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CLINICAL INVESTIGATION

Microwave Ablation in Combination with Chemotherapy for the Treatment of Advanced Non-Small Cell Lung Cancer

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Abstract
Purpose To verify whether microwave ablation (MWA) used as a local control treatment had an improved outcome regarding advanced non-small cell lung cancer (NSCLC) when combined with chemotherapy.
Methods Thirty-nine patients with histologically verified advanced NSCLC and at least one measurable site other than the ablative sites were enrolled. Primary tumors underwent MWA followed by platinum-based doublet chemotherapy. Modified response evaluation criteria in solid tumors (mRECIST) and RECIST were used to evaluate therapeutic response. Complications were assessed using the National Cancer Institute Common Toxicity Criteria (version 3.0).
Results MWA was administered to 39 tumors in 39 patients. The mean and median diameters of the primary tumor were 3.84 cm and 3.30 cm, respectively, with a range of 1.00–9.00 cm. Thirty-three (84.6 %) patients achieved a partial response. No correlation was found between MWA efficacy and clinicopathologic characteristics. For chemotherapy, 11 patients (28.2 %) achieved a partial response, 18 (46.2 %) showed stable disease, and 10 (25.6 %) had progressive disease. The overall objective response rate and disease control rate were 28.2 and 74.4 %, respectively. The median progression-free survival time was 8.7 months (95 % CI 5.5–11.9). The median overall survival time was 21.3 months (95 % CI 17.0–25.4). Complications were observed in 22 (56.4 %) patients, and grade 3 adverse events were observed in 3 (7.9 %) patients.
Conclusions Patients with advanced NSCLC could benefit from MWA in combination with chemotherapy. Complications associated with MWA were common but tolerable.

Keywords Non-small cell lung cancer · Microwave ablation · Chemotherapy

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Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide [1]. Non-small cell lung cancer (NSCLC), comprised of adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, accounts for nearly 80–85 % of this disease. Although diagnosis and treatment has improved dramatically, the overall 5-year survival rate is still 15 % [2]. This dismal prognosis is mainly because nearly two-thirds of patients are diagnosed at an advanced stage, losing the opportunity for radical surgery.

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Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) and anaplastic lymphoma kinase (ALK) inhibitor (crizotinib) have dramatically improved the response and progression-free survival (PFS) times of NSCLC patients harboring EGFR-sensitive mutations [3–7] and the echinoderm microtubule-associated protein like-4 (EML4)-ALK fusion gene [8, 9]. However, for patients without these sensitive gene exchanges chemotherapy, particularly platinum-based doublet chemotherapy, is still the mainstay of treatment.

Microwave ablation (MWA) as a local tumor control treatment has been applied recently. This modality involves the use of electromagnetic waves to produce tissue-heating effects. The microwave energy spectrum has a very high frequency between 300 MHz and 300 GHz, which results in a large zone of active heating [10]. Once the temperature of the ablation zone reaches 65–160 °C, coagulation necrosis will occur. Several studies have demonstrated that MWA could be an alternative approach for early-stage NSCLC patients who are high-risk for surgery [11–13].

However, no reports have explored whether MWA treatment of primary tumors, as an adjuvant to platinum-based doublet chemotherapy, could improve the response and survival of advanced NSCLC patients. We conducted this retrospective study with the objective of assessing the efficacy and safety of MWA in combination with chemotherapy for the treatment of advanced NSCLC.

Table 1 Clinicopathologic characteristics of the 39 NSCLC patients

Characteristics	Number of patients	Percentage
Gender		
Male	22	56.4
Female	17	43.6
Average age (year)	57 (35–88)	
Smoking history		
Smokers	19	48.7
Nonsmokers	20	51.3
Pathology		
ADC	27	69.2
Non-ADC	12	30.8
Stage		
IV	35	89.7
IIIB	4	10.3
ECOG		
0–1	36	92.3
2	3	7.7
Weight loss		
≥ 5 %	8	20.5
< 5 %	31	79.5
Tumor size (cm)		
≥ 3	21	53.8
< 3	18	46.2

Materials and Methods

Inclusion and Exclusion Criteria

Patients with histologically verified stage IIIB or IV NSCLC were included in this study. They all received microwave ablation in combination with platinum-based doublet chemotherapy and had at least one measurable site besides the ablative sites. Other inclusion criteria were as follows: age $\geq$ 18 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; and adequate hepatic, renal, and hematologic function. Patients with the following characteristics were excluded: a life expectancy of 3 months; symptomatic brain metastases; the occurrence of other malignant tumors within the past 5 years; and prior percutaneous thermal ablation or chemotherapy. The study was approved by the Research Ethics Committee of the Institute of Shandong Provincial Hospital affiliated to Shandong University. Written, informed consent was obtained from all patients.

