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A pilot study of conformal radiotherapy combined with erlotinib-based multimodality therapy in newly diagnosed metastatic non-small-cell lung cancer

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Abstract. – OBJECTIVE: Lung cancer is the leading cause of cancer-related death in the world, particularly in major cities in China. We aimed to determine the benefit of survival and toxicity of Conformal Radiotherapy (CRT) combined with erlotinib-based multimodality therapy in newly diagnosed metastatic non-small-cell lung cancer (NSCLC).

PATIENTS AND METHODS: Newly diagnosed metastatic NSCLC patients were treated with CRT and erlotinib, with or without chemotherapy matched protocol. The patients received CRT with a dose of 30-66Gy. Erlotinib was used at least one 28-day cycle. The primary end point was overall survival (OS).

RESULTS: Thirty-two patients were analyzed. The median OS was 517 days. Patients with only one metastasis showed longer survival than patients with multi-metastases (986 vs. 380 days, n = 8 vs. 24, p = .009). Patients with multiple metastases in brain conferred worse survival for patients without and with sole brain metastasis (321 vs. 700 days, n=11 vs 21, p = .006). There was no significant difference in median survival whether erlotinib was used as a first-, second- or third-line therapy (380 vs. 700 vs. 310 days, n = 10 vs. 15 vs 7, respectively. p = .179). Patients with TTCRT > 90 days had longer OS than patients with TTCRT ≤ 90 days (749 vs. 322 days, n = 11 vs. 21, p = .012). Patients tolerated treatment with limited Grade 1/2 toxicity.

CONCLUSIONS: In this study, patients with newly diagnosed metastatic NSCLC had survival benefits when erlotinib was used combined with CRT. Further prospective trials are needed to derive maximal benefit from the drug treatment.

Key Words:
Conformal radiotherapy, Non-small-cell lung cancer, Erlotinib, Metastatic, Survival.

Introduction

Lung cancer is the leading cause of cancer-related death in the world, particularly in major cities in China. It is estimated that more than one million Chinese people will die of lung cancer by 2025[1,2]. Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all newly diagnosed lung cancers, almost one-half of which have metastasized at diagnosis[3]. Chemo-radiotherapy has become the standard treatment for good performance status (PS) patients with metastatic NSCLC. However, survival outcomes are still poor, with a median survival of 4-6 months and a 2-year survival rate of 5%[4,5].

Erlotinib (Tarceva; F. Hoffmann-La Roche, Basel, Switzerland) is a highly potent, orally active EGFR tyrosine-kinase inhibitor (TKI)[6]. In the phase III BR.21 study[7], erlotinib significantly improved overall survival (OS) and progression-free survival versus placebo, and it also provided significant symptomatic and quality-of-life benefits. Two randomized phase III trials were designated to study whether concurrent administration of erlotinib with standard chemotherapy could enhance survival in advanced or metastatic NSCLC patients. However, the combined therapy did not improve survival compared with chemotherapy alone[8,9].

Conformal radiotherapy (CRT) for metastatic NSCLC is generally administered with palliative intent and common indications include pain due to bony metastases, respiratory distress secondary to airway compression, hemoptysis, and

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neurological symptoms caused by brain metastases or spinal cord compression[5]. A prospective Phase III trial of patients with head-and-neck tumors found that the combined RT with the anti-EGFR antibody cetuximab increased both local tumor control and overall survival[10]. Another prospective phase I trial that combined whole-brain radiation therapy (WBRT) and concurrent erlotinib for the treatment of brain metastases NSCLC revealed that it was well tolerated in patients with RT and erlotinib[11]. Therefore, we hypothesized the combined treatment of RT and erlotinib might improve the current dismal prognosis of patients with metastatic NSCLC. To provide data to test the hypothesis, we conducted a retrospective analysis for patients with radiotherapeutics for their metastatic NSCLC, who received erlotinib with or without chemotherapy.

Patients and Methods

Patient Selection

The study was approved by Southern Medical University Ethic Committee and all patients gave written, informed consents. Patients were ≥18 years of age with histologically or cytologically confirmed metastatic NSCLC. Additional inclusion criteria included Eastern Cooperative Oncology Group (ECOG) PS scores of 0-3, assessable lesions defined by Response Evaluation Criteria in Solid Tumors, and life expectancy more than 4 weeks. Exclusion criteria included any active gastrointestinal disorder and severe interstitial pneumonia.

