Int J Clin Exp Med 2018;11(11):11521-11534
www.ijcem.com /ISSN:1940-5901/IJCEM0074398

Review Article

Thermal ablation for colorectal pulmonary metastases: a meta-analysis

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Received February 10, 2018; Accepted October 9, 2018; Epub November 15, 2018; Published November 30, 2018

Abstract: Previous studies have demonstrated ablation therapy is a safe and effective treatment in patients with pulmonary metastases from colorectal cancer, but the survival varied widely. The aim of this meta-analysis was to evaluate the overall efficacy of ablation therapy for colorectal pulmonary metastases (CPM). A total of 18 studies were included in this meta-analysis. Six of the studies were prospective, others were retrospective. Primary outcomes were the overall survival (OS), progression-free survival (PFS) and local control rate (LCR). The 1-, 2-, 3-, 4-, 5-year OS of CPM treated with ablation were 88.9%, 66.6%, 56.9%, 31.0%, 43.4% respectively. The 1-, 3-, 5-year PFS of CPM treated with ablation were 52.4%, 15.8%, 11.8% respectively. The 1-, 3-, 5-year LCR of CPM were 86.8%, 76.7%, 76.1% respectively. CPM patients after pulmonary ablation had a similar survival outcome with pulmonary metastasectomy. The data from the subgroups (tumor size ≤ 3 cm, without extrapulmonary metastasis and CEA negative) showed significantly better 1-year OS and 3-year OS in CPM patients who received pulmonary ablation. CPM with a single tumor had a better 3-year OS than those with multiple tumors, while their 1-year OS had no statistical difference. Those patients of CPM with a tumor size ≤ 3 cm, a single tumor, normal CEA level and without extrapulmonary metastasis are most likely to benefit from ablation treatment.

Keywords: Ablation, colorectal pulmonary metastases, meta-analysis, overall survival

Introduction

Colorectal cancer is the third common cancer in male and the second common cancer in female worldwide [1]. In China, the morbidity and mortality of colorectal cancer increase every year. Colorectal pulmonary metastasis (CPM) is the second common site of metastases following the liver and occurs in approximately 10-20% of patients with colorectal cancer [2]. The majorities of patients with CPM who were treated with chemotherapy had a 5-year OS of less than 10% [3]. Pulmonary metastasectomy has been accepted as a curative option with limited sites of disease and prolongs the survival rate. Recent studies have shown a 5-year survival rates were about 55% after pulmonary metastasectomy [4]. However, only a minority of patients are eligible for surgical resection due to medical co-morbidities or prior metastasectomy, rendering further resection technically challenging. Currently, several studies have demonstrated the ablation therapy is an alternative choice for the unresectable CPM.

Thermal ablation of lung tumors is a fast developing area within interventional oncology. Radiofrequency, laser, microwave and cryotherapy have all been proven to be effective. 5-year OS of patients with ablation for CPM has recently been reported as 19.9-70% [5, 6]. Thermal ablation had a similar survival outcome with pulmonary metastasectomy. But it may lead to a better quality of life for CPM. The advantages of ablation treatment are obvious, such as minimal invasiveness, better safety, equivalent local control and survival to lung resection. However, the reported survival data of those patients who accepted pulmonary ablation

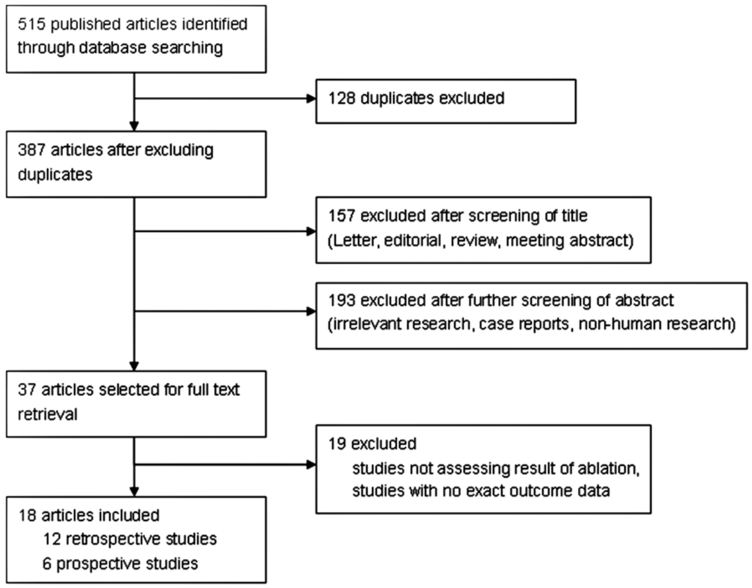


Figure 1. Flow diagram of literature retrieval and screening.

were varied. The prognostic factors, such as tumor size, the number of tumors, pathologic characteristics, level of CEA, were controversial. Questions that still need to be answered include who will benefit from pulmonary ablation treatment and which factors are associated with prolonged survival. We performed a meta-analysis for the questions above.

Materials and methods

Search strategy

A literature search was performed in PubMed and Web of Science up to May 30, 2017. We limited our search to studies published in English. We used the following query: ablation AND (tumor OR neoplasm OR cancer) AND (lung OR pulmonary) AND (metastases OR metastasis) AND (colorectal OR colon OR rectal). If more than one publication were found for the same trial, the most complete, recent, and updated report of the clinical trial was included in the meta-analysis.

Inclusion criteria, exclusion criteria and data extraction

Two independent reviewers determined the eligibility of all selected studies, and divergences were resolved through consulting with a third reviewer. The following criteria were fulfilled for the studies included in the meta-analysis: the studies about the methods of pulmonary ablation, such as radiofrequency, laser, and microwave for CPM; the studies about OS, PFS and LCR of CPM; the studies about tumors which could provide detailed data of CPM.

The following studies were excluded: the original studies only assessing results of other therapies such as radiotherapy for CPM; the studies which could not offer exact data, such as OS, PFS, LCR of CPM; review articles, letters, comments, case reports.

