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TOPIC HIGHLIGHT

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Radiofrequency ablation as treatment for pulmonary metastasis of colorectal cancer

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Abstract

Radiofrequency ablation (RFA) causes focal coagulation necrosis in tissue. Its first clinical application was reported in 2000, and RFA has since been commonly used in both primary and metastatic lung cancer. The procedure is typically performed using computed tomography guidance, and the techniques for introducing the electrode to the tumor are simple and resemble those used in percutaneous lung biopsy. The most common complication is pneumothorax, which occurs in up to 50% of procedures; chest tube placement for pneumothorax is required in up to 25% of procedures. Other severe complications, such as pleural effusion requiring chest tube placement, infection, and nerve injury, are rare. The local efficacy depends on tumor size, and local progression after RFA is not rare, occurring in 10% or more of patients. The local progression rate is particularly high for tumors > 3 cm. Repeat RFA may be used to treat local progression. Short- to mid-term survival after RFA appears promising and is approximately 85%-95% at 1 year and 45%-55% at 3 years. Long-term survival data are sparse. Better survival may be expected for patients with small metastasis, low carcinoembryonic antigen levels, and/or no extrapulmonary metastasis. The notable advantages of RFA are that it is simple and minimally invasive; preserves pulmonary function; can be repeated; and is applicable regardless of previous treatments. Its most substantial limitation is limited local efficacy. Although surgery is still the method of choice for treatment with curative intent, the ultimate application of RFA may be to replace metastasectomy for small metastases. Randomized trials comparing RFA with surgery are needed.

Key words: Radiofrequency ablation; Pulmonary metastases; Colorectal cancer; Ablation therapy; Lung

Core tip: Radiofrequency ablation (RFA) for pulmonary metastasis of colorectal cancer is technically simple. The procedure rarely results in death. The most common complication is pneumothorax, which occurs in up to 50% of patients. Severe complications are rare. Local progression after RFA is not rare and occurs in 10% or more of cases. The short- to mid-term survival after RFA appears promising and is approximately 85%-95% at 1 year and 45%-55% at 3 years. Long-term survival data are sparse. Better survival may be expected for patients with small metastasis, low carcinoembryonic antigen levels, and/or no extrapulmonary metastasis.

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INTRODUCTION

Colon cancer is the third most common cancer and the second most common cause of cancer-related mortality in the United States, and 10%-30% of patients with colon cancer have pulmonary metastasis at presentation[1,2]. Even if metastasis is not initially present, the cancer may recur in the lungs after curative resection of the primary cancer. Kobayashi *et al*[3] surveyed 5230 patients who underwent curative resection for colorectal cancer and found that 906 patients (17%) developed recurrence at a median of 1.4 years after surgery. The first recurrence site in 250 patients (5%) was the lungs, which was the second most common site of recurrence after the liver (373 patients, 7%). Although lung recurrence is usually accompanied by recurrence at other sites, recurrence was confined to the lungs in 2%-10% of patients who develop distant metastases[4,5].

A meta-analysis demonstrated that patients with untreated locally advanced or metastatic colorectal cancer had a median survival of 8 mo[6]. The International Registry of Lung Metastases[7] revealed that the 5-year survival rate for patients who underwent complete resection of lung metastasis was 36%, compared to 13% for patients who did not undergo complete resection. A large-scale, multicenter retrospective study in Japan[3] also reported significantly better survival in patients who underwent resection for pulmonary recurrence. Thus, surgery is considered the treatment of choice for curative intent. However, that study[3] also indicated that less than half (38%) of the patients with pulmonary recurrence underwent surgical resection. Mitry *et al*[2] reported that only 4% of patients with synchronous pulmonary metastases and 14% of patients with metachronous pulmonary metastases were curatively resected. These data indicate that many patients with pulmonary metastases are not considered suitable for surgery. Therefore, the development of less invasive local therapies, such as radiofrequency ablation (RFA), may be attractive.

