Original Article

Efficacy and safety of thermal ablation of lung malignancies: A Network meta-analysis

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Abstract:

OBJECTIVE: The objective of this study was to compare the efficacy and safety of radiofrequency ablation (RFA), cryoablation, and microwave ablation (MWA) for patients with lung malignancies.

METHODS: We performed a network meta-analysis to identify both direct and indirect evidence from relevant trials by searching PubMed, Embase, and the Cochrane Library to December 31, 2017, for the treatment of malignant lung tumors with the use of RFA, MWA, or cryoablation. We extracted the relevant information from the published studies with a predefined data sheet and assessed the risk of bias with the Cochrane risk of bias tool. The primary outcomes were efficacy (local progression rate and overall survival rate) and safety (major complications rate). We did a random-effects network meta-analysis within a Bayesian framework as well as assessed the quality of evidence contributing to each network estimate using GRADE framework.

RESULTS: We collected 34 studies eligible which included 1840 participants and 2520 lung malignancies (1318 primary lung cancer and 1202 pulmonary metastatic tumors). The quality of evidence was rated as very low in most comparisons. From the point of local progression rate, RFA and MWA were significantly more effective than cryoablation with odds ratio (OR) of 0.04 (95% confidence interval [CI]: 0.004, 0.38; $P = 0.005$) and 0.02 (95% CI: 0.002, 0.24; $P = 0.001$), respectively. No significant difference was found between MWA and RFA with an OR of 0.63 (95% CI: 0.04, 10.39; $P = 0.745$). Regarding the major complications, RFA, MWA, and cryoablation showed the comparable safety ($P > 0.05$).

CONCLUSION: RFA and MWA offer an advantage over cryoablation for patients with malignant lung tumors.

Keywords:

Cryoablation, lung tumors, microwave ablation, radiofrequency ablation

Primary lung cancers are the most common malignancies and the leading cause of cancer-related death worldwide. In addition, the lung is also the second-most common site of metastasis.[1] Surgical resection is universally accepted as the first-line therapy in an early-stage non-small cell lung cancer (NSCLC) and selected metastatic lung tumors. However, surgery is not suitable for most patients due to strict surgical criteria. Although chemotherapy, radiation therapy, and a combination of these modalities are alternative treatments for such patients, complete tumor remission is rarely achieved.[2]

During recent decades, thermal ablation has increasingly been performed on solid tumors of the liver, kidney, mammary, adrenal glands, and also for lung tumors.[3] Image-guided thermal ablation offers clinicians and patients a repeatable, effective, low-cost, and safe treatment for effective palliation and in some cases, cure of both primary and metastatic thoracic malignancies. The principal modalities

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in clinical practice are radiofrequency ablation (RFA), cryoablation, and microwave ablation (MWA). RFA, currently the most widely used ablative technique, uses a high-frequency current to heat and coagulate tissues.[4] Cryoablation uses extreme cold to cause tissue destruction through a complex combination of cellular damage during a freezing and thawing cycles.[5] MWA is a relatively new form of ablation treatment for lung tumors by increasing polar water molecules kinetic energy and converting this energy into heat which increases tissue temperatures to cytotoxic levels.[6]

It is clear that patients who have lung malignancies with limited treatment options are benefiting from image-guided ablation therapy.[7] However, the exact subset of patients who will benefit the most from such procedures and with ablative technology remains unknown. The purpose of this current study is to systematically evaluate and compare the efficacy (local tumor control or progression and survival rates) and safety (major complications rates) of radiofrequency, cryoablation, and MWA for patients with lung malignancies.

Methods

For this network meta-analysis, we searched PubMed, Embase, and the Cochrane Library through December 31, 2017, using the following medical terms are: ("radiofrequency" OR "cryoablation" OR "microwave" OR "thermal ablation") AND "lung". Reference lists of obtained articles were searched as well.

Inclusion and exclusion criteria

We included studies as follows: patients with primary lung cancer or pulmonary metastases from other primary tumors; thermal ablation (radiofrequency, microwave, or cryoablation) was used to treat these patients; and studies reported outcomes of patients after thermal therapy which included local control or progression rates, survival rates, and/or major complications (medical intervention required for pneumothorax, effusion, hemoptysis, pneumonia, severe pain and bronchopleural fistula, and procedure-related death). Studies that used other treatments combined with thermal ablation were excluded from the study.

