Thoracic stereotactic body radiation therapy plus first-line tyrosine kinase inhibitors for patients with epidermal growth factor receptor-mutant polymetastatic non-small-cell lung cancer
A propensity-matched retrospective study

Xia Wang, MD\textsuperscript{a}, Zhiqin Lu, MD\textsuperscript{a}, Zhimin Zeng, MD\textsuperscript{a,b}, Jing Cai, MD\textsuperscript{a}, Peng Xu, MD\textsuperscript{a}, Anwen Liu, MD, PhD\textsuperscript{a,b,}\textsuperscript{*}

Abstract
The role of thoracic stereotactic body radiation therapy (SBRT) in addition to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in EGFR-mutant polymetastatic non-small-cell lung cancer (NSCLC) has not been well established. This retrospective study aimed to evaluate the efficacy and safety of EGFR-TKIs with thoracic SBRT for the treatment of this patient group.

Polymetastatic NSCLC was defined as having >5 metastatic lesions. Patients with polymetastatic NSCLC harboring positive EGFR mutations after initial TKI therapy for at least 8 weeks were eligible for SBRT between August 2016 and August 2019. Eligible patients were treated with thoracic SBRT, and TKIs were administered for the duration of SBRT and continued after SBRT until they were considered ineffective. The control group was treated with TKI monotherapy. Propensity score matching (ratio of 1:4) was used to account for differences in baseline characteristics. Progression-free survival (PFS), overall survival, and treatment safety were evaluated.

In total, 136 patients were included in the study population. Among them, 120 patients received TKIs alone, and 16 patients received TKIs with thoracic SBRT. The baseline characteristics did not significantly differ between the two cohorts after propensity score matching. The median PFS was 17.8 months in the thoracic SBRT group and 10.8 months in the control group ($P = 0.033$). In the multivariate analysis, a Cox regression model showed that thoracic SBRT was an independent statistically significant positive predictor of improved survival, with a hazard ratio of 0.54 ($P = .046$). We recorded no severe toxic effects or grade 4 to 5 toxicities.

Real-world data demonstrate that thoracic SBRT significantly extends PFS in EGFR-mutant polymetastatic NSCLC patients with tolerable toxicity. Given these results, randomized studies are warranted.

Abbreviations: AEs = adverse events, EGFR = epidermal growth factor receptor, ES-SCLC = extensive stage small cell lung cancer, HR = hazard ratio, LCT = local consolidation therapy, NSCLC = non-small-cell lung cancer, OS = overall survival, PFS = progression-free survival, PSM = propensity score matching, RECIST = Response Evaluation Criteria in Solid Tumors, SBRT = stereotactic body radiation therapy, TKIs = tyrosine kinase inhibitors.

Keywords: epidermal growth factor receptor tyrosine kinase inhibitors, non-small-cell lung cancer, propensity score matching, stereotactic body radiation therapy
1. Introduction

Lung cancer is the leading cause of cancer-associated death globally, and non-small-cell lung cancer (NSCLC) accounts for 80% to 85% of cases.[1] Approximately 40% of Asian patients with NSCLC exhibit epidermal growth factor receptor (EGFR) mutations, which plays a widespread role in signal transduction and in oncogenesis. Multiple generation EGFR tyrosine kinase inhibitor (TKI), such as erlotinib, gefitinib, or afatinib, can bind to the active form of EGFR.[2,3] The TKI has become the standard treatment for patients harboring EGFR active mutations.[4–6] Despite the remarkable initial responses to EGFR-TKIs, patients invariably develop acquired resistance.[7,8] Therefore, a search for new strategies to prevent the emergence of resistance is urgently needed.