Two independent reviewers extracted all data from eligible studies. Extracted data included the name of first author's, the year of publication, study design, interventions, participants and participants' demographics (age, sex), clinical data (tumor size, number of tumors, extrapulmonary metastasis, level of plasma CEA), surgical data (methods of ablation, number of lesions treated), and survival (OS, PFS, LCR).

Quality assessment

Quality evaluation of each study included in the meta-analysis was performed using the Methodological Index for Non Randomized Studies (MINORS) [7]. MINORS is a tool to evaluate the methodological quality of non-randomized surgical studies, whether comparative or non-comparative, which included 12 items: the first eight were used for non-comparative studies and the remaining four items were applied to comparative studies.

Prognosis factors

The OS of 4 subgroups were evaluated: the maximal tumor diameter was more or less than 3 cm; the number of tumors; with or without extrapulmonary metastasis; CEA negative or positive.

Statistical analysis

We did all statistical analyses with comprehensive meta-analysis software version 2.0

Table 1. Characteristics of included trials

Study	Country	Design	Methods	No. of patients	Mean ages (years)	No. of lesions treated	Mean tumor size (cm)	Mean tumor number	Follow up (months)	MINORS Score
Simon 2007	USA	Retrospective	RFA	18	NA	21	NA	NA	27.5 (5-61)	12
Gillams 2013	UK	Prospective	RFA	122	68 (29-90)	398	1.7 (0.5-4)	3.3 (1-15)	Until Death	10
Chua 2010	Australia	Retrospective	RFA	100	65 ± 11	NA	NA	NA	23 (1-96)	10
Ferguson 2015	Australia	Prospective	RFA	157	64 (28-86)	434	3.82	2.18	60	10
Omae 2016	Japan	Retrospective	RFA	52	66 (37-94)	NA	1.2 (0.3-3.3)	2	50 (9-128)	10
Yamakado 2007	Japan	Retrospective	RFA	71	64 (40-87)	155	2.4 (0.5-6.0)	2.2 (1-5)	19 (4-42)	10
Yamakado 2009	Japan	Retrospective	RFA	78	66.1 ± 9.8	198	2.0 ± 1.0	2.6 ± 1.8	24.6 ± 17.6	12
Akhan 2016	Turkey	Retrospective	RFA	16	NA	NA	NA	NA	NA	10
Petre 2013	USA	Prospective	RFA	45	63 (43-81)	69	0.4-3.5	1 (1-3)	NA	12
Lencioni 2008	Italy	Prospective	RFA	53	63.1 ± 11.8	NA	1.4 ± 0.7	2.2 ± 1.6	15 (1-30)	10
Baère 2015	France	Prospective	RFA	293	NA	NA	NA	NA	35.5 (20-53)	12
Hiraki 2007	Japan	Retrospective	RFA	27	61.6 (43-80)	49	1.5 (0.3-3.5)	NA	20 (11.2-47.7)	10
Hiraki 2010	Japan	Retrospective	RFA	40	62.5 ± 9.9	117	11.6 ± 6.2	NA	16.4 ± 9.2	10
Vogl 2016	Germany	Retrospective	MWA	47	64.6 ± 11.5	125	0.5-5	NA	NA	10
			LITT	21	72.9 ± 10.4	31	1-4.5	NA	NA	
			RFA	41	71 ± 10	75	0.8-4.2	NA	NA	
Yan 2007	Australia	Retrospective	RFA	30	64 ± 8	74	NA	NA	23 (5-50)	10
Yan 2006	Australia	Prospective	RFA	55	62 ± 11	NA	2.1 ± 1.1	2 ± 2	24 (6-40)	10
Huo 2016	Australia	Retrospective	RFA/MWA	182	64.17 (20-86)	NA	NA	NA	27 (24.49-31.5)	10
Matsui 2015	Japan	Retrospective	RFA	84	65 ± 11.4	172	NA	NA	37.5 (5.4-130.0)	10

MWA, microwave ablation; LITT, laser-induced thermotherapy; RFA, radiofrequency ablation.

(Biostat, Englewood, NJ, USA). OS, PFS and LCR were considered as time-to-event variables. To measure overall heterogeneity across the included cohorts, we calculated I^2 to test heterogeneity (0-40% means little or no heterogeneity; 40-60% means moderate heterogeneity; 50-90% indicates substantial heterogeneity; and 75-100% indicates considerable heterogeneity according to Cochrane handbook). When I^2 beyond 40%, data were analyzed using a random-effects model, while I^2 was below 40%, fixed-effect model was employed. Subgroup analyses were assessed by tumor size, tumor number, CEA level and extrapulmonary metastasis, and then proportions between subgroups were compared using χ^2 tests [8]. Results were considered significant if P value was < 0.05. All confidence intervals (CIs) had two-sided probability coverage of 95%.

Results

Study selection and characteristics

A total of 515 published articles were identified from the database search. After excluding duplicates, 387 articles were reviewed. In the initial screening, 350 trials, including letters, editorials, reviews, meeting abstracts, case reports and studies about experiment in vitro were excluded. A total of 37 potentially relevant articles were selected for full-text retrieval. After reading the content of the full articles, a total of 18 studies were included in the meta-analysis (**Figure 1**) [5, 6, 9-24]. 12 articles were retrospective studies and 6 articles were prospective studies. One study mentioned three kinds of ablation treatment: microwave ablation (MWA), laser-induced thermotherapy (LITT) and radiofrequency ablation (RFA); one study mentioned MWA and RFA, the other 16 studies only mentioned RFA. Totally, 1516 subjects were involved in this meta-analysis. More information about the characteristics of the included studies was summarized in **Table 1**.