Study Procedures and Treatment

Treatment-planning CT scans were performed using a maximum of 5 mm cuts and intravenous contrast if possible. The gross tumor volume (GTV) was defined as the total volume of the primary, nodal tumor masses visualized and the metastases on any radiographic images. The clinical target volume (CTV) was defined as the GTV plus a 0.8 cm margin, and the planning target volume (PTV) was defined as the CTV plus a 1 cm to 1.5 cm margin for setup uncertainty and respiratory motion. The regional lymph nodes were not electively irradiated. All CRT treatment plans for patients were designed on the RT planning system (Xio, FOCUS, CMS, St Louis, MO, USA) to deliver the prescribed dose to 95% of the planning target volume. Four or five fields were usually used in the treatment plan[12].

The spinal cord dose was limited to 50 Gy anywhere, and the total left ventricle dose was limited to 40 Gy. An attempt was made to limit the lung volume receiving > 20 Gy (V20) to < 35%. Although not specifically required, the length of esophagus receiving a full radiation dose was kept as short as possible. The treatment was given with a daily fractionation of 2.0 Gy, 5 days per week. The total radiation dose for the whole group ranged from 30 Gy to 66 Gy. Patients with brain metastases received whole brain irradiation (WBI) with a dose of 30 Gy, and an increased GTV dose of 50-60 Gy while the number of brain metastases did not exceed 3. All quoted doses had incorporated inhomogeneity corrections into the dose calculations. Time to CRT (TTCRT) means time until conformal radiotherapy (CRT) from final diagnosis.

Patients were treated with 150 mg of erlotinib daily without interruption until disease progression, severe or intolerable toxicity, or withdrawal of consents. During the process of treatment, patients could accept various chemotherapies: gemcitabine (1,000 mg/m^2, days 1 and 8 each 28-day cycle), or paclitaxel (175 mg/m^2, days 1 each 28-day cycle), or pemetrex (500 mg/m^2, days 1 each 21-day cycle) and either cisplatin (20 mg/m^2, day 1 to 4 each 28-day cycle) or carboplatin (area under the curve (AUC) 5, day 1 each 28-day cycle).

Assessments

All patients were examined by a thoracic radiologist, pulmonologist, thoracic surgeon, radiation oncologist, and medical oncologist before treatment. Baseline assessment included a historical and physical examination, standard laboratory studies, electrocardiograms (ECG), brain MRIs, either PET/CTs or radionuclide bone scans and staging chest CT scans which included full visualization of the liver and adrenal glands. Quality-Of-Life (QOL) assessment was performed using the patient scale of the Lung Cancer Symptom Scale. After each 4-week cycle, patients underwent an assessment of PS scores, adverse events, and QOL and a physical examination and laboratory studies. After the first cycle of administration of erlotinib, CT was required to ascertain if erlotinib was effective. Tumor assessment by CT was evaluated after every two cycles of therapy. PET/CT scan and/or brain MRI were performed when necessary. The response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). Toxicity was graded by the National Cancer Institute Common Toxicity Criteria, ver-

sion 2.0.

Statistical Analysis

The primary end point was the OS that was calculated from first diagnosis to disease progression or death irrespective of causes. The secondary endpoint was the time to progression (TTP) calculated from the start of erlotinib treatment to the progression of the disease, clinical response rate (RR), toxicity, and QOL. Survival data was analyzed using Kaplan-Meier methods. $p < 0.05$ was considered statistically significant.

Results

Patients

Between August 2006 and April 2009, thirty-two patients with metastatic NSCLC were treated with CRT and erlotinib. There was no patient lost to follow-up with a minimum potential follow-up period of 12 months. Characteristics of these patients are shown in Table I. In the overall study population, 43.8% of patients had over 5 metastasis lesions. Twenty-seven patients had chemotherapies before or after erlotinib.All patients had at least one 28-day cycle of erlotinib and at least one course of CRT.

