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# Additional local consolidative therapy has survival benefit over EGFR tyrosine kinase inhibitors alone in bone oligometastatic lung adenocarcinoma patients

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ABSTRACT

*Objectives:* Whether epidermal growth factor receptor tyrosine-kinase inhibitors (EGFR-TKIs) plus local consolidative therapy (LCT) has survival benefit over EGFR-TKIs alone in lung adenocarcinoma patients with EGFR mutation and bone oligometastases remains controversial.

*Materials and methods:* We conducted a retrospective study to assess the effects of LCT in lung adenocarcinoma patients with bone oligometastases and EGFR mutation. The primary endpoint was overall survival (OS); the secondary endpoints was progression-free survival (PFS).

*Results:* A total of 127 lung adenocarcinoma patients with EGFR mutation and bone oligometastases were assessed, including 65 patients received EGFR-TKIs alone (monotherapy group) and 62 patients received EGFR-TKIs plus local consolidative therapy (LCT) (combination group). Addition of LCT was associated with significantly longer OS (36.3 *vs.* 21.0 months, P = 0.01; hazard ratio [HR] = 0.537, 95% confidence interval [CI]: 0.360-0.801, p = 0.01) and PFS (14.0 *vs.* 8.1 months, P = 0.01; HR = 0.613, 95%CI: 0.427-0.879, p = 0.01) in the whole cohort.

*Conclusion:* In lung adenocarcinoma patients with EGFR-mutation and bone oligometastases, LCT plus EGFR-TKIs therapy is associated with significantly longer OS and PFS compared with EGFR-TKIs therapy alone, indicating that LCT plus EGFR-TKIs therapy might be a better therapeutic option for this patient population.

## 1. Introduction

The bone is one of the most common sites of distant metastases in advanced lung adenocarcinoma patients, which results in poor survival [1]. Currently, the strategies for managing bone metastases include local radiotherapy, bisphosphonate administration, or surgery of metastases sites, either alone or in combination with other systemic anticancer therapeutics [2]. With the development of lung cancer biology, oligometastases can be observed in certain group patients, among whom metastatic sites are limited to three organs and all distant metastases add up to 5 or less [3,4]. Bone oligometastases refers to the distant metastatic sites confined to the bone, with metastatic lesions not exceeding five.

The discovery of EGFR mutation has been an important milestone in the management of lung cancer in the past decade, shifting the treatment paradigm of classical platinum-based chemotherapy in sensitive EGFR-mutant patients [5,6]. Currently, some retrospective and prospective studies have confirmed that the therapeutic efficacy of EGFR can be further improved by combination with chemotherapy or anti-antiangiogenic treatment [7–10]. Specifically, TKIs combined with

*Abbreviations:* EGFR, epidermal growth factor receptor; TKIs, tyrosine-kinase inhibitors; LCT, local consolidative therapy; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; SREs, skeletal-related events; ARMS, amplification refractory mutation system; CT, computed tomography; MRI, magnetic resonance imaging; PS, performance status; SRT, stereotactic radiotherapy; SRS, stereotactic radiosurgery; 3D-CRT, three dimensional conformal RT; IMRT, intensity Modulated RT

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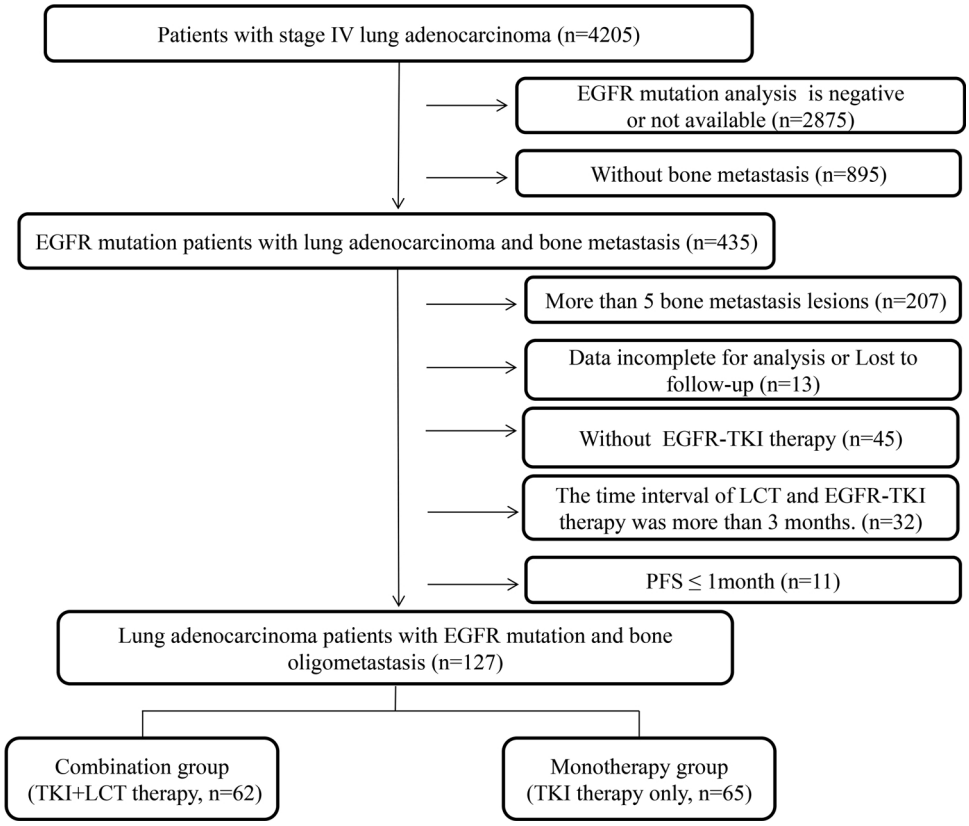


