Efficacy and Failure Patterns of Early SBRT to the Primary Tumor in Advanced EGFR Mutation-Positive Lung Cancer with EFGR-TKI treatment: A Prospective, Single Arm, Phase II Study

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Research Article

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Abstract

Introduction:
Early stereotactic body radiation therapy (SBRT) to the primary tumor combined with EGFR-TKI treatment may increase progression-free survive (PFS) by delaying resistance in patients with advanced EGFR-mutant NSCLC.

Methods
In this prospective, single arm phase II study, patients with advanced NSCLC were treated with EGFR TKI (Icotinib125mg tid or gefitinib 250mg qd) for one month followed by SBRT (40-60Gy/5-8F/5-10d) to the primary tumor with concurrent EGFR TKI until disease progression. The primary endpoint was PFS and the patterns of failure. Overall survival (OS) and adverse effects (AEs) were second endpoints.

Results
Overall 41 advanced NSCLC patients with EGFR mutations received treatment with 24.42 months of median follow-up time. On average, SBRT was initiated 1.49 months after EGFR-TKI administration. Tumors were found to have an average shrinkage rate of 42.50%. Median PFS was 15.23 months (95% CI 13.10-17.36), while median OS was 27.57 months (95% CI 23.05–32.09). Thirty-three patients were found to have disease progression, of which new site failure (NF) (22 patients, 66.66%) was the most common pattern, followed by original site failure (OF) (7 patients, 21.21%) and Simultaneous OF/NF (ONF) (4 patients, 12.12%). There was no AEs equal to or greater than grade 3 with the most frequent AE being radiation pneumonitis.

Conclusions
Administering therapy targeted at the primary tumor using early SBRT after EGFR-TKI initiation is a new potential safe and effective approach to treat EGFR-mutant advanced NSCLC.

Introduction
As one of the most common cancers worldwide, lung cancer makes up approximately a quarter of all cancer deaths\(^1\). There are approximately 55.9% of advanced lung adenocarcinoma patients in eastern China have activating epidermal growth factor receptor (EGFR) mutations according to our previous cohort study\(^2\). Tyrosine kinase inhibitors (TKI) which target EGFR were the standard treatment for metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutations\(^3\). Compared to traditional chemotherapy, first-generation EGFR-TKI treatment can significantly improve the survival rate,
progression-free survive (PFS) and overall survival (OS), allowing for a 5-year survival rate of approximately 20%, 9–13 months of PFS and 19–30 months of OS\textsuperscript{4,5}.

However, acquired targeted resistance was encountered, the mechanisms of which include those dependent on the EGFR signaling pathway, those independent of the EGFR signaling pathway, and small cell transformation\textsuperscript{6}. The most common resistance mechanism was found to be the T790M mutation with 36.51\% (69/189) plasma detected rate reported previously\textsuperscript{7}.

Several studies reported that initial progression of TKI-treated in lung cancer occurred predominantly at original disease sites\textsuperscript{8,9}. Furthermore, the size of the primary lung tumor was strongly associated with the incidence of failure at the original site. EGFR- TKI was found to be radiosensitive both in vivo and in vitro. EGFR- TKI Afatinib combined with radiotherapy significantly increases the anti-tumor effect of radiation in PC-9-GR cells harboring acquired T790M\textsuperscript{10}.