Clinical Data

From February 2010 to January 2013, 69 lung cancer patients who received MWA combined with doublet chemotherapy were screened. Thirty patients were excluded. Among them, 20 patients had stage I-II disease, 5 had received prior anticancer therapies, and 5 had small cell lung cancer. Of the 39 patients enrolled, 22 (56.4 %) were men with a mean age of 57 (range 35–88) years; 19 (48.7 %) were former or current smokers, 27 (69.2 %) had adenocarcinoma, 35 (89.7 %) had stage IV disease, 36 (92.3 %) had an ECOG of 0–1, 31 (79.5 %) had experienced weight loss 5 %, 21 (53.8 %) had a tumor size $\geq$ 3 cm, and 7 had recurrence after radical surgery. A total of 39 lung nodular lesions from 39 patients were detected using CT. The baseline characteristics of the 39 enrolled patients are detailed in Table 1.

Among the 39 patients, primary tumors in the right lung were observed in 24 patients. The mean and median tumor diameters were 3.84 and 3.30 cm respectively, with a range of 1.00–9.00 cm. Twenty-eight patients had lymph node metastases and 35 had distant metastases. The lung, bone, pleural, and pericardium were the common metastatic sites. Table 2 details the characteristics of the disease.

MWA Procedure

A GE-lightspeed 64 V spiral CT machine was used for the scanning of all patients. The MWA instrument used was a

Table 2 Characteristics of the disease

Characteristics	Number of patients	Percentage
Primary tumor sites		
Right upper lobe	15	38.5
Right middle lobe	4	10.2
Right lower lobe	5	12.8
Left upper lobe	9	23.1
Left lower lobe	6	15.4
Primary tumor size		
Median (cm)	3.30	
Mean (cm)	3.84	
Range (cm)	1.00–9.00	
Lymph node metastases		
Yes	28	71.8
No	11	28.2
Distant metastasis location		
Lung	6	15.4
Liver	4	10.3
Bone	9	23.1
Brain	3	7.7
Adrenal	5	12.8
Pleura	11	28.2
Pericardium	6	15.4
Other sites	4	10.3
Distant metastases		
No	4	10.3
One site	17	43.6
Two or three sites	18	46.2

MTC-3C (YZB 1408-2003. No: SFDA (III) 20073251059: Nanjing Qiya Medical Equipment Co., Jiangsu, China). The microwave emission frequency was 2,450 ± 50 MHz, and output level adjustable continuous wave ranged between 0 and 100 W. The microwave antenna had an effective length of 100–180 mm and an outside diameter of 14–20 G, with a long tapered pointed end; a water circulation cooling system was used to reduce the surface temperature of the antenna. MWA with an output of 60–80 W has an ablative zone of nearly 3.5 × 3 cm^2. For tumors 3.5 cm, the ablation was conducted in several positions with an ablative needle. Local anesthesia and preemptive analgesia were used [14]. Preoperative localization was confirmed by observation of CT images and patient movement into different positions. After the achievement of satisfactory anesthesia, the MWA procedure was performed by cutting the skin at the punctured point, puncturing the ablation microwave antenna through the deeper layers of tissue to the nodular lesion; this was performed according to the preoperative-planned channel, with the puncture depth as the preoperative-planned "target-skin distance." MWA could be performed after the cold circulating pipes and circulating pumps had been connected to the MWA antenna and MWA machine with a cable. After this procedure, the microwave ablation antenna was extracted, local disinfection was performed, and a bandage was used to seal the wound. CT scan was performed immediately after MWA had taken place to observe the size, shape relation organs close to the nodular lesion, as well as to determine if there were any signs of pneumothorax, bleeding, or other problems. The proposed ablative margin was 0.5 cm.

