



Efficacy of Local Consolidative Therapy for Oligometastatic Lung Adenocarcinoma Patients Harboring Epidermal Growth Factor Receptor Mutations

Fang Hu,¹ Jianlin Xu,¹ Bo Zhang,¹ Changhui Li,¹ Wei Nie,¹ Ping Gu,¹ Ping Hu,² Huimin Wang,¹ Yujun Zhang,¹ Yinchen Shen,¹ Shuyuan Wang,¹ Xueyan Zhang¹

Abstract

Evidence on the superiority of local consolidative therapy (LCT) for oligometastatic lung adenocarcinoma patients is scarce. We retrospectively reviewed a total of 231 patients with stage IV lung adenocarcinoma harboring sensitive mutation of epidermal growth factor receptor (EGFR) who received EGFR–tyrosine kinase inhibitor (EGFR-TKI) or EGFR-TKIs plus LCT, and analyzed the progression-free survival (PFS) and overall survival (OS) of the 2 groups. Compared to only EGFR-TKI, LCT improved PFS and overall OS. Survival benefit was regardless of EGFR mutation type.

Background: For oligometastatic lung adenocarcinoma patients with sensitive epidermal growth factor receptor (EGFR) mutations, the role of local consolidative therapy (LCT) remains debatable. The purpose of this study was to investigate the efficacy of LCT in oligometastatic lung adenocarcinoma patients. **Patients and Methods:** We conducted a retrospective study to assess the effects of LCT on progression-free survival (PFS) and overall survival (OS). Patients with advanced-stage oligometastatic lung adenocarcinoma harboring sensitive mutation of epidermal growth factor receptor (EGFR) who received EGFR–tyrosine kinase inhibitor (TKI) or EGFR-TKI plus LCT were admitted to Shanghai Chest Hospital from January 2010 to December 2016. The PFS and OS of the 2 groups were accordingly analyzed. **Results:** A total of 231 patients (143 patients who received LCT plus EGFR-TKI [combination group] and 88 patients who only received EGFR-TKI only [monotherapy group]) were included in this study. Median PFS was significantly longer in the combination group (15 months; 95% confidence interval [CI], 13.611–16.389) than in the monotherapy group (10 months; 95% CI, 8.936–11.064; hazard ratio = 0.610; 95% CI, 0.461, 0.807; $P = .000$). The median OS in the combination group was 34 months (95% CI, 27.889, 40.111) versus 21 months (95% CI, 18.445, 23.555) in the monotherapy group (hazard ratio = 0.593; 95% CI, 0.430–0.817; $P = .001$). **Conclusion:** LCT combined with TKIs therapy was a feasible method that significantly improved PFS and OS among oligometastatic lung adenocarcinoma patients with EGFR mutations, and it thus might be considered as an important medical treatment during clinical management.

Clinical Lung Cancer, Vol. 20, No. 1, e81-90 © 2018 Elsevier Inc. All rights reserved.

Keywords: Oligometastasis, OS, PFS, Real-world treatment, Retrospective study

Introduction

Lung cancer is one of the most common cancer worldwide both in terms of incidence (1.8 million new cases estimated in 2012) and

mortality (1.6 million annual deaths).^{1,2} Multiple distant metastasis of the whole body often indicates a poor prognosis, and more than 80% of metastasis occur within the first 2 years.³ Postoperative

F.H., J.X. and B.Z. contributed equally to this article, and all should be considered first author.

¹Department of Pulmonary, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, PR China

²Internal Medicine, Shangyu People's Hospital, Shangyu, Zhejiang Province, PR China

Submitted: Jun 2, 2018; Revised: Aug 21, 2018; Accepted: Sep 15, 2018; Epub: Sep 24, 2018

Address for correspondence: Xueyan Zhang, Department of Pulmonary, Shanghai Chest Hospital, Shanghai Jiaotong University, 241 Huaihai West Road, Xuhui District, Shanghai 200030, China
Fax: +86 62821990; e-mail contact: zyxchest@163.com

Local Consolidative Therapy

relapse occurs in about 45% of patients, even after complete resection of primary lung tumor.⁴ In advanced stage of disease, the 5-year survival rate is only 4%.⁵

In clinical practice, oligometastasis can be observed in certain subgroups of patients. Among those with distant metastatic recurrence, the metastasis is always limited in both number and organ, termed oligometastases.⁶ Previous studies have suggested that although patients diagnosed with oligometastasis can be classified as having stage IV disease, this is a particular state between locally advanced stage and the extensive stage IV transition.⁷

Targeted therapy has represented an important breakthrough in the field of palliative care for advanced lung cancer in the past decade.⁸ Several studies have suggested that therapeutic efficacy of first-line tyrosine kinase inhibitor (TKI) treatment can be further improved when combined with either chemotherapy or antiangiogenic treatment.⁹⁻¹² For the special group of patients diagnosed with oligometastasis, there exists another potential choice: TKI combined with local consolidative therapy (LCT). Some retrospective and small prospective trials have indicated that patients with advanced stage cancer with limited metastatic sites could benefit from the LCT.¹³⁻¹⁷ However, the sample sizes were small and the results sometimes controversial. Thus, more evidence is required to create a more tailored therapy.

In this study, we summarized clinical data of oligometastatic lung adenocarcinoma patients who harbored epidermal growth factor receptor (*EGFR*) mutations, and we also investigated the efficacy of TKI combined with LCT in lung adenocarcinoma patients diagnosed with oligometastasis.

Patients and Methods

Patients

The clinical data of lung adenocarcinoma patients who were diagnosed with oligometastasis at Shanghai Chest Hospital (Shanghai, China) between January 2010 to December 2016 were identified and reviewed.

