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ORIGINAL PAPER

Microwave ablation plus chemotherapy improved progression-free survival of advanced non-small cell lung cancer compared to chemotherapy alone

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Abstract The aim of the study was to determine survival benefit of the microwave ablation (MWA)/chemotherapy combination compared with chemotherapy alone. Patients with untreated, stage IIIB or IV NSCLC and at least one additional measurable site other than the ablative site were enrolled. They were divided into MWA/chemotherapy group and chemotherapy group. The primary endpoint was progression-free survival (PFS); secondary endpoints included response, time to local progression (TTLP), overall survival (OS), and adverse events (AEs). Forty-six and twenty-eight patients were enrolled in the MWA/chemotherapy group and chemotherapy group, respectively. Complete ablation was observed in 84.8 % patients in the MWA/chemotherapy group. Median TTLP was 27.0 months. Objective response rate and disease control rate in MWA/chemotherapy group were 21.7 and 76.1 %, and in the chemotherapy group were 32.1 % ($p = 0.320$) and 75.0 % ($p = 0.916$), respectively. MWA/chemotherapy combination prolonged PFS [MWA/chemotherapy group 10.9 (95 % CI 5.1–16.7) ms vs. chemotherapy group 4.8 (95 % CI 3.9–5.8) ms, $p = 0.001$] and tended to improve OS [MWA/chemotherapy group 23.9 (95 % CI 15.2–32.6) ms vs. chemotherapy group 17.3 (95 % CI 15.2–19.3) ms, $p = 0.140$]. Multivariate analyses showed that MWA was an independent prognostic factor of PFS and primary tumor size was an independent prognostic factor of OS. AEs of MWA were observed in 67.4 % patients. Chemotherapy-associated AEs were observed in 39.1 and 53.6 % of patients in the MWA/chemotherapy and chemotherapy group, respectively. MWA/chemotherapy combination improved PFS of advanced NSCLC compared to chemotherapy alone, and the combination did not increase the adverse events of chemotherapy.

Keywords Microwave ablation · Chemotherapy · Progression-free survival · Overall survival · Time to local progression

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Introduction

Lung cancer is the leading cause of cancer-related mortality in China [1]. Nearly 85 % of cancer-related deaths are attributed to non-small cell lung cancer. Two-thirds of NSCLC patients are diagnosed at an advanced disease stage, no longer being eligible for curative surgery. The prognosis of these patients is extremely poor, with a 5-year survival rate of approximately 15 %.

Platinum-based, doublet chemotherapy remains the first-line treatment option for patients with advanced NSCLC, especially those without epidermal growth factor receptor-sensitive mutations, echinoderm microtubule-associated

protein-like 4-anaplastic lymphoma kinase fusion genes. Progression-free survival ranges from 3.6 to 4.8 months, and overall survival ranges from 7.9 to 10.3 months [2, 3].

Several studies have attempted the application of local control methods besides chemotherapy to treat NSCLC. It was demonstrated that irradiation, ^{125}I seed implantation, and radiofrequency ablation (RFA) combined with chemotherapy relieved symptoms and improved the objective response rate [4–6].

Microwave ablation, a new thermal ablation method, has been applied for early-stage NSCLC as an alternative to radical surgery with the intent of curing poor surgery candidates due to cardiopulmonary function and/or comorbidities [7–9]. Compared with RFA, MWA has several advantages, particularly larger ablative regions, shorter treatment time, and less heat-sink effect [10, 11].

Our previous study showed that MWA in combination with chemotherapy was effective and safe for advanced NSCLC treatment [12]. However, lack of comparison with chemotherapy alone influenced our conclusion. Thus, we conducted this retrospective study to evaluate whether MWA as a supplementary treatment method in combination with chemotherapy could improve the survival when compared with chemotherapy alone.

Materials and methods

Inclusion and exclusion criteria

Chemotherapy-naive patients with cytologically or histologically verified stage IIIB or IV NSCLC were retrospectively enrolled. Those with Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 and at least 18 years of age were included. Adequate hepatic, liver, and bone marrow reserve functions were also required. Further, all enrolled patients had at least one measurable lesion other than the primary tumor lesion treated with MWA.