Quality assessment

All studies in this meta-analysis were non-comparative, and then the quality of 18 studies was assessed according to the eight items of MINORS. Prospective calculation of the study size and blind evaluation of objective endpoints were not mentioned in all studies in this meta-analysis. Consecutive patients have been included in 4 studies (Simon2007, Yamakado2009, Petre2013, and Baère2015), other studies did not reported inclusion of con-

Table 2. Raw data of each included study

Study	Number of patients	OS					PFS			LCR		
		1 y	2 y	3 y	4 y	5 y	1 y	3 y	5 y	1 y	3 y	5 y
Simon 2007	18	87%	78%	57%	57%	57%	NA			NA		
Gillams 2013	122	NA	NA	57%	NA	NA	NA			NA		
Chua 2010	100	87%	66%	50%	NA	30%	NA			NA		
Ferguson 2015	157	89%	NA	44%	NA	19.9%	60.5%	14.4%	7%	NA		
Omae 2016	52	98%	89%	84%	76%	70%	56%	35%	30%	NA		
Yamakado 2007	71	84%	62%	46%	NA	NA	NA	NA	NA	NA		
Yamakado 2009	78	83.9%	NA	56.1%	NA	34.9%	NA	NA	NA	89.9%	79.4%	79.4%
Akhan 2016	16	94%	80%	68%	23%	NA	32%	12%	NA	NA	NA	NA
Petre 2013	45	95%	72%	50%	NA	NA	NA			92%	77%	NA
Lencioni 2008	53	89%	66%	NA	NA	NA	NA			NA		
Baère 2015	Colon 191	92.9%	NA	76.1%	NA	56.0%	37.6%	17.0%	14.8%	89.1%	83.8%	83.8%
	Rectum 102	93.6%	NA	64.9%	NA	49.6%	30.4%	8.6%	6.4%	85.5%	69.3%	69.3%
Hiraki 2007	27	96%	NA	54%	NA	48%	NA			72%	56%	56%
Hiraki 2010	117	NA					NA			88%	NA	NA
Vogl 2016	MWA 47	82.7%	67.5%	NA	16.6%	NA	54.6%	10.0%	NA	89.4%	NA	NA
	LITT 21	95.2%	47.6%	NA	23.8%	NA	96.8%	24.0%	NA	80%	NA	NA
	RFA 41	76.9%	50.8%	NA	8.0%	NA	77.3%	30.8%	NA	80%	NA	NA
Yan 2007	30	75%	63%	45%	NA	NA	NA			NA		
Yan 2006	55	85%	64%	46%	NA	NA	NA			NA		
Huo 2016	182	92%	NA	46%	NA	30%	52%	14%	9%	NA		
Matsui 2015	84	95.2%	NA	65.0%	NA	51.6%	NA			88.3%	84.1%	82.1%

OS, overall survival; PFS, progress free survival; LCR, local control rate; MWA, microwave ablation; LITT, laser-induced thermotherapy; RFA, radiofrequency ablation.

secutive patients. The quality assessment results of the 18 included studies are shown in **Table 1**.

OS, PFS and LCR

The outcome of raw data of each included study was shown in **Table 2**. No heterogeneity was observed in the 1-year LCR of all studies ($P = 0.308$, $I^2 = 14.686$). Thus, the fixed-effect model was used; heterogeneity was observed in every other outcome data. On this basis, the random-effect model was used. 17 studies reported the data of OS rates, except Hiraki2010. The results showed that there were heterogeneity in 1-, 2-, 3-, 4-, 5-year OS rates for the included studies ($I^2 = 48.801$, $P = 0.009$; $I^2 = 48.627$, $P = 0.029$, $I^2 = 80.032$, $P < 0.01$, $I^2 = 90.214$, $P < 0.01$, $I^2 = 83.072$, $P < 0.01$, respectively). The 1-, 2-, 3-, 4-, 5-year OS rates of CPM treated with ablation were 88.9%, 66.6%, 56.9%, 31.0%, 43.4% respectively (**Figure 2**). 6 studies reported the data of PFS. The 1-, 3-, 5-year PFS rates of CPM treated with ablation were 52.4%, 15.8%, 11.8% and the heterogeneity were $I^2 = 85.352$, $P < 0.01$, $I^2 = 63.756$, $P < 0.01$, $I^2 = 89.278$, $P < 0.01$ respectively (**Figure 3**). 7 studies reported the data of LCR. The 1-, 3-, 5-year LCR were 86.8%, 76.7%, 76.1% and the heterogeneity were $I^2 = 14.686$, $P = 0.308$, $I^2 = 70.562$, $P = 0.005$, $I^2 = 74.891$, $P = 0.003$ respectively (**Figure 4**).

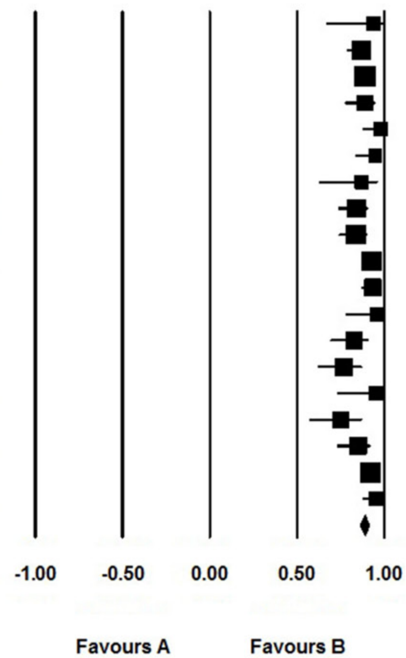
The prognosis factors

Several clinical prognostic factors affecting the outcomes have been described. 8 studies conducted the survival analysis of subgroups, including tumor size, the number of tumors, extrapulmonary metastasis and levels of CEA. The statistical data was significantly favorable to the subgroup of tumor size ≤ 3 cm at 1-year OS rate (88.9% vs 62.1%, $P < 0.01$) and 3-year OS rate (56.2% vs 25.1%, $P = 0.006$). The heterogeneity in 1-year OS rate and 3-year OS rate for the subgroup of tumor size ≤ 3 cm were $I^2 = 0.00$, $P = 0.611$ and $I^2 = 4.799$, $P = 0.350$. CPM with a single tumor had a better 3-year OS rate than those with multiple tumors (55.7% vs 40.1%, $P = 0.01$). The heterogeneity in 3-year OS rate for a single tumor group and multiple tumors group were $I^2 = 34.545$, $P = 0.205$ and