The inclusion criteria were as follows: (1) All lung adenocarcinoma patients included in this study diagnosed histopathologically or cytologically. (2) Patients with stage IV lung adenocarcinoma with oligometastatic (only transferred to one organ, and ≤ 5 lesions, not including the primary tumor were included) disease.^{6,18} The state of oligometastasis was assessed by computed tomography of the chest, magnetic resonance imaging of the brain, bone scan, abdominal ultrasound, or whole-body ¹⁸F-fludeoxyglucose tumor imaging. (3) Patients with *EGFR* mutation. (4) Treatment with *EGFR*-TKIs. (5) The interval between patients treated with TKI therapy and LCT was within 3 months.

The exclusion criteria were as follows: (1) Patients treated with second- or third-generation of TKI. (2) Patients who did not undergo a systemic examination before enrollment onto this study. (3) Incorporation of LCT after progression. (4) Progression-free survival (PFS) ≤ 2 months should be excluded to reduce selection bias. In addition, patients without complete medical records or follow-up information were also excluded. The patient selection steps are shown in Supplemental Figure 1.

A total of 231 patients were ultimately included in this study and were divided into 2 groups: receipt of LCT treatment (combination group) or TKI only (monotherapy group). Non-small-cell lung

cancer staging was performed according to the 8th edition lung cancer tumor, node, metastasis classification and staging system.¹⁹ The study was approved by the institutional review board of Shanghai Chest Hospital (Shanghai, People's Republic of China).

Treatment

First-generation *EGFR*-TKI including gefitinib, erlotinib, and icotinib were provided orally at doses of 250 mg daily, 150 mg daily, and 125 mg 3 times daily, respectively. LCT, which should be incorporated before progression, included operation (local resection of the oligometastasis lesion) and radiotherapy (eg, whole-brain radiotherapy, brain stereotactic radiotherapy, local radiotherapy, gamma knife, cyber knife), and were decided on the basis of patients' and/or investigators' discretion. Clinical follow-up examinations mainly included imaging examination, routine laboratory tests, and physical examination, which were performed every 4 to 8 weeks. PFS was defined as the date from the initiation of *EGFR*-TKI treatment until the date of progression or last follow-up visit (January 18, 2018). Overall survival (OS) was defined from the same date until the date of death or last follow-up visit.

Statistical Analysis

Demographic and clinical data were analyzed, in which continuous abnormally distributed variables were presented by medians, and categorical variables were summarized by counts and percentages. The Kaplan-Meier method was used to perform univariate survival analyses, and data were compared by log-rank test. Positive variables were further analyzed by Cox proportional hazards regression analysis. The first date of treating with *EGFR*-TKIs for the matched pair was defined as the index date. Statistical significance was defined as $P < .05$ with 2 sides. SPSS 24.0 (IBM, Armonk, NY) was used to calculate statistical analyses.

Results

Patient Characteristics

According to the inclusion and exclusion criteria, 231 eligible lung adenocarcinoma patients were enrolled onto this study. Of the 231 *EGFR* mutation-positive oligometastatic lung adenocarcinoma patients, 143 received TKI and LCT, while the other 88 cases received TKI monotherapy. Clinical characteristics were well balanced between the 2 groups except for a statistically higher proportion of patients who underwent brain radiotherapy in the combination group ($P = .000$, Table 1). Treatment details of LCT are shown in Figure 1A. Oligomeric metastasis location is shown in Figure 1B. The proportions and types of progress of the 2 groups are shown in Figure 1C. Moreover, there were 2 subsets of oligometastatic patients included in this study. Ninety-six of them were stage IV lung adenocarcinoma patients with oligometastatic when diagnosed. The other 135 patients had surgical pointers at the time of initial diagnosis and had undergone primary lung resection, but as the disease progressed, these patients developed oligometastasis after surgery and then were included in our study.

Comparison of Efficacy of Treatment Methods

The median follow-up time of the whole study cohort was 24 months (range, 2-75 months). For the 231 *EGFR* mutation-positive oligometastatic lung adenocarcinoma patients, treatment with *EGFR*-TKIs combined with LCT ($n = 143$) led to significantly

Table 1 Demographic Data of 231 Patients and Comparison of Clinical Characteristics Between 2 Groups

Characteristic	LCT + TKI (N = 143)	TKI (N = 88)	P	Total
Age (years), median (range)	59 (38-78)	60 (33-80)	.583	59 (33-80)
Sex				
Male	64 (44.8)	31 (35.2)	.153	95 (41.1)
Female	79 (55.2)	57 (64.8)		136 (58.9)
Smoking Status				
Smoker	45 (31.5)	26 (29.5)	.758	71 (30.7)
Never-smoker	98 (68.5)	62 (70.5)		160 (69.3)
EGFR Mutation Status				
19del	66 (46.2)	38 (43.2)	.888	104 (45.0)
21L858R	62 (43.3)	41 (46.6)		103 (44.6)
Other	15 (10.5)	9 (10.2)		24 (10.4)
Performance Status				
0~1	122 (85.3)	73 (83.0)	.631	195 (84.4)
≥ 2	21 (14.7)	15 (17.0)		36 (15.6)
Previous Therapy^a				
Yes	88 (61.5)	47 (53.4)	.223	135 (58.4)
No	55 (38.5)	41 (46.6)		96 (41.6)
Location of Oligometastasis				
Bone	50 (35.0)	37 (42.0)	.000	87 (37.7)
Brain	63 (44.0)	17 (19.3)		80 (34.6)
Lung	22 (15.4)	29 (33.0)		51 (22.1)
Others	8 (5.6)	5 (5.7)		13 (5.6)
No. of Oligometastases				
1-3	116 (81.1)	73 (83.0)	.725	189 (81.8)
4-5	27 (18.9)	15 (17.0)		42 (18.2)
Nodal Status				
N0-1	61 (42.7)	29 (33.0)	.143	90 (39.0)
N2-3	82 (57.3)	59 (67.0)		141 (61.0)
Initial Response While Receiving EGFR-TKI Therapy^b				
CR	1 (0.6)	0 (0.0)	.735	1 (0.4)
PR	102 (71.3)	59 (67.0)		161 (69.7)
SD	34 (23.8)	24 (27.3)		58 (25.1)
Unevaluable	6 (4.2)	5 (5.7)		11 (4.8)

Data are presented as n (%) unless otherwise indicated.

