

Percutaneous ablation for adrenal metastasis from non-small-cell lung cancer: comparison between cryoablation and microwave ablation

Wei Zhang¹, Wei Liu², Zheng-Long Wu³, Zhi-Yong Zhao⁴, Wei-Ming Ma⁵

¹Department of Liver Disease, Daxing Hospital, Xi'an, China

²Department of Oncology, Xuzhou Central Hospital, Xuzhou, China

³Department of Radiology, Xuzhou Central Hospital, Xuzhou, China

⁴Department of Ultrasound, Shenzhen Hospital, Beijing University of Chinese Medicine, Shenzhen, China

⁵Department of Urological Surgery, Xuzhou Central Hospital, Xuzhou, China

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Abstract

Introduction: While cryoablation (CA) and microwave ablation (MWA) have both been implemented as approaches to the treatment of adrenal metastasis (AM), the outcomes associated with these two therapeutic strategies remain unclear.

Aim: To compare the safety and efficacy of CA and MWA as treatments for AM in patients with non-small-cell lung cancer (NSCLC).

Material and methods: Consecutive patients with AM secondary to NSCLC from January 2015 to December 2020 underwent CA or MWA. Treatment-related outcomes and complications were retrospectively compared between these groups.

Results: In total, 68 NSCLC patients with isolated AM were enrolled in this study, of whom 35 and 33 underwent treatment with CA and MWA, respectively. Primary complete ablation rates in the CA and MWA groups were 91.4% (32/35) and 93.9% (31/33) respectively ($p = 1.000$), while a 100% secondary complete ablation rate was observed for both groups. Hypertensive crisis incidence affected 11.4% (4/35) and 9.1% (3/33) of patients in the CA and MWA groups ($p = 1.000$), respectively, while 8 (22.9%) and 8 (24.2%) patients in these corresponding groups experienced local progression after ablation that was detected during the follow-up period ($p = 0.893$). Patients in the CA and MWA groups exhibited a median progression-free survival of 18 and 22 months, respectively ($p = 0.411$), while the corresponding median overall survival of patients in these groups was 25 and 29 months ($p = 0.786$).

Conclusions: CT-guided CA and MWA appear to exhibit similar safety and efficacy profiles when employed to treat isolated AM in NSCLC patients.

Key words: cryoablation, microwave ablation, adrenal, metastasis.

Introduction

The adrenal glands are a major site of metastasis in patients with tumors of the lungs, liver, colon, kidneys, and other organs [1–3]. Non-small-cell lung

cancer (NSCLC) is a highly prevalent primary tumor type often characterized by adrenal metastasis (AM), with NSCLC as the primary tumor type in 13–58% of AM patients [1, 2].

Address for correspondence

Wei-Ming Ma, Department of Urological Surgery, Xuzhou Central Hospital, Xuzhou, China, e-mail: xzmaweiming@163.com

AM patients often face poor outcomes, but no clinical trials to date have sought to clarify the benefits of the local treatment of these metastatic lesions [4]. Several reports, however, have indicated that adrenalectomy can improve AM patient overall survival (OS), with a post-surgery median OS of 23–30 months [5, 6]. Together with the design of mini-invasive therapeutic techniques, imaging-guided ablation strategies have successfully been utilized to treat AM [2–4]. Liu *et al.* [1] additionally determined that imaging-guided ablation and adrenalectomy can achieve comparable OS for AM lesions under 5 cm in size.

Currently, radiofrequency ablation (RFA), cryoablation (CA), and microwave ablation (MWA) have all been established as effective and safe treatment strategies for AM. However, the ablation mechanisms of these methods are different. Whereas MWA and RFA rely on thermal ablation, CA is instead based on the freezing of target lesions. The main advantage of microwave is shorter procedural time and the main advantage of cryoablation is that it is less painful than heat-based ablation [7]. At present, the relative advantages of CA and MWA as treatments for AM remain to be established.

Aim

This study sought to compare the safety and efficacy of CA and MWA as treatments for isolated AM in patients with NSCLC.

Material and methods

This was a retrospective analysis of patients from two centers that received approval from the Ethics Committee of Daxing Hospital and Xuzhou Central Hospital, which waived the need for written informed consent.