A **1-year OS** **Meta Analysis**

Model	Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
	Akhan2016	0.940	0.666	0.992	2.614	0.009
	Chua2010	0.870	0.789	0.923	6.393	0.000
	Ferguson2015	0.890	0.831	0.930	8.197	0.000
	Lencioni2008	0.890	0.774	0.950	4.762	0.000
	Omae2016	0.980	0.875	0.997	3.929	0.000
	Petre2013	0.950	0.833	0.986	4.305	0.000
	Simon2007	0.870	0.629	0.964	2.712	0.007
	Yamakado2007	0.840	0.736	0.908	5.122	0.000
	Yamakado2009	0.839	0.740	0.905	5.358	0.000
	Baère2015#	0.929	0.883	0.958	9.127	0.000
	Baère2015*	0.936	0.869	0.970	6.631	0.000
	Hiraki2007	0.960	0.778	0.994	3.236	0.001
	Vogl2016-M	0.827	0.692	0.911	4.057	0.000
	Vogl2016-R	0.769	0.617	0.873	3.246	0.001
	Vogl2016-L	0.952	0.728	0.993	2.926	0.003
	Yan2007	0.750	0.568	0.873	2.606	0.009
	Yan2006	0.850	0.730	0.922	4.593	0.000
	Huo2016	0.920	0.871	0.952	8.939	0.000
	Matsui2015	0.952	0.879	0.982	5.853	0.000
Random		0.889	0.859	0.913	15.235	0.000

Event rate and 95% CI



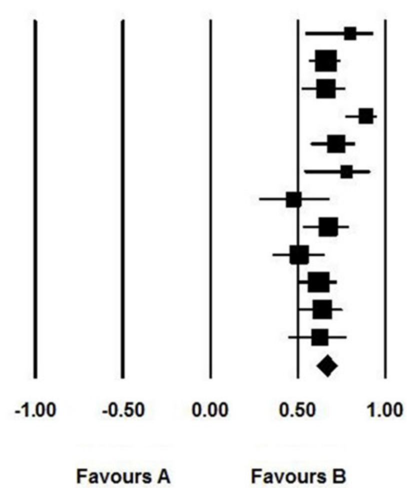
Test of heterogeneity : I^2=48.801 P=0.009

Meta Analysis

B **2-year OS** **Meta Analysis**

Model	Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
	Akhan2016	0.800	0.540	0.932	2.218	0.027
	Chua2010	0.660	0.562	0.746	3.142	0.002
	Lencioni2008	0.660	0.524	0.774	2.287	0.022
	Omae2016	0.890	0.772	0.951	4.717	0.000
	Petre2013	0.720	0.573	0.831	2.845	0.004
	Simon2007	0.780	0.538	0.915	2.224	0.026
	Vogl2016-L	0.476	0.278	0.681	-0.220	0.826
	Vogl2016-M	0.675	0.530	0.793	2.347	0.019
	Vogl2016-R	0.508	0.359	0.656	0.102	0.918
	Yamakado2007	0.620	0.503	0.725	2.002	0.045
	Yan2006	0.640	0.506	0.755	2.048	0.041
	Yan2007	0.630	0.448	0.781	1.407	0.159
Random		0.666	0.605	0.722	5.085	0.000

Event rate and 95% CI

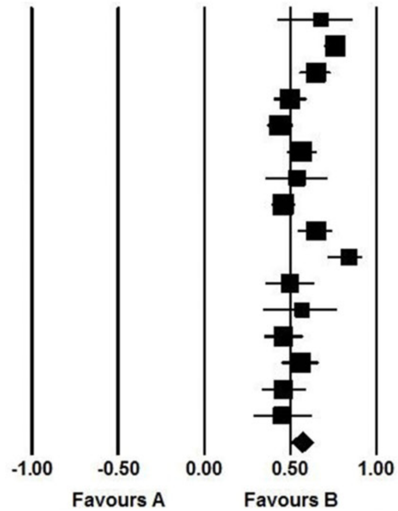


Test of heterogeneity : I^2= 48.627 P=0.029

Meta Analysis

C **3-year OS** **Meta Analysis**

Model	Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
	Akhan2016	0.680	0.426	0.859	1.406	0.160
	Baère2015#	0.761	0.695	0.816	6.826	0.000
	Baère2015*	0.649	0.552	0.735	2.963	0.003
	Chua2010	0.500	0.403	0.597	0.000	1.000
	Ferguson2015	0.440	0.364	0.518	-1.500	0.134
	Gillams2012	0.570	0.481	0.655	1.541	0.123
	Hiraki2007	0.540	0.355	0.714	0.415	0.678
	Huo2016	0.460	0.389	0.533	-1.078	0.281
	Matsui2015	0.650	0.543	0.744	2.706	0.007
	Omae2016	0.840	0.714	0.917	4.384	0.000
	Petre2013	0.500	0.358	0.642	0.000	1.000
	Simon2007	0.570	0.343	0.771	0.592	0.554
	Yamakado2007	0.460	0.348	0.576	-0.673	0.501
	Yamakado2009	0.561	0.450	0.667	1.075	0.282
	Yan2006	0.460	0.334	0.591	-0.593	0.553
	Yan2007	0.450	0.285	0.627	-0.547	0.585
Random		0.569	0.504	0.633	2.067	0.039