**Fig. 1.** Patient flowchart.
Flow diagram of patient selection steps. LCT, local consolidative therapy; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; PFS, progression-free survival.

local consolidative therapy (LCT) represents another treatment of choice. In bone metastasis, LCT could alleviate symptoms and delay the onset of skeletal-related events (SREs) [2,11,12]. Our previous study found that in patients with bone oligometastasis, additional application of local consolidation therapy results in improved survival trend compared with targeted monotherapy. However, this survival advantage did not reach statistical differences due to insufficient sample size [13]. Hence, in lung adenocarcinoma patients with EGFR mutation and bone oligometastases, whether the combination of EGFR-TKIs and LCT has better survival benefit over EGFR-TKIs alone remains controversial. Emerging evidence suggests that local consolidative therapy could provide clinical benefits in lung adenocarcinoma patients with oligometastatic disease [8,14–16]. However, most reports focused on intracranial or lung oligometastases [17,18]. As bone oligometastasis is one of the most common metastases of advanced lung cancer, it is necessary to evaluate the role of LCT in the management of bone oligometastases.

Therefore, we conducted this retrospective study to investigate whether local consolidative therapy combined with EGFR-TKIs could provide survival benefits in EGFR-mutant lung adenocarcinoma patients with bone oligometastases compared with EGFR-TKIs alone.

## 2. Materials and methods

### 2.1. Patients

One hundred and twenty-seven patients were identified in Shanghai Chest Hospital from January 2010 to January 2018. The major criteria for patient selection were: (1) histological/pathological confirmation of lung adenocarcinoma; (2) AJCC 8th Edition Stage IV disease (The TNM status of patients diagnosed earlier was reassessed through the 8$^{th}$ edition of the guidelines); (3) EGFR mutations tested by amplification refractory mutation system (ARMS); (4) radiological confirmation of bone oligometastases (radiological evidence included but was not limited to chest computed tomography (CT), bone scan, brain magnetic resonance imaging (MRI) or CT, abdominal ultrasound or PET-CT instead of the above examination.). Firstly, patients with stage IV lung adenocarcinoma were identified. Then, those with bone oligometastases and sufficient clinical data were selected. Thirdly, only patients with EGFR-mutant lung adenocarcinoma and bone oligometastases were selected for the subsequent analysis. Finally, eligible patients were divided into subgroups according to their therapeutic data. Local consolidative therapy included surgery of metastatic sites and local radiotherapy.

Exclusion criteria were: (1) no treatment with first-generation of EGFR-TKIs; (2) more than 5 bone metastatic lesions; (3) incomplete medical records or follow-up information; (4) time interval of LCT and EGFR-TKI therapy exceeding 3 months. The patient selection steps are shown in Fig. 1.

The study was approved by the ethics committee and institutional review board of Shanghai Chest Hospital (Shanghai, China).

