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ORIGINAL ARTICLE

CT-guided percutaneous radiofrequency ablation for lung metastases from colorectal cancer

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Abstract

Background Radiofrequency ablation (RFA) can be a minimally invasive therapeutic option in patients with lung metastasis from colorectal caner. We aimed to elucidate the safety and survival benefit of computed tomography (CT)-guided percutaneous RFA for lung metastasis from colorectal cancer.

Methods A total 188 lesions were ablated in 43 patients from 2005 to 2017. The clinicopathological and survival data of patients were collected retrospectively. The short- and long-term outcomes and prognostic factors were analyzed.

Results Eight patients (18.6%) had viable extrapulmonary metastasis at RFA treatment. The median number of treated lung tumors was 2, and the median maximum diameter was 12 mm. Complications, such as pneumothorax, pleural effusion and subcutaneous emphysema, occurred in 24 (55.8%) patients. Although chest tube drainage for pneumothorax was needed in 6 patients (14.0%), there were no mortalities. Repeated RFA for lung recurrence after primary RFA was performed in 14 patients (32.6%). In a median follow-up of 24.3 months, the median progression-free and overall survival (OS) were 6.8 months and 52.7 months, respectively. The presence of extrapulmonary metastasis and a maximum tumors size of > 15 mm were independently associated with a worse disease-free survival and OS. The OS of patients who underwent repeated RFA was significantly better than that of patients who underwent RFA only once.

Conclusion CT-guided percutaneous RFA for lung metastasis from colorectal cancer is a safe and effective procedure in patients not eligible for surgery, particularly for lesions smaller than 1.5 cm without extrapulmonary metastasis.

Keywords RFA · Colorectal cancer · Lung metastasis · Prognosis

Introduction

The lung is the second-most common site of colorectal cancer metastasis after the liver. During the course of the disease, nearly 20% of diagnosed patients develop solitary or multiple lung metastasis, and less than 5% remain alive at 5 years if untreated [1–8]. Even though the treatment of metastatic colorectal cancer is based mainly on systemic therapy, surgical resection has often been used to achieve a cure in recent years. The efficacy of surgical metastasectomy is reasonable, with a 5-year survival rate of 26–69% depending on several factors, such as the histology of the primary tumor, the completeness of resection and the number of lesions [9–12]. However, surgical resection can sometimes appear too aggressive for patients that are affected by systemic diseases. In addition, patients with systemic comorbidities or respiratory disorder due to previous lung surgery are not suitable for surgical metastasectomy with general anesthesia.

For these reasons, in the last decade, several non-surgical treatments have been developed. One of these new approaches is radiofrequency ablation (RFA), which was defined in an international study in 2004 as a minimally invasive tool for local disease control, with negligible mortality, low morbidity, short hospital stay and a gain in the

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quality of life [13]. Several studies have shown that lung RFA is feasible, but the long-term outcomes have rarely been reported [14–16].

The aim of this retrospective study was to elucidate the short- and long-term outcomes of computed tomography (CT)-guided percutaneous RFA for lung metastasis from colorectal cancer. The possible risk factors affecting the overall survival (OS) and progression-free survival (PFS) were analyzed. The prognosis of patients who underwent lung RFA repeatedly for lung recurrence after primary RFA was also analyzed.

Patients and methods

Patients

The study population was 43 Japanese colorectal cancer patients who underwent CT-guided percutaneous RFA for lung metastasis at Kumamoto University Hospital between August 2005 and April 2017. The local ethics committee's approval and signed informed consent were obtained. Investigations before RFA treatment included a clinical assessment, CT, ^{18}F-deoxyglucose positron emission tomography (FDG-PET) and the estimation of serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels (cut-off levels of 3.4 ng/ml, 37 U/ml, respectively). The patients undergoing lung RFA were judged to be inoperable because of the distribution, number or bilaterality of the lesions, comorbid disease, uncorrectable coagulopathy or refusal of surgery. At our institution, the indication for lung RFA is not determined by the number of tumors or bilaterality of the lesions. In principle, lung metastases located in the bilateral lungs are treated with multiple courses of lung RFA to avoid severe complications. Patients with respiratory disorder due to a previous lung surgery are not suitable for surgical metastasectomy with general anesthesia and are instead indicated for lung RFA, which has little effect on the respiratory function. Patients with progressive extrapulmonary metastasis were excluded. Patients with lung recurrence after RFA (new lesion or recurrence at the therapeutic site) without progressive extrapulmonary metastasis can be a good candidate of repeated RFA. The 43 patients with 127 lung metastases were treated, and in 14 of these 43 patients, 61 lung recurrences after RFA were treated with repeated RFA.