Abbreviations: CR = complete response; EGFR = epidermal growth factor receptor; LCT = local consolidative therapy; PD = progressive disease; PR = partial response; SD = stable disease; TKI = tyrosine kinase inhibitor.

^aPrevious lung cancer sites of resection before enrollment onto this study.

^bNo patient had PD on initial response while receiving EGFR inhibitor after excluding patients who experienced quick progression (PFS ≤ 2 months).

improved PFS (15 months vs. 10 months, hazard ratio [HR] = 0.610; 95% confidence interval [CI], 0.461, 0.807; $P = .000$; Figure 2A) and OS (34 months vs. 21 months, HR = 0.593; 95% CI, 0.430-0.817; $P = .001$; Figure 2D) compared to treatment with only EGFR-TKI ($n = 88$). OS and PFS benefit was regardless of EGFR mutation type (Figure 2B, 2C, 2E and 2F). In 13 cases of other-location oligometastasis, there was no statistical difference of PFS and OS between the 2 groups (Supplemental Figure 2).

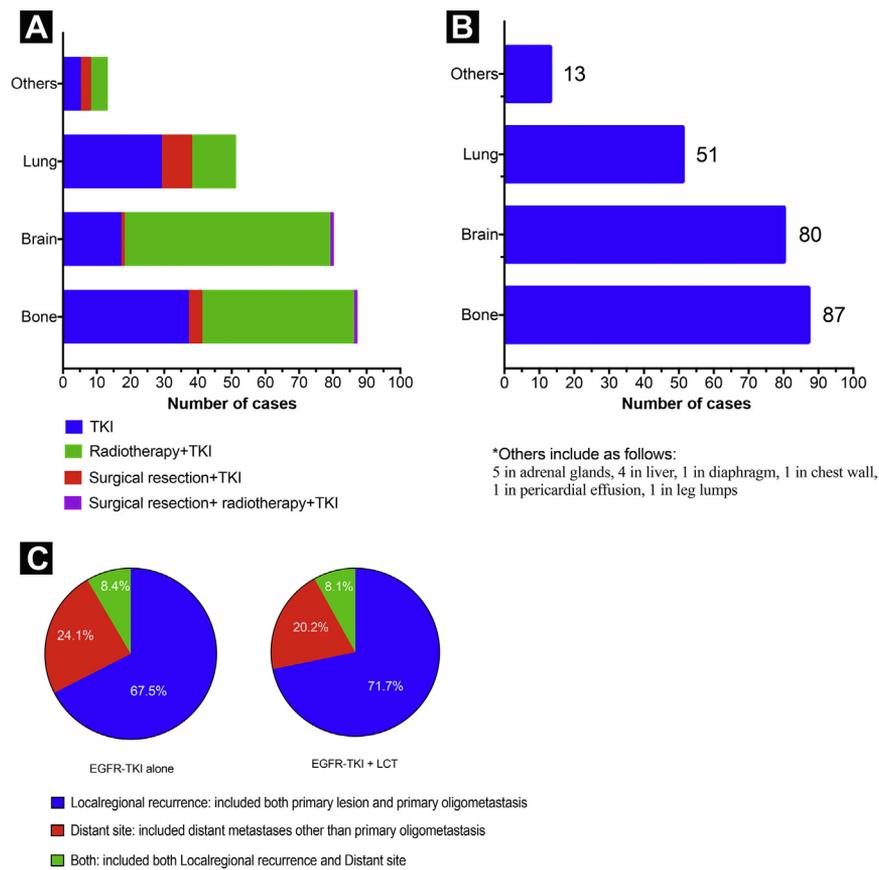
Progression-Free Survival

In univariate analysis of the all patients included, the TKI plus LCT group ($P = .000$) and the previous-therapy group ($P = .022$)

were significantly associated with longer PFS. Multivariate analysis suggested that incorporating LCT to clinical management is an independent prognostic factor (HR = 0.593; 95% CI, 0.441-0.797; $P = .001$) (Table 2). For those 19del EGFR mutation-positive patients included in this study, treatment with TKIs plus LCT had a significantly superior PFS (Figure 2B) than those without LCT. Similar results were also observed in patients with 21L858R (Figure 2C). In addition, the combination group showed significantly improved PFS in the subpopulation of those with brain and lung oligometastases (brain, HR = 0.582; 95% CI, 0.306-1.107; $P = .040$, Figure 3B; lung, HR = 0.504; 95% CI, 0.283-0.899; $P = .010$, Figure 3C). Among lung adenocarcinoma patients with bone

Local Consolidative Therapy

Figure 1 Treatment Details (A), Oligomeric Metastasis Location (B), and Different Patterns of Progression After Treatment With EGFR-TKI With or Without LCT (C)



Abbreviations: *EGFR* = epidermal growth factor receptor; LCT = local consolidative therapy; TKI = tyrosine kinase inhibitor.

oligometastases, the PFS was not significant between the combination group (13.5 months) and monotherapy group (10 months) (HR = 0.743; 95% CI, 0.468-1.178; $P = .175$, Figure 3A).