Treatment

Twenty-six patients received thoracic irradiation. All patients with brain metastases received WBI. Seven patients with 1-3 brain metastases increased the brain metastases dose to 50-60 Gy. Seventeen patients with pain caused by bone metastases received a dose of 30-40 Gy; the patients with sole bone metastasis increased the dose to 54-66 Gy. The median TTCRT for the entire group was 24.5 days (range from 0-843 days). Eleven patients had TTCRT > 90 days, and twenty-one patients had TTCRT ≤ 90 days.

Thirty-one patients received 150 mg of erlotinib daily. One patient who didn't quit smoking during treatment gradually increased the dose to 300 mg daily for 3 months with the assessment of PR. Of the surviving patients, only this patient remains progression free on therapy with erlotinib.

Twenty-seven patients received chemotherapy. The most frequently prescribed chemotherapeutics was paclitaxel (15/27), and then docetaxel (10/27), gemcitabine (9/27), pemetrex (9/27) and vinorelbine (3/27). The most used platinum was cisplatin (17/27), and then oxaliplatin (8/27), carboplatin (6/27) and nedaplatin (5/27).

Table I. Characteristics of study patients.

Characteristic	Erlotinib+CRT (n = 32)
Sex, No. of patients	
Female	6 (18.8%)
Male	26 (81.3%)
Age, years	
Median	55
Range	34-80
ECOG performance score, %	
N = 0,1,2	29 (90.6%)
N=3	3 (9.4%)
Smoking status, %	
Current	23 (71.9%)
Former	1 (3.1%)
Never	8 (25.0%)
Number of metastases	
n=1	8 (25%)
1 < n ≤ 3	9 (28.1%)
3 < n ≤ 5	1 (3.1%)
n ≥ 5	14 (43.8%)
Metastases, %	
Brain	14 (43.8%)
Bone	21 (65.6%)
Lung	10 (31.3%)
Adrenal gland	6 (18.8%)
Liver	4 (12.5%)
Skin	1 (3.1%)
Number of brain metastasis	
n = 1	3/14 (21.4%)
1 < n ≤ 3	4/14 (28.6%)
n > 3	7/14 (50%)
Tumor histology, %	
Adenocarcinoma	23 (71.9%)
Squamous	8 (25.0%)
Mixed type	1 (3.1%)
TTCRT (days)	
n ≤ 90	21 (65.6%)
N > 90	11 (34.4%)
Chemotherapy	
No	5 (15.6%)
Yes	27 (84.4%)
Role of treatment	
First-line	10 (31.3%)
Second-line	15 (46.9%)
Third-line	7 (21.9%)
Concurrent CRT and erlotinib	
No	20 (62.5%)
Yes	12 (37.5%)
Dose of erlotinib	
150 mg	31 (96.9%)
300 mg	1 (3.1%)

Response Rate and QOL

The percent of patients with complete responses (CR) was 12.5%. There were nine partial responses (PR) among the patients. Six patients

achieved stable disease (SD), whereas thirteen patients had PD as their worst clinical response. The overall disease control rate (CR+PR+SD) defined as no-PD subgroup was 59.4%.

The proportion of patients with improved QOL was 68.8%. Nine patients achieved stable QOL, whereas one patient had worse QOL. Among the improved QOL patients, cough (81.8%), pain (59.1%) and hemoptysis (36.4%) were the most commonly relieved symptom.

Overall Survival

Six patients were confirmed alive and twenty-six patients had confirmed deaths. The median OS was 517 days (range from 66 to 1027 days). The 6-, 10-, 12-, 18- and 24-month survival rates were 78.1%, 68.8%, 50.0%, 28.1% and 18.8%, respectively. The female patients had significantly longer median OS than the male patients (1011 *vs*. 380 days, $p = .016$). There was no difference between squamous and no-squamous NSCLC patients (610 *vs*. 423 days, $p = .950$). The median OS of patients with sole metastasis were on average longer than the patients with multi-metastases (968 vs. 380 days, $p = .009$). Patients with brain multiple metastases conferred a slightly worse survival rate than patients with or without sole brain metastasis (321 vs. 700 days, $p = .006$). Figure 1(A) showed the non-PD (progressive disease) subgroup of had longer survival than the PD subgroup (749 vs. 278 days, $p = .006$). The survival showed no difference between the first-line,