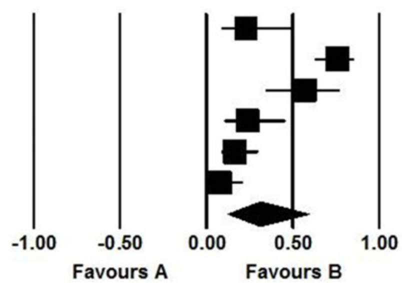


Test of heterogeneity : I^2=80.032 P=0.000

Meta Analysis

D **4-year OS** **Meta Analysis**

Model	Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
	Akhan2016	0.230	0.085	0.489	-2.034	0.042
	Omae2016	0.760	0.626	0.857	3.550	0.000
	Simon2007	0.570	0.343	0.771	0.592	0.554
	Vogl2016-L	0.238	0.103	0.460	-2.271	0.023
	Vogl2016-M	0.166	0.085	0.300	-4.118	0.000
	Vogl2016-R	0.080	0.027	0.212	-4.243	0.000
Random		0.310	0.122	0.593	-1.334	0.182

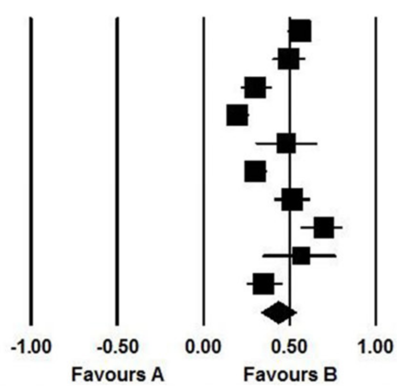


Test of heterogeneity : I^2=90.214 P=0.00

Meta Analysis

E **5-year OS** **Meta Analysis**

Model	Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
	Baère2015#	0.560	0.489	0.629	1.654	0.098
	Baère2015*	0.496	0.400	0.592	-0.081	0.936
	Chua2010	0.300	0.218	0.397	-3.883	0.000
	Ferguson2015	0.199	0.144	0.269	-6.966	0.000
	Hiraki2007	0.480	0.303	0.663	-0.208	0.835
	Huo2016	0.300	0.238	0.370	-5.238	0.000
	Matsui2015	0.516	0.410	0.621	0.293	0.769
	Omae2016	0.700	0.563	0.809	2.800	0.005
	Simon2007	0.570	0.343	0.771	0.592	0.554
	Yamakado2009	0.349	0.252	0.461	-2.624	0.009
Random		0.434	0.334	0.539	-1.238	0.216



Test of heterogeneity : I^2=83.072 P=0.00

Meta Analysis

Figure 2. Meta-analysis results of overall survival (OS).

I^2 = 71.151, P = 0.008; while their 1-year OS rate had no statistical difference (90.7% vs 85.3%, P = 0.159). The subgroup without extrapulmonary metastasis of CPM had a better survival time than those with extrapulmonary metastasis at 1-year OS rate (96.4% vs 75.5%, P < 0.01) and heterogeneity were I^2 = 0.00, P = 0.641 and I^2 = 72.736, P = 0.012 and 3-year OS rate (64.7% vs 8.6%, P < 0.01) and heterogeneity were I^2 = 0.00, P = 0.472 and I^2 = 73.356, P = 0.010. CPM with CEA negative had a better 1-year OS rate (92.5% vs 79.1%, P = 0.001) and 3-year OS rate (75.3% vs 26.4%, P < 0.01) than those with CEA positive. The heterogeneity in 1-year OS rate and 3-year OS rate for the subgroup of CEA negative were I^2 = 0.00, P = 0.455 and I^2 = 33.672, P = 0.197. The related prognostic factors were summarized in **Table 3**.

Discussion

It is widely accepted that pulmonary metastasectomy is the treatment of choice for patients with CPM [25-27]. The suitable criteria for resection of the CPM include the following: control of the primary tumor, possibility of complete resection and adequate pulmonary reserve to tolerate the planned resection [28]. However, many patients are considered ineligible for the conditions above. The study of Mitry et al showed that only 4.1% of synchronous CPM and 14.3% of metachronous CPM were eligible for resection [29]. Furthermore, those who are suitable for the surgery may not be willing to accept the operation, because of its physical trauma, effect on quality of life, long hospital stay and long post-procedure recovery. Lastly, the operation cannot be performed repeatedly for recurrence of the tumor. The recurrence rate after operation was up to 68%, and the remaining lung was the most common site of recurrence [30, 31]. Based on these, the therapy of pulmonary ablation offers a potential solution.

Thermal ablation is a kind of less invasive interventional therapy. It was first used in normal liver in 1990 [32, 33]. The first clinical application in lung cancer was reported in 2000 [34] and now pulmonary ablation is a widely accepted treatment for pulmonary metastases and some lung primary tumors. The therapy of ablation has less effect on pulmonary function or quality of life, which is more acceptable for patients [16]. Furthermore, pulmonary ablation can be performed repeatedly if tumor recurs [35]. The reported 5-year OS after surgical resection ranged from 35.1 to 67.8% [36-38]. The 5-year OS after pulmonary ablation could reach 19.9-70% [5, 6]. However, chemotherapy only showed a 5-year OS of less than 10% [3]. In our meta-analysis study, the 5-year OS of CPM treated with pulmonary ablation was 43.4%, and the 1-, 2-, 3-, 4-year OS were 88.9%, 66.6%, 56.9%, 31.0% respectively. The result of 4-year OS lower than the 5-year OS was probably caused by statistical bias. Maybe it is because that 4-year OS was not mentioned in some articles. Compared with the poor OS of CPM patients after the treatment of chemotherapy, the outcomes after pulmonary ablation were encouraging. CPM patients after pulmonary ablation had a similar survival outcome with surgery. Pulmonary metastasectomy was limited to the timing of tumor metastases, the lymph nodal involvements, the location (unilateral or bilateral) and the tumor TNM stages. Compared with pulmonary metastasectomy, the indications of pulmonary ablation were more relaxed.

