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CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

Local Thermal Ablation with Continuous EGFR Tyrosine Kinase Inhibitors for EGFR-Mutant Non-small Cell Lung Cancers that Developed Extra-Central Nervous System (CNS) Oligoprogressive Disease

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Abstract

Background Most epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) patients treated with tyrosine kinase inhibitors (TKIs) experience oligoprogressive disease. Local ablation for isolated resistant sites continued with the original EGFR-TKI showed good efficacy in these patients. We conducted this multicenter retrospective study to investigate the potential benefit of thermal ablation in NSCLC patients that developed extra-central nervous system (CNS) oligoprogressive disease during TKI treatment.

Methods A total of 71 EGFR-mutant patients treated with EGFR-TKIs were identified. Progression-free survival 1 (PFS1) was calculated from the initiation of TKI treatment to first progression. Patients with metastatic sites ≤ 3 in less than 3 extra-CNS organs suitable for local ablation therapy received either radiofrequency ablation or microwave ablation to these sites and continued on the original TKIs. PFS2 was defined from the first progression to second progression after ablation.

Results The median PFS1 for all patients was 11.8 months. Eighty extra-CNS oligoprogressive lesions in 71 patients were ablated. Thirty-six of 71 patients progressed after thermal ablation and 31 of whom died during the study period. The median PFS2 after thermal ablation was 10.0 months, and the median overall survival was 26.4 months. PFS1 and PFS2 were highly correlated with OS, whereas PFS1 was not correlated with PFS2. The numbers of oligoprogressive lesions were significantly and independently associated with PFS2.

Conclusion Local thermal ablation for the oligoprogressive lesions with continuous EGFR-TKI treatment is associated with additional 10 months of disease control and should be recommended in TKI acquired resistant-NSCLC patients.

Keywords Thermal ablation · Microwave ablation · Radiofrequency ablation · EGFR-TKI acquired resistance · Oligoprogression

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Introduction

Lung cancer remains as the leading cause of cancer-related deaths in men and women worldwide [1]. Approximately 50% of Eastern Asian patients and 11–18% of Caucasian patients with adenocarcinomas harbor activating epidermal growth factor receptor (EGFR) mutations [2]. With the superior efficacy over chemotherapy, EGFR tyrosine

kinase inhibitors (EGFR-TKIs) such as gefitinib, erlotinib and afatinib are approved as the first-line treatment for EGFR-mutant advanced non-small cell lung cancer (NSCLC) [3–6]. Unfortunately, despite initial dramatic responses, most patients ultimately develop acquired resistance after a median of about 10 months [7, 8]. Continued TKI treatment beyond disease progression in this setting has been suggested to delay the need for chemotherapy, while stopping treatment prematurely may result in a risk of disease flare [9, 10]. Clinically, slow or asymptomatic progression at one or few distant sites without involvements of new organ systems, termed as oligoprogressive disease, is frequently observed when acquired resistance initially develops [11]. Local treatment such as surgery and radiotherapy can be considered in oligoprogressive disease, which might lead to survival prolongation [12, 13].

Image-guided percutaneous thermal ablation techniques—including radiofrequency ablation (RFA) and microwave ablation (MWA), have been developed to treat primary and secondary solid tumors, initially applied to liver tumors and then to lung tumors [14–17]. Over the past decades, thermal ablation as a minimally invasive technique has played an important role in the treatment of both primary and secondary pulmonary malignancies. In our recently published pilot study, we reported that MWA with continued EGFR-TKIs treatment was effective and safe in treating patients who developed EGFR-TKIs acquired resistance [18]. With the purpose to describe the outcomes of thermal ablation in EGFR mutated patients who progressed to first-line TKI, we conducted this multicenter retrospective study and evaluate the clinical efficacy of thermal ablation for EGFR-TKIs acquired resistance patients.