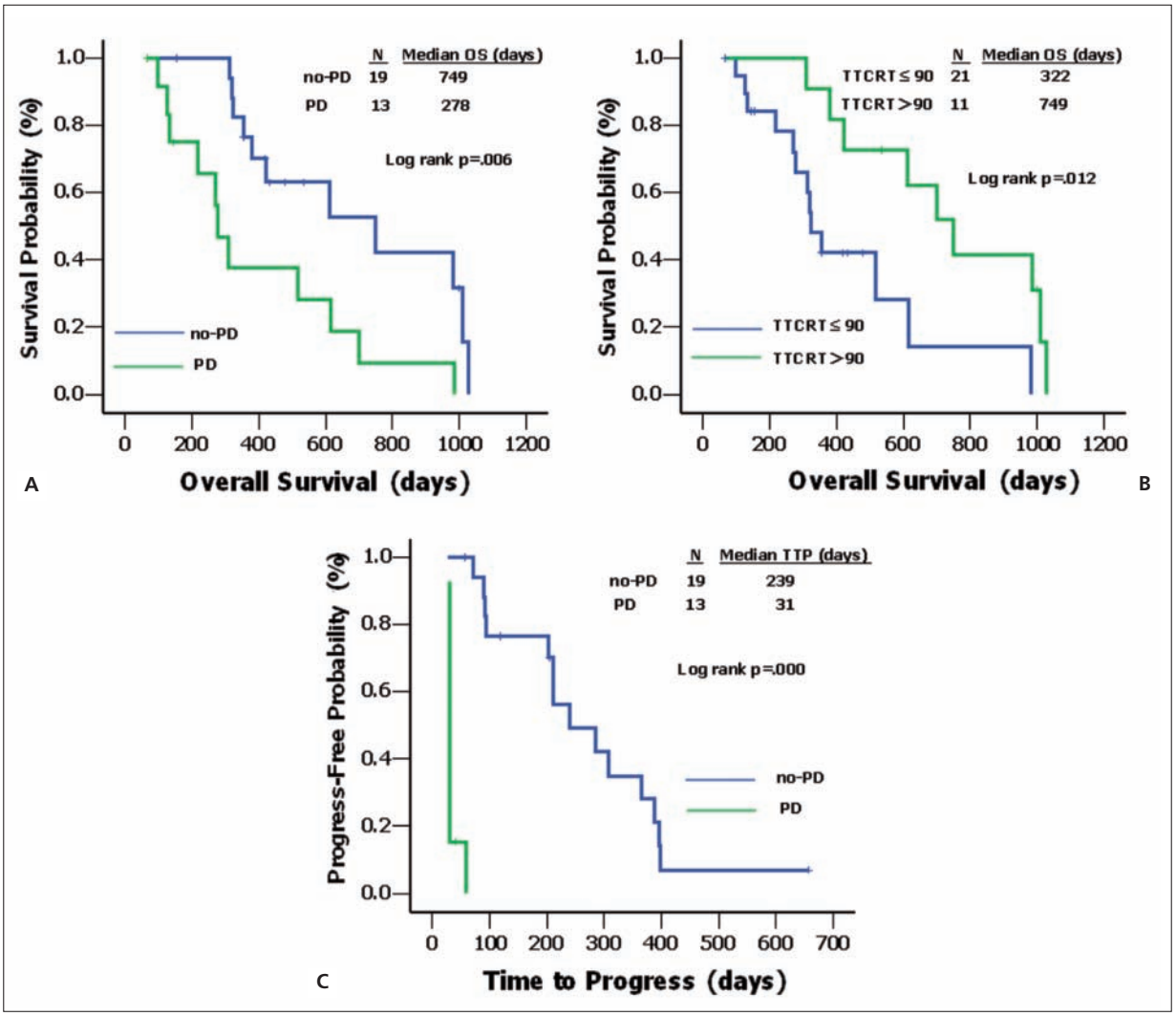

Figure 1. Clinical benefit on patients treatment with combined CRT and Erlotinib. ***A,*** Non-PD subgroup of had longer overall survival(OS) than the PD subgroup. ***B,*** Patients with TTCRT > 90 days had longer OS than the patients with TTCRT ≤ 90 days. ***C,*** Non-PD subgroup showed longer TTP than PD subgroup.