### 2.2. Data collection

Follow-up was performed by hospital visits or through telephone conversations. Major clinicopathological characteristics, including demographic information (age and sex), smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), nodal stage, numbers of bone metastases, location of bone oligometastases, course of LCT and EGFR-TKIs therapy, EGFR mutational status and the status of osimertinib administration, were collected. LCT was only performed against the metastatic sites. EGFR mutations mainly referred to exon 19Del and 21L858R. The EGFR-TKIs used in this study included gefitinib, erlotinib and icotinib, and were orally administered at 250 mg

**Table 1**
Demographic data of 127 patients and comparison of baseline characteristics between two groups.

| Characteristic | Patients (n = 127) | | | |
|---|---|---|---|---|
| | LCT + TKI(n = 62) | TKI(n = 65) | P value | Total |
| **Median age (range)** | 61 (39–78) | 60 (30–82) | 0.82 | 60 (30–82) |
| **Sex** | | | | |
| Male | 32 (51.6%) | 23 (35.4%) | 0.07 | 55 (43.3%) |
| Female | 30 (48.4%) | 42 (64.6%) | | 72 (56.7%) |
| **Smoking status** | | | | |
| Smoker[a] | 24 (38.7%) | 22 (33.8%) | 0.59 | 46 (36.2%) |
| Never-smoker | 38 (61.3%) | 43 (66.2%) | | 81 (63.8%) |
| **Location of bone oligometastasis** | | | | |
| Spine | 26 (41.9%) | 18 (27.7%) | 0.04 | 44 (34.6%) |
| Outside of the spine | 10 (16.1%) | 23 (35.4%) | | 33 (26.0%) |
| Both | 26 (41.9 %) | 24 (36.9%) | | 50 (39.4%) |
| **Number of metastatic lesions** | | | | |
| 1–2 | 30 (48.4%) | 40 (61.5%) | 0.14 | 70 (55.1%) |
| 3–5 | 32 (51.6%) | 25 (38.5%) | | 57 (44.9%) |
| **EGFR mutation status** | | | | |
| 19del | 30 (48.4%) | 27 (41.5%) | 0.10 | 57 (44.9%) |
| 21L858R | 30 (48.4%) | 36 (55.4%) | | 66 (52.0%) |
| Others | 2 (3.2%) | 2 (3.1%) | | 4 (3.1%) |
| **T stage** | | | | |
| T1-2 | 48 (77.4%) | 49 (75.4%) | 0.84 | 97 (76.4%) |
| T3-4 | 14 (22.6%) | 16 (24.6%) | | 30 (23.6%) |
| **N stage** | | | | |
| N0-1 | 22 (35.5%) | 14 (21.5%) | 0.08 | 36 (28.3%) |
| N2-3 | 40 (64.5%) | 51 (78.5%) | | 91 (71.7%) |
| **Performance status** | | | | |
| 0~1 | 54 (87.1%) | 55 (84.6%) | 0.80 | 109 (85.8%) |
| ≥2 | 8 (12.9%) | 10 (15.4%) | | 18 (14.2%) |
| **Type of bone oligometastasis** | | | | |
| Synchronous | 31 (50.0%) | 48 (73.8%) | 0.01 | 79 (62.2%) |
| Metachronous | 31 (50.0%) | 17 (26.2%) | | 48 (37.8%) |
| **Symptoms of bone metastasis** | | | | |
| Yes | 40 (64.5%) | 22 (33.8%) | 0.00 | 62 (48.8%) |
| No | 22 (35.5%) | 43 (66.2%) | | 65 (51.2%) |
| **Local therapy** | | | | |
| Radiotherapy | 57 (91.9%) | – | – | 57 (91.9%) |
| Surgery | 3 (4.8%) | – | | 3 (4.8%) |
| Radiotherapy + Surgery | 2 (3.2%) | – | | 2 (3.2%) |

Abbreviations: LCT, local consolidative therapy; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.
[a] Smoker: The defination of "smoker" in our study means the patient who has smoked > 100 cigarettes during their lifetime.

daily, 150 mg daily, and 125 mg three times daily, respectively. Radiotherapy included both stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS). SRT mainly referred to three dimensional conformal RT (3D-CRT) and intensity Modulated RT (IMRT), and SRS to X-knife, gamma knife (Y knife) and cyber knife. The therapeutic effect was assessed mainly according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The treatment response was evaluated one month after the initiation of EGFR-TKIs therapy and then every 8–12 weeks. Bone scans were performed every 3–6 months. (when symptoms of bone metastasis were suspected, bone scan was performed immediately.).

The primary endpoint of this study was overall survival (OS). The secondary endpoint was progression free survival (PFS). The last patient was enrolled on January 10, 2018, and the last follow-up occurred on January 21, 2019. The median follow-up time for the whole study cohort was 28 months. PFS was determined from EGFR-TKI treatment initiation to the date of progression or last follow-up visit. Overall survival (OS) was determined from EGFR-TKI treatment initiation to the date of death or last follow-up visit.