CT-guided percutaneous RFA protocol

All procedures were performed under conscious sedation and local anesthesia using CT guidance. The patients' vital signs were monitored continuously during the procedure. The electrode needle was inserted and positioned toward the targeted area. The needle was deployed to start ablation. For tumors ≤ 20 mm or > 20 mm in size, a needle with a 20-mm and 30-mm expandable tip, respectively, was used. We used an RF 2000 generator and LeVeen electrodes (Boston Scientific Corporation, Natick, MA, USA). Initially, the RF power was set at 20 W for tumors ≤ 20 mm and 30 W for tumors > 20 mm and then increased by 5 W at 2-min intervals. The maximum RF power was 80 W. Ablation was completed at ''roll-off'', at which point the impedance reaches its maximum and RF is automatically shut off. Several power applications of lung RFA for a single mass to ablate the entire tumor mass (known as overlapping ablation [17]) were performed for large tumors or tumors located near large vessels. The proximity of large vessels (> 3 mm) dissipates the energy of RFA, creating a heat sink effect and causing treatment failure [18]. We therefore believe that lung metastasis near large vessels is a good indication for surgical resection. If patients cannot undergo surgery for some reason, overlapping ablation that is several power applications of lung RFA for a single mass can be performed to maximize the therapeutic effect.

Patients were admitted to the hospital for at least 1 day for observation. Chest CT was performed the following day to exclude pneumothorax. Patients who had large or clinically significant pneumothorax required chest drains. Small and asymptomatic pneumothoraces were managed conservatively.

Follow-up

After lung RFA, patients were followed up at 1 month and at 3–6 month intervals for 5 years unless the clinical need changed during the intervening period. The levels of CEA and CA19-9 were tested every follow-up, and CT was performed every 6 months. Recurrence was defined as the development of new distant pulmonary and extrapulmonary lesions with increasing size over time, enhancement of the tumor on contrast-enhanced CT, an abnormal FDG uptake on PDG-PET, and the development of such lesions at the treatment site following established involution after lung RFA.

Statistical analyses

Survival curves were plotted according to the Kaplan–Meier method, with the differences between two curves analyzed using the log-rank test. The independent factors associated with the PFS and OS were evaluated using a Cox regression analysis. All statistical analyses were performed using the SPSS software program (version 11; IBM, Chicago, IL, USA). P values of < 0.05 were considered to indicate statistical significance.

Results

The characteristics of the patients who underwent CT-guided percutaneous RFA for lung metastasis from colorectal cancer are summarized in Table 1. Seventeen of the 43 patients (39.5%) had comorbidities, such as hypertension, diabetes mellitus, cerebral infarction, hepatitis or autoimmune disease. Respiratory disorder was seen in 16 of the 43 patients (37.2%; obstructive disorder: 7, restrictive disorder: 8, mixed: 1). Primary colorectal cancer was located at the right-side colon (cecum, ascending colon and transverse colon) in 8 patients (18.6%) and left-side colon (descending colon, and sigmoid colon) and rectum in 35 patients (81.4%). Eight patients (18.6%) had viable extrapulmonary metastasis (liver, adrenal gland, bone, ovary, lymph node, peritoneal dissemination, local recurrence) at RFA treatment. Lung resection and liver resection for colorectal cancer metastasis had been previously performed in 18 (41.9%) and 15 (34.9%) patients, respectively.

