Erlotinib as second-line treatment in patients with advanced non-small-cell lung cancer and asymptomatic brain metastases: a phase II study (CTONG–0803)†

Y.-L. Wu1*, C. Zhou2, Y. Cheng3, S. Lu4, G.-Y. Chen5, C. Huang6, Y.-S. Huang1, H.-H. Yan1, S. Ren2, Y. Liu3 & J.-J. Yang1

1Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou; 2Shanghai Pulmonary Hospital, Shanghai; 3Jilin Tumor Hospital, Changchun; 4Shanghai Chest Hospital affiliated to Shanghai JiaoTong University, Shanghai; 5The Affiliated Tumor Hospital of Harbin Medical University, Harbin; 6Fujian Tumor Hospital, Fuzhou, China

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Background: This phase II, open-label study evaluated the efficacy and safety of erlotinib as second-line therapy in non-small-cell lung cancer (NSCLC) patients with brain metastases (BM).

Patients and methods: Forty-eight patients aged 18–75 years with Eastern Cooperative Oncology Group performance status 0–2, confirmed adenocarcinoma or activating epidermal growth factor receptor (EGFR) mutation-positive NSCLC, and asymptomatic BM without extracranial progressive disease after first-line platinum-doublet chemotherapy were recruited. Treatment comprised erlotinib 150 mg/day. The primary end point was progression-free survival (PFS) determined by RECIST.

Results: The median PFS was 10.1 months [95% confidence interval (CI) 7.1–12.3] for intracranial progression and 9.7 months (95% CI 2.5–17.8) for intracranial and systemic progression. Patients with EGFR mutation-positive disease had significantly longer median PFS versus EGFR wild-type disease [15.2 months (95% CI 8.3–22.2) versus 4.4 months (95% CI 0.0–11.6); P = 0.02]. The median overall survival was 18.9 months (95% CI 14.4–23.4); 6-month and 1-year survival rates were 85% and 73%, respectively. Overall response rate was 58.3%. Most common adverse events were rash (77.1%), paronychia (20.8%), hyperbilirubinemia (16.7%), and diarrhea (14.6%); these were predominantly of grade 1/2.

Conclusions: Single-agent erlotinib was active and well tolerated in NSCLC patients with BM. Further studies are warranted.

Key words: brain metastases, carcinoma, erlotinib, non-small-cell lung, phase II clinical trial, second-line therapy

introduction

The brain is a common site of metastases among patients with non-small-cell lung cancer (NSCLC); the prognosis for patients with brain metastases (BM) is extremely poor with 1-year survival rates around 10% despite therapy [1, 2]. Evidence suggests that the brain is the first site of disease recurrence in approximately one quarter of all patients with NSCLC and 50% of patients eventually develop BM [3, 4]. The incidence of lung cancer with BM has increased in recent years largely as a result of improvements in the diagnosis and systemic treatment of extracranial disease [5].

Available therapeutic approaches for BM include whole-brain radiotherapy (WBRT), surgery, stereotactic radiosurgery (SRS), chemotherapy, and symptomatic and supportive treatment [5–7]. However, despite advances in the treatment of NSCLC BM in recent years, survival rates are poor [6]. The role of systemic chemotherapy is particularly controversial because of the limited ability of most potential agents to cross the blood–brain barrier (BBB) [8].

The epidermal growth factor receptor (EGFR) plays an important role in NSCLC and has been explored as a novel therapeutic target in lung cancer [9]. Erlotinib is an oral EGFR tyrosine kinase inhibitor (TKI) that demonstrated a significant survival benefit versus placebo in patients with advanced NSCLC after failure on chemotherapy in a pivotal trial (BR.21) [10], leading to the approval of erlotinib for patients with locally advanced or metastatic NSCLC who have failed at least one prior chemotherapy regimen [11]. Erlotinib is also approved in Europe as first-line therapy for locally advanced or metastatic NSCLC with EGFR activating mutations and as
maintenance treatment in patients with stable disease (SD) after first-line standard platinum-based chemotherapy [11]. EGFR mutation status has emerged as an important predictor of response and survival benefit following treatment with EGFR TKIs [10, 12–14] and consequently erlotinib is specifically recommended for the treatment of NSCLC patients with EGFR-activating mutations [11].