Overall Survival

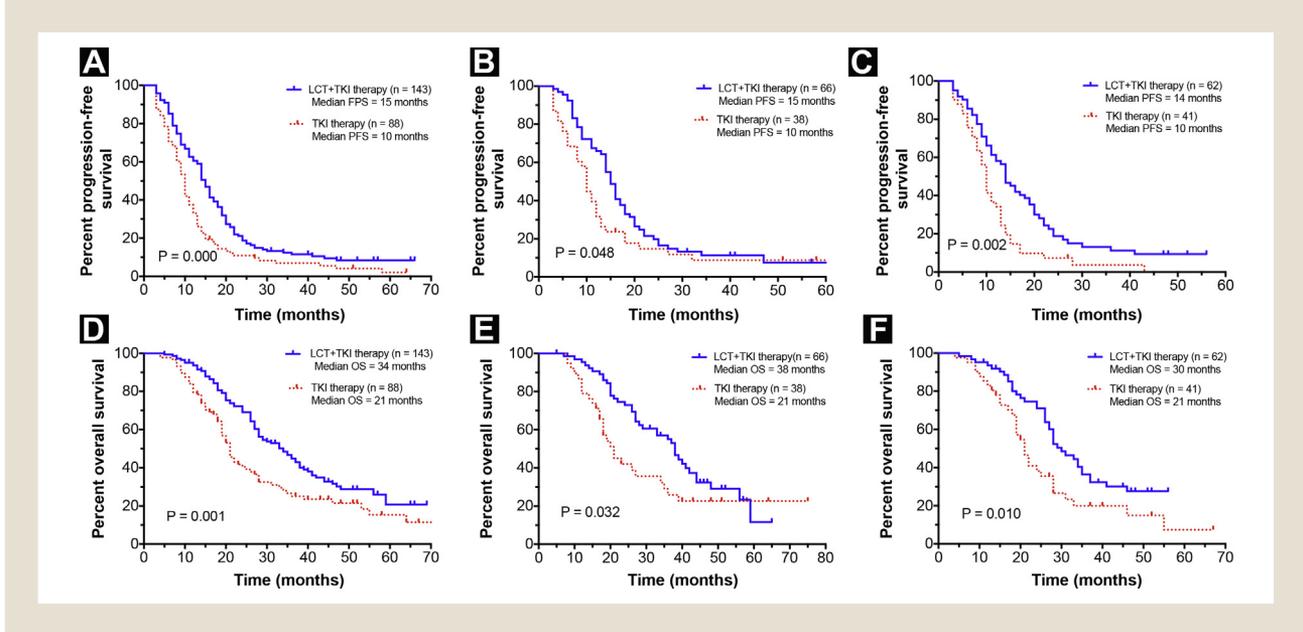
Univariate analysis showed that combination therapy ($P = .001$), age < 60 years ($P = .042$), and being a never-smoker ($P = .018$) contributed to significantly longer OS than the comparison group. In multivariate analyses, OS was significantly related to treatment ($P = .001$) and smoking status ($P = .036$) (Table 2). For those 19del *EGFR* mutation-positive patients, significant differences in OS were observed between the combination and monotherapy treatment groups (Figure 2E). Similar results were also found in patients with 21L858R (Figure 2F). In addition, the combination group showed significantly improved PFS in the population of brain and lung oligometastases (brain, HR = 0.541; 95% CI, 0.254-1.153; $P = .048$, Figure 3E; lung, HR = 0.449; 95% CI, 0.229-0.879; $P = .022$, Figure 3F). Among lung adenocarcinoma patients with bone oligometastases, the OS was 33 months in the combination group, which was longer than the 21 months in the monotherapy group; however, it failed to reach statistical significance (HR = 0.744; 95% CI, 0.436-1.268; $P = .250$) (Figure 3D).

Discussion

The efficacy of LCT in oligometastatic lung adenocarcinoma patients with *EGFR*-mutant disease has remained a controversial topic.²⁰ In this study, we examined the efficacy of LCT in oligometastatic lung adenocarcinoma patients with *EGFR* mutations and found that both PFS and OS were longer in patients who received the combination of LCT and TKI therapies than in patients who received TKIs only, regardless of *EGFR* mutation. The location of the oligometastasis was not balanced between 2 groups because there were more brain oligometastatic patients in the combination group, and it was consistent with the fact that brain oligometastatic patients tended to choose more active treatment in a real-world setting. Patients whose disease quickly progressed were not appropriate candidates for LCT. Thus, there is almost certainly selection bias in those patients who were referred for aggressive local therapy versus those who were not. Therefore, to reduce this selection bias, we excluded patients whose PFS was ≤ 2 months in this study.

The theory of oligometastases was first proposed in 1995 by Hellman and Weichselbaum⁶ as an inference to the spectrum theory of cancer development.¹⁸ Oligometastases often occur after the visible tumor tissue has been resected and subclinical tumor disease eradicated through systematic chemotherapy, and may serve as a

Figure 2 Survival of Oligometastatic Lung Adenocarcinoma Patients. (A) PFS and (D) OS of 2 Groups for all Patients. (B) PFS and (E) OS of 2 Groups for 19 del *EGFR* Mutation Patients. (C) PFS and (F) OS of 2 Groups for 21L858R *EGFR* Mutation Patients



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

nidus for the further dissemination.^{6,21} This concept is based on the hypothesis that the primary tumor has limited metastatic capacity: it presents a stepwise metastatic spread in time and degree, providing a window of treatment for a cure.²⁰

The results of this study are in accordance with some previous studies that reported treatment with LCT to metastatic sites in oligometastatic non-small-cell lung cancer patients whose disease was controlled and who had primary tumors, which could prolong PFS and OS.^{14,17,22,23} In a retrospective study, 309 patients with ≤ 5 metastases who were treated with stereotactic radiotherapy were analyzed to determine which factors influenced survival. The study found some risk factors, including nonadenocarcinoma histology, intracranial metastasis, male sex, and synchronous disease.¹⁴ Furthermore, some retrospective studies demonstrated that primary or postoperative oligometastatic recurrence in lung could obviously benefit from LCT.^{24,25} In comparison, a retrospective study conducted by Yano et al¹⁷ investigated the prognostic impact of local treatment and showed that local therapy could be considered first-line treatment in patients with postoperative oligometastatic recurrence, especially those with a disease-free interval of > 1 year. A pooled analysis conducted by Ashworth et al²⁶ identified that the median OS for patients with 1 to 5 synchronous or metachronous metastases treated with LCT was 26 months, 1-year OS rate was 70.2%, and 5-year OS rate was 29.4%. Patients with multiple metastases in other locations were selected in the study of Ashworth et al, while only *EGFR*-positive patients with 1 to 5 metastases and disease limited to one organ were selected in our study. The patients enrolled onto our study were in better condition, which explained why OS in the combination group was longer than that of the OS of Ashworth et al. Another study found that radiotherapy plus *EGFR*-TKI did not have superior survival benefit

than *EGFR*-TKI alone in *EGFR*-positive non-small-cell lung cancer patients with brain metastases.²⁷ Such different conclusions may be due to differences in patient selection. The number of lesions in patients with brain metastases included in their study was not limited. However, our study only included patients with brain oligometastasis.