Patients with the following characteristics were excluded: (1) previous anticancer treatments including chemotherapy, irradiation, surgery, targeted therapy, thermal ablation, and radioactive seed implantation; (2) second primary malignant tumors within the previous 5 years; (3) symptomatic brain metastases or life expectancy $\leq$3 months; and (4) severe hepatic, liver, and hematologic functions unfit for MWA or chemotherapy.

The study was approved by the Research Ethics Committee of the Institute of Shandong Provincial Hospital affiliated to Shandong University. Written informed consents were obtained from all patients.

Treatment regimen

All enrolled patients were divided into two groups. The chemotherapy group included patients treated with chemotherapy alone. The MWA/chemotherapy group included patients treated with chemotherapy and MWA. In the chemotherapy group, patients were treated with gemcitabine 1,250 mg/m^2 on days 1 and 8, paclitaxel 175 mg/m^2 on day 1, docetaxel 75 mg/m^2 on day 1, or pemetrexed 500 mg/m^2 on day 1, followed by cisplatin 75 mg/m^2 on day 1 and 2 or carboplatin dosed to a target area under the curve of 5 on day 1. In the MWA/chemotherapy group, patients were treated with the former chemotherapy regimens, and MWA was administered before or after chemotherapy. In both groups, chemotherapy was administered every 3 weeks and up to six cycles were conducted.

MWA procedure

MWA procedures were performed under computed tomography guidance. The detailed procedure was described in a previous publication [12]. One antenna was applied for tumors <3.5 cm in diameter, and two for those $\geq$3.5 cm in diameter simultaneously. The antenna has a single slot. MWA with an output of 60–80 W and an ablative zone of nearly 3.5 $\times$ 3 cm was used, with a proposed ablative margin of 0.5 cm.

Follow-up

Chest contrast computed tomography was administered within 15 days before treatment, at 24-h, 1-, 3-, 6-, 12-, 18-, 24-, and 36-month follow-up visits after MWA. Response to chemotherapy was evaluated every two cycles.

Response and survival assessment

Response to MWA was classified as complete or incomplete ablation [13]. The response to chemotherapy was classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to RECIST 1.1 [14].Survival was assessed by TTLP, PFS, and OS. TTLP was calculated from the time of ablation of primary tumors to local progression. PFS was calculated from the start of anticancer treatment, including chemotherapy and MWA, to disease progression, including progression in ablative sites, distant metastases, or death. OS was calculated from the start of anticancer treatment to death. Complications of MWA and chemotherapy were assessed according to the National Cancer Institute Common Toxicity Criteria version 3.0.

Statistical analyses

All analyses were performed using SPSS for Windows Version 17.0 (IBM, Chicago, IL, USA). Chi-square test was used to evaluate the correlation between clinical characteristics and response to MWA or chemotherapy. The correlation between adverse events (AE) and clinical characteristics was also evaluated using Chi-square test. Kaplan–Meier univariate analysis with log-rank test was used to assess the correlation between TTLP, PFS, and OS with clinical characteristics. Those characteristics with a p value <0.1 in univariate analysis and previously verified prognostic factors were used to conduct Cox regression multivariate analysis. The analyses were all two-sided, and p value <0.05 was considered statistically significant.

Results

Patients

From January 2011 to December 2013, 74 patients were enrolled in this study. Among them, 46 patients were enrolled in the MWA/chemotherapy group and 28 in the chemotherapy group. Patients had a mean age of 58.5 years, 37 patients were male, 69 had ECOG PS of 0–1, 31 had smoking history, and 60 had stage IV adenocarcinoma. Clinical characteristics of the patients in both groups were similar as shown in Table 1.

In the MWA/chemotherapy group, 26 primary tumors were located in the right lung, and 32 in the upper and middle lobes. The mean diameter of primary tumors was 3.7 (range 1.0–7.0) cm. In the chemotherapy group, 13 primary tumors were located in the right lung, and 17 in the upper and middle lobes. The mean diameter of primary tumors was 4.3 (range 1.2–11.0) cm.