Several clinical trials have shown that local consolidation therapy (LCT), such as surgery or stereotactic body radiation therapy (SBRT), can prolong progression-free survival (PFS) in patients with NSCLC and delay drug resistance to EGFR-TKIs in the setting of select metastatic diseases, particularly oligometastases.[9–11] SBRT allows the delivery of high-precision and dose-escalated treatment to targets throughout the body and has been commonly used in selected patients with or without metastatic lesions, with excellent rates of local control and acceptable toxicity.[12–14] Our previous study demonstrated that the combination of brain stereotactic radiosurgery and TKIs resulted in increased intracranial PFS and overall survival (OS) compared to TKIs alone in EGFR-mutant lung adenocarcinoma patients with asymptomatic brain metastasis.[15]

Nevertheless, although the potential effects of SBRT on NSCLC are obvious, few studies have explored the benefits of thoracic SBRT combined with TKIs on EGFR-mutant polymetastatic disease. Information regarding the role of thoracic SBRT in addition to TKIs in polymetastatic NSCLC is limited. In one pattern of failure analysis of EGFR-mutant patients, almost 50% of recurrences after TKI therapy occurred first in primary or preexisting metastatic sites.[16] Published data have indicated that thoracic radiotherapy in addition to chemotherapy improved survival in patients with extensive stage small cell lung cancer (ES-SCLC) or polymetastatic NSCLC.[17–20]

Herein, we hypothesized that thoracic SBRT could prolong the PFS of patients with polymetastatic disease treated with EGFR-TKIs and conducted a retrospective study to describe a single institution’s experience using thoracic SBRT after initial TKI therapy and the continuation of TKIs to treat polymetastatic NSCLC patients.

2. Patients and methods

2.1 Patients

This single-center, retrospective study was approved by the Institutional Ethics Committee of the Second Affiliated Hospital of Nanchang University (No. R2021.041). The requirement for informed consent was waived due to the retrospective study design. From the clinical records database of our center, we reviewed a total of 1485 patients diagnosed with NSCLC between August 2016 and August 2019 with adequate follow-up data. The eligibility criteria included the following: histological diagnosis of polymetastatic stage IV NSCLC; in the thoracic SBRT group, disease in the lung was limited to ≤3 sites; lung lesions’ maximum diameter <3 cm;[16,21] the presence of activating EGFR mutations; age >18 years; and the following treatment regimens: TKIs alone or TKIs plus thoracic SBRT. In the 1:4-matched cohort, the patients who received TKIs plus SBRT were individually matched with four control patients who received TKIs alone. The variables used in propensity score matching (PSM) included brain metastasis and bone metastasis.[22] Patients with initial brain metastases were eligible if they were treated with local treatment (surgery or radiotherapy) and remained clinically stable for at least 8 weeks. The major exclusion criteria included other previous thoracic radiotherapy, prior TKI therapy or local therapy elsewhere during TKI therapy. Oligometastatic disease was defined as the presence of ≤5 lesions in 1 to multiple organs at the initiation of TKIs, whereas polymetastatic disease was defined as >5 metastatic lesions.[23]

2.2 Treatment

Sixteen patients with 25 lung lesions treated with at least 8 weeks of first-line TKIs (erlotinib, gefitinib or icotinib) followed by SBRT before progression were identified as the thoracic SBRT group, while 120 patients treated with first-line TKIs alone were identified as the control group. In the thoracic SBRT group, TKIs were administered for the duration of SBRT and continued after SBRT until they were considered ineffective or the patient developed unacceptable toxicity. SBRT planning was performed using the Monaco planning system and was delivered using the Elekta Versa HD medical linear accelerator. The total dose of SBRT was 70 Gy administered in 10 fractions, 60 Gy administered in 8 fractions, or 50 Gy administered in 5 fractions. The treatment was administered once a day, 5 days per week. The baseline laboratory analyses (hematologic and biochemical profiles) were evaluated every 4 weeks. Magnetic resonance imaging of the brain, chest computed tomography (CT), and upper abdominal CT were performed 1 and 3 months after SBRT and then every 2 months until death or the last follow-up. The radiologic response was assessed by an independent review according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). PFS, OS, and treatment safety were evaluated.

2.3 Statistical analysis

PFS was defined from the start date of TKI therapy to disease progression or death. OS was defined from the time of TKI initiation to the date of death or the last follow-up. The data are presented as the median (range) and n (%). The baseline characteristics were compared using Fisher exact test (categorical variables) and the 2-sample t test or the Mann–Whitney U test (continuous variables) as appropriate. Survival was evaluated by Kaplan-Meier plots and the Cox log-rank test. A Cox proportional hazards model was used to conduct multivariable analyses of variables with P values ≤.20 in the univariate analyses. P values <.05 were considered indicative of significant differences. The statistical software packages R (http://www.R-project.org, The R Foundation) and Empower Stats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA) were used to analyze all data.