Data extraction and quality assessment

Two investigators (a radiologist and a pneumologist) independently abstracted data using a predefined sheet and the final decision was made by consensus of the all authors. We extracted the following data: author, year of publication, design of study (prospective or retrospective and single-arm or case–control.), population region, age, gender, sample size, tumor size, follow-up duration, and clinical outcomes including tumor local control rates, survival rates, and major complications. The risk of bias was assessed with the Cochrane risk of bias tool.[8] We also assessed the quality of evidence contributing to each network estimate using the GRADE framework (Grade Working Group, USA).

Statistical analysis

Direct pairwise meta-analysis was not performed for unavailable head-to-head comparisons. Bayesian hierarchical modeling of the present network meta-analysis complied with the National Institute for Health and Excellence Decision Support Units guidelines. Count statistics of the local progression rate and major complications rate was analyzed using a Bayesian random effects model to calculate relative effects expressed as Odds Ratios (OR) with a 95% of confidence interval (CI) for pairwise comparisons of different ablation modalities. We assessed statistical heterogeneity with the I^2 statistic and P value as well as publication bias with an Egger's test. We did not fit the survival curves because that the detailed 5-year survival data were unavailable.

To determine whether the results were affected by study characteristics, we performed subgroup network meta-analyses by the following variables: study design (prospective/retrospective), population region (Europe/America, East Asia), sample size, tumor size, gender ratio, age, and follow-up duration. The Stata version 14.0 (StataCorp LP, Texas, USA) was used in this network meta-analysis, and the level of statistical significance was set at $\alpha = 0.05$.

Results

There were 34 studies[9-42] identified in this network meta-analysis [Figure 1]. These included 17 studies from Europe/America and 17 studies from East Asia. These

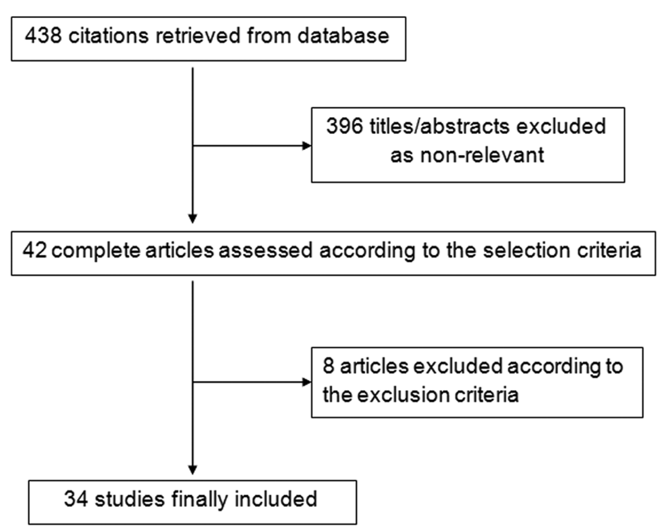

Figure 1: Flow diagram of the reviewing process

studies included a total of 1840 patients (mean age, 67.9; male, 64.5%) with 1318 primary lung tumors and 1202 pulmonary metastatic tumors. The median follow-up was 29 months [Table 1]. Of the 34 studies, only three studies were direct pairwise comparisons design [Figure 2]. The quality of evidence was rated as very low.

Local progression

The weighted average local progression rate of thermal ablation was 19.2% (19.8% to RFA, 23.7% to cryoablation, and 10.9% to MWA, respectively) [Table 2]. RFA and MWA were significantly more effective than cryoablation with an OR of 0.04 (95% CI: 0.004, 0.38; P = 0.005) and 0.02 (95% CI: 0.002, 0.24; P = 0.001), respectively. In addition, a comparable efficacy was found between MWA and RFA with an OR of 0.63 (95% CI: 0.04, 10.39; P = 0.745). The I^2 value was 75.1% ($P < 0.001$). Meta-regression identified the study design (P = 0.02) and population region (P = 0.015) were significantly associated with local progression.