### 2.3. Statistical analysis

Demographic and clinical data were analyzed. Differences in baseline characteristics between the different treatment groups were assessed by the $X^2$ test. The chi-square test or Fisher's exact test was used to compare categorical variables. The Kaplan-Meier method was used to derive median OS and PFS. Hazard ratio (HR) and the corresponding 95% confidence intervals (CIs) were calculated by the Cox proportional hazards model. Statistical significance was defined as two-sided $P < 0.05$. All statistical analyses were performed with the SPSS statistical software, version 24.0(SPSS Inc., Chicago, IL, USA).

## 3. Results

### 3.1. Patient characteristics

A total of 127 patients were included and analyzed according to the above inclusion criteria. Patients selection steps are shown in Fig. 1. Of the 127 EGFR mutation-positive bone oligometastatic lung adenocarcinoma patients, 62 received LCT and EGFR-TKIs therapy, while the remaining 65 underwent EGFR-TKIs monotherapy. The baseline characteristics of the two groups were well balanced except for significantly higher proportions of patients with spine metastasis ($p = 0.04$) and symptoms of bone metastasis ($p = 0.00$) in the combination group, and more individuals with synchronous bone oligometastasis in the monotherapy group ($p = 0.01$). The baseline characteristics of both groups are listed in Table 1.

In this study, 57 patients (91.9%) were treated with radiotherapy as LCT, while 2 cases underwent radiotherapy plus surgery as LCT. Of the 59 patients receiving radiotherapy, 52 (88.1%) underwent SRT radiotherapy and the remaining 7 (11.9%) received SRS for local treatment. Of the patients treated with SRT, 45 received a radiotherapeutic

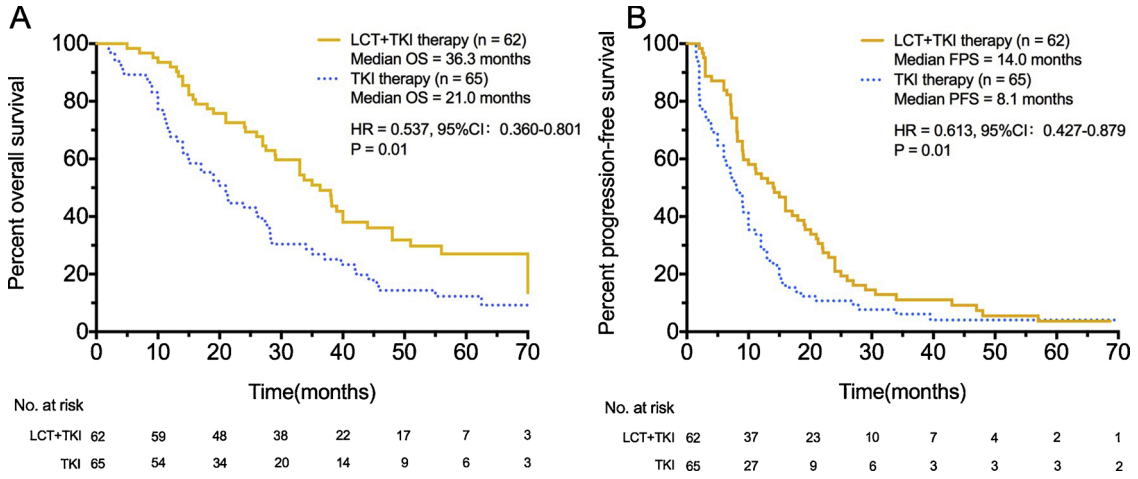


**Fig. 2.** Overall survival and progression-free survival in the combination and monotherapy groups of lung adenocarcinoma patients with bone oligometastases. (A) Kaplan–Meier curve of overall survival (OS); (B) Kaplan–Meier curve of progression-free survival (PFS).
LCT, local consolidative therapy; TKIs, tyrosine kinase inhibitors; HR, hazard ratio; CI, confidence interval.

regimen of 30 Gy/10fx (86.5%), and the remaining 7 had radiotherapeutic regimens of 36–40 Gy/11fx-20fx (13.5%).

Among the patients with symptoms of bone metastases, 37 patients (92.5%) showed relieved symptoms after treatment in the combination group, while 14 cases (63.6%) were relieved after treatment with EGFR-TKIs in the monotherapy group (Supplementary Fig. 1).