Materials and Methods

Patients Selection

The inclusion criteria for the ablation therapy were: histologically diagnosed with NSCLC; tumor which harbors EGFR mutations associated with TKI sensitivity and objective clinical benefit (complete response (CR) or partial response (PR), or durable stable disease (SD) over 6 months) from treatment with EGFR-TKIs (first-line treatment); determination of progressive disease (PD) of extra-CNS oligoprogressive disease (metastatic sites $\leq$ 3 in less than 3 organs) while on continuous treatment with an EGFR-TKI within the last 30 days; Eastern Cooperative Oncology Group (ECOG) Scale of performance status (PS) of 0–2; no intervening systemic therapy between cessation of TKIs and initiation of thermal ablation for oligoprogressive lesions.

The treatment protocol was approved by the ethics committees of each center. Written informed consent was obtained from all patients.

Treatment

All patients were treated with EGFR-TKI including gefitinib, erlotinib, icotinib and afatinib which were administrated by regular doses of 250, 150 mg qd, 125 mg tid and 40 mg qd, respectively. The oligoprogression date was defined based on routine surveillance imaging and/or symptomatic progression that prompted earlier radiographic evaluation with routine imaging every 2–3 months for most patients. When extra-CNS oligoprogressive diseases were identified, patients received thermal ablation for all progressive lesions with continued EGFR-TKI treatment, which would minimally continue until next progression of disease. Detailed ablation procedures were as we previously described [18, 19]. One month after ablation, contrast-enhanced computed tomography (CT) and/or magnetic resonance (MR) imaging was performed and served as a new baseline for subsequent surveillance. Local response was determined as complete ablation or incomplete ablation based on criteria as we previously described [20]. Patients received contrast-enhanced CT or MR scan every 3 months after ablation to assess their response to treatment and to identify adverse events.

Statistical Analysis

Median progression-free survival (PFS1) was calculated from time of initiation of TKI treatment to first progression of disease (as assessed by clinician). PFS2 was defined from the time of first progression to second progression after ablation. Overall survival (OS) was calculated from the time of diagnosis to the date of last follow-up or death from any case. Kaplan–Meier analysis was used as an estimate for patient survival. Patients who did not experience progression or death during the study time were censored at the time of the last available follow-up. The data were evaluated using the Spearman rank correlation coefficient and linear regression analyses to examine potential correlation among PFS1, PFS2 and OS. Cox proportional hazards regression models were used to assess the association between each of the variables and PFS2.

Table 1 Patients and tumor characteristics

Variables	Total
Numbers of patients	71
Numbers of lesions	80
Gender	
Male	33
Female	38
Age	
Median	60
Range	29–91
Smoking history	
Never smoker	60
Former smoker	11
Pathology types	
Adenocarcinoma	68
Squamous cell carcinoma	3
Stage at initial diagnosis	
II	9
IIIA	10
IIIB + IV	52
ECOG PS at PFS1	
0–1	63
2	8
EGFR mutation type	
Exon 19 deletion	39 (54.9%)
Exon 21 L858R	28 (39.4%)
Other	4 (5.6%)
EGFR-TKI	
Erlotinib	25
Gefitinib	36
Icotinib	6
Afatinib	4
Procedures	
MWA	43
RFA	28
Site of metastatic disease at PFS1	
Lung	45
Lymph node	4
Adrenal gland	9
Liver	15
Pleura	7
Tumor size at ablation	
Mean	3.3
Range	1–10.5

Results

Patients Characteristics

From June 2009 to March 2017, 71 patients who received EGFR-TKIs and developed acquired resistance were enrolled in this study. Patients and lesions characteristics are summarized in Table 1. Most patients (68 of 71, 96%) had adenocarcinoma histology, and the median age was 60 years. EGFR mutations were confirmed in all patients, with exon 19 deletion mutation being most common (54.9%), followed by exon 21 L858R mutation (39.4%) and other types of mutation (5.6%). Sixty-five patients and 6 patients showed PR and SD longer than 6 months, respectively, in the treatment of initial EGFR-TKIs treatment. All 71 patients received EGFR-TKIs as a first-line treatment. A total of 80 extra-CNS oligoprogressive lesions were identified and treated with thermal ablation. All patients had extra-CNS oligoprogressive disease (≤ 3 sites) at the time of thermal ablation. Forty-three patients received MWA while 28 patients received RFA as the local therapy for progressive lesions. After local thermal ablation, all patients continuously received the original EGFR-TKIs.