PRINCIPLE AND TECHNIQUES OF LUNG RFA

RFA causes focal coagulation necrosis in tissue via the delivery of energy in the form of an alternating electrical current with a frequency of 460-500 kHz in the radio wave range. The alternating electrical current causes the agitation of ionic dipolar molecules in surrounding tissue and fluids, resulting in frictional heating. The exposure of cells to temperatures of 50-52 ℃ for 4-6 min may induce cytotoxicity[8]. Between 60 ℃ and 100 ℃, there is a near instantaneous induction of protein coagulation, which irreversibly damages key cytosolic and mitochondrial enzymes, as well as nucleic acid-histone protein complexes[8]. Thus, the aim of the RFA procedure is to generate temperatures > 50 ℃ in cancer cells.

Since Dupuy *et al*[9] reported the first clinical use of RFA to treat lung cancer in 2000, RFA has been commonly used as a treatment for both primary and metastatic lung cancer. The thermal and electrical conductivity of air are low, and thus the effects of RFA on the lungs may be tissue-specific. Accordingly, it has been demonstrated that a given quantity of RF current produces a larger volume of ablation of tumors in the lungs than in subcutaneous tissues or the kidneys[10]. Conversely, alveolar air and ventilation may limit the ablation zone in the surrounding parenchyma, as saline infusion into the lung parenchyma to reduce alveolar air and bronchial balloon occlusion enlarged the ablation zone in animal experiments[11,12]. This difficulty in ablating the marginal parenchyma may account for the relatively high frequency of local progression after RFA of lung cancer.

RFA is indicated in patients who are considered non-surgical candidates and for whom the treatment of lung cancer is expected to contribute to prolonged survival. The procedure is not indicated in patients with poor performance status (*e.g.*, PS $\geqslant$ 3), leucocyte count < 3000 cells/μL, uncorrected coagulopathy (*e.g.*, a platelet count < 50000/μL or a prothrombin time-international ratio > 1.5), poor pulmonary function (*e.g.*, predicted forced respiratory volume in 1 sec $\leqslant$ 1000 mL), poor cardiac function (*e.g.*, New York Heart Association Class $\geqslant$ III), uncorrected diabetes (*e.g.*, HbA1c $\geqslant$ 7), and uncontrollable extrapulmonary cancer. The procedure is feasible, but patients with tumors in contact with the heart and aorta are at a higher risk of local progression[13].

The electrode used for lung RFA is usually either a multitined expandable electrode or an internally cooled electrode[14]. The multitined expandable electrode, which is more commonly used for lung RFA, consists of an array of multiple electrode tines that expand from a single, centrally positioned large needle cannula. The internally cooled electrode consists of dual-lumen needles with non-insulated active tips, in which internal cooling is achieved by continuous perfusion with chilled saline.

We suggest that the procedure should be performed by physicians who are familiar with both computed tomography (CT)-guided intervention and RFA. The procedure is usually conducted under local anesthesia, but epidural or general anesthesia may also be used. CT is the only image-guidance modality that can be used for lung RFA. CT fluoroscopy permits a near real-time image display, thereby facilitating the procedure. The techniques used to introduce the electrode into the tumor under CT guidance are simple and similar to those used in percutaneous lung biopsy. A prospective multicenter clinical trial showed that treatment was successfully completed in 99% (105/106) of patients[15]. Multiplanar reconstruction of CT images is useful for confirming proper positioning of the electrode. After introducing the electrode into the tumor, a given RF energy is applied for a variable duration. In our institution, an ablation algorithm based on electrode type is used; this algorithm has been described in the literature[16]. The procedure should aim to obtain an ablative margin of at least 0.5 cm around the tumor to treat the microscopic extension of cancer cells around