### 3.2. Efficacy and survival

In 127 EGFR mutation-positive bone oligometastatic lung adenocarcinoma patients, treatment with EGFR TKIs combined with LCT (n = 62) led to significantly longer OS (36.3 *vs.* 21.0 months, HR = 0.537, 95%CI 0.360-0.801, p = 0.01; Fig. 2A) and PFS (14.0 *vs.* 8.1 months; HR = 0.613, 95%CI 0.427-0.879, p = 0.01; Fig. 2B), compared with the monotherapy group (n = 65).

In univariate analysis, addition of local therapy was significantly associated with improved OS (36.3 *vs*. 21.0 month; HR = 0.537, 95%CI 0.360-0.801, p = 0.01) (Table 2) and PFS (14.0 *vs*. 8.1 month; HR = 0.613, 95%CI, 0.427-0.879, p = 0.01) (Table 3) compared with EGFR-TKIs alone. Besides, univariate analysis also showed that metachronous bone oligometastasis (p = 0.00), PS score of 0–1(p = 0.00), and osimertinib treatment (p = 0.00) were significantly associated with prolonged OS (Table 2). Meanwhile, metachronous bone oligometastasis (p = 0.00), PS score of 0–1(p = 0.00) and treatment with osimertinib (p = 0.01) were significantly associated with improved PFS (Table 3).

Multivariate analysis used the Cox model to examine the impact of important clinical characteristics on OS and PFS, including treatment strategy (EGFR-TKIs plus LCT *vs.* EGFR-TKIs), type of bone oligometastasis, performance status, and treatment with osimertinib. The results showed that the HR of OS and PFS for the combination group *vs.* the monotherapy group was 0.646(95%CI, 0.426–0.978; p = 0.04) and 0.675 (95%CI, 0.468–0.974; P = 0.04), respectively. In addition, metachronous bone oligometastasis (HR = 0.627, 95%CI, 0.392–1.000, p = 0.05), PS score of 0–1 (HR = 0.361, 95%CI, 0.210–0.620, p = 0.00) and treatment with osimertinib (HR = 0.265, 95%CI, 0.155–0.452, p = 0.00) were independent prognostic factors of improved OS (Table 2). In multivariate analysis, PFS was significantly associated with the type of bone oligometastasis (HR = 0.581, 95%CI, 0.385–0.877, p = 0.01), performance status (HR = 0.388, 95%CI, 0.228–0.660, p = 0.00) and treatment with osimertinib (HR = 0.587, 95%CI, 0.391–0.881, p = 0.01) (Table 3).

**Table 2**
Univariate and Multivariate Analyses of Clinical Characteristics on Overall Survival Outcomes between two groups.

| Factor | Overall survival | | | |
|---|---|---|---|---|
| | Univariate Analysis | | Multivariate Analysis | |
| | Hazard Ratio | P Value | Hazard Ratio | P Value |
| **Treatment strategy** (TKI + LCT/TKI) | 0.537 (95%CI, 0.360–0.801) | 0.01 | 0.646 (95%CI, 0.426–0.978) | 0.04 |
| **Age** ( < 60/ ≥ 60) | 0.963 (95%CI, 0.648–1.430) | 0.85 | – | – |
| **Sex** (Male/ Female) | 0.948 (95%CI, 0.637–1.413) | 0.79 | – | – |
| **Smoking status** (Never-smoker/ Smoker) | 0.682 (95%CI, 0.455–1.022) | 0.06 | – | – |
| **Location of bone oligometastasis** (Spine/ Outside of the spine/ Both) | 0.805 (95%CI, 0.509–1.275)/ 0.788 (95%CI, 0.476–1.305) | 0.35/ 0.35 | – | – |
| **Type of bone oligometastasis** (Metachronous/ Synchronous) | 0.534 (95%CI, 0.348–0.821) | 0.00 | 0.627 (95%CI, 0.392–1.000) | 0.05 |
| **Number of oligometastatic lesions** (1-2/3-5) | 0.981 (95%CI, 0.660–1.459) | 0.93 | – | – |
| **EGFR mutation status** (19del/21L858R) | 0.851 (95%CI, 0.569–1.274) | 0.43 | – | – |
| **Performance status** (0~1/ ≥ 2) | 0.350 (95%CI, 0.209–0.587) | 0.00 | 0.361 (95%CI, 0.210–0.620) | 0.00 |
| **T stage** (T1-2/ T3-4) | 0.783 (95%CI, 0.493–1.242) | 0.29 | – | – |
| **N stage** (N0-1/ N2-3) | 0.667 (95%CI, 0.423–1.052) | 0.08 | – | – |
| **Treatment with Osimertinib**[a] (Yes/ No) | 0.313 (95%CI, 0.186–0.524) | 0.00 | 0.265 (95%CI, 0.155–0.452) | 0.00 |

Abbreviations: PFS, progression-free survival; OS, overall survival; LCT, local consolidative therapy; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

[a] The patient chose to use Osimertinib for treatment after the disease progressed (Osimertinib was adopted at a dose of 80 mg per day when the first generation EGFR-TKIs was resistant).