Table 1: Characteristics for thermal ablation studies included in the present meta-analysis

Reference	Country	Study design	Patient (*n*)	Male (%)	Age (range) (years)	Sample size (*n*)		Follow-up (range) (months)
						Primary	Metastasis	
Radiofrequency ablation								
Belfiore *et al*., 2004[9]	Italy	Retrospective	33	79	66 (44-75)	33	0	12
Fernando *et al*., 2005[10]	America	Retrospective	18	55.6	75 (58-86)	21	0	14 (3-25)
Simon *et al*., 2007[14]	America	Retrospective	153	57	69 (17-94)	116	73	21 (3-74)
Lencioni *et al*., 2008[15]	Multi-center	Prospective	106	66	65 (29-82)	38	145	15 (1-30)
Pennathur *et al*., 2009[16]	America	Retrospective	21	42	78 (68-88)	21	0	24 (12-43)
Okuma *et al*., 2010[17]	Japan	Retrospective	72	78	70 (31-94)	12	126	12 (3-60)
Zemlyak *et al*., 2010[18]	America	Retrospective	12	66.7	74 (62-83)	12	0	33
Ambrogi *et al*., 2011[19]	Italy	Prospective	57	79	74 (40-88)	59	0	47 (12-82)
Hess *et al*., 2011[20]	France	Retrospective	15	60	64 (42-82)	11	9	17.6 (2-31)
Hiraki *et al*., 2011[21]	Japan	Retrospective	50	58	75 (52-88)	52	0	37 (2-88)
Kim *et al*., 2012[23]	Korea	Retrospective	8	88	72 (61-78)	8	0	108
Lanuti *et al*., 2012[24]	America	Retrospective	45	40	70 (51-89)	45	0	32 (2-75)
Lee *et al*., 2012[25]	Korea	Retrospective	40	75	73 (65-81)	40	0	46 (6-64)
Palussiere *et al*., 2015[34]	France	Retrospective	87	78	69 (45-86)	97	0	30.5 (16.7-51)
Vogl *et al*., 2016[35]	Germany	Retrospective	41	68.3	71 (50-90)	0	65	24
Gobara *et al*., 2016[36]	Japan	Prospective	33	82	72 (48-85)	33	15	37 (1-55)
Maxwell *et al*., 2016[38]	America	Retrospective	4	55.5	73.8 (50-86)	1	4	16 (3-48)
Omae *et al*., 2016[39]	Japan	Retrospective	123	84	66 (34-94)	0	123	53 (2-129)
Macchi *et al*., 2017[41]	Italy	Prospective	28	71.4	70 (40-82)	28	0	_
Cryoablation								
Wang *et al*., 2005[11]	China	Retrospective	187	73.3	61 (41-83)	196	38	_
Kawamura *et al*., 2006[13]	Japan	Prospective	20	60	57 (36-75)	0	35	21 (9-28)
Zemlyak *et al*., 2010[18]	America	Retrospective	27	59.3	74 (59-88)	27	0	33
Yamauchi *et al*., 2011[22]	Japan	Retrospective	24	70.8	62 (36-82)	0	55	40
Yamauchi *et al*., 2012[26]	Japan	Retrospective	22	50	72	34	0	29 (12-68)
Zhang *et al*., 2012[27]	China	Retrospective	46	76.1	65 (36-82)	46	0	24
Niu *et al*., 2013[29]	China	Retrospective	31	41.9	59 (36-81)	31	11	78
Pusceddu *et al*., 2013[30]	Italy	Retrospective	32	75	67 (42-81)	11	23	_
Yashiro *et al*., 2013[31]	Japan	Retrospective	71	60.6	58.8 (20-82)	11	199	19 (2.6-82.2)
Colak *et al*., 2014[32]	Australia	Retrospective	8	37.5	59 (28-76)	2	9	31.5 (3-62)
Microwave ablation								
He *et al*., 2006[12]	China	Retrospective	12	58.3	47.6 (31-69)	6	10	20 (6-40)
Liu *et al*., 2013[28]	Australia	Retrospective	16	73.3	73 (52-87)	16	0	12 (6-18)
Acksteiner *et al*., 2015[33]	Australia	Retrospective	10	60	79 (75-88)	11	0	12 (30)
Vogl, 2016[35]	Germany	Retrospective	47	61.7	64.6 (34-86)	0	193	24
Li *et al*., 2016[37]	China	Retrospective	80	61	64.1 (28-87)	59	21	_
Maxwell *et al*., 2016[38]	America	Retrospective	5	55.5	73.8 (50-86)	2	3	16 (3-48)
Zheng, 2016[40]	China	Retrospective	183	63.4	61.5 (19-85)	138	45	34.5 (24.7-51.8)
Macchi *et al*., 2017[41]	Italy	Prospective	24	70.8	68 (40-87)	52	0	_
Wei *et al*., 2017[42]	China	Retrospective	61	49.2	_	61	0	16.9 (2.5-36.5)
Summary	_	_	1840	64.5	67.9 (17-94)	1318	1202	29.1 (12-108)

Publication bias presented using the Egger's test (P = 0.007).