Optimal central nervous system (CNS) penetration is a critical issue in the treatment of patients with BM with systemic drug therapy. Recently published data showing high concentrations of erlotinib in the cerebrospinal fluid with subsequent regression of BM following erlotinib administration suggest suitable BBB permeability that warrants further investigation as a potential treatment for NSCLC-associated BM [15–19]. The CTONG-0803 phase II study was designed to prospectively evaluate the efficacy and safety of erlotinib as second-line therapy in NSCLC patients with BM.

methods
study design
This was a Chinese, phase II, non-randomized, open-label, multicenter, single-arm clinical trial in patients with advanced NSCLC who had progressed with asymptomatic BM after achieving SD, partial response (PR), or complete response (CR) in extracranial lesions following standard chemotherapy treatment.

The trial was approved by the medical ethics committee of each participating center and was carried out in accordance with the principles of the Declaration of Helsinki and Guidelines for Good Clinical Practice. All patients provided written informed consent before any study-related procedure (ClinicalTrials.gov identifier: NCT00663689).

patients
Patients were eligible for inclusion in the study if they were aged 18–75 years, of Asian origin, had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, confirmed adenocarcinoma or activating EGFR mutation-positive NSCLC (detected by DNA direct sequencing), asymptomatic BM (one or more lesions of ≥10 mm diameter or more than three lesions of <10 mm) revealed during systemic screening, without extracranial progressive disease (PD) after 2–6 cycles of first-line platinum-doublet chemotherapy, and a life expectancy of >3 months. BM were defined as asymptomatic if there were no signs of increased intracranial pressure, nausea or vomiting, headache, cognitive and affective disorder, epilepsy, or focal neurologic symptoms. The main exclusion criteria for the study were any unstable systemic condition (including active infection, poorly controlled hypertension, unstable angina, congestive heart failure, and hepatic, renal, or metabolic disease); prior EGFR inhibitor therapy; prior radiotherapy for BM; significant ophthalmologic abnormalities; active peptic ulcer; and abnormal blood cell count, liver function tests, or creatinine clearance. During the study, patients were not permitted to receive the following drugs: phenytoin, carbamazepine, rifampicin, phenobarbital, and itraconazole because of their potential to affect the metabolism of erlotinib and reduce its plasma concentration.

study treatment
Patients received erlotinib 150 mg/day until morphologically verified intracranial PD or the development of clinically symptomatic BM or extracranial systemic progression.

efficacy and safety analyses

The primary end point was progression-free survival (PFS) defined as the time from starting erlotinib to the occurrence of either clinically symptomatic BM (intracranial progression-free survival, PFSi) or confirmed morphologically proven intracranial PD [presence of at least one key symptom in combination with radiologic evidence including computed tomography (CT) or magnetic resonance imaging (MRI) of PD in the brain on follow-up] or extracranial PD (PFS). Systemic PD was defined as disease progression based on RECIST version 1.0 [20] without intracranial PD. Patients with disease that progressed outside the brain were followed for the occurrence of intracranial PD. Secondary end points included overall response rate (ORR), 6-month and 1-year overall survival (OS) rates, and safety. Tumor response was assessed using RECIST version 1.0. Chest CT and brain MRI were carried out 6 weeks after the start of erlotinib therapy; if a patient had non-PD at week 6 they were then followed up every 3 months. Measurable lesions were defined as lesions that could be accurately measured in at least one dimension with the longest diameter of ≥20 mm, using conventional techniques, or >10 mm with a spiral CT scan.

Tumor tissue specimens were collected for biomarker analysis, and EGFR mutation was detected by DNA direct sequencing. Efficacy results were evaluated according to the EGFR mutation status (wild-type, mutation) and also the number of BM (≥3 versus ≤3). Physical examination, hematology, and biochemistry tests were carried out, and the performance status and vital signs were assessed at baseline, every 6 weeks during treatment, and then 30 days after the completion of study treatment.