Chemotherapy

All patients were treated with MWA, followed by chemotherapy during the subsequent 7 days. The protocol was broadly in accordance with the sequence of radiofrequency ablation combined with chemotherapy used in the treatment of advanced NSCLC. The chemotherapy regimens included gemcitabine (1,250 mg/m^2) on days 1 and 8, or docetaxel (75 mg/m^2) on day 1, or pemetrexed (500 mg/m^2) on day 1. Platinum-based doublet chemotherapies involved the combination of the former three anticancer drugs with cisplatin (75 mg/m^2) on days 1 and 2 or carboplatin with an area under curve of 5 on day 1. All regimens were repeated every 3 weeks. Up to six cycles of chemotherapy were administered.

Follow-up Schedule

At 48 h and 1, 3, 6, 9, and 12 months after MWA patients received a CT scan to assess their response to treatment and to identify adverse events; the CT scan taken after 1 month of MWA was used as the baseline scan for evaluation of the response to treatment. The assessment of response to chemotherapy was conducted every two cycles. For patients who completed the established regimens, follow-up was performed every 3 months.

Clinical Evaluation

Change in the size of the primary tumor after treatment with MWA was used for the assessment of response. Measurable tumor sites other than the primary tumor site were used to assess the response to chemotherapy. The response to MWA was classified as a complete response, a partial response (PR), stable disease (SD), and progressive disease (PD) according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST; Table 3) [15, 16]. The response to chemotherapy was evaluated based on RECIST 1.1 [17]. Assessment of complications associated with MWA was in accordance with the National Cancer Institute Common Toxicity Criteria version 3.0 (CTC3.0).

Table 3 Modified RECIST criteria used to evaluate treatment response

Response	Size of CT mass	Quality of CT mass	PET
Complete (any 2)	Disappearance of the lesion or a presence of a scar 25 % of its original size	Cyst or cavity formation. Low density of the entire lesion	SUV 2.5
Partial (any 1)	Decrease of 30 % in LD of target lesion	Central necrosis or central cavitation with liquid density	Decreased SUV or area of FDG uptake
Stable lesion (any 1)	Decrease of 30 % in LD of target lesion	Mass with solid appearance, no central necrosis or cavity	Unchanged SUV or area of FDG uptake
Progression (any 2)	Increase of 20 % in LD of target lesion	Solid mass and invasion of adjacent structures	Higher SUV

Target lesions represent tumors treated with RFA

SUV standard uptake value for fluorodeoxyglucose F18 in the PET scan; *LD* largest diameter of target lesion; *FDG* fluorodeoxyglucose F18

Statistical Analysis

The correlations between therapeutic response to MWA and clinicopathological characteristics were assessed using the χ^2 test. PFS was calculated from the date of diagnosis or recurrence after surgical resection to the date of progression or death. Overall survival (OS) was calculated from the time of diagnosis to the time of death or the last follow-up. Kaplan–Meier analysis was applied for the assessment of survival. All tests were two-sided, and $p < 0.05$ was considered as being statistically significant. All analyses were performed using SPSS for Windows Version 17.0 (IBM, Chicago, IL).

Results

Response to MWA and Chemotherapy

All patients who were enrolled in the study received MWA at their primary tumor sites. A total of 39 percutaneous MWAs for 39 tumors were administrated in the 39 patients. Four (10.3 %) patients were treated with 60 W MWA, and 35 (89.7 %) with 70 W MWA. The median ablation time was 6 (range 4–11) min. Thirty-three (84.6 %) patients achieved a PR, and six (15.4 %) patients exhibited SD (Fig. 1). No correlation was found between the response to MWA and the following clinicopathologic characteristics: gender ($p = 0.0578$); smoking history ($p = 0.946$); pathology ($p = 0.883$); stage ($p = 0.374$); ECOG PS ($p = 0.177$); and weight loss ($p = 0.796$). All patients were treated with platinum-based doublet chemotherapy post-MWA, with a median of four (range 2–6) cycles. Eleven patients (28.2 %) achieved a PR, 18 (46.2 %) showed SD, and 10 (25.6 %) had PD. The objective response rate (ORR) for the combined treatments was 28.2 % and the disease control rate (DCR) was 74.4 %.

Survival

At the last follow-up on April 14, 2013, which represented a median follow-up time of 11.2 (range 2.5–29.2) months, 23 patients (59.0 %) exhibited tumor progression and 9 patients (23.1 %) had died. Among the patients with disease progression, 7 had progressed at ablative sites, 15 had developed metastases in lobes other than at the ablative sites or distant sites, and 1 had metastases at both the ablative site and a distant site. The median PFS time was 8.6 months (95 % CI 5.5–11.9) in patients treated with MWA in combination with chemotherapy (Fig. 2). The median OS time was 21.3 months (95 % CI 17–25.4; Fig. 3).