Patient inclusion

Between January 2015 and December 2020, consecutive NSCLC patients with AM who underwent CA or MWA treatment were enrolled in this study. To be eligible for inclusion, patients needed to have: (1) a definitive diagnosis of AM secondary to NSCLC; (2) undergone surgical resection for primary NSCLC tumors; (3) AM lesions < 5 cm in size; and (4) refused to undergo adrenalectomy. Patients were excluded in the following cases: (1) extra-adrenal

tumors; (2) conditions which were not suitable for ablation; (3) an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 3 ; (4) refusal of ablation; or (5) incomplete clinical data.

The conditions not suitable for ablation were: (1) AM with adjacent vascular, organ, or tissue invasion; or (2) patients with significant dysfunction of blood coagulation, active infection, and/or active bleeding. Both centers performed both of the MWA and CA treatments.

The collected data included patients' age, gender, tumor history, diameter of AM, side of AM, complete response rate, treatment-related complications, and follow-up outcomes.

Diagnosis criteria

Isolated AM secondary to NSCLC was diagnosed based on a review of each patient's history, abdominal computed tomography (CT) results, and biopsy findings. The tumor size and side were determined and observed on the CT images.

CT-guided CA

CA was performed under local anesthesia with guidance from a 16-row CT instrument (Philips, OH, USA) using an argon-helium CA device (CryoHit, Galil Medical, Israel). Patients were placed in the prone position, and cryoprobe numbers and distributions were selected in accordance with target tumor position, shape, and size. In cases where the target lesions abutted critical structures, small volumes of ethanol were injected using an 18G needle to displace these structures prior to CA. Electrocardiogram monitoring was maintained throughout the CA procedure.

After cryoprobe placement, tumors underwent two freeze/thaw cycles (freeze for 10 min, thaw for 3 min). Rapid argon gas expansion in sealed cryotubes was used to achieve freezing, achieving a minimum tip temperature of -140°C in seconds. Argon was then displaced by helium to enable thawing. After CA was complete, abdominal CT scanning was repeated to evaluate the patient for evidence of immediate necrosis.

CT-guided MWA

MWA was performed under local anesthesia with a 16-row CT instrument and the KY-2450B MWA system (Kangyou, Nanjing, China). Ablation antennas

were placed using the same strategy as was employed for CA treatment, and electrocardiogram monitoring was maintained throughout the MWA procedure.

An ablation power level of 60–70 W and an ablative duration of 4–8 min were selected. Following MWA, abdominal CT scanning was repeated to evaluate the patient for evidence of immediate necrosis.

Follow-up

Patients in this study were hospitalized and monitored for complications, and were discharged within 24 h if they remained complication-free. Long-term follow-up was conducted after 1 week, 1, 3, and 6 months, and every 6 months thereafter. Follow-up analyses included chest and abdominal CT scans, full-body examinations, and brain MRI scans. In addition, bone emission CT was performed every 6 months after ablation. The follow-up was conducted until patients' death or the point of setting this study (June 2023).

Definitions

Treatment effectiveness was assessed by contrast-enhanced CT and ablation was considered complete if no tumor enhancement was detectable on contrast-enhanced CT scans at 1 week after ablation [8]. If enhancement was still evident, ablation was considered partial. Local progression was defined by evidence of new tumor enhancement in the ablated region [8]. Progression-free survival (PFS) was the in-

terval between ablation and local or extra-adrenal recurrence or progression. OS was the interval from ablation to death or the last follow-up. Hypertensive crisis was defined by a systolic pressure ≥ 180 mm Hg or a diastolic pressure ≥ 110 mm Hg [9, 10].

Statistical analysis

Normally (non-normally) distributed data were presented as means \pm standard deviations (medians), and were compared with Student's *t*-test (Mann-Whitney *U* test). Categorical data were compared with the χ^2 test and presented in the form of percentages. Median OS and PFS (mOS and mPFS) were compared with the log-rank test. Survival curves were generated by the Kaplan-Meier method. If a patient was lost to follow-up, the PFS and OS were calculated from ablation to the date of the last visit. Predictors of OS were identified via a Cox regression analysis approach. A multivariate analysis was then performed incorporating those variables significantly predictive of OS in univariate analyses ($p < 0.1$). Potential sources of bias were addressed via subgroup analyses. $P < 0.05$ served as the cut-off to define significance. SPSS 16.0 (SPSS Inc., IL, USA) was utilized for all statistical testing.