MWA in primary tumor sites

In the MWA/chemotherapy group, 46 patients underwent 46 MWA sessions corresponding to 72 antennas for 46 primary tumor sites. Among them, 20 patients were treated with one antenna and 26 with two antennas. Thirty-five (76.1 %) patients were treated with MWA initially, followed by chemotherapy. Eleven patients (23.9 %) were treated with chemotherapy first. Complete ablation was observed in 39 (84.8 %) patients, and incomplete ablation was observed in seven (15.2 %) patients. Further analyses showed that the response of MWA did not correlate to baseline characteristics, including gender ($p = 0.682$), age ($p = 1.000$), ECOG PS ($p = 1.000$), smoking history ($p = 1.000$), histology ($p = 0.983$), stage ($p = 1.000$), and tumor sizes ($p = 1.000$) (Table 2).

Response to chemotherapy

All patients enrolled were treated with first-line, platinum-based doublet chemotherapy. In the MWA/chemotherapy group, 19 patients were treated with pemetrexed, 16 with docetaxel, 7 with gemcitabine, and 4 with paclitaxel. Twenty-six (56.5 %) patients received chemotherapy for ≥4 cycles. CR, PR, SD, and PD were observed in 0, 10, 25, and 11 patients, respectively. Objective response rate (ORR) was 21.7 %, and disease control rate (DCR) was 76.1 %. In the chemotherapy group, 9 patients were treated with pemetrexed, 6 with docetaxel, 10 with gemcitabine, and 3 with paclitaxel. Twenty-two (78.6 %) patients received chemotherapy for ≥4 cycles. CR, PR, SD, and PD were observed in 0, 13, 8, and 7 patients, respectively. ORR was 32.1 %, and DCR was 75.0 %. ORR ($p = 0.320$) and DCR ($p = 0.916$) were similar in two groups.

Survival

Until the last follow-up on March 27, 2014, the median follow-up was of 21.0 (range 5.1–39.2) months. In the MWA/chemotherapy group, nine patients presented progression in ablative sites, 30 presented progression in metastatic sites, and 16 patients died. In the chemotherapy group, 28 patients presented progression in primary and metastatic sites, and 19 patients died.

In the MWA/chemotherapy group, the median TTLP was 27.0 (95 % CI 22.2–31.7) ms. Patients in the MWA/chemotherapy group had better PFS [MWA/chemotherapy group, 10.9 (95 % CI 5.1–16.7) ms vs. chemotherapy group, 4.8 (95 % CI 3.9–5.8) ms, $p = 0.001$] (Fig. 1). The median OS in MWA/chemotherapy group was 23.9 (95 % CI 15.2–32.6) ms, and in the chemotherapy group, 17.3 (95 % CI 15.2–19.3) ms, but the difference was not significant ($p = 0.140$) (Fig. 2). Those with primary tumors <3.0 cm in diameter had better PFS [<3.0 cm, median 12.2 (95 % CI 5.2–19.2) ms vs. ≥3.0 cm, median 6.2 (95 % CI 4.8–7.5) ms, $p = 0.085$] (Fig. 3) and OS [<3.0 cm, mean 43.4 (95 % CI 34.1–52.6) ms vs. ≥3.0 cm, median 19.1 ms, 95 % CI 15.0–23.2 ms, $p = 0.000$] (Fig. 4) than those with tumors ≥3.0 cm in diameter. Univariate analyses failed to show the correlation between PFS or OS with other clinical characteristics (Table 3). Factors such as gender, ECOG, pathology, stage, MWA treatment, and tumor size were conducted for multivariate analyses. MWA treatment was the independent prognostic factor of PFS ($p = 0.001$), and tumor size was the independent prognostic factor of OS ($p = 0.000$), but not the MWA treatment ($p = 0.108$) (Table 4).

AEs

MWA-associated AEs were observed in 31 patients (67.4 %). They included pneumothorax, pleural effusion,

Table 1 Baseline clinicopathological characteristics of study patients

	MWA/chemotherapy group		Chemotherapy group		*p*
	Number	Percent	Number	Percent	
Gender					
Male	27	58.7	18	64.3	0.055
Female	19	41.3	10	35.7	
Age					
<60	19	41.3	17	60.7	0.105
≥60	27	58.7	11	39.3	
ECOG					
0–1	43	93.5	26	92.9	1.000
2	3	6.5	2	7.1	
Smoking history					
Smokers	21	45.7	18	64.3	0.401
Non-smokers	25	54.3	10	35.7	
Pathology					
ADC	36	78.3	24	85.7	0.427
Non-ADC	10	21.7	4	14.3	
Stage					
IIIB	8	17.4	6	21.4	0.667
IV	38	82.6	22	78.6	
Primary tumor site					
Right lung	26	56.5	13	46.4	0.399
Left lung	20	43.5	15	53.6	
Primary tumor site					
Upper and middle lobe	32	69.6	17	60.7	0.713
Lower lobe	14	30.4	11	39.3	
Primary tumor size					
Mean	3.7	(1.0–7.0)	4.3	(1.2–11.0)	0.145
<3.0 cm	17	37.0	5	17.9	
≥3.0 cm	29	63.0	23	82.1	
Metastases					
Lymph node	35		22		
Intrapulmonary	14		5		
Distant	38		22		
Metastases					
1	11	23.9	5	17.9	0.356
≥2	35	76.1	23	82.1	