Although the advantages of pulmonary ablation are obvious, the greatest disadvantage of ablation might be its limited local efficacy. In our meta-analysis, the 1-, 3-, 5-year PFS of CPM treated with ablation were 52.4%, 15.8%, 11.8% respectively and the 1-, 3-, 5-year LCR of CPM were 86.8%, 76.7%, 76.1% respectively. The LCR reported after wedge resection or segmentectomy was approximately 72% and after video-assisted thoracoscopic surgery was about 92%. The LCR of pulmonary metastasectomy was associated with pathologically and a malignant positive surgical margin [39, 40]. The LCR of pulmonary ablation was similar with pulmonary metastasectomy. However, the factors affect LCR of pulmonary ablation should be further investigated.

Some studies also analyzed the prognostic factors, which will be helpful in establishing valuable treatment guidelines for pulmonary ablation by identifying patients who will benefit from pulmonary ablation. Similar with lung metastat-

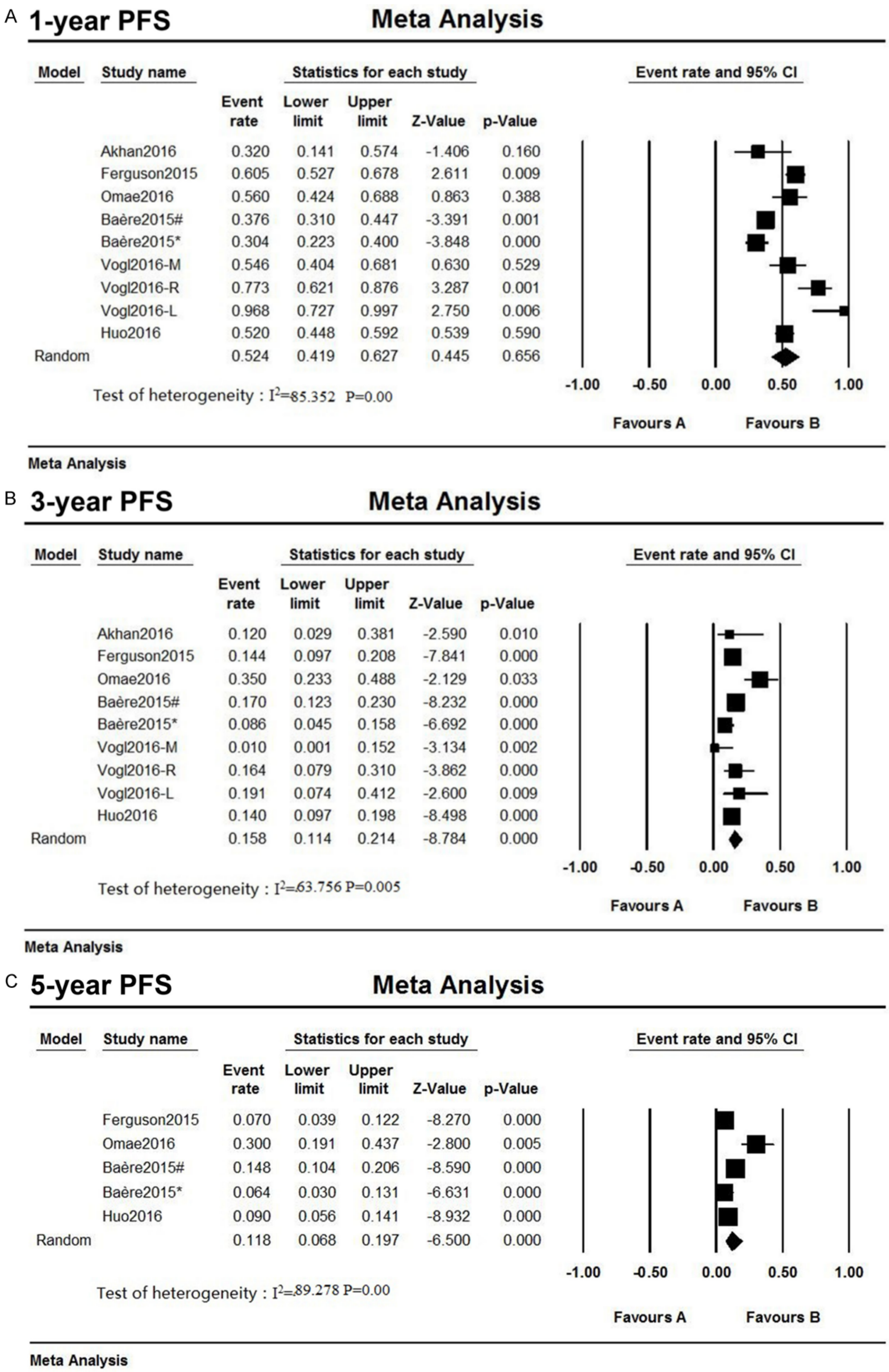

A
1-year PFS
Meta Analysis
Model
Study name
Statistics for each study
Event rate and 95% CI
Event rate
Lower limit
Upper limit
Z-Value
p-Value
Akhan2016 0.320 0.141 0.574 -1.406 0.160
Ferguson2015 0.605 0.527 0.678 2.611 0.009
Omae2016 0.560 0.424 0.688 0.863 0.388
Baère2015# 0.376 0.310 0.447 -3.391 0.001
Baère2015* 0.304 0.223 0.400 -3.848 0.000
Vogl2016-M 0.546 0.404 0.681 0.630 0.529
Vogl2016-R 0.773 0.621 0.876 3.287 0.001
Vogl2016-L 0.968 0.727 0.997 2.750 0.006
Huo2016 0.520 0.448 0.592 0.539 0.590
Random 0.524 0.419 0.627 0.445 0.656
-1.00 -0.50 0.00 0.50 1.00
Test of heterogeneity : I2=85.352 P=0.00
Favours A
Favours B
Meta Analysis
B
3-year PFS
Meta Analysis
Model
Study name
Statistics for each study
Event rate and 95% CI
Event rate
Lower limit
Upper limit
Z-Value
p-Value
Akhan2016 0.120 0.029 0.381 -2.590 0.010
Ferguson2015 0.144 0.097 0.208 -7.841 0.000
Omae2016 0.350 0.233 0.488 -2.129 0.033
Baère2015# 0.170 0.123 0.230 -8.232 0.000
Baère2015* 0.086 0.045 0.158 -6.692 0.000
Vogl2016-M 0.010 0.001 0.152 -3.134 0.002
Vogl2016-R 0.164 0.079 0.310 -3.862 0.000
Vogl2016-L 0.191 0.074 0.412 -2.600 0.009
Huo2016 0.140 0.097 0.198 -8.498 0.000
Random 0.158 0.114 0.214 -8.784 0.000
-1.00 -0.50 0.00 0.50 1.00
Test of heterogeneity : I2=63.756 P=0.005
Favours A
Favours B
Meta Analysis
C
5-year PFS
Meta Analysis
Model
Study name
Statistics for each study
Event rate and 95% CI
Event rate
Lower limit
Upper limit
Z-Value
p-Value
Ferguson2015 0.070 0.039 0.122 -8.270 0.000
Omae2016 0.300 0.191 0.437 -2.800 0.005
Baère2015# 0.148 0.104 0.206 -8.590 0.000
Baère2015* 0.064 0.030 0.131 -6.631 0.000
Huo2016 0.090 0.056 0.141 -8.932 0.000
Random 0.118 0.068 0.197 -6.500 0.000
-1.00 -0.50 0.00 0.50 1.00
Test of heterogeneity : I2=89.278 P=0.00
Favours A
Favours B
Meta Analysis

Figure 3. Meta-analysis results of progression-free survival (PFS).

ic surgical resection [41], the mentioned good prognostic factors after pulmonary ablation were: the small volume lesion, a cutoff of tumor diameter maybe ≤ 3 cm, the single lung metastasis, tumors without extrapulmonary metastasis; normal serum CEA. However, the prognostic data were conflicting. Our meta-analysis focused on this aspect. Among the literatures included in our study, there were 8 conducted the prognostic analysis. Because of the insufficient data of 5-year OS in these literatures, we only evaluated 1-year and 3-year OS. Most studies suggested patients of CPM might gain a better survival when the small volume lesion was treated by pulmonary ablation. Yamakado's study showed a 3-year OS 46% after pulmonary ablation for that unresectable CPM. When the tumor was less than 3 