Table 1 Patients' characteristics

Factor	Variable	Value
Age at RFA, years	Mean (range)	64.8 (34–83)
Gender	M/F	28/15
Comorbidity	Absent/present	26/17
Respiratory disorder	Absent/present	27/16
Primary tumor location	Cecum	1
	Ascending colon	4
	Transverse colon	3
	Descending colon	2
	Sigmoid colon	10
	Rectum	23
Lung metastasis	Synchronous	8
	Metachronous	35
Extrapulmonary metastasis	Absent/present	35/8
Previous lung resection	−/+	25/18
Previous liver resection	−/+	28/15
Chemotherapy for lung metastasis prior to RFA	−/+	14/29
CEA	Negative/positive	27/16
CA19-9	Negative/positive	39/4

RFA radiofrequency ablation

The details about lung metastasis treated with RFA and short-term outcome are summarized in Table 2. The median number of treated lung tumors was 2 (range 1–16), and the median maximum diameter was 12 mm (range 5–34 mm). Lung tumors in the bilateral lungs were treated in 19 patients (44.2%). Complications, such as pneumothorax, pleural effusion and subcutaneous emphysema, occurred after RFA in 24 (55.8%) patients. Although chest tube drainage for pneumothorax was needed in 6 patients (14.0%), there were no mortalities. Diaphragm injury is reportedly a serious adverse event that occurs after liver and lung RFA when the tumor is located directly under the diaphragm [19]; however, no patients in the present study experienced diaphragm injury. Repeated RFA for lung recurrence after primary RFA was performed in 14 patients (32.6%), and the median RFA frequency was 2 (range 2–9).

Figure 1 shows the Kaplan–Meier analysis for the PFS and OS of the 43 patients after lung RFA. During follow-up after RFA (median follow-up time: 24.3 months), 35 patients (81.4%) had recurrence. Twenty-seven patients (62.8%) experienced lung recurrence. Among them, only 4 patients (9.3%) showed local recurrence at the therapeutic site, and the other 23 patients experienced new lesions in the lung. The median PFS was 6.8 months (Fig. 1a), and the median OS was 52.7 months (Fig. 1b).

Tables 3 and 4 show the Cox regression analysis findings for the PFS and OS. Among the factors listed in the tables, the presence of extrapulmonary metastasis and a maximum tumor size exceeding 15 mm were associated a worse PFS in the univariate analysis, and both were independent

Table 2 RFA for colorectal cancer lung metastasis

Factor	Variable	Value
Number of treated tumors	Median (range)	2 (1–16)
Maximum diameter of tumors (mm)	Median (range)	12 (5–34)
Location	Unilateral/bilateral	24/19
Complications	None	19
	Pneumothorax[a]	22
	Pleural effusion	1
	Subcutaneous emphysema	1
Hospital stay after RFA	Median (range)	4 (1–51)
Mortality		0
Repeated RFA for lung recurrence[b]	−/+	29/14

RFA radiofrequency ablation

[a]Chest tube drainage for pneumothorax was needed in 6 patients (14.0%)

[b]The median RFA frequency in patients who underwent repeated RFA was 2 (range 2–9)

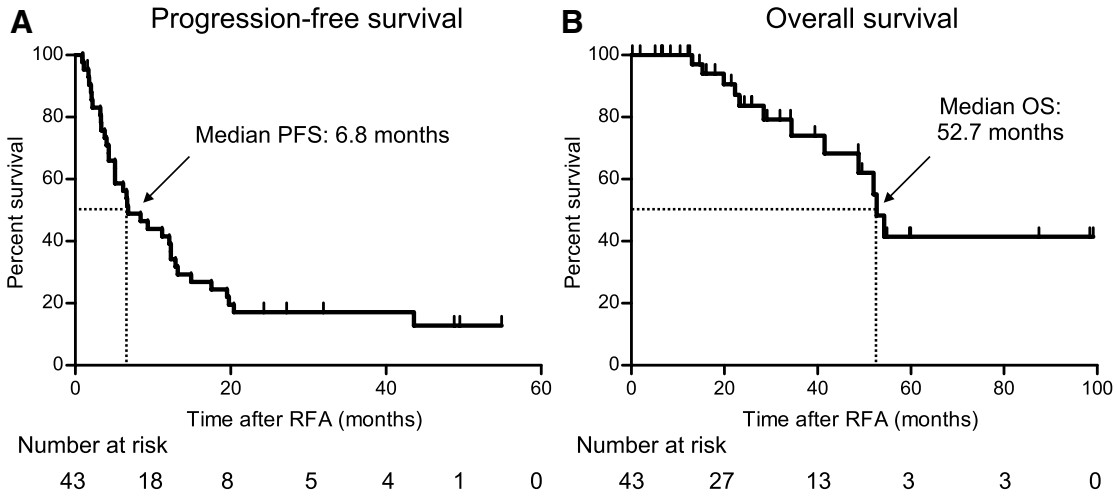

Fig. 1 The survival of 43 patients after lung RFA. The Kaplan–Meier analysis shows the progression-free survival (PFS) (**a**) and overall survival (OS) (**b**) after lung RFA. The median follow-up time was 24.3 months. The median PFS was 6.8 months (**a**), and the median OS was 52.7 months (**b**)