ADC adenocarcinoma, *non-ADC* non-adenocarcinoma, *ECOG* Eastern Cooperative Oncology Group, *MWA* microwave ablation

infection, and hemothorax, which were observed in 18, 15, 9, and 7 patients, respectively. Most AEs were grades 1 and 2; only three patients (6.5 %) presented with grade 3 AEs, consist of pneumothorax that required chest tube drainage.

Chemotherapy-associated AEs were observed in 18 (39.1 %) and 15 (53.6 %) patients in the MWA/chemotherapy group and chemotherapy group, respectively. Bone marrow inhibition and gastrointestinal reactions were the most common AEs, which were seen in 11 and 5 patients in the MWA/chemotherapy, but 9 and 8 patients in the chemotherapy groups. Grade 3 AEs were more common in the chemotherapy group (4/28, 14.3 %) than in the MWA/chemotherapy group (2/46, 4.3 %).

Discussion

This study was conducted to evaluate whether MWA, in combination with chemotherapy, could improve the survival of advanced NSCLC patients compared with chemotherapy alone. Complete ablation was observed in 84.8 % of patients. The median TTLP was 27.0 months. MWA combined with chemotherapy prolonged PFS and

Table 2 Correlation between response to MWA and clinical characteristics

	Complete ablation	Incomplete ablation	*p*
Gender			0.682
Male	22	5	
Female	17	2	
Age			1.000
<60	23	4	
≥60	16	3	
ECOG			1.000
0–1	36	7	
2	3	0	
Smoking history			1.000
Smokers	18	3	
Non-smokers	21	4	
Pathology			0.983
ADC	30	6	
Non-ADC	9	1	
Stage			1.000
IIIB	7	1	
IV	32	6	
Diameter of primary tumors			1.000
<3.0 cm	15	2	
≥3.0 cm	24	5	

ADC adenocarcinoma, *ECOG* Eastern Cooperative Oncology Group, *MWA* microwave ablation

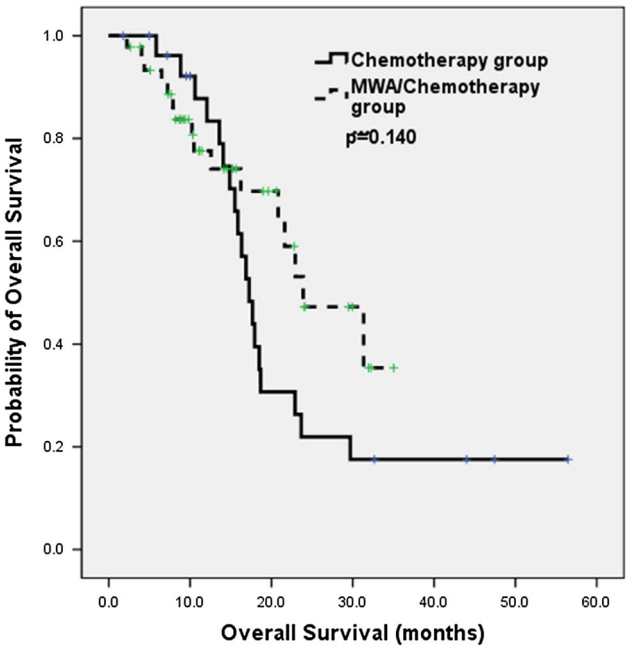

Fig. 2 Kaplan–Meier of OS in MWA/chemotherapy group and chemotherapy group. The median OS was 23.9 ms (95 % CI 15.2–32.6 ms) in MWA/chemotherapy group ($n = 46$) and 17.2 ms (95 % CI 15.2–19.3 ms) in chemotherapy group ($n = 28$). *CI* confidence interval, *OS* overall survival