Results

Patients

From January 2015 to December 2020, there were 182 NSCLC patients with AM in our centers. This study enrolled 68 patients (Figure 1), of whom 35 and 33 underwent treatment with CA and MWA, respectively (Table I). Baseline patient and tumor data did not differ between these two ablation groups, and each patient exhibited a single isolated AM lesion.

Treatment efficacy

Primary complete ablation rates in the CA and MWA groups were comparable at 91.4% (32/35) and 93.9% (31/33), respectively ($p = 1.000$) (Table II). In patients who experienced partial primary ablation, secondary complete ablation rates were 100% in both groups.

Complication rates

Hypertensive crisis incidence rates in the CA and MWA groups were comparable at 11.4% (4/35) and

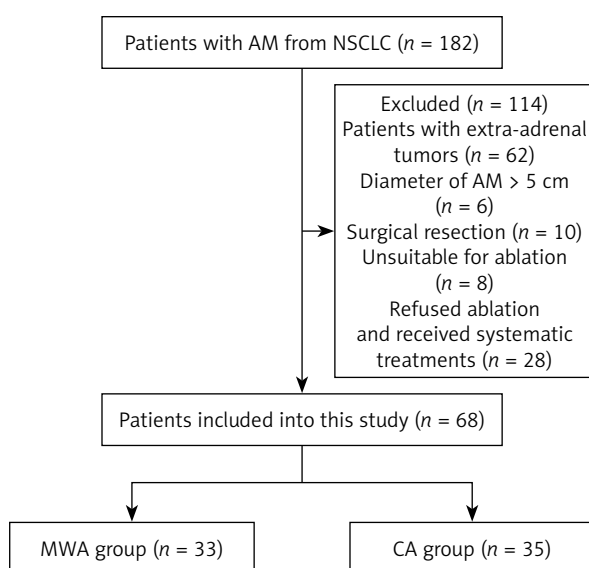


Figure 1. Study flowchart

Table I. Baseline data of the patients

Parameter	CA	MWA	P-value
Patients number	35	33	–
Age [years]	55.2 ± 8.8	56.3 ± 8.5	0.603
Gender:			0.222
Male	27	21	
Female	8	12	
Primary cancer types:			0.819
Squamous cell carcinoma	16	16	
Adenocarcinoma	19	17	
Primary cancer stages:			0.437
I	12	10	
II	13	17	
III	10	6	
Preoperative chemotherapy	18	13	0.319
Time from initial surgery to onset of AM [months]	15.2 ± 3.9	14.9 ± 3.6	0.773
Tumor size [cm]	3.1 ± 0.5	2.9 ± 0.6	0.127
Tumor side:			0.486
Left	13	15	
Right	22	18	

AM – adrenal metastasis, CA – cryoablation, MWA – microwave ablation.

9.1% (3/33) ($p = 1.000$). In these cases, procedures were suspended and β -blocker, α -blocker, hydralazine hydrochloride, and sodium nitroprusside treatments were administered until blood pressure levels had returned to the normal range, at which time ablation was resumed. Local hemorrhage occurred only in a single patient in the CA group, and this case

was managed through hemostasis and anti-inflammatory treatments.

Long-term outcomes

No patients were lost to follow-up after ablation and the median follow-up period was 27 months (11–66 months) for all patients (Table II). Overall,

Table II. Treatment outcomes

Parameter	CA	MWA	P-value
Number of patients	35	33	–
Primary complete ablation (%)	91.4% (32/35)	93.9% (31/33)	1.000
Secondary complete ablation (%)	100% (35/35)	100% (33/33)	–
Procedure-related complications:			
Hypertensive crisis (%)	11.4% (4/35)	9.1% (3/33)	1.000
Local hemorrhage (%)	2.9% (1/35)	0% (0/33)	1.000
Postoperative chemotherapy	18	13	0.319
Local progression (%)	22.9% (8/35)	24.2% (8/33)	0.893
Extra-adrenal progression (%)	14.3% (5/35)	15.2% (5/33)	1.000
PFS [months]	18	22	0.411
OS [months]	25	29	0.786

CA – cryoablation, MWA – microwave ablation, PFS – progression-free survival, OS – overall survival.