**Table 3**
Univariate and Multivariate Analyses of Clinical Characteristics on Progression-Free Survival Outcomes between two groups.

| Factor | Progression-free survival | | | |
|---|---|---|---|---|
| | Univariate Analysis | | Multivariate Analysis | |
| | Hazard Ratio | P Value | Hazard Ratio | P Value |
| **Treatment strategy** (TKI + LCT/ TKI) | 0.613 (95%CI, 0.427–0.879) | 0.01 | 0.675 (95%CI, 0.468–0.974) | 0.04 |
| **Age** ( < 60/ ≥ 60) | 0.995 (95%CI, 0.696–1.423) | 0.98 | – | – |
| **Sex** (Male/ Female) | 0.823 (95%CI, 0.574–1.182) | 0.28 | – | – |
| **Smoking status** (Never-smoker/ Smoker) | 0.876 (95%CI, 0.605–1.268) | 0.48 | – | – |
| **Location of bone oligometastasis** (Spine/ Outside of the spine/ Both) | 0.776 (95%CI, 0.511–1.178)/ 0.774 (95%CI, 0.487–1.230) | 0.23/ 0.27 | – | – |
| **Type of bone oligometastasis** (Metachronous/ Synchronous) | 0.512 (95%CI, 0.346–0.759) | 0.00 | 0.581 (95%CI, 0.385–0.877) | 0.01 |
| **Number of oligometastatic lesions** (1-2/3-5) | 0.952 (95%CI, 0.665–1.362) | 0.78 | – | – |
| **EGFR mutation status** (19del/21L858R) | 0.748 (95%CI, 0.517–1.082) | 0.12 | – | – |
| **Performance status** (0~1/ ≥ 2) | 0.336 (95%CI, 0.199–0.567) | 0.00 | 0.388 (95%CI, 0.228–0.660) | 0.00 |
| **T stage** (T1-2/ T3-4) | 0.889 (95%CI, 0.585–1.350) | 0.57 | – | – |
| **N stage** (N0-1/ N2-3) | 0.763 (95%CI, 0.512–1.138) | 0.18 | – | – |
| **Treatment with Osimertinib** (Yes/ No) | 0.597 (95%CI, 0.399–0.893) | 0.01 | 0.587 (95%CI, 0.391–0.881) | 0.01 |

Abbreviations: PFS, progression-free survival; OS, overall survival; LCT, local consolidative therapy; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

All subgroup analyses showed that the combination group had significantly longer OS compared with the monotherapy group (except for the subgroup with performance status score ≥2), especially for subgroups of age ≥ 60, non-smokers, cases with 1–2 bone oligometastasis lesions and PS score of 0–1 (Fig. 3A). All subgroup analyses suggested PFS benefit for the combination therapy group (Fig. 3B).

Notably, patients with 1–2 bone metastatic lesions showed a trend of longer PFS and OS benefit from the LCT compared with those with 3–5 bone metastatic lesions (median PFS of 16.0 *vs*. 9.0 months; HR = 0.799, 95%CI: 0.478–1.335, p = 0.38; median OS of 38.1 *vs*. 27.0 months; HR = 0.735, 95%CI: 0.399–1.352, p = 0.31). Besides, patients with 1–2 bone metastatic lesions had significantly longer PFS (16.0 *vs*. 8.0 months; HR = 0.542, 95%CI: 0.345-0.853, p = 0.01) and OS (38.1 *vs*. 21.0 months; HR = 0.456, 95%CI: 0.270-0.770, p = 0.01) compared with the monotherapy group. Meanwhile, a trend was found but not significant between the patients with 3–5 bone metastases lesions administered LCT and monotherapy (median PFS of 9.0 *vs*. 8.0 months, HR = 0.717, 95%CI: 0.464–1.108, p = 0.12; median OS 27.0 *vs*. 21.0, HR = 0.645, 95%CI: 0.399–1.042) (Supplemental Fig. S2).