The blood-brain barrier is the main interface between circulating blood and the central nervous system, and it selectively limits many substances, including TKI drugs, from entering the brain.²⁸ This may explain the poor prognosis in patients with brain oligometastases in this study. There were more brain oligometastatic patients in LCT combined with TKI, and such a distribution could further demonstrate the efficacy of LCT. Recently, the BRAIN study, a randomized phase 3 trial, found that their icotinib treatment group had better PFS than their whole-brain irradiation plus chemotherapy group. The median PFS in the TKI group in our study was 9.0 months which, is consistent with the BRAIN study. (The PFS in the icotinib treatment group was 10 months in the BRAIN study.)²⁹ Another study found that radiotherapy plus *EGFR*-TKI did not result in a survival benefit superior to that of *EGFR*-TKI alone in *EGFR*-positive non-small-cell lung cancer patients with brain metastases.²⁷ In addition, the prognosis of patients with brain metastasis is also related to other factors—for example, whether the metastatic site is in a functional area, whether it results in symptoms, what the graded prognostic assessment is, and so on.³⁰

Bone metastases are a general secondary localization of disease in patients with lung adenocarcinoma. For bone metastasis, local radiotherapy is one of the most commonly used methods to prevent and delay the onset of skeletal-related events.³¹ Previous studies have pointed out that local radiotherapy for bone metastases can

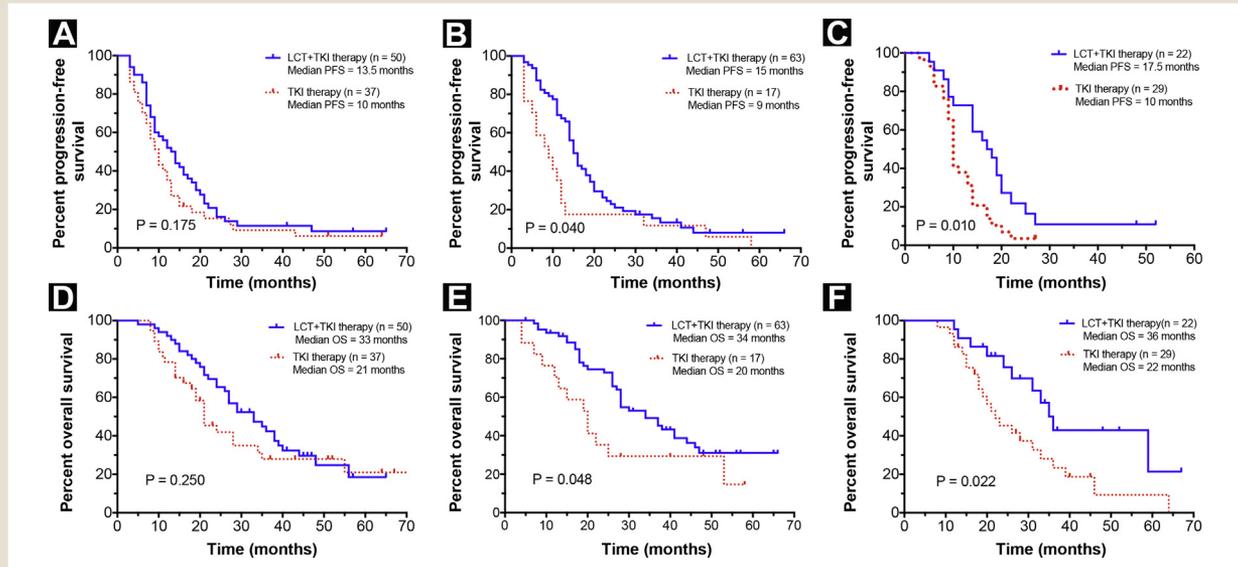
Table 2 Univariate and Multivariate Analyses of Clinical Parameters on PFS and OS Outcomes

