* tyrosine kinase inhibitors (TKIs), erlotinib, gefitinib, and afatinib, with response rates of 55–83% and progression-free survival (PFS) of 9.7–13.1 months (6–12). However, their tumors eventually grow back during *EGFR*-TKI therapy due to the development of acquired resistance, eventually leading to tumor progression (13). The duration of disease control from *EGFR*-TKI therapy can range from 4 months to 4 years or longer (13). In this context, objective early markers of tumor response during *EGFR*-TKI therapy are needed to identify patients who can safely remain on therapy and those who are unlikely to have long-term control and may potentially benefit from an early introduction of additional or alternative agents.

Imaging remains as the principal method to objectively characterize the tumor burden during cancer therapy (2). Prior studies have demonstrated the limitations of the conventional diameter-based approach according to Response Evaluation Criteria in Solid Tumors (RECIST) and indicated the need

Acad Radiol 2016; 23:329–336

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http://dx.doi.org/10.1016/j.acra.2015.11.005

for volumetric tumor assessment (2,14–20). The previous studies evaluated tumor volume measurements in patients with advanced NSCLC treated with *EGFR*-TKIs using Food and Drug Administration-approved, commercially available software and published the high reproducibility of the technique (14). By applying this technique to patients with *EGFR*-mutant NSCLC treated with the first-line erlotinib or gefitinib, the study demonstrated that greater tumor volume decrease at 8 weeks of therapy is significantly associated with longer overall survival (OS), with a cut-off value of 38% volume decrease at 8 weeks best differentiating patients with longer OS and PFS (21). The 8-week volume change as a predictor of survival has a potential role in identifying patients who may benefit from additional or alternative therapy in the early course of therapy, and help in maximizing the benefit of targeted therapy and in improving the clinical outcome. Tumor volume analysis was also applied to characterize the rate of tumor growth in patients with *EGFR*-mutant NSCLC after they reach their volume nadir (the smallest tumor volume since baseline), which is another important aspect in assessing benefit of cancer therapy (22–27). A prior study reported a reference value of the volumetric tumor growth rate among these patients after their volume nadir, which helps to differentiate slow versus fast progressors among those who are on *EGFR*-TKI therapy, thus contributing to provide an objective guidance about when to keep patients on the *EGFR*-TKI after progression (28).

Given the promising utility of tumor volume analysis, it is necessary to reproduce the results in independent cohorts to propose the approach to be used in clinical practice. The purpose of the present study is to validate (1) the association between the 8-week tumor volume decrease and longer OS and (2) the volumetric tumor growth rate after the volume nadir, in an independent cohort of patients with advanced NSCLC harboring sensitizing *EGFR* mutations treated with first-line erlotinib or gefitinib. Retrospective analysis of an independent cohort also provides an opportunity to assess how these approaches contribute in a real-life clinical setting.

MATERIALS AND METHODS

Patients

The study cohort included 58 patients with advanced *EGFR*-mutant NSCLC treated with first-line erlotinib or gefitinib monotherapy between 2002 and 2012, who had a baseline computed tomography (CT) performed before initiating therapy demonstrating at least one measurable lung lesion, and had at least one follow-up chest CT. All patients had histologically or cytologically confirmed NSCLC with sensitizing *EGFR* mutations, which were defined as deletions, duplications, and deletions-insertions of exon 19, L858R point mutation, L861Q point mutation, and G719 mis-sense point mutations, as described previously (21,28–30). The patients were initially treated with gefitinib or erlotinib, and the clinicians made decisions about changing therapies based on the symptoms, signs, and radiographic tumor assessments. Measureable lung lesions were defined as lesions measuring at least 10 mm in the longest diameter and were chosen based on the review of baseline CT images by a thoracic radiologist (M.N.) (21,28).

CT Tumor Volume Measurements during TKI Therapy

Baseline and follow-up chest CT scans were performed to assess the response to *EGFR*-TKI therapy as a part of their clinical care. A thoracic radiologist (M.N.; 10 years of experience in thoracic and oncologic imaging) performed the tumor volume and size (the longest diameter) measurements of a dominant lung lesion (1 lesion per patient) on baseline and all follow-up CT scans during therapy, using the previously validated technique on the volume analysis software (Vitrea 2; Vital Images, Minnetonka, MN) (14,21,28,31). In the workflow of tumor volume measurement, axial chest CT images were loaded and displayed in a lung window setting (level = −500; width = 1500). The radiologist (M.N.) manually selected a small region of interest within a lesion on a CT image, which showed the longest diameter of the lesion by a mouse click. The software automatically segmented the lesion from the surrounding normal lung and adjacent structures such as vessels and pleura, using a three-dimensional seed-growing algorithm. The boundary of the segmented lesion was then displayed on the CT images. The radiologist visually assessed if the automated algorithm accurately segmented the lesion excluding adjacent structures such as vessels, pleura, atelectasis, and effusion. The radiologist manually adjusted the boundary of the tumor on each image if needed, determining the boundary between the lesion and the adjacent structures by visual assessment. After segmentation and manual correction, the volume of the segmented lesion was automatically calculated by the software, and the volume of the segmented tumor was provided. The reader also manually measured the longest diameter of the lesion on a CT image using a caliper-type measurement tool on the Vitrea Workstation. The intra- and interobserver measurement variability of the technique has been studied in detail and previously published; therefore, the radiologist measured the lesion once at each time point for the present study.

The 8-week Tumor Volume Analysis

The proportional tumor volume and size changes (%) at 8 weeks of therapy were calculated in reference to the baseline tumor volume and size (21). Follow-up scans performed at 8 ± 2 weeks of therapy were allowed for the 8-week scans as in the prior study (21). The patients who did not have a follow-up CT at 8 ± 2 weeks of therapy were excluded from the 8-week volume analysis.

Volumetric Tumor Growth after the Nadir

Based on the review of the longitudinal tumor volume measurements during therapy, the volume nadir (smallest tumor volume recorded from baseline to TKI termination/last follow-up) was determined in each patient. Patients who experienced