3. Results

3.1 Patient characteristics

Between August 2016 and August 2019, a total of 1485 patients with NSCLC were hospitalized at our center. A flow chart of the screened patients is presented in Figure 1. Ultimately, 136
patients were included in the study population. Among them, 120 patients received TKIs alone, and 16 patients received TKIs with thoracic SBRT. Using PSM at a ratio of 1:4, the study cohort comprised 16 patients treated with TKIs plus SBRT and 64 patients treated with TKIs only. The patient and tumor characteristics are listed in Table 1. After PSM, there were no significant differences in the clinical characteristics between the thoracic SBRT and control groups.

3.2. Survival outcomes

The median PFS was 17.8 months in the thoracic SBRT group and 10.8 months in the control group, which was significantly different (hazard ratio [HR] = 0.53; \( P = .033 \)) (Fig. 2A). In the multivariate analysis, a Cox regression model showed that thoracic SBRT was an independent statistically significant positive predictor of improved PFS, with an HR of 0.54 (\( P = .046 \)) (Table 2). The median OS was 36.7 months in the thoracic SBRT group and 27.8 months in the control group. The OS data are presently immature; thus, we cannot present any statistical analyses. At the data cut-off, 9 events (56.2%) had occurred in the thoracic SBRT group, and 30 events (46.8%) had occurred in the control group (Fig. 2B).

3.3. Adverse events

The adverse events (AEs) are summarized in Table 3. The addition of thoracic SBRT to TKIs in polymetastatic NSCLC patients was well tolerated, without severe toxicities. There were no grade 4 to 5 toxicities in either group. The rates of grade I/II skin rashes, representing the most frequent grade I/II AEs, were 57.8% and 43.8% in the control group and thoracic SBRT group, respectively (\( P = .312 \)). Meanwhile, radiation pneumonitis, radiation esophagitis, and radiation dermatitis, were observed exclusively in patients treated with SBRT. The grade III/IV AE rates were comparable between the groups: 5 (31.3%) patients in the thoracic SBRT group and 13 (20.3%) patients in the control group (\( P = .349 \)). Grade III radiation pneumonitis occurred in 1 patient (6.2%) after SBRT.

4. Discussion

Lung cancer frequently metastasizes to the bone, brain, lung, and liver, with a high risk of mortality.\(^{[24]}\) Approximately 40% to 60% of patients with NSCLC present with distant metastases at the time of diagnosis.\(^{[25,26]}\) The metastatic status of NSCLC is highly variable. The first theorization of the “oligometastatic” disease state was described in 1995 by Hellman and Weichselbaum\(^{[27]}\) as an intermediate state between localized and polymetastatic disease characterized by a limited number of metastases (usually 1–5) in a few organs (usually 1–3) and indolent behavior.\(^{[28]}\) Evidence from the literature indicates that oligometastatic patients have a better clinical outcome than nonoligometastatic patients.\(^{[17,25,30]}\) Several previous studies\(^{[9–11,31]}\) of patients with oligometastatic NSCLC following

---

**Figure 1.** Flow chart of the screened patients. NSCLC = non-small-cell lung cancer, TKIs = tyrosine kinase inhibitors, EGFR = epidermal growth factor receptor, SBRT = stereotactic body radiation therapy.
### Table 1
Baseline characteristics of the unmatched and matched groups.