Stereotactic body radiation therapy (SBRT), a novel method of radiotherapy, has superior precision, increased potency per fraction for tumors, as well as decreased damage to normal tissue. Recently, SBRT has demonstrated a tremendous role in the treatment of lung cancer\textsuperscript{11,12}. Thus, many researchers hypothesized that SBRT for residual disease could delay subsequent metastatic reseeding, thereby eliminating tumor internal heterogeneity. For instance, in a phase 2 study by Kong et al. it was found during midtreatment PET there was a favorable local regional tumor control for NSCLC receiving radiation with concurrent chemotherapy\textsuperscript{40}. In metastatic disease, studies have shown the potential role of SBRT in achieving high local control in patients with oligo-progressive NSCLC, and there has been increasing interest in SBRT for oligo-metastatic NSCLC, including the cases which involve the lungs, brain, liver, spine, and adrenal glands\textsuperscript{13-15}. Similar results were gained in oligo-progressive and oligo-metastatic NSCLC with EGFR mutations for instance the randomized SINDAS trial which found that preemptive RT before the occurrence of oligoprogression improved OS and PFS in these populations\textsuperscript{42}, although the definition of oligo-metastatic or oligo-progression varied among studies. A phase prospective study demonstrated that radiotherapy to all intrathoracic sites within 2 weeks from the initiation of EGFR-TKI treatment obtained 13.0 months of PFS with well-tolerated side effects\textsuperscript{19}. Furthermore, it was also found that the addition of upfront local therapy with RT followed by TKI treatment statistically improved OFS and OS for EGFR-mutated NSCLC\textsuperscript{41}.

Therefore, we hypothesized that the early SBRT to the primary tumor shortly after treatment with EGFR-TIK therapy could also prevent progression and prolong PFS in EGFR mutation-positive NSCLC by delaying the development of targeted resistance.

**Methods**

**Study design and Participants**
A prospective, single arm, phase trial (ChiCTR-OIN-17013920) was conducted. Approval was obtained from the institutional ethics review board. All participants provided written informed consent.

The key eligibility criteria were as follows: Age ≥ 18 years and ≤ 85 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; Histopathologically or cytologically proven non-small cell lung cancer (NSCLC); Initial treatment of stage IV, or advanced B, or IIIC who refused concurrent radiochemotherapy and other treatments according to TNM version 8; Harboring EGFR mutations (Exon 21 L858R or Exon 19 deletion) by ARMS test; Brain metastases would be eligible if they were asymptomatic or completed treatment (SIB-IMRT in Symptomatic Brain Metastases for NSCLC20) ≥ 14 days before starting study treatment; adequate organ function.

**Treatment**

All patients were administered first-generation EGFR-TKI (Icotinib 125mg tid or Gefitinib 250mg qd, orally). Participants who achieved partial response (PR) or stable disease (SD) after one month of EGFR-TKI treatment according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) received stereotactic body radiation therapy (SBRT) with 40-60Gy/5-8 Fraction/5-10days to the primary tumor while continuing targeted therapy21.

**Assessments**

Tumor imaging was performed at baseline, after one month, and every 3 months thereafter. According to RECIST v1.1, PR was defined as a reduction of ≥30% in the longest diameter of the target tumors measured by computed tomography (CT) compared to the baseline, and progressive disease (PD) was defined as an increase of ≥20% in the maximum diameter of the target tumors compared with these recorded after treatment initiation or the occurrence of one or more new tumors. SD was defined as the intermediate between PR and PD.

As for failure pattern models, it was classified as original site failure (OF) including progression in initial primary or metastatic lesions, or new site failure (NF), respectively. Simultaneous OF/NF was labeled as ONF.

Adverse events (AEs) were recorded throughout treatment and for 30 days thereafter (90 days for serious AEs), including any occurrences of nausea, vomiting, diarrhea, rash, paronychia, transaminitis, increased creatinine, neutropenia, radiation pneumonia, or radiation esophagitis, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0).

Survival was assessed every 4 weeks during follow-up.

**Endpoints**

The primary endpoint was PFS, which was defined as the time from EGFR-TKI treatment to disease progression or death. Secondary endpoints were patterns of failure models, AEs, and OS, which was defined as the time from EGFR-TKI treatment to death.
**Statistical analysis**

All statistical assessments were performed on the statistical package for the social sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). For PFS, OS, and their stratified analysis, event-time distributions were estimated by the Kaplan-Meier method. Cox proportional hazards models were used to assess the contribution of each potential prognostic factor for survival analysis including the hazard ratio (HR) and 95% confidence interval (CIs). Because M stage, pathological stage, and the number of metastases were all inter-dependent, the number of metastases was chosen as the only one to be included in the multivariate analysis. All P values were two-tailed. A P value ≤0.05 was considered statistically significant.