Safety was assessed at each clinical visit using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI CTCAE 3.0). The incidence of serious adverse events, adverse events (AEs) leading to early withdrawal from the study, unexpected erlotinib-related AEs, and erlotinib-related rash was recorded.

statistical analyses

The sample size calculation was based on a one-sample mean test. The time period from the development of asymptomatic BM to symptomatic BM or morphologically confirmed intracranial PD was assumed to follow a normal distribution within 2 standard deviations of the mean, and the natural survival time for patients with lung cancer and BM was considered to be 1 month. Based on these assumptions, and with the prerequisite that erlotinib therapy is effective if it prolongs the end point by at least 1 month, a sample size of approximately 45 patients was required with an α error of 0.05 and a β error of 0.2.

The Kaplan–Meier method was used to determine the 6-month and 1-year cumulative survival rates. The log-rank test was used to compare the median PFS and OS of patients with different characteristics (number of BM ≥3 versus ≤3; EGFR mutation-positive versus EGFR wild-type). Survival data were censored at the time of the last visit for patients who were still alive at the final analysis. The data cut-off date for all analyses was 15 February 2012.

results

patient population
From June 2008 to April 2010, 48 patients were enrolled in the study; one patient who withdrew consent to receive erlotinib after 8 days because of toxicity was not assessable for response. All 48 enrolled patients were included in the safety analysis. Baseline characteristics for the overall population are summarized in Table 1. Of note, a total of 31.3% of patients
were wild-type for EGFR and 16.7% of patients had an EGFR mutation (exon 19 deletion or L858R mutation).

efficacy outcomes

At the time of data cut-off (15 February 2012), nine patients had no evidence of intracranial PD and six patients continued to receive erlotinib therapy. The median PFSi and PFS were 10.1 months [95% confidence interval (CI) 7.1–12.3] and 9.7 months (95% CI 2.5–17.8), respectively (Figure 1). When assessed according to the number of BM, the median PFS was numerically but not statistically longer for patients with ≤3 versus >3 BM [median PFS: 14.9 months, 95% CI 6.9–22.9 and 8.2 months, 95% CI 1.6–14.8, respectively; P = 0.71] (Table 2). The median PFS for patients with EGFR mutation-positive disease was significantly longer compared with EGFR wild-type disease (median PFS: 15.2 months for EGFR mutation subgroup, 95% CI 8.3–22.2; 4.4 months for EGFR wild-type subgroup, 95% CI 0.0–11.6; and 14.9 months unknown status, 95% CI 6.5–23.2). The median OS was 18.9 months [95% CI 14.4–23.4 (Figure 1)]. The 6-month and 1-year cumulative survival rates were 85% and 73%, respectively. Determination of the median OS for the subgroup analyses according to the number of BM (≤3 BM 21.3 months; >3 BM 16.6 months, P = 0.58), smoking status (non-smoker 21.3 months; smoker 5.7 months, P = 0.02), and PS (PS 1, 21.3 months; PS 2, 18.4 months, P = 0.42) revealed a significant difference between the smoking subgroups (Table 2). OS for patients with EGFR mutation-positive disease was numerically but not statistically longer (P = 0.14) compared with wild-type disease and unknown status [median OS was 37.5 months (95% CI not available), EGFR mutation-positive was 18.4 months (95% CI 11.4–25.4), EGFR wild-type was 19.4 months (95% CI 12.9–25.9) unknown EGFR status]. More than half of the patients (54.2%) had a PR, and two patients (4.2%) had a CR, giving an ORR of 58.3% (Table 3). Eight patients (16.7%) had SD. When assessed according to EGFR mutation status, the ORR was higher for patients with an exon 19 deletion (100%, four PRs) or an L858R mutation (50%, one CR, one PR) compared with patients with wild-type disease (33%, five PRs) (Table 3). At data cut-off, 41 patients had PD, the majority of which were intracranial, with intracranial lesions reported in 19 patients and extracranial lesions in 5 patients. Additionally, 16 patients had intracranial morphologic PD simultaneously with extracranial lesions in 5 patients. Eight patients had intracranial morphologic PD simultaneously with extracranial PD and 1 patient experienced extracranial PD simultaneously with intracranial symptoms. WBRT was the most common post-study treatment received (35.4% of patients) followed by chemotherapy (25.0%).

safety and tolerability

A total of 40 patients (83.3%) experienced at least one AE, which were mainly mild or moderate in intensity. A total of 5.5% of AEs reported were of grade 3/4. The most frequently