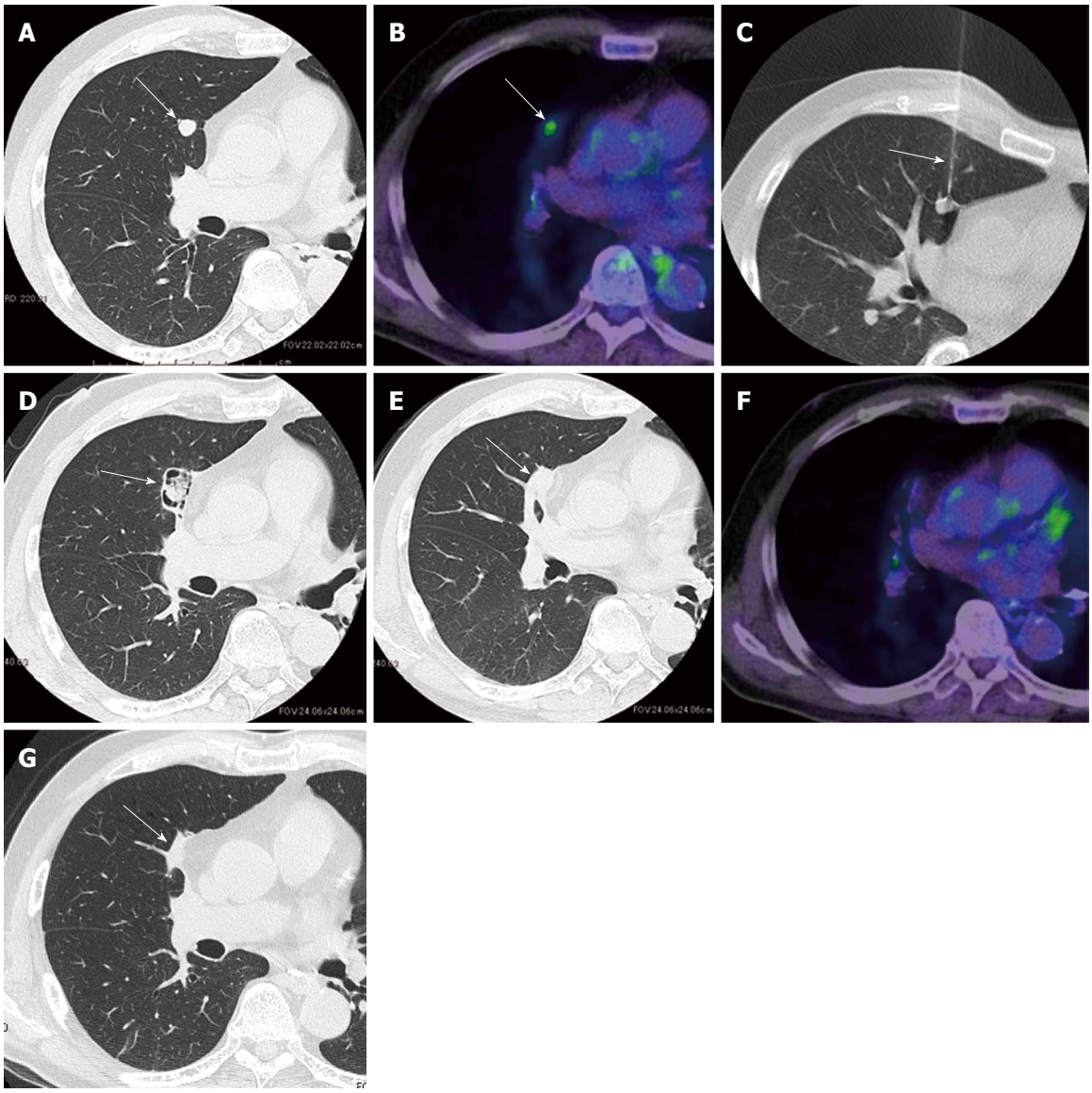

Figure 1 Pulmonary metastasis in a 68-year-old man with colorectal cancer treated with radiofrequency ablation. A: Computer tomography (CT) image before radiofrequency ablation (RFA) showing a tumor (arrow) 1.1 cm in size in the right middle lobe; B: Positron emission tomography (PET) image before RFA showing increased fluorodeoxyglucose (FDG) uptake by the tumor (arrow); C: CT fluoroscopic image obtained during RFA showing the treatment of the tumor with a multitined expandable electrode (arrow); D: CT image 1 mo after RFA showing cavity formation around the ablated tumor (arrow); E: CT image 3 mo after RFA showing cavity collapse and an increase in the size of the ablation zone (arrow) beyond the tumor size before RFA; F: PET image 6 mo after RFA showing the disappearance of FDG uptake; G: CT image 24 mo after RFA showing the shrinkage of the ablation zone (arrow) and its appearance as a focal atelectasis.

the macroscopic mass and thereby decrease the risk of local progression. To obtain an adequate ablative margin, repositioning of the electrode followed by application of RF energy (so-called "multiple overlapping ablations") may be performed.

RADIOLOGICAL EVALUATION OF LOCAL EFFICACY

Figure 1 shows radiological images of a pulmonary metastasis from a colorectal cancer patient treated with RFA. Local efficacy is evaluated primarily by sequential follow-up CT scans. During the first 6 mo after RFA, the size of the ablated lesion may exceed the tumor size before ablation because the lesion includes the ablated marginal parenchyma surrounding the tumor[17-19]. Thus, at a given time point during this period, local efficacy cannot be evaluated by comparing the tumor size with the pretreatment tumor size. Consequently, CT images are first obtained in the early period (*e.g.