Characteristic	Univariate Analysis on PFS		Multivariate Analysis on PFS		Univariate Analysis on OS		Multivariate Analysis on OS	
	HR	P	HR	P	HR (OS)	P	HR (OS)	P
Treatment								
TKI + LCT	0.610 (95% CI, 0.461-0.807)	.000	0.593 (95% CI, 0.441-0.797)	.001	0.593 (95% CI, 0.430-0.817)	.001	0.566 (95% CI, 0.403-0.795)	.001
TKI	1		1		1		1	
Age								
< 60 years	0.840 (95% CI, 0.639-1.103)	.209	—	—	0.719 (95% CI, 0.523-0.989)	.042	0.774 (95% CI, 0.556-1.078)	.130
≥ 60 years	1		—	—	1		1	
Sex								
Male	1.064 (95% CI, 0.807-1.404)	.659	—	—	1.189 (95% CI, 0.863-1.640)	.290	—	—
Female	1		—	—	1		—	—
Smoking Status								
Never-smoker	0.817 (95% CI, 0.610-1.093)	.173	—	—	0.663 (95% CI, 0.475-0.924)	.018	0.695 (95% CI, 0.495-0.976)	.036
Smoker	1		—	—	1		1	
EGFR Mutation Status								
19del	0.767 (95% CI, 0.485-1.215)	.259	—	—	0.821 (95% CI, 0.479-1.407)	.473	—	—
21L858R	0.833 (95% CI, 0.526-1.318)	.435	—	—	0.929 (95% CI, 0.543-1.590)	.789	—	—
Others	1		—	—	1		—	—
Previous Therapy^a								
Yes	0.722 (95% CI, 0.545-0.955)	.022	0.759 (95% CI, 0.567-1.016)	.064	0.758 (95% CI, 0.550-1.045)	.091	0.792 (95% CI, 0.566-1.109)	.174
No	1		1		1		1	
No. of Oligometastases								
1-3	0.884 (95% CI, 0.626-1.248)	.482	0.837 (95% CI, 0.586-1.195)	.328	0.788 (95% CI, 0.528-1.175)	.242	0.740 (95% CI, 0.483-1.135)	.168
4-5	1		1		1		1	
Nodal Status								
N0-1	0.863 (95% CI, 0.651-1.143)	.303	—	—	0.870 (95% CI, 0.628-1.204)	.401	—	—
N2-3	1		—	—	1		—	—
Location of Oligometastases^a								
Bone	1.026 (95% CI, 0.713-1.477)	.890	1.068 (95% CI, 0.730-1.562)	.735	0.978 (95% CI, 0.641-1.492)	.917	1.165 (95% CI, 0.738-1.841)	.512
Brain	1.221 (95% CI, 0.841-1.772)	.293	0.819 (95% CI, 0.448-1.500)	.519	1.177 (95% CI, 0.759-1.825)	.468	1.016 (95% CI, 0.513-2.012)	.964
Lung	1		1		1		1	

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

^aBecause there were only 13 patients with oligometastases in other sites (except bone, brain and lung), sample size was too small and thus is not analyzed here.

Figure 3 Survival of Bone Oligometastatic Patients. (A) PFS and (D) OS of 2 Groups for Bone Oligometastatic Patients. (B) PFS and (E) OS of 2 Groups for Brain Oligometastatic Patients. (C) PFS and (F) OS of 2 Groups With Lung Oligometastatic Patients Included



Abbreviations: LCT = local consolidative therapy; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

alleviate the symptoms of patients and could extend survival for advanced adenocarcinoma patients with *EGFR* mutation.^{32,33} In lung adenocarcinoma patients with bone oligometastases included in this study, the OS was 33 months in the combination group, which was longer than the 21 months in the monotherapy group; the difference was close but not statistically significant. The small sample size might account for the failure of statistical significance.

For lung adenocarcinoma patients with lung oligometastases, surgical resection and local radiotherapy are the most commonly used methods for local metastasis sites. Our study showed that the prognosis of patients with lung oligometastases was significantly improved after LCT. Therefore, it is necessary to include LCT in the routine management of treatment in our clinical work to improve survival for lung oligometastases patients.

There are some limitations and biases that should be acknowledged in this study. First, the number of patients included in our study for final analysis was relatively small, which might affect the statistical analysis. Second, the study was retrospective study, which might suffer from selection bias despite the multivariate analyses we adopted.²⁰ For example, a few patients with oligometastatic non-small-cell lung cancer with poor health status typically would not choose LCT. Third, 21.7% of the patients in this study were classified with lung oligometastases; however, the retrospective nature of data in this study precluded the accurate distinction between oligometastases and second primary lung cancers. Given the rarity of second lung primary lung cancer, we think that this effect is slight. Furthermore, although we tried our best to obtain information regarding adverse events, we missed data regarding adverse events and that therefore could not be analyzed here.

More evidence supporting the efficacy of LCT is needed to permit a strategy of treating oligometastases in routine clinical practice and to gain widespread acceptance of this therapy.²⁰

Conclusion

LCT combined with TKI therapy was feasible and significantly prolonged PFS (from 10 months in the monotherapy group to 15 months in the combination group) and OS time (from 21 months in the monotherapy group to 34 months in the combination group) among oligometastatic lung adenocarcinoma patients. Large prospective studies are required to further confirm the efficacy of LCT in oligometastatic adenocarcinoma patients and to identify the patients who will derive the most benefit from LCT.

Clinical Practice Points

- The efficacy of LCT in oligometastatic lung adenocarcinoma patients treated with *EGFR*-TKI is unknown.
- Our study suggested that LCT combined with TKI therapy could improve PFS and OS.
- Our study also suggested that such survival benefit was not affected by *EGFR* mutation type and metastatic site.
- We provided real-world treatment outcomes of oligometastatic lung adenocarcinoma patients. We recommend considering LCT as an important medical treatment during clinical management.

Acknowledgments

Supported in part by the National Natural Science Foundation of China (grant 81502450) and the Science and Technology Commission of Shanghai Municipality, China (grant 18441904700).

Local Consolidative Therapy

The authors greatly appreciate all the patients who contributed to this study.

Disclosure

The authors have stated that they have no conflict of interest.