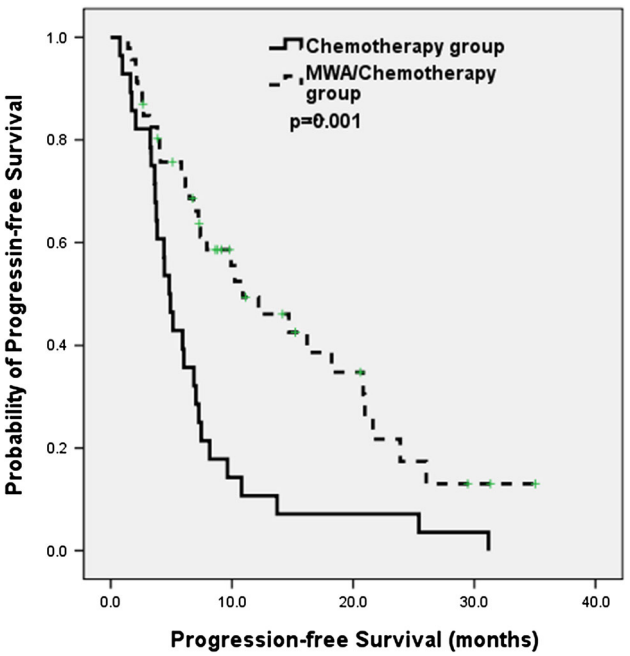

Fig. 1 Kaplan–Meier of PFS in MWA/chemotherapy group and chemotherapy group. The median PFS was 10.9 ms (95 % CI 5.1–16.7 ms) in MWA/chemotherapy group ($n = 46$) and 4.8 ms (95 % CI 3.9–5.8 ms) in chemotherapy group ($n = 28$). *CI* confidence interval, *PFS* progression-free survival

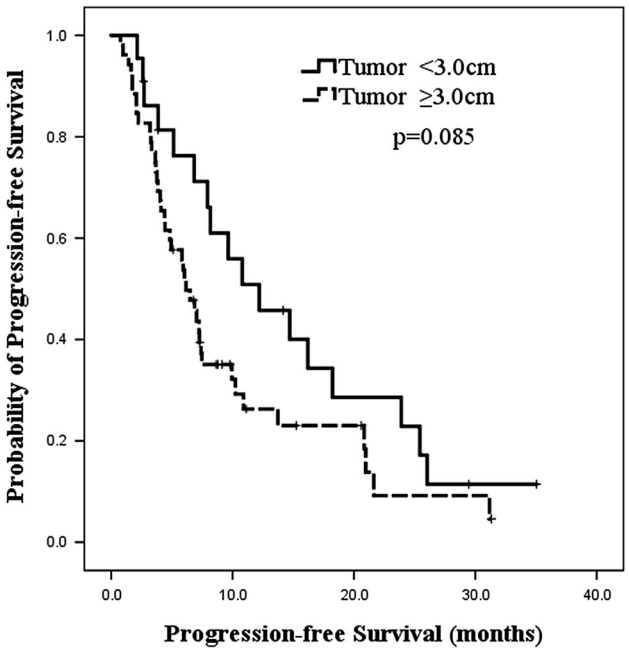

Fig. 3 Kaplan–Meier of PFS between tumor size <3.0 and ≥3.0 cm. The median PFS was 12.2 ms (95 % CI 5.2–19.2 ms) in tumor size <3.0 cm ($n = 22$) and 6.2 ms (95 % CI 4.8–7.5 ms) in tumor size ≥3.0 cm ($n = 52$). *CI* confidence interval, *PFS* progression-free survival