the second-line and the third-line of erlotinib (380 *vs*. 700 *vs*. 310 days, respectively. $p = .179$). The patients with TTCRT > 90 days had longer OS than the patients with TTCRT ≤ 90 days (749 *vs*. 322 days, $p = .012$) (Figure 1B). Whether CRT concurrent with erlotinib had no effect on median OS (322 *vs*. 610 days, concurrent and no-concurrent, respectively. $p = .417$). The patients without chemotherapy seemed had the same median OS with the patients received chemotherapy (311 *vs*. 517 days, $p = .218$).

TTP (Time to Progression)

The median TTP was 94 days (with a range from 28 to 657 days). The 6- and 12-month progress-free rates were 37.5% and 15.6%, respectively. The non-PD patients showed longer TTP than the PD patients (239 *vs*. 31 days in non-PD and PD patients, respectively. $p = .000$) (Figure 1C). There was no difference of TTP between the first-, the second-, and the third line, of erlotinib (92 *vs*. 210 *vs*. 31 days, respectively. $p = .103$). The patients with TTCRT > 90 days had the same TTP as the patients with TTCRT ≤ 90 days (239 *vs*. 89 days, $p = .051$). Whether CRT was concurrent with erlotinib had no influence on TTP (202 *vs*. 89 days, n = 12 *vs*. 20, concurrent and no-concurrent, respectively. $p = .480$).

Toxic Effects

Summary of adverse events that occurred in > 2% of all patients and patients with concurrent erlotinib and CRT during treatment are shown in Table II. The most frequent adverse effects were rashes (59.4%) and diarrhea (43.8%). In general, toxicities were mild (grade 1/2) and easily managed.

Discussion

To our knowledge, there are few randomized controlled trial focused on combine CRT and erlotinib-based multimodality treatment of unselected, newly diagnosed metastatic NSCLC worldwide.

The median OS of thirty-two patients was 517 days. The 6-, 12- and 24-month survival rates were 78.1%, 50.0% and 18.8%, respectively. Our results are in line with other retrospective studies in Chinese population[13,14], and different from the European[15] and American data[16,17].

Moreover, we firstly demonstrated the patients with only one metastasis showed better median OS of 986 days than that with > 2 metastases after the primary and metastatic lesions received radical irradiation with dose of 54-66 Gy (Figure 2A). Patients without or with one brain metastasis had significantly better survival (Figure 2B). This result might echo a truism that greater cancer burdens, number of metastatic organ sites, or number of metastatic lesions were correlated with decreased survival[18]. Patients with one or a few metastases were amenable to radiotherapy, the prognosis could be better because the volume of disease and the source of disease spread was smaller and could be further diminished markedly by local ablative therapies.

Treatment-related toxicity was mainly limited to Grade 1 or 2 that was consistent with the previously documented toxicity profile of erlotinib. The most common treatment-related toxicities were acneiform rash, diarrhea, nausea, fatigue, anorexia, and vomiting[16]. Cutaneous rashes were

Table II. Summary of adverse events occurring in > 2% of all patients and patients with concurrent erlotinib and CRT.

	All patients (n = 32)		Patients with toncurrent treatment (n = 12)	
	All grade No. (%)	Grade3/4 No. (%)	All grade No. (%)	Grade3/4 No. (%)
Rash	19 (59.4)	2 (6.3)	7 (58.3)	0 (0)
Nausea	8 (25.0)	1 (3.1)	4 (33.3)	0 (0)
Anorexia	4 (12.5)	2 (6.3)	2 (16.7)	1 (8.3)
Fatigue	6 (18.8)	1 (3.1)	3 (25.0)	0 (0)
Diarrhea	14 (43.8)	2 (6.3)	4 (33.3)	1 (8.3)
Vomiting	4 (12.5)	1 (3.1)	1 (8.3)	0 (0)
Pulmonary embolism	1 (3.1)	1 (3.1)	1 (8.3)	1 (8.3)
Interstitial pneumonitis	1 (3.1)	1 (3.1)	1 (8.3)	1 (8.3)
Esophagitis	4 (12.5)	0 (0)	4 (33.3)	0 (0)
Anemia	2 (6.3)	0 (0)	1 (8.3)	0 (0)
Lymphocytopenia	2 (6.3)	0 (0)	2 (16.7)	0 (0)