prognostic factors in the multivariate analysis (Table 3). With regard to the OS, the presence of extrapulmonary metastasis, a tumor marker CEA level exceeding 5 ng/ml and a maximum tumor size exceeding 15 mm were associated with a worse OS in the univariate analysis. In the multivariate analysis, only extrapulmonary metastasis and the tumor size were found to be independent prognostic factors, similar to our findings for the PFS (Table 4).

Figure 2 shows a comparison of the OS after lung RFA between patients who underwent RFA once and those who underwent repeated RFA for lung recurrence after primary RFA. The OS of patients who underwent repeated RFA was significantly better than that of patients who underwent RFA only once (log-rank test $P = 0.0123$).

Discussion

In the present study, the treatment outcomes of CT-guided percutaneous RFA for 43 patients with lung metastasis from colorectal cancer were analyzed retrospectively to elucidate the safety and efficacy of the treatment. Although 14% of patients experienced pneumothorax requiring chest tube drainage, there were no mortalities. The median PFS and OS were 6.8 months and 52.7 months, respectively. The presence of extrapulmonary metastasis and a maximum tumor size of > 15 mm were independent prognostic factors for both the PFS and OS. In addition, the OS of patients who underwent repeated RFA was significantly better than that of patients who underwent RFA only once.

The most frequent complication of lung RFA is pneumothorax, which occasionally requires chest tube drainage. In previous reports, although nearly 50% of patients developed pneumothorax, only 20% of those eventually required chest tube placement and remained hospitalized for fewer than 4 days. In addition, the procedure-related mortality rate was very low (< 1%) [20–22]. In the present study, the short-term outcomes, such as the incidence of pneumothorax (51%), the number of patients requiring chest tube drainage (14%), the mortality rate (0%) and the median hospital stay (4 days), were similar to those of previous reports. These findings suggest that lung RFA is a safe and feasible procedure with an acceptable morbidity rate.

With regard to the survival, the prognostic role of RFA for the treatment of lung metastasis from colorectal cancer has been evaluated with an adequate follow-up period. Previous studies reported a median OS of 33 months in 55 patients [15], 33 months in 27 patients [18], 38 months in 78 patients [23], 41 months in 122 patients [24], 46 months in 45 patients [25] and 51 months in 148 patients [26]. The improved results in the present study (median OS: 52.7 months) may be due to several reasons. For example, the size of the lung tumor may be related to the OS. In the present study, the median tumor size was 12 mm, and a tumor size exceeding 15 mm was an independent predictor of a worse prognosis. In contrast, the mean lung tumor size treated by RFA in the previous studies ranged from 15 to 24 mm [15, 18, 24, 25, 27]. This bigger size may have been associated with a worse OS in those studies. Indeed, the tumor size has been reported as an independent prognostic factor in other previous studies as well. Both Yan et al. and Yamakado et al. reported that a tumor size exceeding 3 cm was independently associated with a reduced survival [15, 27]. Our finding that a tumor size exceeding 15 mm was an independent prognostic factor may therefore be a relatively strict criterion for patient selection of lung RFA. Another