31 patients (CA group: 18; MWA group: 13) underwent chemotherapeutic treatment following ablation. In total, 8 (22.9%) and 8 (24.2%) patients in the CA and MWA groups experienced local progression over the course of follow-up ($p = 0.893$), and repeat ablation was performed in all cases. Extra-adrenal metastases were detected in 5 (14.3%) and 5 (15.2%) patients in these respective groups ($p = 1.000$). The mPFS of patients in the CA and MWA groups was 18 and 22 months, respectively ($p = 0.411$, Figure 2 A). The 1-, 3-, and 5-year PFS rates of patients in the CA group were 80%, 22.9%, and 8.6%, respectively, while the corresponding rates in the MWA group were 87.9%, 18.2%, and 0.0%.

All patients died over the course of follow-up, with an mOS of 25 and 29 months in the CA and MWA groups, respectively ($p = 0.786$, Figure 2 B). The 1-, 3-, and 5-year OS rates of patients in the CA group were 94.3%, 25.7%, and 8.6%, respectively, while the corresponding rates in the MWA group were 90.9%, 39.4%, and 6.1%.

Predictors of OS

Univariate Cox regression analyses indicated that lung adenocarcinoma ($p < 0.001$), previous stage III NSCLC ($p = 0.021$), and the absence of postoperative chemotherapy ($p = 0.042$) were all related to shorter OS (Table III). In a multivariate analysis, only a lung

adenocarcinoma diagnosis ($p < 0.001$) was an independent predictor of shorter OS.

Subgroup analyses

A subgroup analysis was next conducted comparing OS outcomes for individuals with different NSCLC subtypes. The mOS of squamous cell carcinoma patients in the CA and MWA groups was 36 and 45 months, respectively ($p = 0.440$, Figure 3). The 1-, 3-, and 5-year OS rates of patients in the CA group were 100%, 56.2%, and 12.5%, respectively, while those of patients in the MWA group were 93.8%, 68.8%, and 12.5%, respectively.

Among adenocarcinoma patients, the mOS in the CA and MWA groups was 22 and 22 months, respectively ($p = 0.667$, Figure 4). The 1-, 3-, and 5-year OS rates of patients in the CA group were 89.5%, 10.5%, and 5.3%, respectively, while those of patients in the MWA group were 88.2%, 11.8%, and 0.0%, respectively.

Discussion

Effectively treating AM can be difficult and necessitates the selection of an appropriate interventional approach. While surgical resection is the optimal treatment for these metastatic lesions, the efficacy of percutaneous ablation has been reported to be similar to that of surgical resection when AM lesions

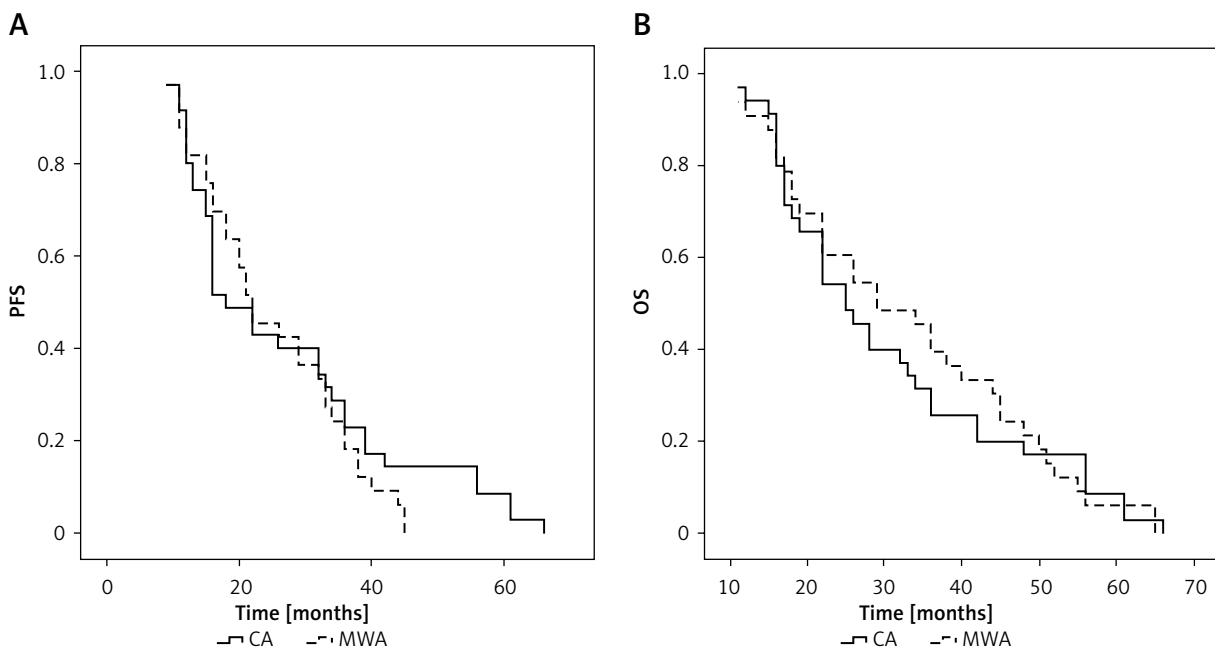


Figure 2. Median PFS (A) and OS (B) compared between CA and MWA groups for all patients