Safety of MWA

Complications associated with MWA included pneumothorax, infection, pleural effusion, and hemothorax; these were observed in 12 (30.8 %), 7 (18.0 %), 7 (18.0 %), and 6 (15.3 %) patients, respectively. In total, 22 patients (56.4 %) suffered from adverse events. No adverse events related to mortality were observed. These adverse events were predominantly of grade 1 or 2 (19/22 [86.4 %]) with the exception of three (13.6 %) patients with grade 3 pneumothorax, which required chest tube intervention. Adverse events associated with the use of MWA were observed in 12 patients, 7 at 48 h post-MWA.

Discussion

For advanced NSCLC, chemotherapy especially third-generation platinum-based doublet chemotherapy remains the standard treatment. However, only 30–40 % of patients benefit from treatment. Most patients exhibit tumor progression during the initial therapy, and even patients who achieve disease control will eventually progress. In NSCLC patients, the failure of chemotherapy is often the result of three major factors. The first is distant metastases, the second uncontrolled local sites, and the third is disruption of immune function. The former and the latter

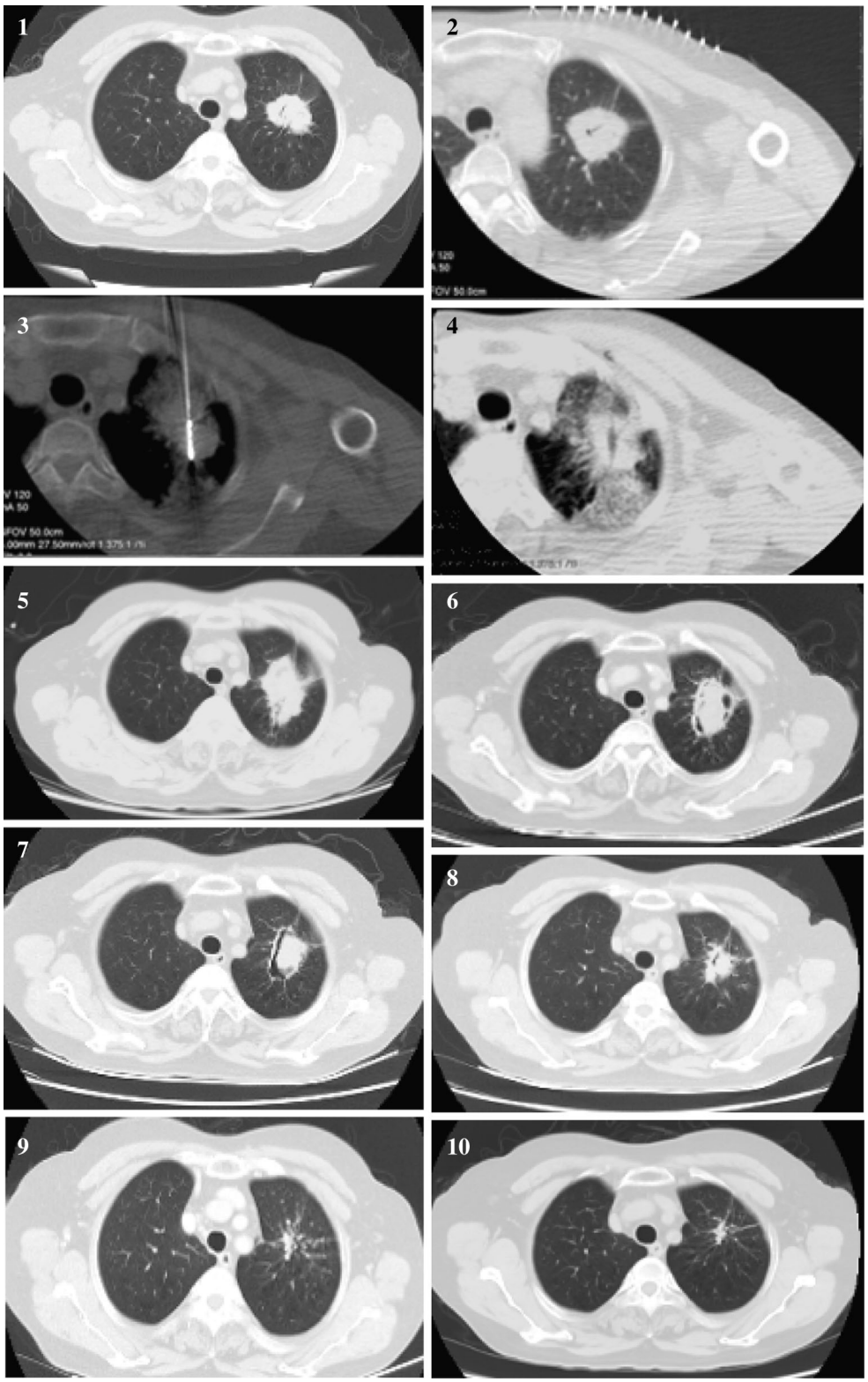

Fig. 1 A 68-year-old female with the diagnosis of left upper lobe adenocarcinoma at stage IIIb (T2N3M0). *1* A primary tumor with a diameter of 3.4 cm. *2* The positioning image before treatment. *3* Puncture of the ablative antenna into the tumor. *4* The image obtained immediately after