## 4. Discussion

The concept of 'oligometastasis' was first proposed in 1995 by Hellman and Weichselbaum [3,4]. This concept is based on the hypothesis that the primary tumor has limited metastatic capacity, providing a window of treatment for early cure [19]. The development of

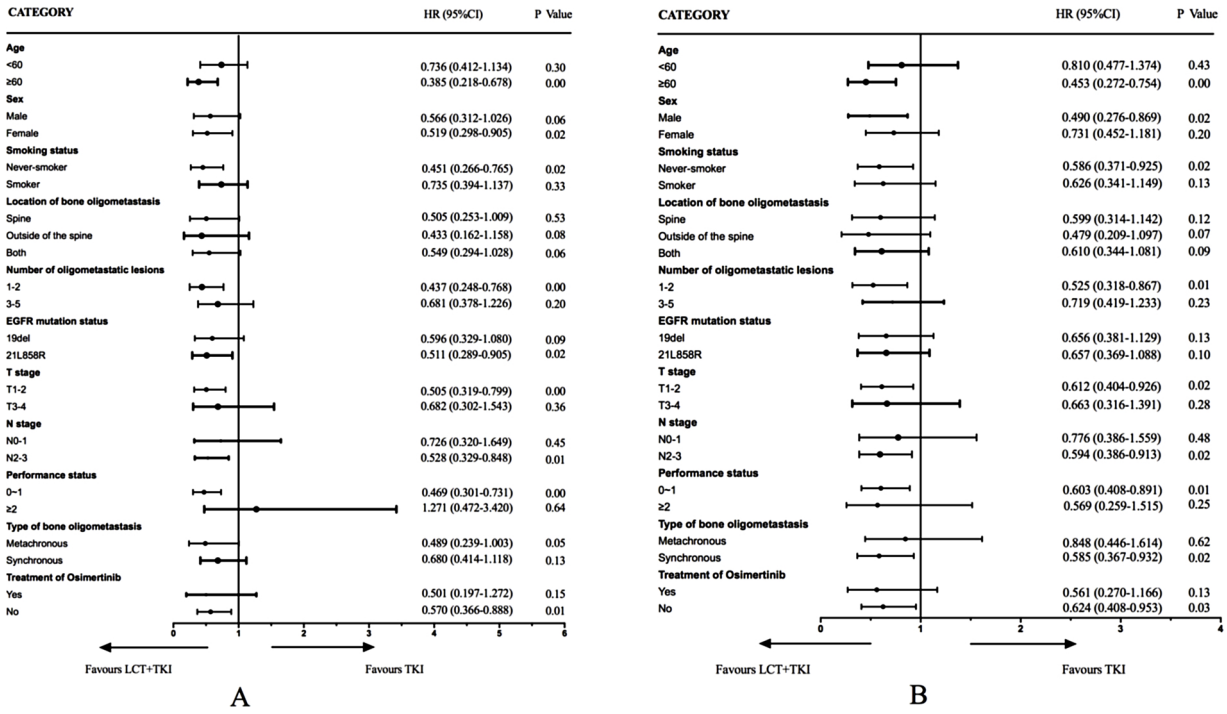


**Fig. 3.** Subgroup analysis of lung adenocarcinoma patients with bone oligometastases.
(A) Overall survival (OS).
(B) Progression-free survival (PFS).
LCT, local consolidative therapy; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; HR, hazard ratio; CI, confidence interval.

diagnostic imaging techniques such as PET-CT and MRI has been helpful in identifying oligometastatic lesions and increasing the detection rate of oligometastases in lung cancer patients [20,21]. There is currently no uniform standard for defining the oligometastatic state. Some researchers classify patients based on the time and progression of metastasis. Oligometastases found at the time of initial diagnosis are called synchronous oligometastases, while those detected after a period of treatment are called metachronous oligometastasis. Our previous study found that patients administered additional LCT have a trend of longer OS (33 *vs.* 21 months; HR = 0.744, 95% CI: 0.436–1.268; p = 0.25) compared with those who received EGFR-TKIs alone [13]. However, due to small sample size, statistical significance was not achieved. Therefore, this study expanded the sample size and focused on patients with bone oligometastases, systematically evaluating the efficacy of LCT on prognosis in bone oligometastatic lung adenocarcinoma patients with EGFR mutations. The current results were consistent with previous studies, demonstrating that both OS and PFS were significantly longer in the combination group compared with the monotherapy group [15,17,22,23]. A randomized phase II trial found that LCT in patients with oligometastatic NSCLC has a prominent PFS benefit. (local consolidative therapy group *vs.* maintenance treatment group: 11.9 *vs.* 3.9 months) [14]. The median PFS in this study was longer than their study. The main reason is that all the patients included in this study were sensitive EGFR-mutant and treated with targeted drugs. In addition, a recent study conducted by Helena A. Yu et al suggested that patients with acquired resistance to EGFR TKIs therapy are also amenable to LCT for treating the oligometastatic disease. LCT followed by continued treatment with EGFR TKIs is well tolerated and associated with improved PFS and OS [24]. In comparison, another research suggested that although local treatment of bone oligometastasis has excellent local control rate and little toxicity, its survival benefits are limited [2].