**Results**

**Patients**

From September 2016 to November 2021, 41 patients were enrolled in total. Baseline characteristics are shown in Table 1.
Table 1
Characteristics of patients (N = 41)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Median, range (years)</td>
<td>66 (46–75)</td>
</tr>
<tr>
<td>&gt; 66</td>
<td>23</td>
</tr>
<tr>
<td>≤ 66</td>
<td>18</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
</tr>
<tr>
<td><strong>Smoke history</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16</td>
</tr>
<tr>
<td>No</td>
<td>25</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td><strong>Mutation type</strong></td>
<td></td>
</tr>
<tr>
<td>L858R</td>
<td>20</td>
</tr>
<tr>
<td>19-del</td>
<td>21</td>
</tr>
<tr>
<td><strong>T</strong></td>
<td></td>
</tr>
<tr>
<td>T1-2</td>
<td>13</td>
</tr>
<tr>
<td>T3-4</td>
<td>28</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td></td>
</tr>
<tr>
<td>N0-1</td>
<td>9</td>
</tr>
<tr>
<td>N2-3</td>
<td>32</td>
</tr>
<tr>
<td><strong>M</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td><strong>Lesions</strong></td>
<td></td>
</tr>
<tr>
<td>1–5</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>33</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>7</td>
</tr>
<tr>
<td>IV</td>
<td>34</td>
</tr>
<tr>
<td><strong>Initial metastasis</strong></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>20</td>
</tr>
<tr>
<td>Brain</td>
<td>6</td>
</tr>
<tr>
<td>Bone</td>
<td>21</td>
</tr>
<tr>
<td>Liver</td>
<td>4</td>
</tr>
<tr>
<td>Adrenal glands</td>
<td>1</td>
</tr>
<tr>
<td>Characteristics</td>
<td>Numbers</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Regional lymph nodes</td>
<td>35</td>
</tr>
<tr>
<td>Distant lymph nodes</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>15</td>
</tr>
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</table>

There were 37 patients with partial response (PR) and 4 patients with stable disease (SD) after one month of treatment with EGFR-TKI (Fig. 1A).

A mean time interval of 1.49 months (0.73–2.47 months) occurred between initiation of EGFR-TKI and SBRT.

**Efficacy**

Overall 41 advanced NSCLC patients with EGFR mutations received treatment with 24.42 months of median follow-up time. On average, tumors were found to have a shrinkage rate of 42.50% (Fig. 1B). As shown in Fig. 2A, the median overall PFS was 15.23 months (95% CI 13.10-17.36). The PFS benefit was observed in subgroups of T1-2, M0, stage III B, number of metastasis (≤ 5 lesions) and 19-del mutation (Fig. 3), and number of metastasis (> 5 lesions vs ≤ 5 lesions, HR 3.97, 95% CI (1.48–10.65), P = 0.006), and type of EGFR mutation (L858R vs 19-del, HR 2.72, 95% CI (1.35–5.49), P = 0.005) as determined by multivariate analysis (Supp Table 1). Thus, the PFS of subgroups in number of metastasis and EGFR mutation were 16.33 months vs 11.13 months (HR 0.45, 95% CI (0.23–0.91), P = 0.016) and 26.69 months vs 13.43 months (HR 0.23, 95% CI (0.12–0.46), P = 0.0017), respectively.

As shown in Fig. 2B, the median OS was 27.57 months (95% CI 23.05–32.09). The OS benefit was observed only in subgroups of 19-del mutation (Fig. 3) and demonstrated by multivariate analysis (Supp Table 2). Thus, the OS of subgroup in number of metastasis and EGFR mutation were undefined vs 18.90 months (HR 0.29, 95% CI (0.12–0.70), P = 0.0056) and undefined vs 25.9 months (HR 0.32, 95% CI (0.12–0.87), P = 0.097), respectively.
<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>All (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation Pneumonitis</td>
<td>27</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>35(85.37)</td>
</tr>
<tr>
<td>Radiation esophagitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/(0.00)</td>
</tr>
<tr>
<td>Transaminase increased</td>
<td>8</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>21(51.22)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6(14.63)</td>
</tr>
<tr>
<td>Rash</td>
<td>14</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16(39.02)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4(9.76)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2(4.88)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2(4.88)</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1(2.44)</td>
</tr>
</tbody>
</table>

**Safety**

The main AEs are outlined in Table 2. Radiation pneumonitis (85.4%), transaminitis (51.2%), and rash (39.0%) were the top three most common side effects. The most common Grade 2 AEs was transaminitis (31.7%). There were no AEs of Grade 3 or above.