MWA; ground glass opacity around the tumor and cavity in the core was observed. *5* The image at 1 month after MWA; the exudate has disappeared. *6* The image at 3 months after MWA; an irregular cavity has been formed. *7* The image at 6 months after ablation; the tumor has shrunken. *8* The image at 9 months after ablation; the tumor has already shrunken and fibrosis has developed. *9* The image at 12 months after ablation; a fibrotic scar has developed. *10* The image at 24 months after ablation; the fibrotic scar has shrunken

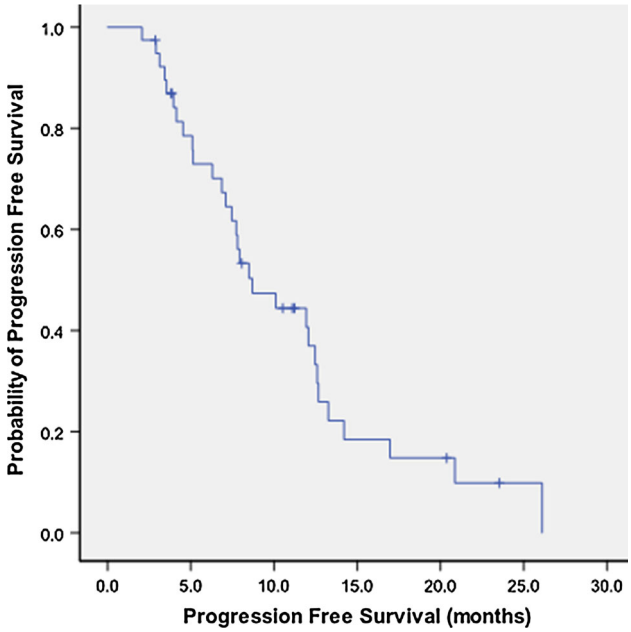

Fig. 2 Kaplan-Meier plot of progression-free survival times

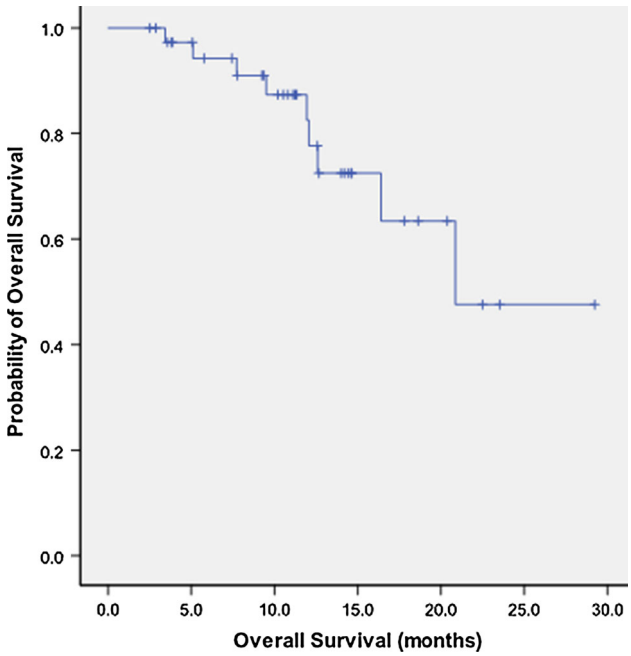

Fig. 3 Kaplan-Meier plot of overall survival times

factors are often unchangeable. Recently, an increasing number of studies have focused on the second factor. Radiotherapy and percutaneous thermal ablation are deemed as the most powerful therapies for achieving local tumor control. Several studies have explored radiotherapy for primary tumor sites in NSCLC patients. Although the optimal radiotherapy dose remains uncertain, there is no doubt that it can improve the local control rate, palliate the symptoms of the disease, and improve survival. This benefit is mainly restricted to patients with good performance status and those with metastatic NSCLC or oligometastatic NSCLC tumors of limited volume [18–21]. However, long treatment times, radiation damage to normal tissues, and the high cost involved limits the application of radiotherapy.