Therapy Response, Survival and Complications

Eighty extra-CNS oligoprogressive lesions in 71 patients were ablated. Of all sites treated, 42 lesions were below 3 cm, 32 lesions between 3 to 5 cm and 5 lesions between 5 to 7 cm. The largest lesion was an oligoprogressive pulmonary disease (10.5 cm). Complete ablation was identified in 75 lesions while incomplete ablation in 5 lesions. The median PFS1 for all patients was 11.8 months (Fig. 1A). Thirty-six of 71 patients progressed after local thermal ablation during the study period, and 31 patients died. The median PFS2 after thermal ablation was 10.0 months (Fig. 1B), with a range from 1 to 82 months. Of the 36 patients who progressed after ablation, 32 progressed with distant metastatic disease, and 4 progressed with locally recurrent disease. The 4 patients who progressed locally received an additional local thermal ablation while the remaining 32 patients received systemic chemotherapy for further treatment. The median overall survival was 26.4 months, with a range from 6 to 86 months (Fig. 1C).

Most thermal ablations were well tolerated. There were no patient deaths related to the procedure or within 30 days after ablation. Pain was the predominant side effect and 27 patients (38.0%) suffered moderate pain after ablation, but no severe post-ablation pain occurred. Post-ablation pneumothorax image findings were observed in 23 patients

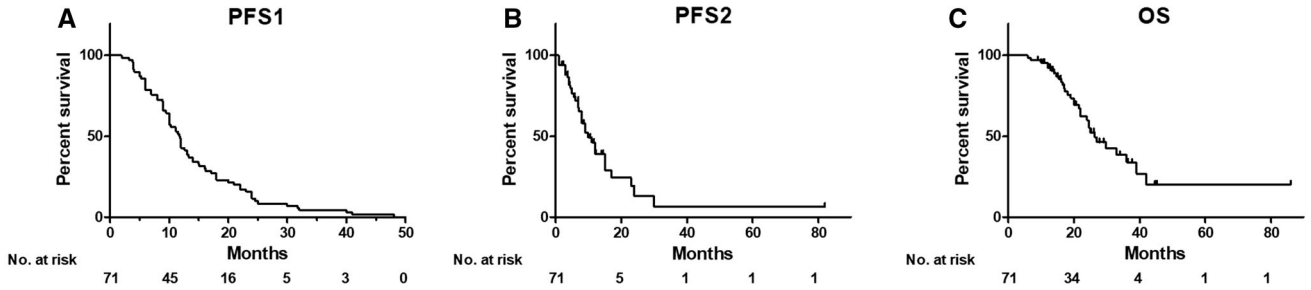

Fig. 1 Kaplan–Meier survival curves of PFS1, PFS2, and OS for all patients. **A** Median PFS1 was 11.8 months. **B** Median PFS2 after thermal ablation was 10.0 months (range 1 to 82 months).**C** Median overall survival was 26.4 months (range 6 to 86 months)