*, 1 mo) after RFA as a point of reference. Thereafter, it is possible to evaluate local efficacy by comparing the size and geometry of the ablation zone with the previous CT images. When the tumor is completely ablated, the ablation zone gradually decreases in size[20] and typically becomes scar-like tissue. Local tumor progression is considered to occur when the ablation zone increases in size[20]. In our experience, in most cases of local tumor progression, a nodule appears in the periphery of the ablation zone that always enlarges

if untreated. Such a nodule generally exhibits some degree of contrast enhancement that distinguishes it from the unenhanced necrotic tumor tissue[20]. Thus, contrast-enhanced CT images can be helpful in confirming the diagnosis of local progression. However, in our experience, local progression is diagnosed by careful observation of the size and geometry of the ablation zones. Therefore, we are of the opinion that contrast-enhanced CT is preferable but not essential for diagnosing local progression.

Positron emission tomography may also be used to evaluate local efficacy. Focal areas of increased fluorodeoxyglucose uptake at the ablated zone are suggestive of local tumor progression. However, attention should be paid to possible false-positive results during the first 3 mo[17,21] or even at 24 mo[22] after RFA, due to inflammation induced by RFA.

REVIEW OF STUDIES ON RFA OF PULMONARY METASTASES FROM COLORECTAL CANCER

A review of the literature was conducted by searching the PubMed database. The results were limited to studies published in English, and the search was performed with the keywords "colorectal", "lung", and "radiofrequency ablation". The citations of all electronically identified articles were further manually searched for potentially relevant studies. Human clinical studies on the efficacy of RFA of pulmonary metastases from colorectal cancer were selected, while animal experiments, case reports, and reviews were excluded. All relevant articles were subsequently evaluated.