| Characteristic                  | Before propensity score matching | After propensity score matching |
|--------------------------------|----------------------------------|--------------------------------|
|                                | Control group | Thoracic SBRT group | P | Control group | Thoracic SBRT group | P |
| Number of patients             | 120            | 16                 | .714 | 64            | 16                 | .902 |
| Median age (range)             | 58.0 (22.0–87.0) | 56.0 (45.0–85.0) | .263 | 60.0 (33.0–87.0) | 56.0 (45.0–85.0) | .140 |
| Sex                            | Female 66 (55.0%) | 12 (75.0%) | .263 | 35 (54.7%) | 12 (75.0%) | .381 |
|                                | Male 54 (45.0%) | 4 (25.0%) | | 29 (45.3%) | 4 (25.0%) | |
| Smoking status                 | Never 81 (67.5%) | 13 (81.2%) | .902 | 45 (70.3%) | 13 (81.2%) | .101 |
|                                | Former or current 39 (32.5%) | 3 (18.8%) | | 19 (29.7%) | 3 (18.8%) | |
| ECOG status                    | 0–1 90 (75.0%) | 15 (93.8%) | .902 | 48 (75.0%) | 15 (93.8%) | .591 |
|                                | 2–3 30 (25.0%) | 1 (6.2%) | | 16 (25.0%) | 1 (6.2%) | |
| Histological type              | Adenocarcinoma 113 (94.2%) | 16 (100.0%) | .805 | 60 (93.8%) | 16 (100.0%) | .620 |
|                                | Adenosquamous carcinoma 4 (3.3%) | 0 (0.0%) | | 3 (4.7%) | 0 (0.0%) | |
|                                | Not otherwise specified 1 (0.8%) | 0 (0.0%) | | 1 (1.6%) | 0 (0.0%) | |
|                                | Squamous carcinoma 2 (1.7%) | 0 (0.0%) | | 0 (0.0%) | 0 (0.0%) | |
| T                              | 1 18 (15.0%) | 5 (31.2%) | .400 | 11 (17.2%) | 5 (31.2%) | .657 |
|                                | 2 66 (55.0%) | 8 (50.0%) | | 35 (54.7%) | 8 (50.0%) | |
|                                | 3 15 (12.5%) | 1 (6.2%) | | 5 (7.8%) | 1 (6.2%) | |
|                                | 4 21 (17.5%) | 2 (12.5%) | | 13 (20.3%) | 2 (12.5%) | |
| N                              | 0 11 (9.2%) | 3 (18.8%) | .574 | 7 (10.9%) | 3 (18.8%) | .445 |
|                                | 1 10 (8.3%) | 2 (12.5%) | | 4 (6.2%) | 2 (12.5%) | |
|                                | 2 86 (71.7%) | 10 (62.5%) | | 48 (75.0%) | 10 (62.5%) | |
|                                | 3 13 (10.8%) | 1 (6.2%) | | 5 (7.8%) | 1 (6.2%) | |
| EGFR mutations                 | Exon19 deletion 70 (58.3%) | 8 (50.0%) | .527 | 37 (57.8%) | 8 (50.0%) | .573 |
|                                | L858R mutation 50 (41.7%) | 8 (50.0%) | | 27 (42.2%) | 8 (50.0%) | |
| Type of EGFR TKIs              | Gefitinib 85 (70.8%) | 10 (62.5%) | .706 | 45 (70.3%) | 10 (62.5%) | |
|                                | Erlotinib 15 (12.5%) | 2 (12.5%) | | 11 (17.2%) | 2 (12.5%) | |
|                                | Icotinib 20 (16.7%) | 4 (25.0%) | | 8 (12.5%) | 4 (25.0%) | |
| Pleural metastasis             | No 96 (80.0%) | 16 (100.0%) | .049 | 48 (75.0%) | 16 (100.0%) | .059 |
|                                | Yes 24 (20.0%) | 0 (0.0%) | | 16 (25.0%) | 0 (0.0%) | |
| Lung metastasis                | No 56 (46.7%) | 10 (62.5%) | .234 | 27 (42.2%) | 10 (62.5%) | |
|                                | Yes 64 (53.3%) | 6 (37.5%) | | 37 (57.8%) | 6 (37.5%) | |
| Kidney metastasis              | No 116 (96.7%) | 16 (100.0%) | 1.000 | 63 (98.4%) | 16 (100.0%) | |
|                                | Yes 4 (3.3%) | 0 (0.0%) | | 1 (1.6%) | 0 (0.0%) | |
| Pancreas metastasis            | No 118 (98.3%) | 16 (100.0%) | 1.000 | 63 (98.4%) | 16 (100.0%) | |
|                                | Yes 2 (1.7%) | 0 (0.0%) | | 1 (1.6%) | 0 (0.0%) | |
| Spleen metastasis              | No 115 (95.8%) | 16 (100.0%) | 1.000 | 62 (96.9%) | 16 (100.0%) | |
|                                | Yes 5 (4.2%) | 0 (0.0%) | | 2 (3.1%) | 0 (0.0%) | |
| Leptomeningeal metastasis      | No 109 (90.8%) | 15 (93.8%) | .699 | 56 (87.5%) | 15 (93.8%) | |
|                                | Yes 11 (9.2%) | 1 (6.2%) | | 8 (12.5%) | 1 (6.2%) | |
| Brain metastasis               | No 51 (42.5%) | 11 (68.8%) | .048 | 44 (68.8%) | 11 (68.8%) | |
|                                | Yes 69 (57.5%) | 5 (31.2%) | | 20 (31.2%) | 5 (31.2%) | |
| Bone metastasis                | No 38 (31.7%) | 1 (6.2%) | .035 | 16 (25.0%) | 1 (6.2%) | |
|                                | Yes 82 (68.3%) | 15 (93.8%) | | 48 (75.0%) | 15 (93.8%) | |
| Liver metastasis               | No 85 (70.8%) | 13 (81.2%) | .383 | 49 (76.6%) | 13 (81.2%) | |
|                                | Yes 35 (29.2%) | 3 (18.8%) | | 15 (23.4%) | 3 (18.8%) | |
| Adrenal metastasis             | No 107 (89.2%) | 15 (93.8%) | .571 | 59 (92.2%) | 15 (93.8%) | |
|                                | Yes 13 (10.8%) | 1 (6.2%) | | 5 (7.8%) | 1 (6.2%) | |