cm and had no extrapulmonary metastasis for a selected subgroup of patients, 3-year OS rose to 78% [13]. Certainly, there were still different viewpoints. Among the 8 included literatures, 3 studies suggested that tumor size had little effect on survival [11, 12, 18]. In these 3 studies, the investigators considered 1.5 cm or 2 cm instead of 3 cm as the critical point of tumor size. In our meta-analysis, we considered 3 cm as the critical point of tumor size. Our result showed pulmonary ablation was more suitable for small volume tumors with a diameter ≤ 3 cm. The diameter of tumor ≤ 3 cm had a significantly better survival rate at 1-year OS (88.9% vs 62.1%, $P < 0.01$) and 3-year OS (56.2% vs 25.1%, $P = 0.006$). The different conclusions between these studies might be caused by the selection of critical point of tumor size. However, some studies have found no significant relationship between the survival rate and the size of CPM treated by pulmonary metastasectomy [42, 43]. The cause might be associated with complete surgical removal. Compared with pulmonary ablation, pulmonary metastasectomy is still the first choice for these patients with tumor size exceeded 3 cm.

Similar to the size of CPM, arguments also existed as to whether the number of metastasis affected the survival rate after pulmonary ablation of CPM. DeBaère's prospective study showed a number of metastases ≥ 3 was significantly associated with OS and Yamakado' study in 2009 reported the similar conclusion [14, 17]. But a study designed by Yamakado in 2007 showed a different result, that the number of pulmonary metastases did not appear to alter the outcome [13]. In our meta-analysis, multiple tumors may be related to a worse prognosis than a single tumor. CPM with a single tumor after pulmonary ablation had a better 3-year OS than those with multiple tumors (55.7% vs 40.1%, $P = 0.01$), while their 1-year OS had no statistical difference (90.7% vs 85.3%, $P = 0.159$). Despite the controversies exist among different studies about the prognostic effect of tumor size and the number of tumors after ablation for CPM, the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) issued the standards of practice based on expert consensus in 2012. The standards stated that, if the therapy of pulmonary ablation would be selected for CPM, the maximum diameter of lesions should not exceed 3 cm and the number of lesions should not exceed 5 [44]. We look forward to perform more large-sample, high-quality prospective studies to confirm the effect of the number of metastatic tumors on OS for CPM after ablation.

Extrapulmonary metastasis is also consistently reported to have a negative impact on survival outcomes. In our meta-analysis, after pulmonary ablation, the subgroup without extrapulmonary metastasis of CPM had a better survival time than those with extrapulmonary metastasis at 1-year survival (96.4% vs 75.5%, $P < 0.01$) and 3-year survival (64.7% vs 8.6%, $P < 0.01$). Elevated serum level of CEA has usually been considered to be an independent negative prognostic factor after ablation [14, 21, 24]. CEA expressed on the apical surface of colonic epithelial cells that is involved in intracellular recognition and adhesion of tumor cells to host cells [45, 46]. Serum CEA level is an indication of the total tumor mass and invasiveness. In our study, CPM with CEA negative had a better 1-year OS (92.5% vs 79.1%, $P = 0.001$) and 3-year OS (75.3% vs 26.4%, $P < 0.01$) than those with CEA positive. Based on our meta-analysis, in summary, tumor size ≤ 3 cm, a single lesion, normal CEA level and without extrapulmonary metastasis were associated with a better prognosis.