Major complications

The weighted average major complications rate of thermal ablation was 11.5% (11.6% to RFA, 4.6% to cryoablation, and 22.5% to MWA, respectively) [Table 2]. However, the network meta-analysis showed the comparable safety between cryoablation and RFA (P = 0.974), microwave and RFA (P = 0.979), respectively. The I^2 value was 76.4% ($P < 0.001$). Meta-regression identified none of the potential factors for major complications. The Egger's test (P = 0.089) indicated no publication bias.

Overall survival rate

The 1, 2, 3, 4, and 5 year-weighted average overall survival rate for RFA was 84.3%, 66.8%, 62.4%, 55.1%, and 43.5%, respectively. The 1, 2, and 3 years weighted average overall survival rate for cryoablation was 86.5%, 73.5%, and 71.2%, respectively. The 1, 2, 3, 4, and 5 years weighted average overall survival rate for MWA was 82.5%, 54.6%, 35.7%, 29.6%, and 16.6%, respectively [Figure 3].

Discussion

In the current network meta-analysis, we conclude that RFA and MWA were more effective to decrease the progression rate of lung malignance than cryoablation with OR of 0.04 (95% CI: 0.004, 0.38; P = 0.005) and 0.02 (95% CI: 0.002, 0.24; P = 0.001), respectively. Regarding the major complications, RFA, MWA, and cryoablation showed comparable safety ($P > 0.05$).

In the past 10 years, different technologies have been developed for image-guided percutaneous thermal ablation of lung malignancies, mainly including RFA, MWA, and cryoablation. These image-guided ablation techniques are considered safe, cost-effective, and minimally invasive for patients that are not eligible for the surgery.[43] RFA is an electric current-based technique that heats tissue due to fractioning electrons at a frequency of 400 KHz. The air-filled lung spaces insulate the heated volume resulting to low thermal inertia and high electrical impedance compared to other tissues. A multi-tined expandable electrode has been shown to reduce the local recurrence rate.[44] MWA is a field-based technology. The electromagnetic field creates frictional heat by rotating water molecules. Therefore, the temperature rises higher and more rapidly with wider active heating zone than RFA. In addition, MWA relies less on conduction into tissues and less influenced using the heat-sink effect, yielding a more uniform ablation zone. Cryoablation damages tumor cells through a complex combination of different mechanisms during tissue freezing and thawing.

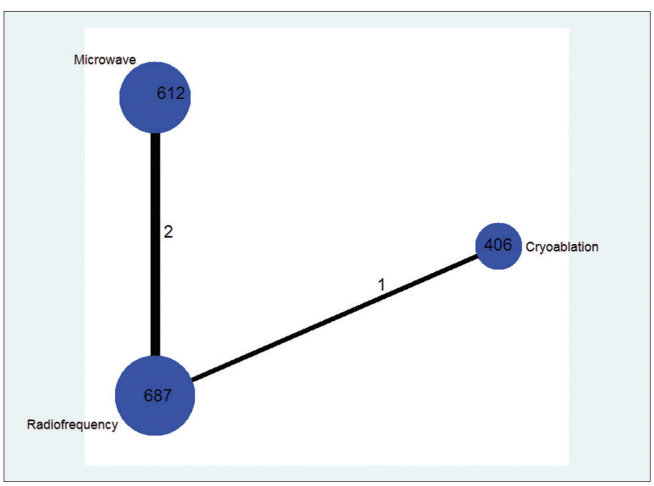

Figure 2: Comparison network of the included studies The width of the lines is proportional to the number of direct comparisons from original studies, and the size of every circle is proportional to the number of randomly assigned participants (sample size)

Our results showed that RFA and MWA were more effective than cryoablation for local control rate, while MWA and RFA showed comparable efficacy. The weighted average local recurrence rate was 23.7% for cryoablation, 19.8% for RFA, and 10.9% for MWA. However, the obvious heterogeneity and publication bias in this network meta-analysis weakened the significance. We also found that study design (prospective or retrospective) and population region (Europe/America or East Asia) influenced the local control rate of thermal ablation.