Data are represented as the median (range) and n (%).

TKIs = tyrosine kinase inhibitors, SBRT = stereotactic body radiation therapy, ECOG = eastern cooperative oncology group, EGFR = epidermal growth factor receptor.

* P < 0.05 was considered significant.
EGFR-TKI therapy demonstrated that local therapy with surgery or radiation may lead to improved outcomes compared to standard therapies, raising the important question of whether this type of “polymetastasis” warrants consideration of LCT.

Studies on the role of thoracic radiotherapy in polymetastatic patients are limited. Presently, pharmacotherapy remains the standard treatment modality for polymetastatic disease, and thoracic radiotherapy is reserved only for the palliation of...
Adverse events.

| Adverse event                  | Grade I/II (%) Control group (n=64) | Thoracic SBRT group (n=16) | P  | Grade III/IV (%) Control group (n=64) | Thoracic SBRT group (n=16) | P  |
|--------------------------------|------------------------------------|-----------------------------|----|--------------------------------------|-----------------------------|----|
| Rash                           | 37 (57.9%)                         | 7 (43.8%)                   | .312 | 6 (9.4%)                             | 2 (12.5%)                   | .657 |
| Diarrhea                       | 16 (25.0%)                         | 5 (31.2%)                   | .611 | 0 (0.0%)                             | 0 (0.0%)                    | .007 |
| Dry skin                       | 18 (28.1%)                         | 4 (25.0%)                   | .802 | 0 (0.0%)                             | 0 (0.0%)                    | .007 |
| Paronychia                     | 13 (20.3%)                         | 3 (18.8%)                   | .889 | 1 (1.6%)                             | 0 (0.0%)                    | 1.000 |
| Mucositis                      | 15 (23.4%)                         | 4 (25.0%)                   | .895 | 0 (0.0%)                             | 0 (0.0%)                    | .007 |
| Anorexia                       | 10 (15.6%)                         | 3 (18.8%)                   | .762 | 0 (0.0%)                             | 0 (0.0%)                    | .007 |
| Elevated aminotransferase      | 18 (28.1%)                         | 6 (37.5%)                   | .464 | 6 (9.4%)                             | 2 (12.5%)                   | .657 |
| Fatigue                        | 6 (9.4%)                           | 4 (25.0%)                   | .091 | 0 (0.0%)                             | 0 (0.0%)                    | .007 |
| Nausea or vomiting             | 6 (9.4%)                           | 2 (12.5%)                   | .657 | 0 (0.0%)                             | 0 (0.0%)                    | .007 |
| Radiation pneumonitis          | 0 (0.0%)                           | 3 (18.8%)                   | .007* | 0 (0.0%)                             | 1 (6.2%)                    | .200 |
| Radiation esophagitis          | 0 (0.0%)                           | 2 (12.5%)                   | .038* | 0 (0.0%)                             | 0 (0.0%)                    | .007 |
| Radiation dermatitis           | 0 (0.0%)                           | 3 (18.8%)                   | .007* | 0 (0.0%)                             | 0 (0.0%)                    | .007 |

Data are represented as n (%). SBRT = stereotactic body radiation therapy. * P<.05 was considered significant.