Table 1. Baseline demographics, clinical characteristics, and biomarker status in the overall population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Erlotinib (N = 48)*</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>Mean (range) 56 (21–75)</td>
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<tr>
<td>Gender, n (%)</td>
<td>Male 19 (39.6)</td>
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<tr>
<td></td>
<td>Female 29 (60.4)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td>1 18 (37.5)</td>
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<tr>
<td></td>
<td>2 30 (62.5)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td>Smoker 9 (18.8)</td>
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<tr>
<td></td>
<td>Non-smoker 39 (81.2)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td>Adenocarcinoma 45 (93.8)</td>
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<tr>
<td></td>
<td>BAC 2 (4.2)</td>
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<tr>
<td></td>
<td>Other 1 (2.1)</td>
</tr>
<tr>
<td>Number of brain metastases, n (%)</td>
<td>≤3 23 (47.9)</td>
</tr>
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<td></td>
<td>&gt;3 25 (52.1)</td>
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<tr>
<td>EGFR mutation status, n (%)</td>
<td>Unknown 25 (52.1)</td>
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<tr>
<td></td>
<td>Wild-type 15 (31.3)</td>
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<td></td>
<td>Mutation positive 8 (16.7)</td>
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<tr>
<td>EGFR mutation type, n (%)</td>
<td>Exon 19 deletion 4 (8.3)</td>
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<tr>
<td></td>
<td>L858R mutation 4 (8.3)</td>
</tr>
<tr>
<td>Response after chemotherapy, %</td>
<td>Stable disease 75</td>
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<tr>
<td></td>
<td>Partial response 22.9</td>
</tr>
<tr>
<td></td>
<td>Complete response 2.1</td>
</tr>
<tr>
<td>Median time from last chemotherapy cycle to start of erlotinib treatment, days (range)</td>
<td>33 (8–319)</td>
</tr>
</tbody>
</table>

BAC, bronchoalveolar carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status.

*From June 2008 to April 2010, 48 patients were enrolled; one patient withdrew consent after 8 days without an efficacy assessment.
The most common AEs reported during erlotinib therapy were rash (77.1%), paronychia (20.8%), hyperbilirubinemia (16.7%), and diarrhea (14.6%). These were predominantly of grade 1/2, with only two cases of rash and one case of paronychia reported as grade 3. One grade 4 AE of gastrointestinal bleeding was reported, which was considered by the investigator to be related to PD. No unexpected AEs or deaths due to AEs were reported.

**discussion**

The treatment of patients with advanced NSCLC and BM remains a significant challenge for clinicians. While the mainstay of therapy is WBRT, the best treatment approach continues to be debated and further clinical studies are warranted [21]. This current study was designed to determine the efficacy and safety of erlotinib as monotherapy after first-line systemic chemotherapy for NSCLC patients with reported AEs (>5% incidence) are summarized in Table 4. The most common AEs reported during erlotinib therapy were rash (77.1%), paronychia (20.8%), hyperbilirubinemia (16.7%), and diarrhea (14.6%). These were predominantly of grade 1/2, with only two cases of rash and one case of paronychia reported as grade 3. One grade 4 AE of gastrointestinal bleeding was reported, which was considered by the investigator to be related to PD. No unexpected AEs or deaths due to AEs were reported.
asymptomatic BM. Eligibility criteria for this study excluded patients >75 years to avoid selection bias, as many elderly patients do not maintain their treatment course; therefore, these patients were excluded to avoid selection bias. As erlotinib is approved for all patients regardless of EGFR mutation status in second line, EGFR mutation testing was not mandatory, and patients with adenocarcinoma were included because, in Chinese patients, a higher rate of EGFR mutations is seen in adenocarcinoma patients. Our results suggest that erlotinib has promising efficacy in this setting with an acceptable safety profile and merits further evaluation in this group of patients. Our data (PFS of 10.1 months, 1-year survival of 73%, and CR/PR in 58%) compare well with survival data reported previously for NSCLC patients with metastatic brain lesions treated with WBRT and/or SRS [6, 22–24]. While WBRT alone results in OS of ~4 months (2.4–4.9 months), in a study of patients with leptomeningeal metastasis, WBRT followed by erlotinib treatment has resulted in OS ranging from 4.4 to 18.6 months [25]. In our study, the median OS was 18.9 months, suggesting erlotinib until PD in asymptomatic patients would be a suitable alternative to WBRT.