Bi *et al*. compared the local control rate of stage I NSCLC between RFA and stereotactic body radiation therapy (SBRT), and reported the uncorrected pooled 1, 2 3, and 5 years local control rate for RFA were all significantly lower than those for SBRT.[45] In addition, Bi *et al*. also reported the pooled 1, 2, 3, and 5 year-overall survival rate, and neither treatment had significant difference. Due to the tremendous heterogeneity, we

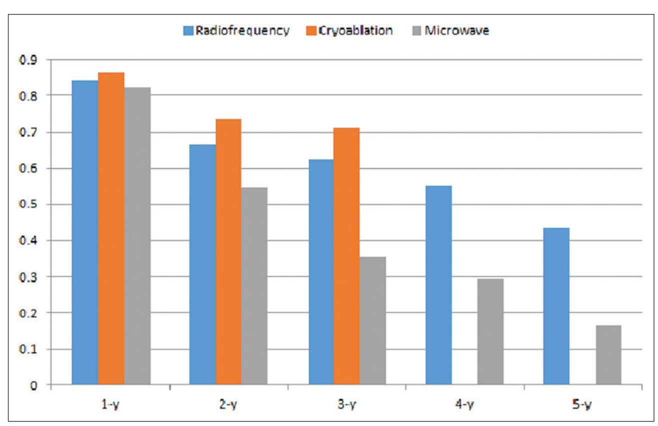

Figure 3: The weighted average overall survival rate

Table 2: Efficacy and safety of thermal ablation studies included in the present meta-analysis

Reference	Ablation	Sample size (*n*)	Tumor size (cm)	Local efficacy		Major complications (*n*)						
				Technical success (%)	Local progression (%)	Pneumothorax	Effusion	Hemoptysis	Pneumonia	Severe pain	Fistula	Procedure-related death
Belfiore *et al*., 2004[9]	Radiofrequency	33	3.3 (1.8-6.0)	100	3	0	0	0	0	0	0	0
Fernando *et al*., 2005[10]	Radiofrequency	21	2.8 (1.2-4.5)	100	9.5	7	0	0	2	0	0	0
Wang *et al*., 2005[11]	Cryoablation	234	_	_	_	3	5	0	0	0	0	0
He *et al*., 2006[12]	Microwave	16	4.2 (3.0-6.0)	100	31.3	0	0	0	0	0	0	0
Kawamura *et al*., 2006[13]	Cryoablation	35	1.3 (0.6-3.0)	100	5.7	1	0	0	0	0	0	0
Simon *et al*., 2007[14]	Radiofrequency	189	3.2 (0.6-19)	_	_	18	0	0	4	0	0	4
Lencioni *et al*., 2008[15]	Radiofrequency	183	1.7 (0.5-3.4)	99	_	27	4	0	0	0	0	0
Pennathur *et al*., 2009[16]	Radiofrequency	21	2.2 (0.9-5.5)	98.1	42.9	10	0	0	0	0	0	0
Okuma *et al*., 2010[17]	Radiofrequency	138	2.1 (0.2-9.0)	_	31.9	3	0	0	16	0	0	0
Zemlyak *et al*., 2010[18]	Radiofrequency	12	_	_	33.3	0	0	1	0	0	0	0
	Cryoablation	27	_	_	11.1	0	0	1	0	0	0	0
Ambrogi *et al*., 2011[19]	Radiofrequency	59	2.6 (1.1-5.0)	100	5.1	4	0	0	0	0	0	0
Hess *et al*., 2011[20]	Radiofrequency	20	1.6 (0.4-3.7)	93	5	6	0	0	1	0	0	0
Hiraki *et al*., 2011[21]	Radiofrequency	52	2.1 (0.7-6.0)	100	30.8	2	1	0	2	0	1	0
Yamauchi *et al*., 2011[22]	Cryoablation	55	1.3 (0.3-3.1)	_	30.9	1	0	0	0	0	0	0
Kim *et al*., 2012[23]	Radiofrequency	8	3.7 (2.0-6.0)	100	50	0	0	0	0	0	0	0
Lanuti *et al*., 2012[24]	Radiofrequency	45	2.0 (0.7-4.5)	100	40	1	0	0	0	0	0	0
Lee *et al*., 2012[25]	Radiofrequency	40	4.3 (1.0-10)	100	40	3	1	1	0	0	0	0
Yamauchi *et al*., 2012[26]	Cryoablation	34	1.4 (0.5-3.0)	_	2.9	1	0	0	0	0	0	0
Zhang *et al*., 2012[27]	Cryoablation	46	_	_	_	2	0	0	0	0	0	0
Liu *et al*., 2013[28]	Microwave	16	2.4 (0.8-4.0)	100	31.3	2	0	1	0	0	0	0

Contd...