Table III. Cox regression analysis for OS

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Age	1.016	0.988–1.045	0.263			
Gender:						
Male	1					
Female	1.025	0.593–1.774	0.928			
Tumor size	1.228	0.816–1.848	0.324			
Side:						
Right	1					
Left	0.917	0.560–1.502	0.730			
Lung cancer:						
Squamous cell carcinoma	1			1		
Adenocarcinoma	2.567	1.535–4.295	< 0.001	2.788	1.638–4.745	< 0.001
Tumor stage at previous surgery:						
I	1			1		
II	1.130	0.645–1.980	0.670	1.063	0.602–1.879	0.833
III	2.203	1.127–4.307	0.021	2.037	1.000–4.148	0.05
Time from initial surgery to onset of AM:						
Preoperative chemotherapy:						
Yes						
No	1.050	0.644–1.711	0.864			
Postoperative chemotherapy:						
Yes	1			1		
No	1.685	1.020–2.785	0.042	1.633	0.957–2.789	0.072
Ablation types:						
CA	1					
MWA	0.938	0.579–1.521	0.796			

AM – adrenal metastasis, CA – cryoablation, MWA – microwave ablation, OS – overall survival.

are smaller than 5 cm [1]. Zhang *et al.* [2] previously noted that extra-adrenal tumors were predictive of a significant reduction in OS. Patients exhibiting isolated AM are considered the most appropriate candidates for percutaneous ablation.

In this study, the safety and efficacy of CA and MWA were compared as treatments for isolated AM secondary to NSCLC. Comparable primary (91.4% vs. 93.9%, $p = 1.000$) and secondary (100% vs. 100%) complete ablation rates were observed for these two techniques, suggesting that both ablation strategies are similarly effective as a means of eliminating AM lesions in patients with NSCLC. CA entails the use of alternating freeze/thaw cycles to promote cell death using a range of techniques [11, 12]. Relative to

MWA and RFA, CA offers an important advantage of causing lower levels of periprocedural pain [12]. The necessary freeze/thaw cycles, however, prolong the CA treatment time as compared to that associated with RFA or MWA. MWA, in contrast, is a thermal ablation strategy that can more quickly disrupt target lesions.

Hypertensive crisis is a unique complication associated with adrenal tumor treatment [13]. Here, similar rates of hypertensive crisis incidence were observed in the CA and MWA groups (11.4% vs. 9.1%), suggesting that the safety profiles of these two ablation strategies are similar when treating NSCLC patients with isolated AM. The rates in this study are also within the range of the rates which

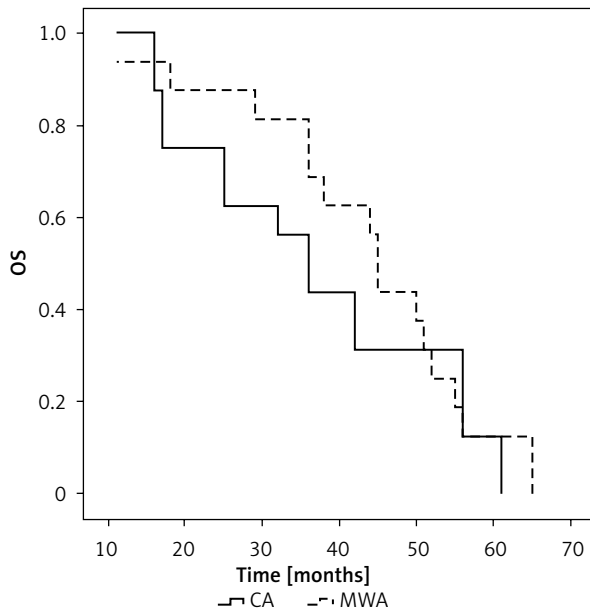


Figure 3. Median OS compared between CA and MWA groups for patients with primary lung squamous cell carcinoma