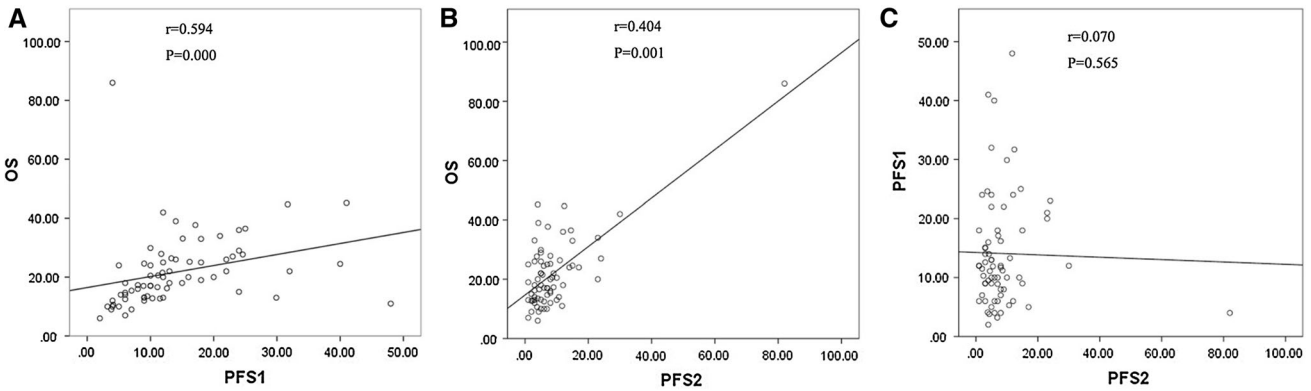

Fig. 2 Relationship of PFS1, PFS2 and OS. **A** Correlation between OS and PFS. **B** Correlation between OS and PFS2. **C** Correlation between PFS1 and PFS2. *r* values represent the Spearman rank correlation coefficient

(32.4%), in which 7 of them received chest tube drainage. Nine patients (12.7%) had pleural effusion (of which 1 case underwent chest tube insertion). Post-ablation syndrome including fever (below 38.5 °C), fatigue, general malaise, nausea, and vomiting, etc., occurred in 20 patients.

The relationships between PFS1 or PFS2 and OS are shown in Fig. 2. According to the Spearman rank correlation coefficient and linear regression analyses, PFS1 and PFS2 were associated with OS (Spearman's $r = 0.594$, $R^2 = 0.085$, $p < 0.001$; Spearman's $r = 0.404$, $R^2 = 0.0513$, $p = 0.001$, respectively), whereas PFS1 was not correlated with PFS2 (Spearman's $r = 0.07$, $R^2 = 5.11\text{E}{-4}$, $p = 0.565$).

Table 2 Results of Cox regression analyses

Factors	PFS2		
	HR	95% CI	*p* value
Univariate Cox regression analysis of patient characteristics			
Gender (male/female)	1.66	0.83–3.33	0.15
Age	1.00	0.98–1.03	0.95
PS	0.35	0.16–0.79	0.01*
Treatment procedure (MWA/RFA)	0.76	0.39–1.50	0.43
Tumor size	1.24	1.00–1.53	0.05
Numbers of ablated lesions	0.20	0.09–0.45	< 0.01*
Multivariate Cox regression analysis			
PS	0.52	0.21–1.30	0.16
Tumor size	1.15	0.90–1.47	0.26
Numbers of ablated lesions	0.26	0.11–0.63	0.003*

*$p < 0.05$

Factors Affecting PFS2

The association between PFS2 and various clinical factors was assessed. As shown in Table 2, univariate analysis revealed that ablated tumor size and the numbers of oligoprogressive lesions were significantly associated with PFS2. We then performed multivariate analysis of these factors and showed that only the numbers of oligoprogressive lesions were significantly and independently associated with PFS2 (Hazard ratios (HR): 0.26, 95% confidence intervals (CI) 0.11–0.63, $p = 0.003$).

Discussion

The management of acquired resistance has become the central challenge in the treatment of patients with EGFR-mutant advanced NSCLC. In the present study, patients

treated with EGFR-TKIs had a median PFS1 of 11.8 months, consistent with previous published studies, especially with the data of East Asian patients [21–23]. For EGFR-positive NSCLC patients who develop less than 3 extra-CNS oligoprogressive lesions, thermal ablation (MWA or RFA) with continuation of the original TKIs may extend median progression-free survival by 10 months. The progression-free survival following ablation is likely also related to continued TKI therapy.