Table 2: Contd...

Reference	Ablation	Sample size (*n*)	Tumor size (cm)	Local efficacy		Major complications (*n*)						
				Technical success (%)	Local progression (%)	Pneumothorax	Effusion	Hemoptysis	Pneumonia	Severe pain	Fistula	Procedure-related death
Niu *et al.*, 2013[29]	Cryoablation	42	_	_	_	0	0	0	0	0	0	0
Pusceddu *et al.*, 2013[30]	Cryoablation	34	2.6 (1.5-6.0)	100	8.8	0	0	0	0	0	0	0
Yashiro *et al.*, 2013[31]	Cryoablation	210	1.3 (0.3-4.2)	79.5	23.8	_	_	_	_	_	_	_
Colak *et al.*, 2014[32]	Cryoablation	11	2.6 (1.0-4.5)	100	45.5	3	1	6	0	0	0	0
Acksteiner *et al.*, 2015[33]	Microwave	11	2.9 (1.5-4.1)	100	27.3	3	0	1	2	0	0	0
Palussiere *et al.*, 2015[34]	Radiofrequency	97	2.1 (1.0-5.4)	89.7	3.1	18	0	0	0	0	0	1
Vogl *et al.*, 2016[35]	Radiofrequency	65	_ (0.8-4.2)	100	30.8	4	0	0	0	0	0	0
	Microwave	193	_ (0.5-5.0)	53.4	6.2	8	0	0	0	0	0	0
Gobara *et al.*, 2016[36]	Radiofrequency	48	1.5 (1.0-2.4)	100	10.4	2	2	0	1	0	0	0
Li *et al.*, 2016[37]	Microwave	80	2.0 (0.9-3.0)	100	0	3	0	1	2	1	0	0
Maxwell *et al.*, 2016[38]	Radio-micro	10	2.3 (1.2-4.8)	100	40	3	0	0	0	0	0	0
Omae *et al.*, 2016[39]	Radiofrequency	123	1.3 (0.2-5.0)	_	_	_	_	_	_	_	_	_
Zheng *et al.*, 2016[40]	Microwave	183	3.4 (1.4-5.4)	100	19.1	29	6	0	5	0	0	0
Macchi *et al.*, 2017[41]	Microwave	52	1.9 (1.0-2.8)	100	1.9	_	_	_	_	_	_	_
	Radiofrequency	28	1.9 (1.0-2.8)	100	7.1	_	_	_	_	_	_	_
Wei *et al.*, 2017[42]	Microwave	61	3.7 (0.8-10)	100	62.3	_	_	_	_	_	_	_

failed to perform a statistic analysis for the pooled 1, 2, 3, 4, and 5 years overall survival rate.

Although thermal ablation of lung tumors is generally safe, it may cause various complications.[46] Most of the complications can be treated conservatively or with minimal therapy. However, the rare but serious complications should be known, including massive hemorrhage, intractable pneumothorax, pneumonitis, pulmonary artery pseudo aneurysm, injury of nearby important tissues, systemic air embolism, lung abscess and empyema, and skin burn.

This study has some limitations. First, we fail to distinguish the subgroups based on different stages (e.g., stage I, stage II, stage III, and stage IV) of primary lung cancer and metastatic lung tumors from different primary malignancies. This may significantly obscure the overall survival rate among different ablations. Second, in the GRADE framework, most of the comparisons are assessed as low or very low quality. Third, the inclusion of retrospective and single-arm studies may introduce the patient selection bias. Finally, details on patient demographics and tumor characteristics (number/size) are not accounted for (especially worthy of note since tumor size is known to be one of the most important factors that limit the efficacy of ablation).

Conclusion

RFA and MWA may offer an advantage over cryoablation for patients with malignant lung tumors.

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Conflicts of interest

There are no conflicts of interest.

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