Table 3 Cox regression analyses for the progression-free survival after lung RFA

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age at RFA (years)				
≤ 64	1	0.242		
≥ 65	1.499 (0.761–2.951)			
Gender				
Male	1	0.192		
Female	0.619 (0.301–1.273)			
Primary tumor location				
Right-side	1	0.743		
Left-side	1.159 (0.479–2.804)			
Lung metastasis				
Synchronous	1	0.904		
Metachronous	0.947 (0.392–2.289)			
Extrapulmonary metastasis				
Absent	1	0.032	1	0.026
Present	2.608 (1.083–6.279)		2.742 (1.130–6.651)	
Previous lung resection				
−	1	0.670		
+	0.861 (0.432–1.715)			
Previous liver resection				
−	1	0.817		
+	1.086 (0.539–2.188)			
Chemotherapy for lung metastasis				
−	1	0.758		
+	0.895 (0.443–1.810)			
CEA (ng/ml)				
< 5	1	0.368		
≥ 5	1.440 (0.651–3.183)			
Number of tumors				
≤ 2	1	0.564		
≥ 3	1.251 (0.584–2.679)			
Maximum size of tumors (mm)				
< 15	1	0.017	1	0.013
≥ 15	2.358 (1.169–4.757)		2.437 (1.202–4.941)	

CI confidence interval, *HR* hazard ratio, *RFA* radiofrequency ablation

reason for the improved survival in our study over previous studies may be the frequency of extrapulmonary metastasis. The presence of extrapulmonary metastasis (8/43: 18.6%) at the time of RFA was an independent predictor of a worse prognosis in the present study. However, the frequency of extrapulmonary metastasis was reported to range from 20 to 47% in previous studies [23–25], and this higher frequency of extrapulmonary metastasis may have resulted in a worse OS than in our study. Furthermore, in our series, 34.9% of patients had experienced liver resection prior to lung RFA, and 67.4% of patients were treated with systemic chemotherapy for lung metastasis before RFA. Although a history of liver resection and systemic chemotherapy were not independent prognostic factors in the present study, recent advances in treatment approaches, such as multidisciplinary treatments for metastatic colorectal cancer, may have imbued a survival benefit in our patients. Other predictive factors of a worse OS, such as ≥ 3 metastases and increased levels of the tumor marker CEA, were identified in previous reports [23, 25, 28]. However, although the CEA level was significantly associated with a poor OS in our univariate analysis, neither the number of metastases nor the CEA level were found to be independent survival predictors. As shown in Table 1, 29 of 43 patients (67.4%) were treated with some kind of systemic chemotherapy for lung metastasis or comorbid extrapulmonary metastasis prior to lung RFA. We wondered if the response to chemotherapy was associated with the prognosis after lung RFA. If the response was indeed associated with the prognosis, patients with a good response to chemotherapy may be good candidates for lung RFA. However, our data did not show a significant association between the response to chemotherapy prior to

Table 4 Cox regression analyses for the cancer-specific survival after lung RFA

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age at RFA (years)				
≤ 64	1	0.785		
≥ 65	0.852 (0.270–2.692)			
Gender				
Male	1	0.484		
Female	1.503 (0.480–4.706)			
Primary tumor location				
Right-side	1	0.866		
Left-side	1.141 (0.247–5.280)			
Lung metastasis				
Synchronous	1	0.117		
Metachronous	0.380 (0.113–1.272)			
Extrapulmonary metastasis				
Absent	1	0.007	1	0.012
Present	4.846 (1.549–15.157)		5.368 (1.438–20.038)	
Previous lung resection				
−	1	0.803		
+	1.160 (0.361–3.729)			
Previous liver resection				
−	1	0.433		
+	0.592 (0.160–2.195)			
Chemotherapy for lung metastasis				
−	1	0.711		
+	0.794 (0.234–2.694)			
CEA (ng/ml)				
< 5	1	0.028	1	0.322
≥ 5	4.493 (1.172–17.227)		2.225 (0.456–10.845)	
Number of tumors				
≤ 2	1	0.875		
≥ 3	1.103 (0.324–3.758)			
Maximum size of tumors (mm)				
< 15	1	0.043	1	0.043
≥ 15	3.262 (1.037–10.263)		3.998 (1.042–15.333)	

CI confidence interval, *HR* hazard ratio, *RFA* radiofrequency ablation

lung RFA and the prognosis (data not shown). The present study is a small-scale retrospective study from a single institute, so a larger-scale prospective study is desired to discuss this issue.