Although the median PFS in our study was longer for patients with ≤3 BM (versus >3), this difference was not statistically significant, suggesting that erlotinib could achieve a clinical benefit regardless of the extent of metastatic spread. The median PFS for patients with EGFR mutation-positive disease was significantly longer compared with that for patients with documented EGFR wild-type disease (15.2 versus 4.4 months); this correlates with the well-established theory that EGFR mutation status is an important predictor of response and survival benefit following treatment with EGFR TKIs [10, 12–14]. Unlike some EGFR TKIs, erlotinib has proven efficacy in both mutation-positive and wild-type patients [12]; therefore, patients with unknown EGFR status are suitable for erlotinib treatment. Contrary to previous studies demonstrating the efficacy of erlotinib in wild-type patients, the preliminary results from the TAILOR study indicated that erlotinib was not associated with a PFS benefit compared with docetaxel in EGFR wild-type patients (median PFS: erlotinib 2.4 months; docetaxel 3.4 months; HR = 0.69, P = 0.01); however, this was a secondary end point—the primary end point of OS has not been presented for this study [26].

Erlotinib was generally well tolerated with a manageable safety profile and no new safety signals. The profile of AEs reported was as expected, with rash, paronychia, hyperbilirubinemia, and diarrhea the most common AEs, and the majority of AEs were of grade 1/2 in severity. Although the efficacy and safety data from this study are promising, it is important to take into consideration the limitations of the study, namely the relatively small number of patients recruited and the non-randomized design, when interpreting the results. Additionally, it may be difficult to determine the clinical impact erlotinib could have on these patients, as screening for BM is only mandatory for early or locally advanced NSCLC, not for stage IV NSCLC; therefore, identifying patients who may benefit would be difficult.

While the efficacy of erlotinib maintenance therapy has been previously established in NSCLC patients and in the Asian subpopulation [12, 27], until now, data on the efficacy of erlotinib in patients with BM from NSCLC have largely been limited to case reports or small retrospective reviews. In a clinical positron emission tomography study using C 11 erlotinib, regression of both BM and the primary lung tumor in a patient harboring an EGFR mutation was reported [19]. A clinical response was also reported in five of six patients (83%) with NSCLC, CNS metastases, and EGFR mutations treated with erlotinib in a small case series [17]. In a retrospective study of patients with NSCLC and BM (n = 69), an objective response rate of 82.4% was reported among 17 patients with an EGFR mutation (versus 0% in unselected patients; P < 0.001). Treatment with erlotinib also resulted in a significant benefit in the median time to progression within the brain (11.7 and 5.8 months; P < 0.05), and the median OS (12.9 versus 3.1 months; P < 0.001) among patients with EGFR mutation-positive NSCLC compared with those with wild-type disease or unknown EGFR status [18]. Another retrospective review of NSCLC patients with BM reported a median PFS of 3.0 months, a median OS of 9.2 months, and disease control rates (DCRs) of 42.5% for extracranial disease and of 62.5% for intracranial disease. Nine surgical tumor specimens were examined retrospectively for EGFR mutations; DCR was 80% in patients with EGFR mutation-positive tumors compared with 25% in patients with EGFR wild-type disease [28]. In common with our study results, these latter two studies suggest that most clinical benefit seen with erlotinib in these patients is associated with the presence of an EGFR mutation.

Several studies have shown that erlotinib reaches the cerebrospinal fluid in concentrations sufficient to cause brain metastasis regression. Dynamic positron-emission tomography with C 11 erlotinib has been used to show sufficient drug accumulation in the brain [19]. Broniscer et al. [15] showed that ~10% of the concomitant plasma concentration of erlotinib was present in the cerebrospinal fluid, which was enough to have an effect on BM.