The historical algorithm for management of patients that progress on TKI therapy is to discontinue original TKIs at the time of clinical progression and switch to cytotoxic chemotherapy. Clinically, indolent or asymptomatic progression can often be observed and an immediate switch in therapy is not necessary in this setting. The ASPIRATION trial prospectively analyzed 207 EGFR mutation-positive NSCLC patients receiving erlotinib therapy and showed that continued erlotinib therapy following progression was associated with an additional 3.1 months of PFS, delaying salvage therapy in selected patients [9]. Several retrospective studies also supported the potential benefits from the same TKI therapy in patients with acquired resistance [10, 24]. Furthermore, local ablation for treatment of oligoprogressive lesions has shown benefit in selected patients with acquired TKI resistance [12, 13]. National Comprehensive Cancer Network (NCCN) guidelines recommend local therapies including radiotherapy or surgery to be used for the site of resistant disease and allow for continuation of the original EGFR-TKI in patients with oligoprogressive disease [7, 25]. Radiotherapy in combination with continuous administration of EGFR-TKI was effective for isolated central nervous system (CNS) metastasis [26, 27], while EGFR-TKI acquired resistance NSCLCs with extra-CNS oligoprogressive lesions can be treated with metastasectomy, which might lead to long PFS and OS [13]. This approach is based on the biological heterogeneous mix of TKI-sensitive and TKI-resistant cells among tumors pre-exists at the time of clinical progression. Furthermore, local ablation to these TKI-resistant oligoprogressive sites, in combination with ongoing use of the same TKI to subclones which are still sensitive to the original TKI, might be clinically beneficial in NSCLC [28]. Similarly, local liver RFA was reported as a useful therapeutic option in the management of gastrointestinal stromal tumors (GIST) patients undergoing targeted tyrosine kinase inhibitor therapy (TKI) for liver metastases [29, 30]. However, there is little published data about the application of percutaneous thermal ablation for oligoprogressive disease on TKIs acquired resistant NSCLCs. In one retrospective study which enrolled 18 patients with EGFR-TKI acquired resistance, two patients received lung RFA post-PFS1 and had not progressed again after over 4 months [13]. In our recently reported pilot study, we showed that treating oligoprogressive lesions with MWA was associated with a longer PFS2 (median: 8.8 months vs. 5.8 months, $p < 0.05$) than systemic chemotherapy in EGFR-TKIs acquired resistance NSCLCs [18]. Our results expand on the knowledge of thermal ablation as a local therapy in EGFR-TKIs acquired resistance NSCLCs that developed extra-CNS oligoprogressive disease.

Thermal ablation possesses unique advantages over other therapy options for tumor treatment. The mortality and major complication rate for thermal ablation has been reported as low as 0.4% and 9.8% [31, 32]. Our results support its safety in EGFR-TKI acquired resistance NSCLC patients. The most common complication observed is post-ablation pain, usually self-limiting. Thermal ablation can be offered to patients who are not candidates for surgical resection as a result of cardiorespiratory comorbidity or insufficient vital lung function. While the acute complications of thermal ablation appear to outweigh those of stereotactic body radiation therapy (SBRT), this relation reverses in the chronic setting, ablation being virtually devoid of complications such as radiation pneumonitis (16.5%), chest (wall) pain beyond the acute phase (6.4%), and symptomatic rib fractures (1.8%) [33]. Late complications seem to be rare following ablation treatment. Another major advantage of thermal ablation is the option to repeat the treatment; as often as indicated, an option radiation therapy is lacking [34]. Four of our patients received repeat ablation for suspected local recurrence and showed good efficacy.

Although the patients reported here had long median PFS2 and OS, there was a wide range of outcomes. We showed that OS was highly associated with PFS1 and PFS2, whereas the correlation between PFS1 and PFS2 was not significant. In addition, the number of oligoprogressive sites was independent prognosticators for PFS2. Therefore, outcomes seemed to be best when the site of local therapy was the only known site of disease. In addition, we did not find significant difference of MWA and RFA for disease control, which indicates that either approach is suitable for oligoprogressive EGFR-acquired resistance NSCLC patients.

In conclusion, thermal ablation with isolated oligoprogressive lesions combined with continuous EGFR-TKI may extend the use of TKI therapy in TKI acquired resistance NSCLC patients. Future investigations in a larger number of patients are required to determine the true extent of benefit of the treatment.

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Compliance with Ethical Standards

Conflict of interest The authors have no conflict of interest to declare.

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