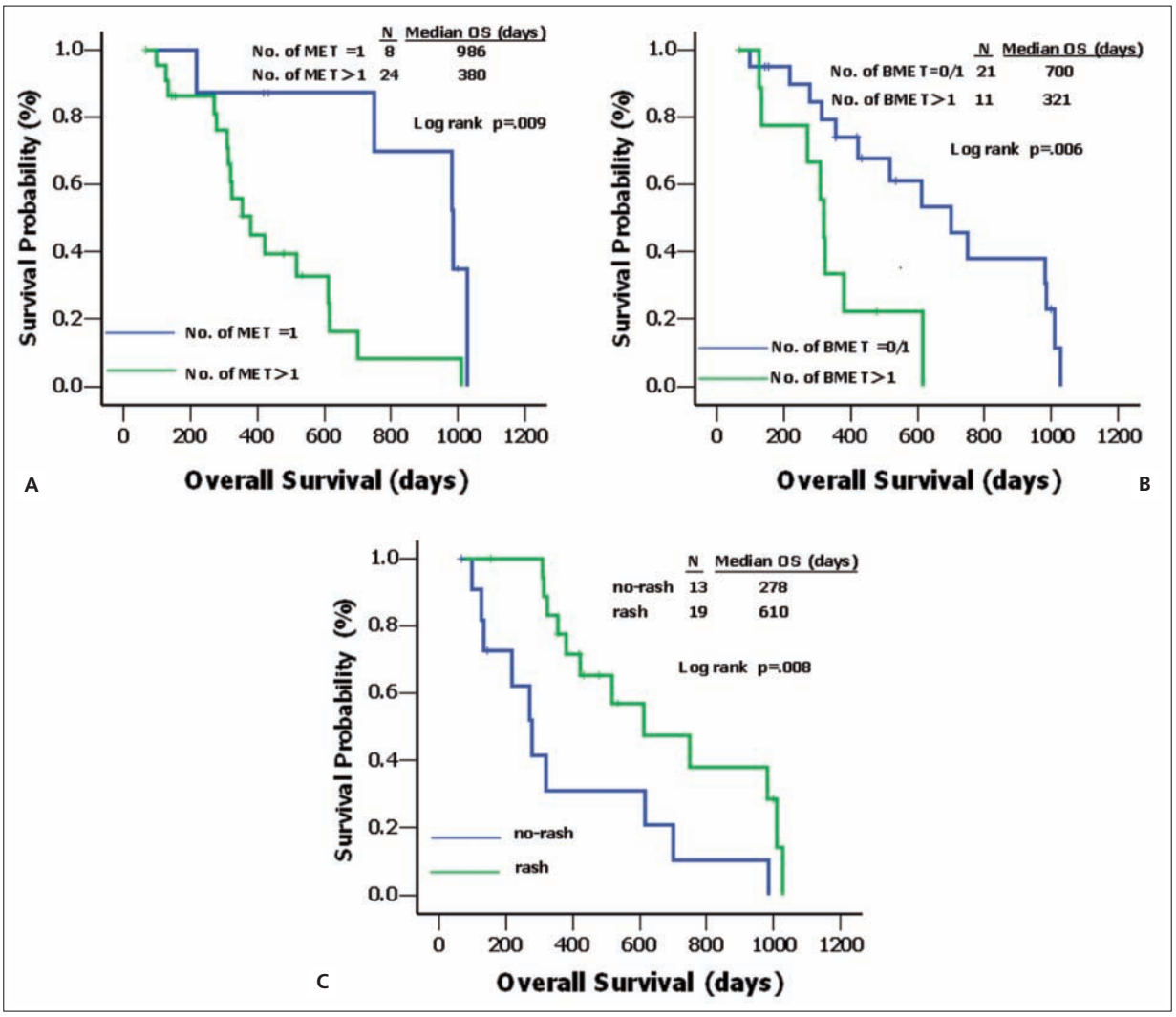

Figure 2. Clinical outcomes were associated with numbers of metastasis and rash presence. ***A,*** Patients with sole metastasis showed better median OS than that with > 2 metastases. ***B,*** Patients without or with one brain metastasis had significantly better survival. ***C,*** Patients with rash showed better survival than patients without rash. Abbreviations: MET, metastasis; BMET, brain metastasis.