**Patterns of failure**

As listed in Table 3, of 33 patients who progressed, 7 (21.21%) had OF, 22 (66.66%) had NF, and 4 (12.12%) had ONF. Lung was the most common site of initial progression.
Table 3  
Patterns of initial failure.

<table>
<thead>
<tr>
<th>Sites of initial failure</th>
<th>All patients (n = 33)</th>
<th>Patients with OF (n = 7)</th>
<th>Patients with NF (n = 22)</th>
<th>Patients with ONF (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Brain</td>
<td>11</td>
<td>33.33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bone</td>
<td>12</td>
<td>36.36</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Liver</td>
<td>2</td>
<td>6.06</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lung</td>
<td>19</td>
<td>57.58</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>Regional lymph nodes</td>
<td>3</td>
<td>9.09</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>12.12</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

OF: original site failure; DF: appearance of new lesions as distant site failure; ONF: Simultaneous OF/DF

Discussion

This was first prospective study to explore the efficacy of early SBRT to the primary tumor in advanced cases of EGFR-mutant NSCLC after first-generation EGFR-TKI and to expound the patterns of failures of this combination therapy. The primary endpoints of our study was to determine PFS, AEs, and OS among this population. Encouragingly, the median PFS of SBRT combined with EGFR-TKI treatment in advanced NSCLC patients were 15.23 months without no serious AEs. The incidence of radiation pneumonitis, the most common AE, was 85.7% and the majority were Grade 1. As for the patterns of failure in the relapsing 37 patients, it failed mainly at new metastatic sites. Overall OS was favorable at 27.57 months. Local SBRT to the primary tumor in the early phase, approximately at first month in our study, seemed to have good local control, with the possibility of eliminating tumor heterogeneity and thereby delaying targeted resistance in advanced EGFR mutation-positive NSCLC treated with EGFR-TKI.

Consistent with previous studies, there was a significant difference of PFS and OS when patients with the 19-del mutation were compared with those who had the L858R mutation. In a study by Yi Tang et al\textsuperscript{22}, patients with the 19-del mutation are more likely to benefit from combination therapy consisting of SBRT and EGFR-TKI. In the NEJ026 study\textsuperscript{23}, bevacizumab plus erlotinib combination therapy could also improve PFS compared with erlotinib alone in patients with EGFR mutation-positive non-squamous NSCLC, especially for patients with the L858R mutation. However, bevacizumab plus erlotinib did not significantly affect OS, and no difference was observed in mutation subtype analysis. Similar results were found in the combination of EGFR-TKI and chemotherapy, but mutation subtype analysis was not performed.
In the subgroup analysis, the number of metastases (≤ 5 lesions) was only a predictor for PFS rather than OS in patients receiving SBRT to the primary tumor combined EGFR TKI, but a trend of improved OS was observed. As previously demonstrated, consolidative therapy confers better survival benefit than maintenance therapy alone\textsuperscript{14}. Numerous prospective and retrospective studies indicated that local radiotherapy combined with continuation of TKI therapy in the limited progression, note as oligo-progression, of naive EGFR mutation with TKI\textsuperscript{33,34}. For instance, in a recent study by Wang et al., it was found that local therapy with RT followed by TKI treatment statistically improved OFS and OS for EGFR-mutated NSCLC\textsuperscript{41}. Wu et al. also proposed local treatment for local progression models. In oligo-metastasis EGFR mutant NSCLC patients with first-line EGFR-TKI before progression\textsuperscript{35}, although the number of metastasis and organ varies in studies. Consistent with our results, in patients with five or fewer metastases, SBRT prolonged PFS with 26.69 months and an increasing trend in OS was observed. Although most patients in this group were IIIB stage, it also was in lined with a multi-center and retrospective study in unresectable advanced NSCLC with EGFR mutation, which revealed that radiotherapy combined with EGFR-RKI could prolong PFS with 21.6 months and OS with 67.4 months when compared with chemoradiotherapy group and EGFR-TKI alone group\textsuperscript{36}.