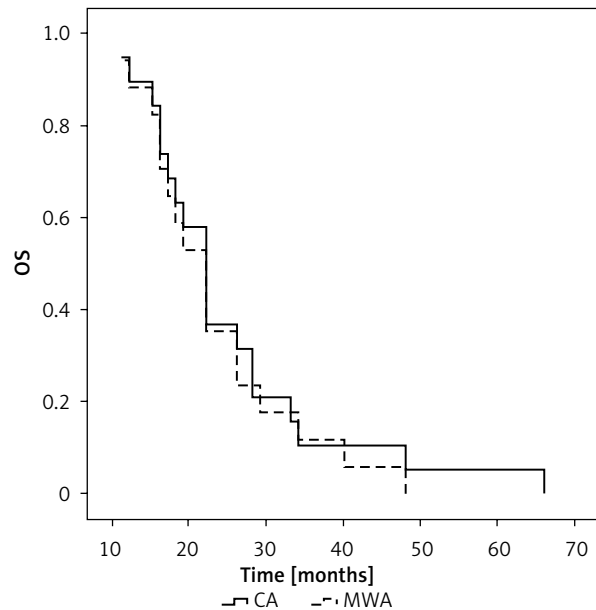


Figure 4. Median OS compared between CA and MWA groups for patients with primary lung adenocarcinoma

were reported in the prior meta-analyses focused on percutaneous ablation of AM (6–21.2%) [6–8].

Similar rates of local progression (22.9% vs. 24.2%, $p = 0.893$) and PFS (18 vs. 22 months, $p = 0.411$) were noted in the CA and MWA groups in this study, suggesting that these ablation techniques can offer similar levels of long-term local control for AM secondary to NSCLC. These rates are comparable to those observed in prior analyses of NSCLC patients with AM undergoing CA (20.5%) and MWA (22.6%) treatment [4, 12]. Botsa *et al.* [14] similarly observed comparable rates of local control for RFA and MWA (77.2% vs. 80.6%) when used to treat AM secondary to NSCLC. Cheng *et al.* [4] also found that different subtypes of NSCLC were not associated with local progression (squamous cell carcinoma: 31.3%; adenocarcinoma: 16.6%, $p = 0.551$).

The mOS of patients in the CA and MWA groups was similar (25 vs. 29 months, $p = 0.786$), suggesting that the selected ablation technique has no impact on patient OS in cases of AM secondary to NSCLC, as supported by the results of Cox regression analyses. Liu *et al.* [1] also observed that the mean OS of NSCLC patients with isolated AM following RFA was 2.3 years, which is similar to the mOS in this study. No relationship between postoperative chemotherapy and OS was detected. This may be because all enrolled patients exhibited isolated AM that was

effectively controlled through local ablation, and because many of these patients had already undergone chemotherapeutic treatment prior to AM onset such that their tumors may have exhibited higher levels of chemoresistance.

Cox regression analyses revealed that a primary squamous cell carcinoma diagnosis was predictive of longer OS. This may be a consequence of the fact that lymph node metastasis is more common in lung adenocarcinoma cases as compared to squamous cell carcinoma [15]. Kawase *et al.* [16] further found that cancer-specific death rates associated with lung adenocarcinoma were higher than those for squamous cell carcinoma. When patients were stratified according to NSCLC subtype, however, the mOS of individuals in the CA and MWA groups remained comparable within cohorts of individuals with both squamous cell carcinoma and adenocarcinoma. This suggests that CA and MWA exhibit similar levels of efficacy when treating different NSCLC subtypes.

There are some limitations to this study. For one, the retrospective design entails a high risk of bias and underscores the need for subsequent validation through randomized controlled trials. Moreover, while these patients were derived from two centers, the operative experience levels of personnel at these institutions may have differed, introducing another possible source of bias. Lastly, the sample size was

relatively small. However, the specific focus on NS-CLC patients with AM may have partially reduced the risk of bias.

Conclusions

CT-guided CA and MWA appear to exhibit comparable safety and efficacy profiles when treating instances of isolated AM secondary to NSCLC. Both of these treatment strategies appear to be most effective in patients with primary lung squamous cell carcinoma.

Acknowledgments

Wei Zhang, Wei Liu, and Zheng-Long Wu contributed equally to this study.

Conflict of interest

The authors declare no conflict of interest.

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