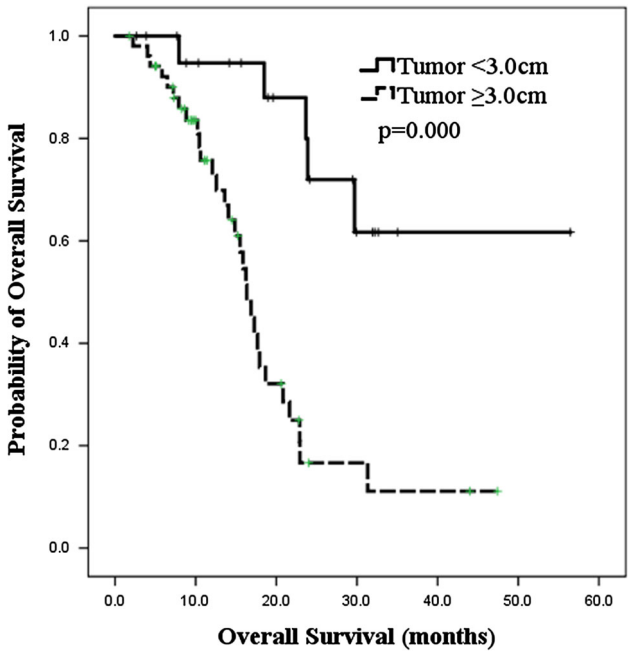

Fig. 4 Kaplan–Meier of OS between tumor size <3.0 and ≥3.0 cm. The mean OS was 43.4 ms (95 % CI 34.1–52.6 ms) in tumor size <3.0 cm ($n = 22$) and 19.1 ms (95 % CI 15.0–23.2 ms) in tumor size ≥3.0 cm ($n = 52$). *CI* confidence interval, *OS* overall survival

tended to improve mean survival time. AEs of MWA were common but tolerable. AEs in the MWA/chemotherapy group were lower than in the chemotherapy group, but ORR and DCR were similar in both groups (Fig. 3).

MWA is a new thermal ablation method in which a microwave of 915 or 2,450 MHz is applied to induce coagulation necrosis [7]. For medically inoperative patients with early-stage NSCLC, MWA is an alternative treatment method, with high efficacy and less AEs [7–9].

In our study, complete ablation was observed in 84.8 % of patients, lower than results obtained in previous studies [7–9], in which patients had early-stage NSCLC with a median maximal tumor diameter ranging from 2.4–2.95 cm [7, 8]. In our study, all patients treated with MWA had advanced NSCLC and the median maximal tumor diameter was 3.5 cm. Nevertheless, patients treated with MWA had better local control rates, with a median TTLP of 27.0 months (Fig. 4).

To the best of our knowledge, no other studies have explored the MWA combination with chemotherapy in patients with advanced NSCLC to date. Although previous studies have explored the efficacy of RFA in advanced-stage patients, one study from Korea showed that a median

Table 3 Correlation between PFS and OS and clinical characteristics

	PFS (ms)		*p*	OS (ms)		*p*
	Median	95 % CI		Median	95 % CI	
Gender						
Male	7.4	3.6–11.2	0.882	21.6	15.1–28.2	0.848
Female	6.9	4.2–9.6		18.5	15.9–21.1	
Age						
<60	7.3	5.2–9.3	0.476	17.9	15.9–20.0	0.288
≥60	7.0	3.1–11.0		29.7	18.9–40.5	
ECOG						
0–1	7.3	5.7–8.8	0.803	20.8	15.2–26.4	0.423
2	7.2	0.0–14.9		16.2	2.8–29.7	
Smoking history						
Smokers	6.9	5.5–8.2	0.739	21.6	15.1–28.2	0.735
Non-smokers	7.5	4.9–10.0		18.5	16.3–20.7	
Pathology						
ADC	7.0	6.0–8.1	0.588	18.7	13.3–24.0	0.927
Non-ADC	8.2	0.0–18.1		23.9	14.9–32.9	
Stage						
IIIB	9.6	5.2–14.1	0.815	18.7	10.5–26.9	0.793
IV	7.2	5.7–8.8		21.6	15.0–28.3	
Treatment						
MWA/CT group	10.9	5.1–16.7	0.001	23.9	15.2–32.6	0.140
CT group	4.8	3.9–5.8		17.3	15.2–19.3	
Primary tumor size						
<3.0 cm	12.2	5.2–19.2	0.085	43.4[a]	34.1–52.6	0.000
≥3.0 cm	6.2	4.8–7.5		19.1[a]	15.0–23.2	

ADC adenocarcinoma, *ECOG* Eastern Cooperative Oncology Group, *MWA* microwave ablation, *OS* overall survival, *PFS* progression-free survival