The time of intervention of local treatment in oligo-metastasis EGFR mutation-positive NSCLC remains controversial. As for patients with limited brain metastases, the sequence of EGFR-TKI and local treatment (for example: SRS, SBRT, or surgery) depended on central nervous system symptomatology. As for lung sites, many proposals suggest introducing local therapy at or near the time of TKI initiation could hold the potential to reduce initial accumulation of malignant clones, decreasing the risk of following metastasis and reducing the injury of normal tissue due to the reduction of lesions burden\textsuperscript{37}. A retrospective study\textsuperscript{22} with 105 subjects indicated that considerable shrinkage from TKI therapy occurs in the first 2 months after TKI initiation; local therapy can therefore be adopted after this timepoint and before disease progression, especially for EGFR mutation-positive patients. In the study by Wu et al, the median response time after TKI treatment was 7.4 weeks\textsuperscript{38}. In the present study, there were 33 PR and 4 SD. The median response time was 1.49 (0.73–2.47) months, similar to that of previous studies. Another study by Wei et al. 2021 showed that preemptive RT to the primary lung tumor before occurrence of oligo-metastasis significantly improved PFS, also suggesting the benefit on survival with early intervention of RT \textsuperscript{42}. However, future prospective studies of radiotherapy in the early phase of TKI initial treatment in NSCLC are imperative as it remains unknown whether or not RT before or after chemo provides better survival outcomes in patients with EGFR-mutant NSCLC.

In metastases resulting from EGFR mutation-positive NSCLC, reports of radiotherapy mainly focus on alleviating symptoms and multi-brain metastasis. Several studies demonstrated that whole brain radiotherapy (WBRT) with EGFR-TKI would not improve OS, with greater impaired cognitive function and decreased quality of life. As for lung tumors, Zheng et al\textsuperscript{19} demonstrated that concurrent EGFR-TKI and radiotherapy within 2 weeks from targeted therapy as the first-line treatment for advanced NSCLC harboring the EGFR mutation showed a long-term control of primary lung lesion and acceptable serious AEs, with 13.0 months of PFS and a 57.1% 1-year PFS rate. Conforming with our research, patients with
more than 5 metastases were found to have 13.43 months of PFS and 25.9 months of OS, although SBRT was administered approximately 1 months after TKI and only for the primary tumor in the lung. A significantly lower rate of progression was observed at the site of the primary tumor, which was consistent with the study by Hani Al-Halabi et al\textsuperscript{8}. However, some studies demonstrated that all forms of RT could obtain PFS and OS benefit rather than part-RT or RT alone\textsuperscript{35}. The role of radiotherapy in combination therapy is still under controversy and there is no consensus guidelines for the use of RT in EGFR-mutant NSCLC\textsuperscript{39}.

The mechanism underlying the efficacy of concomitant SBRT and EGFR-TKI remains unclear. Notably, of progression in 37 patients, a total of 24/37 (64.86\%) were under second gene detection, and the T790M mutation was detected in 21/37 patients (56.76\%), including 14 patients (66.67\%) with the initial 19-del mutation and 7 patients (33.33\%) with the L858R mutation. It was consistent with the occurrence rate of T790M after targeted therapy and in line with the phenomenon of the 19-del mutation developing from T790M rather than L858R\textsuperscript{24–26}.