In this study, locations of bone oligometastases, symptom of bone metastasis and types of bone oligometastases were not balanced between the two groups. Because the risk of paraplegia in patients with spinal oligometastasis is relatively high, these individuals tended to undergo more active treatments. In addition, patients with bone metastasis symptoms were more likely to select LCT for symptom relief. Thus, there were more patients with spinal oligometastasis and pain symptoms in the combination group. Besides, metachronous oligometastasis usually develops slowly, and most affected patients have undergone primary lung surgery, with the systemic tumor burden relatively low; therefore, such patients are more inclined to choose LCT for bone oligometastases. Moreover, patients with quick disease progression are not LCT candidates, so we excluded such cases (PFS ≤ 1 months) to reduce selection bias. We further conducted a subgroup analysis of OS and PFS according to the performance status (PS score 0–1 *vs.* ≥ 2), and cases with PS scores of 0–1 significantly benefited from LCT while those with PS scores ≥2 did not. These findings suggested that patients with bone oligometastasis whose PS scores are greater than or equal to 2 should not be treated with LCT based on EGFR-TKIs monotherapy, except for some special cases (such as individuals at high risk of paraplegia). Since bone metastasis symptoms such as pain and numbness are evaluated by subjective feelings of patients, this study did not include this factor in subsequent survival statistical analysis, but evaluated it based on the patient's subjective experience: the relief of bone metastasis symptoms. In addition, univariate analysis in this study showed that metachronous oligometastases had a better outcome than synchronous counterparts, corroborating previous studies. The causes of metachronous oligometastasis are currently considered to include the presence of underlying clonal heterogeneity and external selection pressures, such as the use of targeted therapy. Compared with synchronous oligometastasis, the metachronous type is more inert in biological behavior and develops more slowly [25].

The survival advantage of the combination group over the monotherapy group could have some explanations. First, from the tumor burden perspective, local radiotherapy can destroy tumor cells in bone oligometastases, further reducing systemic tumor burden based on targeted drug therapy, to improve patient prognosis [26]. Secondly, previous studies have shown that local radiotherapy is effective in targeted drug-resistant patients since it could directly damage cancer cell DNA and stimulate the body's anti-tumor immune response, indicating that LCT plus EGFR-TKIs could enhance the efficacy of targeted drugs and delayed drug resistance [12,24]. Finally, local radiotherapy for spinal oligometastasis effectively alleviates the disease development process at the bone metastatic site and prevents the occurrence of adverse events such as paraplegia that seriously affect the quality of life and survival time, to significantly improve the patient's quality of life and survival time [27].

The major limitation of this study was its retrospective nature, with potential selection bias. Besides, the number of patients enrolled in this study was relatively small. Furthermore, additional prospective evidences elucidating the efficacy of LCT are needed to implement the LCT strategy in bone oligometastases as a routine clinical practice with widespread acceptance. Finally, both subjective evaluations and objective assessments were used to estimate side effects. However, subjective descriptions (such as erythra and paronychia) are scarce in our medical record system, and large errors would be caused by using telephone follow-up and patient evaluation. Therefore, adverse reactions werennot assessed in this research.

In conclusion, this study showed that in patients with EGFR-mutant lung adenocarcinoma and bone oligometastasis, the combination of EGFR-TKIs and LCT is associated with significantly prolonged OS and PFS. This survival advantage was found in different subgroups except for patients with PS scores greater than or equal to 2. Therefore, in bone oligometastatic patients with good performance status score and EGFR-positive lung adenocarcinoma, LCT combined with EGFR-TKIs may be a better therapeutic option compared with EGFR-TKIs alone.

## Declaration of Competing Interest

All authors have no conflict of interest to disclose.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.07.024.

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