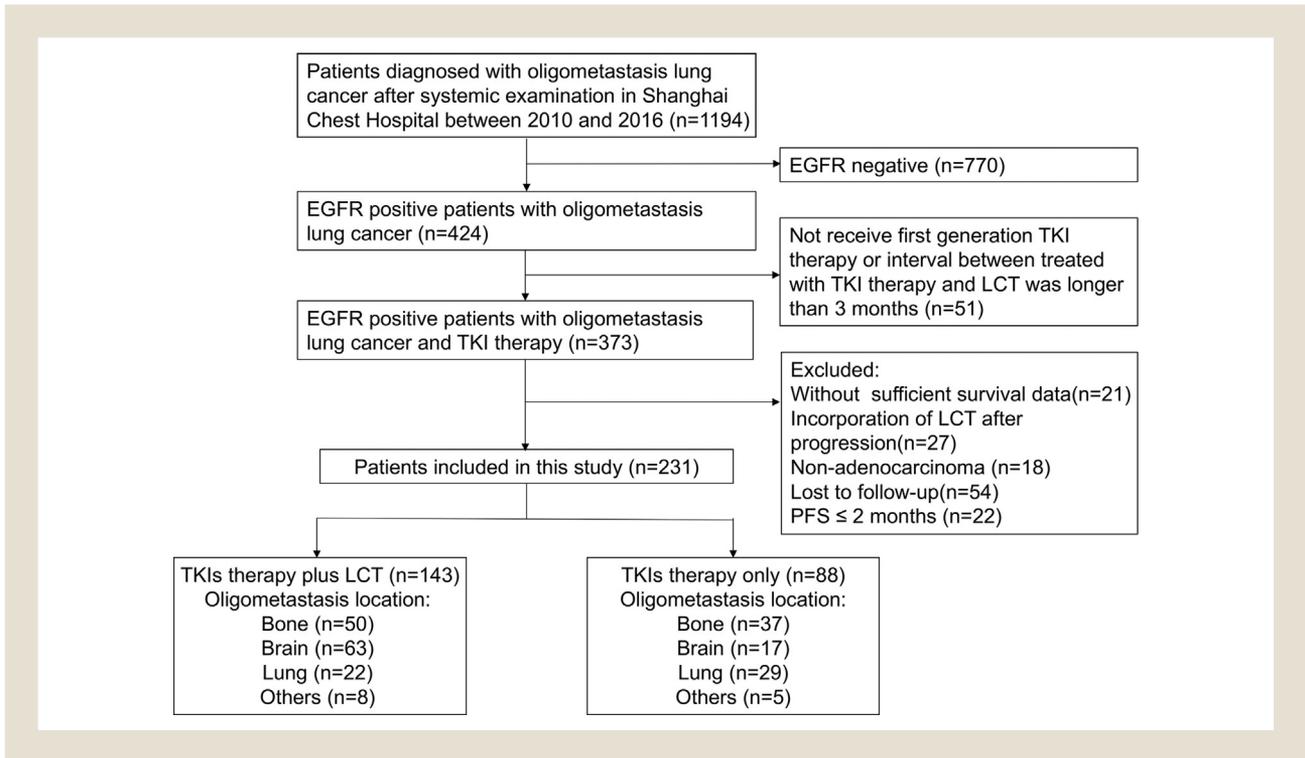
Supplemental Data

Supplemental figures accompanying this article can be found in the online version at <https://doi.org/10.1016/j.clcc.2018.09.010>.

References

1. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; 66:115-32.
2. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65:87-108.
3. Riihimaki M, Hemminki A, Fallah M, et al. Metastatic sites and survival in lung cancer. *Lung Cancer* 2014; 86:78-84.
4. Yano T, Hara N, Ichinose Y, et al. Local recurrence after complete resection for non-small-cell carcinoma of the lung. Significance of local control by radiation treatment. *J Thorac Cardiovasc Surg* 1994; 107:8-12.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; 66:7-30.
6. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995; 13:8-10.
7. Heitmann J, Guckenberger M. Perspectives on oligometastasis: challenges and opportunities. *J Thorac Dis* 2018; 10:113-7.
8. Forde PM, Erttinger DS. Targeted therapy for non-small-cell lung cancer: past, present and future. *Expert Rev Anticancer Ther* 2013; 13:745-58.
9. Herbst RS, Ansari R, Bustin F, et al. Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): a double-blind, placebo-controlled, phase 3 trial. *Lancet* 2011; 377:1846-54.
10. Seto T, Kato T, Nishio M, et al. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. *Lancet Oncol* 2014; 15:1236-44.
11. Wu YL, Lee JS, Thongprasert S, et al. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FAS-TACT-2): a randomised, double-blind trial. *Lancet Oncol* 2013; 14:777-86.
12. Goldberg SB, Oxnard GR, Digumarthy S, et al. Chemotherapy with erlotinib or chemotherapy alone in advanced non-small cell lung cancer with acquired resistance to EGFR tyrosine kinase inhibitors. *Oncologist* 2013; 18:1214-20.
13. Salama JK, Chmura SJ, Mehta N, et al. An initial report of a radiation dose-escalation trial in patients with one to five sites of metastatic disease. *Clin Cancer Res* 2008; 14:5255-9.
14. Inoue T, Katoh N, Aoyama H, et al. Clinical outcomes of stereotactic brain and/or body radiotherapy for patients with oligometastatic lesions. *Jpn J Clin Oncol* 2010; 40:788-94.
15. Pfannschmidt J, Dienemann H. Surgical treatment of oligometastatic non-small cell lung cancer. *Lung Cancer* 2010; 69:251-8.
16. Khan AJ, Mehta PS, Zusag TW, et al. Long term disease-free survival resulting from combined modality management of patients presenting with oligometastatic, non-small cell lung carcinoma (NSCLC). *Radiat Oncol* 2006; 81:163-7.
17. Yano T, Haro A, Yoshida T, et al. Prognostic impact of local treatment against postoperative oligometastases in non-small cell lung cancer. *J Surg Oncol* 2010; 102:852-5.
18. Weichselbaum RR, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol* 2011; 8:378-82.
19. Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016; 11:39-51.
20. Palma DA, Salama JK, Lo SS, et al. The oligometastatic state—separating truth from wishful thinking. *Nat Rev Clin Oncol* 2014; 11:549-57.
21. Patel PR, Yoo DS, Niiibe Y, Urbanic JJ, Salama JK. A call for the aggressive treatment of oligometastatic and oligo-recurrent non-small cell lung cancer. *Pulm Med* 2012; 2012:480961.
22. Gomez DR, Blumenschein GR Jr, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* 2016; 17:1672-82.
23. Wong AC, Watson SP, Pitroda SP, et al. Clinical and molecular markers of long-term survival after oligometastasis-directed stereotactic body radiotherapy (SBRT). *Cancer* 2016; 122:2242-50.
24. De Leyn P, Moons J, Vansteenkiste J, et al. Survival after resection of synchronous bilateral lung cancer. *Eur J Cardiothorac Surg* 2008; 34:1215-22.
25. He J, Li Y, An J, Hu L, Zhang J. Surgical treatment in non-small cell lung cancer with pulmonary oligometastasis. *World J Surg Oncol* 2017; 15:36.
26. Ashworth AB, Senan S, Palma DA, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer* 2014; 15:346-55.
27. Jiang T, Su C, Li X, et al. EGFR TKIs plus WBRT demonstrated no survival benefit other than that of TKIs alone in patients with NSCLC and EGFR mutation and brain metastases. *J Thorac Oncol* 2016; 11:1718-28.
28. Lin KH, Hong ST, Wang HT, Lo YL, Lin AM, Yang JC. Enhancing anticancer effect of gefitinib across the blood-brain barrier model using liposomes modified with one alpha-helical cell-penetrating peptide or glutathione and Tween 80. *Int J Mol Sci* 2016; 17.
29. Yang JJ, Zhou C, Huang Y, et al. Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): a multicentre, phase 3, open-label, parallel, randomised controlled trial. *Lancet Respir Med* 2017; 5:707-16.
30. Baykara M, Kurt G, Buyukberber S, et al. Management of brain metastases from non-small cell lung cancer. *J Cancer Res Ther* 2014; 10:915-21.
31. D'Antonio C, Passaro A, Gori B, et al. Bone and brain metastasis in lung cancer: recent advances in therapeutic strategies. *Ther Adv Med Oncol* 2014; 6:101-14.
32. Collen C, Christian N, Schallier D, et al. Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic nonsmall-cell lung cancer patients. *Ann Oncol* 2014; 25:1954-9.
33. Qu BL, Cai BN, Yu W, et al. Radiotherapy effects on brain/bone metastatic adenocarcinoma lung cancer and the importance of EGFR mutation test. *Neoplasma* 2016; 63:158-62.