In term of further generations of EGFR-TKI therapy, the second generation of EGFR-TKI in clinical application was limited, although it could prolong PFS by 11 to 14.7 months, owing to its relatively higher potency. Outstanding performance was demonstrated by the third-generation EGFR-TKI agent osimertinib, which is the first-line treatment for EGFR mutation-positive NSCLC, especially for patients with the T790M mutation and brain metastasis\textsuperscript{27}. The FLAURA trial suggests improvement in PFS and OS with Osimertinib compared with gefitinib or erlotinib in EGFR mutant NSCLC\textsuperscript{41}. Tiantian Guo et al\textsuperscript{28} analyzed the pattern of recurrence, finding 50\%, 22\% and 28\% for OF, NF and ONF, respectively, in metastatic EGFR mutation-positive NSCLC treated with osimertinib. The authors hypothesized that consolidative SBRT to all residual disease sites as an addition to EGFR-TKI therapy holds promise for delaying disease progression and even for improving OS.

With the advent of era of immunotherapy, 5-year survival of NSCLC patients was approximately 30\%, which was a victory over conventional chemotherapy. However, the immunotherapy as first-line therapy was aborted in advanced NSCLC harboring the EGFR mutation in many clinical trials\textsuperscript{29}, despite a few positive results in IMpower150\textsuperscript{30} and ATLANTIC\textsuperscript{31}. However, immunotherapy in advanced EGFR mutation-positive NSCLC after EGFR-TKI resistance was developed in clinical trials, and its outcomes could be anticipated, due to the theory that immune escape mediated by upregulation of PD-L1 was one of the targeted resistance mechanisms in vivo and in vitro\textsuperscript{32}. To our knowledge, this was the first prospective study to evaluate the effectiveness and patterns of failures in concurrent early phase SBRT to the primary tumor after first-generation EGFR-TKI treatment in EGFRm NSCLC. However, there are several limitations in our study. First, a limited number of patients were studied, and no control group receiving EGFR-TKI alone was available as per a phase 2 trial. A larger, multi-center, and prospective phase III research is of great need. Secondly, resistance mechanisms underlying this regimen have not been explored, which may guide further treatment development.
In summary, early phase SBRT for the primary lung tumor combined with EGFR-TKI followed by RT may be an alternative choice for advanced NSCLC harboring the EGFR mutation, which has the potential to alter the natural history of disease progression and to delay targeted resistance, as well as increasing OS without serious AEs. The lung was the most common site of initial progression. It remains to be determined whether or not SBRT before or after chemo is more beneficial for survival in EGFR mutant NSCLC. The role of SBRT during treatment of EGFRm NSCLC with osimertinib also deserves further consideration.

Declarations

Prior presentation

Presented in part at the World Conference on Lung Cancer (WCLC), Toronto, September 23 – 26, 2018; and the World Conference on Lung Cancer (WCLC), Barcelona, September 7-10, 2019; and the 2021 American Society of Clinical Oncology (ASCO).

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Clinical trial information

ChiCTR-OIN-17013920

Author's disclosure of potential conflicts of interest and data availability statement

Author's contributions

Haihua Yang: Conceptualization, Supervision, Funding acquisition, Investigation, Methodology, Project administration, Formal analysis, Writing - review & editing. Dongqing Lv: Conceptualization, Supervision, Investigation, Methodology, Project administration, Validation. Xiaofeng Chen: Conceptualization, Methodology, Data curation, Formal analysis, Writing - review & editing. Yangyang Shi: Roles/Writing - original draft, Validation, Data curation, validation. Hailing Xu: Roles/Writing - original draft, investigation, software, Data curation. William Y. Raynor: Roles/Writing - Original draft, Formal analysis, Writing - review & editing. Jiapei Ding: investigation, Validation. Ling Lin: investigation, Data curation. Chao Zhou: investigation, Data curation. Wei Wang: investigation, Data curation. Yinnan Meng: investigation, validation. Xiaomai Wu: investigation, Data curation

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Author's disclosures of potential conflicts interest

none.

References

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**Figures**

![Figure A](image1.png)

![Figure B](image2.png)
Figure 1

Follow-up time of patients. A. changes of treatment in different times; B. distribution of objective response in patients.

Figure 2

Survival analysis of patients in the whole group. A. median PFS; B. median OS.

Figure 3

Survival analysis of patients in subgroups. A. PFS in EGFR mutation subtype group; B. PFS in the number metastasis subtype group; C. OS in EGFR mutation subtype group; D. OS in the number metastasis subtype group.
Supplementary Files

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