As an alternative to radical surgery, thermal ablation has been used to treat early-stage patients in the past decade [11–13, 22–25]. Multiple studies have verified MWA as a simple, efficient, and safe cancer treatment modality. MWA administered to early-stage NSCLC patients has achieved complete ablation in 95–100 % of patients. Adverse events were observed in 47 % of patients. The median time to recurrence at ablative sites was 16.2 ± 1.3 months. One-year, 2-year, and 3-year survival rates were 65, 55, and 45 %, respectively [11–13].

In the present study, a partial response to MWA was observed in 33 (84.6 %) patients, which was lower than reported in previous studies [11–13]. We consider that two factors resulted in this significant difference. First was the MWA dose and mean treatment time, which were 60–70 W and 6.7 min, respectively; however, in a previous study they were 70–80 W and 7–12 min, respectively. Second was the type of patient enrolled in the study; in our study, they were primary NSCLC patients, but in previous studies some had metastatic lung malignancy.

We explored the efficacy of MWA in combination with chemotherapy in advanced NSCLC patients. The ORR was 28.2 % and the DCR was 74.4 %. The ORR was similar to that reported in previous studies involving first-line doublet platinum-based chemotherapy in advanced NSCLC patients. However, the DCR in our study was superior to that reported in previous studies.

We also attempted to determine whether MWA in combination with first-line platinum-based chemotherapy could improve survival. The median PFS of enrolled patients was 8.7 months. In previous studies the median PFS in the Chinese population treated with platinum-based doublet chemotherapy was reported to range from 4.6 to 6.8 months [7, 26]. The combination of MWA and chemotherapy seemed to improve the PFS dramatically. To date, there have been no reports regarding the efficacy of MWA combined with chemotherapy in the treatment of advanced NSCLC. Several studies concerning the combination of radiofrequency ablation and chemotherapy in advanced NSCLC have shown that this approach could improve OS compared with chemotherapy alone; the median OS time ranged from 16.8 to 42 months [27–29]. In the current study the median OS time was 21.3 months, which was similar to that reported in previous studies. We suppose that the improved PFS was mainly due to the

decrease in tumor burden and the synergistic interaction between MWA and chemotherapy. Lee et al. [30] verified that 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging could be used to assess the prognostic value of tumor burden. An increase in total metabolic tumor volume (MTV) was associated with increased risk of progression and death [31]. For nonsurgical NSCLC patients, MTV, total lesion glycolysis and the standardized uptake value could be used as prognostic factors for OS independent of clinical stage [32]. Moreover, the Ki-67 level in the ablative sites could be utilized as an independent predictive factor regarding survival [33]. When NSCLC was treated using MWA, pathological analysis showed the formation of necrosis in the ablative zones [34, 35], and PET scans revealed no residual FDG activity in the ablated tumor sites [36]. Furthermore, tumor ablation will increase the level of interleukin (IL)-6 and IL-10; IL-6 promotes the progression of tumors. However, subsequent chemotherapy will inhibit tumor progression [37]. The decrease in tumor burden and the synergistic interaction between MWA and chemotherapy lead to the survival benefits.

Complications were observed in 22 (56.4 %) patients, which was a higher number than reported in previous studies involving early-stage lung cancer [11–13]; perhaps the baseline pulmonary disease and the advanced disease stage of patients resulted in this difference. However, serious adverse events were observed with a frequency of only 13.6 %. Consequently, the overall toxicity was tolerable. Considered overall, advanced NSCLC patients could benefit from MWA in combination with chemotherapy.

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Conflict of interest Zhigang Wei, Xin Ye, Xia Yang, Aimin Zheng, Guanghui Huang, Xiang Ni, Wenhong Li, Jiao Wang, and Xiaoying Han have no conflicts of interest or financial disclosures to report.

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