seen in 59.4% of patients on the face, neck, or upper torso. The patients with rashes showed better survival than the patients without rashes (278 *vs*. 610 days, $p = .008$) (Figure 2(C)), similar to the early studies. One patient died of confirmed interstitial pneumonitis on the 119th day from administration of erlotinib. Though 12% prevalence were observed in the Japanese phase II study[19] and 1% was observed in each arm of the BR.21 trial[7], we could not definitively associate interstitial pneumonitis with erlotinib and concurrent CRT yet. This was because of the patient's high individual risks: (1) elder age of 73 years; (2) had smoked for 50 years and 30 to 40 tobacco daily; (3) had a 63 mm diameter mass at the left hilum of lung and obstructive pneumonia before treatment; (4) had a V20 of 34.7%; (5) the past history included chronic obstructive pulmonary diseases. It was still unclear whether lymphangitic spread of a tumor that was systemically progressing. Another patient died of confirmed pulmonary embolism on the 57th day from the administration of erlotinib. The possibly pathogenetic causes of pulmonary embolism in this case were discussed. The treatment including WBI, erlotinib, or chemotherapy combined paclitaxel with cisplatin which might accelerate the development of pulmonary embolism, even though D-dimer of the patient increased about 20-fold (5295 μg/L) compared with the normal

level (0 to 256 μg/L) before treatment and cancer might likely be the main cause of the thrombotic complication. New guideline for prophylaxis is a low-molecular-weight heparin (LMWH) that is preferred as an effective and safe means. The advantages of an LMWH include increased survival and quality of life, a low occurrence of thrombocytopenia[21].

In our study, one patient, who had smoked for 30 years with 20 to 30 tobaccos used daily and continued to smoke during treatment, received erlotinib 300 mg daily for three months after the dose was increased from standard 150 mg daily to 225 mg daily. There was no other Grade 3/4 toxic effect seen in the patient except paronychia on the first 28-day cycle. The patient remains progression free on therapy with erlotinib for 204 days, and has survived for 417 days up to the deadline of follow-up. A recent dose escalation study established 300 mg daily as the recommended Phase II dose in patients who continue to smoke. It was confirmed that theses active smokers rapidly metabolized erlotinib and experienced lower drug exposure when treated with standard doses. Steady-state trough plasma concentrations and appearance of rash and diarrhea in smokers at 300 mg were similar to those in former or never smokers receiving 150 mg in the BR.21 trial. An exploratory survival analysis found a trend towards longer median survival for smokers receiving a high dose of erlotinib. Based on the findings of this study, the 300 mg daily dose should be further investigated in current smokers in order to confirm any potential improvement in outcome as well as assess patient safety at the higher dose[22,23].

There were five patients who did not subject to chemotherapy in the study. Of note, the median age of these patients was 73 years old, range from 64 to 80 years. Survival analysis didn't find a trend towards longer median OS for the patients receiving chemotherapy (517 *vs*. 311 days. n = 27 *vs*. 5, chemotherapy *vs*. no-chemotherapy, respectively. $p = .218$). In this study, patients with better PS or younger age or been recommended doublet chemotherapy, which might introduce a negative selection bias. Single-agent chemotherapy is considered the standard of care for most elderly patients, but it seemed that elderly patients and their physicians were less willing to accept even mild toxicity, and this led to more elderly patients receiving elotinib as first-line. In a phase II clinical trial of chemotherapy naive patients > 70 years of age treated with erlotinib for advanced NSCLC, a median survival time of 10.9 months (47 weeks) compared favorably with the survival times achieved in elderly patients receiving vinorelbine (6.5 to 8.5 months), paclitaxel (5.5 months), and cisplatin-based combination therapy (8.0 to 8.5 months)[24]. In our study, erlotinib combined with CRT was active and relatively well tolerated in chemotherapy naive elderly patients with metastatic NSCLC. The combined treatment merits consideration for further investigation as a therapeutic option in elderly patients with metastatic NSCLC.