[a] The data presented are mean values

Table 4 Multivariate analyses of PFS and OS using Cox regression

	PFS		*p*	OS		*p*
	OR	95 % CI		OR	95 % CI	
Gender	0.873	0.492–1.548	0.643	0.785	0.371–1.662	0.527
ECOG	0.872	0.289–2.632	0.808	1.020	0.267–3.900	0.977
Pathology	0.993	0.508–1.944	0.985	0.930	0.393–2.201	0.869
Stage	1.592	0.778–3.257	0.203	0.957	0.420–2.183	0.918
Treatment	0.373	0.207–0.672	0.001	0.801	0.363–1.767	0.583
Primary tumor size	1.644	0.879–3.075	0.120	5.795	2.055–16.338	0.001

CI confidence interval, *ECOG* Eastern Cooperative Oncology Group, *OR* odds ratio, *OS* overall survival, *PFS* progression-free survival

OS of 42.0 months was achieved after combination treatment [15]. Two studies from China applied RFA in combination with gemcitabine/cisplatin and paclitaxel/carboplatin, and the median OS ranged from 16.8–17.4 months [16, 17]. Another study from China administered RFA as a supplemental treatment for NSCLC patients without progression after chemotherapy, and the PFS and OS were 16 weeks and 14 months, respectively [6]. These studies validated the premise that RFA combined with chemotherapy could be an effective treatment method for advanced NSCLC.

We found that patients in the MWA/chemotherapy group had better ORR and similar DCR compared with the chemotherapy group. The difference may be explained mainly by the different chemotherapy cycles. In the MWA/chemotherapy group, 56.5 % of patients received ≥4 cycles of chemotherapy, but 78.6 % of patients in the chemotherapy group received ≥4 chemotherapy cycles.

In our study, patients treated with MWA and CT had better PFS and OS. PFS and OS of the MWA/chemotherapy group were 10.9 and 23.9 months, respectively. The PFS in our study was in agreement with the PFS found in a previous study [6]. Notably, the OS achieved in our study was better than in previous studies [15–17].The difference of PFS between two groups was of great statistical significance ($p = 0.001$), although the difference of OS was not significant ($p = 0.140$). MWA in combination with chemotherapy improved the survival especially in terms of PFS of patients with advanced NSCLC. Perhaps several mechanisms could clarify the benefit. First was the tumor burden reduction. MWA induces coagulation necrosis, and thus, the standardized uptake value decreases to normal levels in the ablative zones when evaluated by PET/CT [18–20]. Second was the improvement of immune function. One study showed a transient peripheral increase in T helper cells (CD3+ and CD4+) and B cells after MWA treatment [21]. Another study detected the increased infiltration of lymphocytes (predominantly CD3+ T cells, CD56+ NK cells, and macrophages) after MWA [22]. Third was the strong synergistic effect between thermal ablation and chemotherapy. Preclinical studies had showed that RFA, in combination with doxorubicin and liposomal doxorubicin, could increase high-temperature-based coagulation and tumor destruction [23–25]. The effect has been attributed to cellular stress through the production of oxidative damage to DNA, nitrative damage to proteins, and lipid injury, as well as activation and acceleration of apoptosis [26]. Further, the induced hyperthermia of thermal ablation was observed to increase the release and intracellular attachment of doxorubicin in human tumor xenograft models [27].

With respect to the sequence of chemotherapy and thermal ablation, there are no conclusions. Previous studies applied RFA followed by chemotherapy and others applied chemotherapy followed by RFA [6, 16, 17], although the former was more common. A preclinical study recommended administration of RFA first [27]. In our study, most patients (76.1 %) underwent MWA first. Eleven patients underwent chemotherapy followed by MWA mainly due to the existence of pleural effusion or refusal of MWA at the beginning of treatment.

In terms of safety, MWA AEs were observed in 67.4 % of patients, pneumothorax being the most common AE, which is concordant with earlier studies [7–9]. However, only 6.5 % of AEs were grade 3 and required intervention. In both MWA/chemotherapy and chemotherapy groups, bone marrow inhibition and gastrointestinal reactions were the most common AEs (39.1 and 53.6 % of patients, respectively).

In conclusion, MWA, as a supplementary treatment method, was able to improve the PFS of advanced NSCLC patients when combined with chemotherapy. MWA in combination with chemotherapy did not increase the AEs of chemotherapy.

Conflict of interest The authors declare no conflict of interest.

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