Local symptoms (hemoptysis, cough, or pain) and is used to improve quality of life. To the best of our knowledge, no previous study has examined the role of thoracic SBRT in conjunction with TKIs in EGFR-mutant NSCLC with polymetastases.

In the present study, we retrospectively reviewed the clinical database of our center and found that patients who were treated with TKIs plus SBRT exhibited longer PFS than patients who were treated with TKIs alone (17.8 vs 10.8 months, respectively, P = .030). Thoracic SBRT plus TKIs was well tolerated, without severe toxicities or grade 4 to 5 toxicities in either group. This positive result is consistent with findings from studies of patients with oligometastatic NSCLC, suggesting that combining LCT with TKI leads to a significant improvement in PFS.

In a retrospective review of patients with EGFR-mutant stage IV NSCLC, 129 patients were treated with first-line TKIs, and 12 patients were treated with TKIs followed by LCT (primarily radiotherapy or SBRT to the primary tumor). The patients who received a TKI plus LCT had longer PFS than those who received a TKI alone (36 vs 14 months, P = .0024). A single-arm phase II prospective study enrolled 16 patients with EGFR-mutant NSCLC, treated with stereotactic ablative radiotherapy. The screen failure cohort (n = 48) treated with EGFR-TKI alone. Again, PFS favored patients treated with radiotherapy (15.2 vs 11.1 months, P = .043).

Additionally, our results are broadly consistent with retrospective and randomized studies of thoracic radiotherapy in ES-SCLC. In a retrospective study of 270 ES-SCLC cases, 78 patients had oligometastases, and 192 patients had polymetastases, among which 93 polymetastatic patients received thoracic radiotherapy. The 2-year OS rates in the polymetastatic patients treated with chemotherapy plus thoracic radiotherapy and chemotherapy alone were 10.0% and 6.8% (P = .030). Thoracic radiotherapy improved OS of patients with polymetastases.

In a phase 3 randomized controlled trial of patients with ES-SCLC who responded to chemotherapy, the 2-year OS was significantly different between groups, as follows: 13% (95% CI 9–19) in the thoracic radiotherapy group and 3% (95% CI 2–8) in the control group (P = .004). The 2 abovementioned studies also demonstrated that aggressive thoracic radiotherapy might be a suitable addition to systemic therapy when treating patients with polymetastatic disease.

Intrathoracic tumor control remains a major difficulty in NSCLC. The lung is the most common site of initial progression in metastatic EGFR-mutant lung cancer treated with TKIs, and 40% to 45% of patients progressed in the primary site. A retrospective study and a phase II study reported a significant improvement in local control following thoracic radiotherapy, which Wang et al treated 14 NSCLC patients with disease progression after platinum-based chemotherapy with gefitinib plus SBRT, and the 1-year local control rate was 83.9%. Investigators of a phase II study including 10 patients who received EGFR-TKIs plus thoracic radiotherapy reported that the 1-year objective response rate was 50% and that the disease control rate was 100%. Because 42% of patients exhibited progression in new sites, the addition of radiotherapy to extrathoracic sites is also an important consideration. In a hypothesis-generating article, a new treatment approach was proposed for the use of multisite radiation therapy as systemic therapy for polymetastatic disease.

Although these results are encouraging, we acknowledge several limitations to our study. First, this study was based on a relatively small sample size and a retrospective analysis performed at a single center, with potential hidden biases. The adoption of PSM balanced baseline patient characteristics between groups, and multivariate regression was used to minimize some weaknesses associated with a retrospective study. Second, patients treated with the third-generation EGFR-TKI osimertinib were not included in the analysis. Therefore, large prospective studies are needed to confirm the findings.

5. Conclusions

In this retrospective study, TKIs plus thoracic SBRT conveyed superior PFS over TKIs alone in patients with EGFR-mutant polymetastatic NSCLC, with acceptable toxicity in clinical practice. Therefore, thoracic SBRT might be a suitable addition to TKIs in patients with EGFR-mutant polymetastatic NSCLC. The optimal options for thoracic SBRT in polymetastatic NSCLC need to be prospectively investigated to obtain more convincing evidence.
Acknowledgments
The authors kindly thank the editor and reviewers for their careful review and valuable comments, which have significantly improved the manuscript.