In the study, we analyzed the prescription patterns and outcomes related to erlotinib use for metastatic NSCLC to define the maximal benefit from erlotinib. Among the thirty two patients, erlotinib was given first line in 10 (31.3%), second line in 15 (46.9%) and third line in 7 (21.9%) patients. OS and TTP after erlotinib administrated was not different, whether used as first-, second- or third-line therapy (OS: $p = .179$; TTP: $p = .103$), whether patients had concurrent with CRT or not (OS: $p = .417$; TTP: $p = .480$). Of note, patients were given erlotinib as a first-line treatment based on poor PS, elderly age at the time of presentation, and perceived inability to tolerate the cytotoxic chemotherapy. The response rates to erlotinib were found no difference between the three groups. Further prospective trials are needed to better define the role of erlotinib in the treatment of metastatic NSCLC and the population segment that may derive maximal benefit from its use[25].

Most previous studies on time to treatment (TTT) were derived from single-in-situation experiences with heterogeneous patient cohorts composed of both early and advanced stage lung cancer patients treated with older RT techniques. Knowledge of the possible influence of TTCRT on survival and the factors associated with TTCRT in a large cohort of metastatic NSCLC patients treated with modern CRT techniques would be clinically valuable. The survival analysis found that the patients with TTCRT > 90 days had longer OS than the patients with TTCRT ≤ 90 days (749 *vs*. 322 days, $p = .012$). Surprisingly, the outcome in this study was completely different from the previous studies[26-29]. From a biological point of view, prolonged TTCRT might result in increased tumor burdens, which would have a potential negative effect on prognosis when the patients had early stage or local NSCLC. One possible explanation for the nega-

tive correlation between TTCRT and outcome was that 43.8% of patients had exceeded 5 metastases; therefore, the patients might have more severe systematical symptoms that required earlier initiation of the treatment. Further survival analysis of the patients with sole metastasis did not show any effect of TTCRT on OS (982 *vs*. 986 days. n = 4 *vs*. 4, TTCRT ≤ 90 days, TTCRT > 90 days, respectively. $p = .174$). Thus, the dominant factor affecting TTCRT associated with survival in this study was the number of metastases.

In this study, only seven patients consented to EGFR mutation status analysis and only one patient was found EGFR mutation (1/7, 14.3%). The results were inconsistency with higher rate of EGFR mutation frequencies in the population in China. One of the main causes was short of enough cases, and another possibility might be the heterogeneity of genetic abnormalities in the tumors, therefore tumor biopsy specimens might not carry the EGFR mutations that came from different parts of the tumors. Furthermore, we found it was very difficult to obtain tumor tissues for such analysis, particularly from patients with refractory NSCLC. In routine clinical practice, a number of factors impacted the use of genetic tests in metastatic NSCLC patients, such as the technical complexity, high costs of the tests, and the inability to obtain tumor tissues. Therefore, there would be a long period to popular EGFR tests in China where the patient population is large and health care resources are limited, even though the physicians actually know the important correlation between mutations in the kinase domain of EGFR gene and the sensitivity to EGFR TKIs, such as erlotinib[30].

Conclusions

We believe that the benefit of survival and acceptable toxicity with CRT combined with erlotinib-based multimodality therapy in newly diagnosed metastatic NSCLC was observed, whether erlotinib was given as first-, second- or third-line therapy, whether the patients had concurrent with CRT or not, whether patients went with or without other chemotherapies. We found the patients with sole metastasis showed longer median survival of 986 days after the primary and metastatic lesions received radical irradiation with dose of 54-66Gy. The number of metastasis had a higher correlation with the time to CRT (TTCRT) on survival. Further prospective trials are needed to better define the role of erlotinib, the juncture of CRT, combined chemotherapies, individual dosage and the patient population segment may derive a maximal benefit in the treatment of metastatic NSCLC.

Acknowledgements

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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