An increasingly large amount of evidence has shown that colorectal tumors proximal and distal to the splenic flexure are distinct clinical and biological entities [29]. The location of the primary tumor seems to influence the outcome with adjuvant therapy and the survival with palliative chemotherapy or targeted therapy in patients with metastatic or recurrent disease. Previous studies have shown a better outcome for left-sided diseases than right-sided diseases [30–32]. However, few reports have analyzed the treatment outcome of lung RFA for colorectal cancer metastasis comparing left-sided and right-sided diseases. In the present study, tumor sidedness (left versus right) was not associated with the PFS or OS after lung RFA. This finding suggests that lung RFA may be a therapeutic option for colorectal cancer metastasis regardless of the sidedness of the primary tumor.

Lung metastases from colorectal cancer are usually of a multifocal nature and consequently pose a high risk of intrapulmonary de novo recurrence after therapy. Therefore, the treatment for lung metastasis must be repeatable and should preserve as much of the parenchyma as possible to preserve the pulmonary function. The repeatability of the procedure may also be a great advantage of RFA. The influence of RFA on the pulmonary function was found to be minimal, allowing RFA to be applied regardless of the treatment history. Yan et al. demonstrated that the OS of patients who underwent repeated RFA for pulmonary recurrence was significantly better than that of patients with non-repeated RFA [15]. In the present

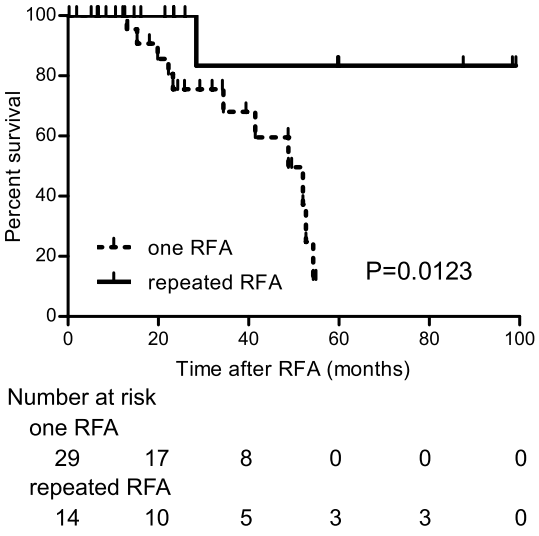

Fig. 2 A comparison of the OS between RFA once and repeated RFA patients. The Kaplan–Meier curves shows a comparison of the OS after lung RFA between patients who underwent RFA once and those who underwent repeated RFA for lung recurrence after primary RFA. A log-rank test was used

study, 14 of the 43 patients (32.6%) underwent repeated RFA for lung recurrence, and the OS of these patients was favorable, consistent with Yan's report. Patients with lung recurrence often have extrapulmonary metastases. If these metastases are controlled by local therapy, such as surgical resection and radiotherapy, or by systemic therapy, such as chemotherapy, these patients may be candidates for lung RFA. Therefore, there is selection bias in determining indications for repeated RFA for recurrent lung tumors, and the fact that the prognosis of patients who underwent repeated RFA was better than that of patients who did not is not surprising. It is important to select appropriate candidates for repeated RFA considering the patients' respiratory function and systemic disease status.

Several limitations associated with the present study warrant mention. First, this study was a retrospective analysis conducted at a single center, and the small number of patients did not allow for a meaningful analysis of the advantages of lung RFA compared with other treatments, such as lung resection or systemic chemotherapy. Selection bias could not be avoided in the patients' enrollment, as lung RFA is presently considered only for non-surgical candidates, i.e., patients with comorbidities and/or who refuse to undergo surgery. In this regard, we need to conduct a prospective, randomized trial in a large cohort of patients in the future. Another limitation is the lack of RAS/BRAF information. Recent studies have shown that the mutation status of RAS/BRAF influences the response to systemic therapies and the prognosis in colorectal cancer patients [33]. We need to gather such information in future studies, as the RAS/BRAF mutation status may influence the treatment outcome of lung RFA.

Conclusion

The results of our study confirm that CT-guided percutaneous RFA for lung metastasis from colorectal cancer is a safe and minimally invasive procedure with an acceptable morbidity, offering the possibility to safely repeat the treatment and achieve a favorable prognosis. In patients not eligible for surgery, lung RFA offers good local control of lung metastasis, even in the long-term period, particularly for lesions smaller than 1.5 cm without extrapulmonary metastasis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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