Author contributions
Funding acquisition: Anwen Liu.
Investigation: Jing Cai, Anwen Liu.
Resources: Zhiqin Lu, Jing Cai.
Software: Peng Xu.
Supervision: Anwen Liu.
Writing – original draft: Xia Wang, Zhimin Zeng.
Writing – review & editing: Anwen Liu.

References
[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68:394–424.
[2] Roskoski RJ. Properties of FDA-approved small molecule protein kinase inhibitors. Pharmacol Res 2019;144:19–50.
[3] Gelati ACZ, Drilon A, Santini FC. Optimizing the sequencing of tyrosine kinase inhibitors (TKis) in epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC). Lung Cancer (Amsterdam, Netherlands) 2019;137:113–22.
[4] Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–57.
[5] Schuler M, Tan EH, O’Byrne K, et al. First-line afatinib versus gefitinib for patients with EGFR mutation-positive NSCLC (LUX-Lung 7): impact of afatinib dose adjustment and analysis of mode of initial progression for patients who continued treatment beyond progression. J Cancer Res Clin Oncol 2019;145:1569–79.
[6] Schuler M, Tan EH, O’Byrne K, et al. First-line afatinib versus gefitinib for patients with EGFR mutation-positive NSCLC (LUX-Lung 7): impact of afatinib dose adjustment and analysis of mode of initial progression for patients who continued treatment beyond progression. J Cancer Res Clin Oncol 2019;145:1569–79.
[7] Reck M, Rabe KF. Precision diagnosis and treatment for advanced non-small-cell lung cancer. N Engl J Med 2017;377:849–61.
[8] Rusthoven KE, Kavanagh BD, Burri SH, et al. First-line afatinib vs geﬁtinib for patients with EGFR mutation-positive NSCLC: Doublet Chemotherapy in Patients with EGFRm T790 M NSCLC Who Have Progressed after EGFR-TKI. Clin Drug Invest 2018;38:319–31.
[9] Kissel M, Martel-Lafay I, Lequesne J, et al. Stereotactic ablative radiotherapy and systemic treatments for extracerebral oligometastases. Oligo-recurrence, oligopersistence and oligoprogression from lung cancer. BMC Cancer 2019;19:1237.
[10] Mann H, Andersohn F, Bodnar C, et al. Adjusted Indirect Comparison Using Propensity Score Matching of Osimertinib to Platinum-Based Doublet Chemotherapy in Patients with EGFRm T790 M NSCLC Who Have Progressed after EGFR-TKI. Clin Drug Invest 2018;38:319–31.
[11] Wang Z, Zhu XX, Wu XH, et al. Geﬁtinib combined with stereotactic radiosurgery in previously treated patients with advanced non-small cell lung cancer. Am J Clin Oncol 2012;35:1081–89.
[12] Rusthoven KE, Cavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. J Clin Oncol 2009;27:1579–94.
[13] Wang et al. Medicine (2021) 100:37 www.md-journal.com
[14] Lu X, Gu W, Zhang H, et al. Local consolidative therapy for locally advanced unresectable and metastatic pancreatic cancer. World J Gastroenterol 2015;21:8156–62.
[15] Jumeau R, Vilotte F, Durham AD, Ozsahin EM. Current landscape of palliative radiotherapy for non-small-cell lung cancer. Transl Lung Cancer Res 2019;8(suppl 2):S192–201.
[16] Wang Z, Zhu XX, Wu XH, et al. Gefitinib combined with stereotactic radiosurgery in previously treated patients with advanced non-small cell lung cancer. Am J Clin Oncol 2014;37:148–53.
[17] Zheng L, Wang Y, Xu Z, et al. Concurrent EGFR-TKI and thoracic radiotherapy as first-line treatment for stage IV non-small cell lung cancer harboring EGFR active mutations. The oncologist 2019;24:1031–e1612.
[18] Peterson RR, Verma V, Burszttein H, et al. Use of multi-site radiation therapy as systemic therapy: a new treatment approach personalized by patient immune status. Int J Radiat Oncol Biol Phys 2021;109:352–64.