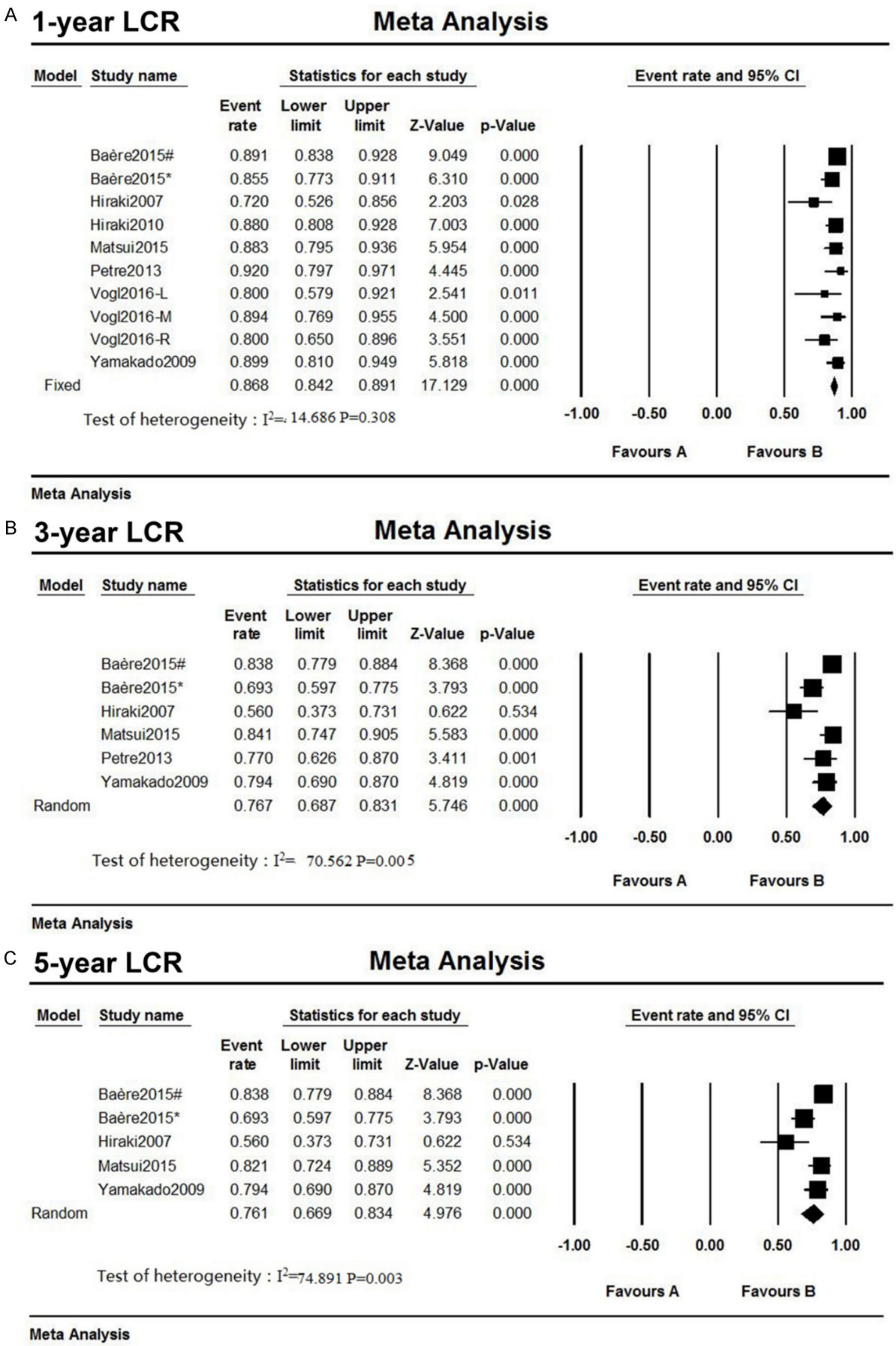


Figure 4. Meta-analysis results of local control rate (LCR).

Table 3. The prognosis factors affected the outcomes

OS	T ≤ 3 cm	T > 3 cm	*P*	Single tumor	Multiple tumor	*P*	Extrapulmonary metastasis (-)	Extrapulmonary metastasis (+)	*P*	CEA (-)	CEA (+)	*P*
1 year	88.9% (n = 173)	62.1% (n = 31)	< 0.01	90.7% (n = 144)	85.3% (n = 161)	0.159	96.4% (n = 156)	75.5% (n = 104)	< 0.01	92.5% (n = 160)	79.1% (n = 172)	0.001
3 year	56.2% (n = 173)	25.1% (n = 21)	0.006	55.7% (n = 133)	40.1% (n = 161)	0.01	64.7% (n = 156)	8.6% (n = 104)	< 0.01	75.3% (n = 149)	26.4% (n = 172)	< 0.01

OS, overall survival; T, tumor size.

In conclusion, ablation is a kind of simple, safe treatment for CPM. It may gain a similar OS and LCR with pulmonary metastasectomy. Those patients of CPM with a tumor size ≤ 3 cm, a single lesion, normal CEA level and without extrapulmonary metastasis are most likely to benefit from ablation treatment. However, this meta-analysis has some limitations. The OS is not a very suitable indicator for the efficacy of treatment, because OS is highly influenced by the patients selected for ablation. The inherent differences in the selected patients could affect OS, such as different treatments before or after ablation, the level of the operation. Compared with OS, LCR is probably a better marker. However, factors associated with the LCR of thermal ablation need be further investigated. Some other limitations still existed in our meta-analysis. The studies included were deficient in randomized control trials, and only 6 out of 18 studies involved were prospective. The lack of prospective randomized controlled trials made the effect of ablation still controversial. We look forward to perform more large-sample, high-quality prospective randomized control studies to confirm the effect of pulmonary ablation for CPM. Furthermore, randomized trials comparing ablation with surgery or chemotherapy or observation are also needed collectively.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (Grant No. 81502279).

Disclosure of conflict of interest

None.

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