To further improve the concentration of erlotinib in the cerebrospinal fluid, weekly high-dose ‘pulses’ of erlotinib have been used to increase CNS accumulation. A 1500 mg weekly dose resulted in CNS concentrations of 130 nM, which is sufficient to inhibit 50% of growth in cancer cell lines [29]. In a retrospective analysis, the use of high-dose pulses to treat brain metastasis was also effective and well tolerated [30]. It is of interest to compare the results obtained with erlotinib in metastatic NSCLC with data in NSCLC patients with BM treated with the EGFR TKI gefitinib. In studies of gefitinib, response rates of 10% to 60% have been reported with the median PFS and OS data of 3 to 9 months and 5 to 15 months, respectively [31–35]. It should be noted, however, that almost half of all patients included in these analyses were pretreated with radiotherapy (predominantly WBRT) and some patients were included as early as 1 month following radiotherapy. There are currently insufficient data to allow any clear conclusions to be drawn regarding the relative efficacy of erlotinib and gefitinib in patients with advanced NSCLC and BM. In a recently published randomized phase II study of erlotinib versus gefitinib in patients with locally advanced, metastatic NSCLC who had failed first-line chemotherapy, both drugs demonstrated comparable clinical activity, with no
significant difference in response rate or PFS, and an acceptable safety profile [36].

In conclusion, erlotinib has promising clinical activity in patients with NSCLC with BM and is well tolerated. Further studies are now warranted to fully elucidate the role of erlotinib in this setting and to determine which patients may benefit most from erlotinib treatment.

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disclosure

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Disease volumes as a marker for patient response in malignant pleural mesothelioma

Z. E. Labby1, A. K. Nowak2,3, J. J. Dignam4, C. Straus1, H. L. Kindler5 & S. G. Armato III1*  

1Department of Radiology, The University of Chicago, Chicago, USA; 2Department of Medical Oncology, Sir Charles Gardner Hospital, Nedlands; 3School of Medicine and Pharmacology, University of Western Australia, Crawley, Western Australia, Australia; Departments of 4Health Studies; 5Medicine, The University of Chicago, Chicago, USA

Background: The goal of this study was to create a comprehensive model for malignant pleural mesothelioma patient survival utilizing continuous, time-varying estimates of disease volume from computed tomography (CT) imaging in conjunction with clinical covariates.

Patients and methods: Serial CT scans were obtained during the course of clinically standard chemotherapy for 81 patients. The pleural disease volume was segmented for each of the 281 CT scans, and relative changes in disease volume from the baseline scan were tracked over the course of serial follow-up imaging. A prognostic model was built using time-varying disease volume measurements in conjunction with clinical covariates.

Results: Over the course of treatment, disease volume decreased by an average of 19%, and median patient survival was 12.6 months from baseline. In a multivariate survival model, changes in disease volume were significantly associated with patient survival along with disease histology, Eastern Cooperative Oncology Group performance status, and presence of dyspnea.

Conclusions: Analysis of the trajectories of disease volumes during chemotherapy for patients with mesothelioma indicates that increasing disease volume was significantly and independently associated with poor patient prognosis in both univariate and multivariate survival models.

Key words: chest CT, malignant pleural mesothelioma, therapy response assessment

Introduction

Any image-based response evaluation method has two components; the first describes a protocol for making measurements, and the second describes how to classify patients into response categories once those measurements are available. Tumor response assessment with medical images has focused on reducing the dimensionality of the first component and discretization of the second component, beginning with the World Health Organization [1] bi-dimensional measurement technique that used the product of two linear measurements as a quasi-two-dimensional metric to assess tumor response across serial scans. Progressive disease (PD) was considered an increase of ≥25% from the minimum of previous tumor measurements, and partial response (PR) was considered a decrease of 50% or more from the baseline tumor measurement. Tumors not meeting the criteria for either PD or PR were classified as stable disease. The Response Evaluation Criteria In Solid Tumors, or RECIST, criteria were developed to simplify this measurement process to a single longest tumor diameter [2], and the threshold criteria were derived from a geometrical relationship between the cross-sectional area and the diameter of a sphere, leading to the current −30%/+20% RECIST classification criteria [3, 4].

*Correspondence to: Dr S. G. Armato III, Department of Radiology, The University of Chicago, 5841 S Maryland Ave., MC 2026, Chicago, IL 60637, USA. Tel: +1-773-834-3044; Fax: +1-773-702-0371; Email: s-armato@uchicago.edu

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