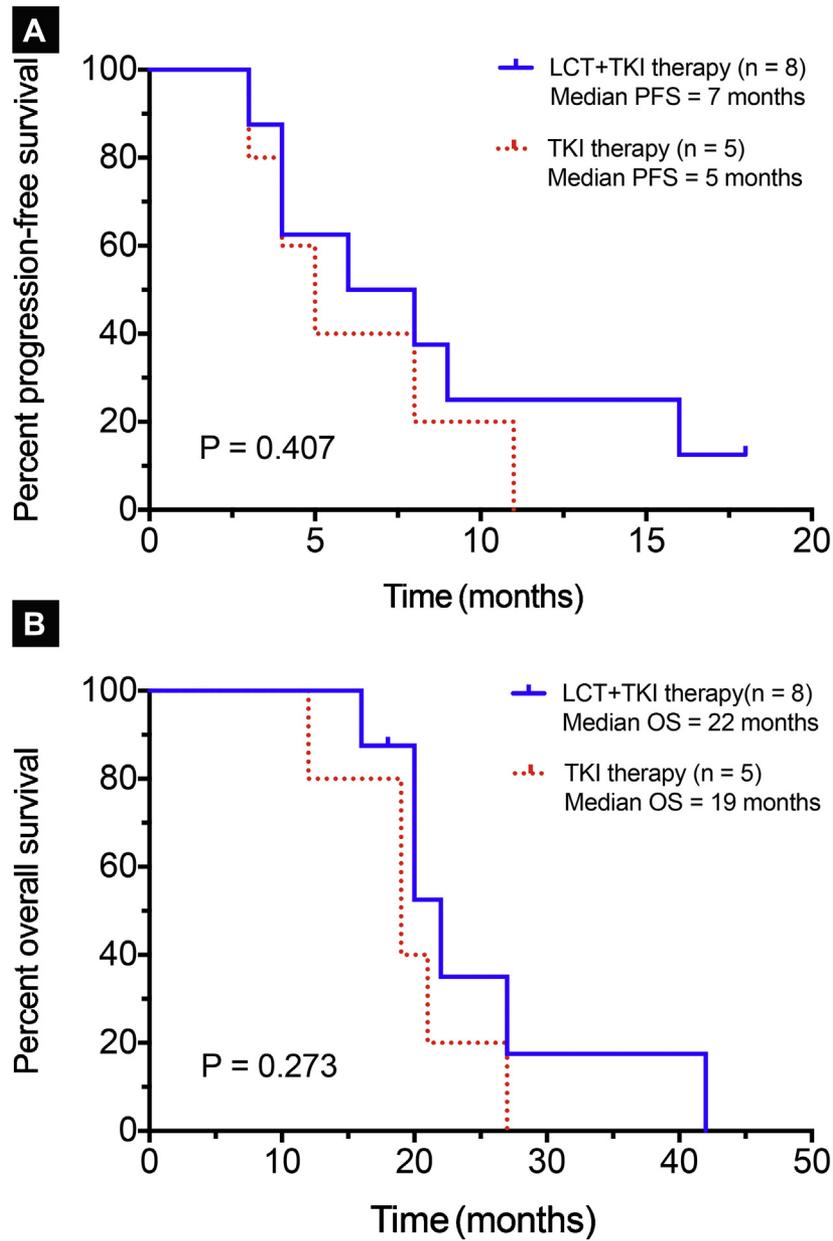
Supplemental Figure 1 Flow Diagram of Patients' Selection Steps for 1194 Individuals



Abbreviations: EGFR = epidermal growth factor receptor; LCT = local consolidative therapy; TKI = tyrosine kinase inhibitor.

Local Consolidative Therapy

Supplemental Figure 2 (A) PFS and (B) OS of 2 Groups of Oligometastases Sites Other than Bone, Brain, and Lung



Abbreviations: LCT = local consolidative therapy; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.