Table 1 summarizes the results for the use of RFA to treat pulmonary metastases in patients with colorectal cancer. A group at St. George Hospital in Australia published several reports on the use of RFA to treat pulmonary metastases in patients with colorectal cancer[18,23-28]. In 2003, Steinke *et al*[18] published their preliminary study, which mainly focused on morbidity. In total, 20 nonsurgical candidates with 41 pulmonary metastases from colorectal cancer were treated with RFA. The procedure resulted in technical failure for 1 tumor. A total of 10 (50%) patients developed pneumothorax, and 5 patients (25%) required chest tube placement. Intrapulmonary hemorrhage occurred in 3 (7.5%) of the 40 tumors, but all cases were self-limiting. In 2007, Yan *et al*[26] reported the mid-term outcomes of 55 nonsurgical candidates, including morbidities, local efficacy, and survival. No hospital mortality was reported. The periprocedural morbidity rate was 42%, which included intrapulmonary bleeding (9%), pneumothorax (29%), pleural effusion (7%), and persistent pleuritic chest pain for more than 1 wk (4%). Some patients experienced more than 1 adverse event. In total, 9 patients had pneumothorax that required chest tube placement (16%). The median duration of hospital stay was 1 d, and the median follow-up period was 24 mo. The proportion of local progression at the time of the study was 38%. The 1-, 2-, and 3-year overall survival rates were 85%, 64%, and 46%, respectively, and the median overall survival was 33 mo. The 1- and 2-year local progression-free survival rates were 74% and 56%, respectively. The 1- and 2-year local progression-free survival rates were 88% and 69%, respectively, for the patients in which the largest lung metastasis was $\leqslant$ 3 cm, and 27% and 18%, respectively, for the patients in which the largest lung metastasis was > 3 cm. The 1- and 2-year overall progression-free survival rates were 61% and 34%, respectively. The median overall progression-free survival was 15 mo. Univariate analyses identified the following factors as significant for local progression-free survival: the size of the largest lung metastasis, the location of the lung metastases, and post-RFA carcinoembryonic antigen (CEA) levels at 1 and 3 mo. According to multivariate analysis, a largest lung metastasis of > 3 cm (HR = 8.3) and post-RFA CEA level of > 5 ng/mL at 1 mo (HR = 3.5) were independently associated with reduced local progression-free survival. Two factors were found to be significant for overall progression-free survival: sex and size of the largest lung metastasis. In multivariate analysis, only a largest lung metastasis of > 3 cm (HR = 5.1) was independently associated with reduced overall progression-free survival. Yan *et al*[27] also reported a learning curve for RFA in which morbidity was reduced. The same group[28] reported the outcomes of an open-label prospective trial of RFA for 148 nonsurgical candidates with lung metastases from several primary cancers; 73% of these patients had primary colorectal cancer. Although the data for the colorectal cancer patient subgroup was limited, the median overall survival for patients with colorectal cancer was found to be 60 mo.

Simon *et al*[29] reported a mixed population comprising 153 nonsurgical candidates with 189 lung cancers, including 18 patients with pulmonary metastasis from colorectal cancer. Although the data from the colorectal cancer subgroup were scarce, the 1-, 2-, 3-, and 5-year survival rates for those patients were 87%, 78%, 57%, and 57%, respectively. Lencioni *et al*[15] performed a prospective, multicenter clinical trial of RFA using a mixed population comprising 106 nonsurgical candidates with primary lung cancer and pulmonary metastasis from various primary cancers. In total, 53 patients had metastases from colorectal cancer. No procedure-related deaths occurred. Complete treatment was confirmed for $\geqslant$ 1 year in 91% of the patients with pulmonary metastases from colorectal cancer. The 1- and 2-year overall survival rates for the patients with colorectal metastases were 89% and 66%, respectively. The cancer-specific 1- and 2-year survival rates were 91% and 68%, respectively.

Hiraki *et al*[30] assessed the outcomes of 27 nonsurgical candidates with pulmonary metastases from colorectal cancer; these patients comprised a total of 41 RFA sessions. There was no mortality or sequela. Pneumothorax occurred after 49% of the sessions, and chest tube placement was required after 7.3% of the sessions. Pleural

Table 1 Summary of studies reporting outcomes of radiofrequency ablation of pulmonary metastases from colorectal cancer

Ref.	Center	Year	*n*	Patient age (yr)	No. of tumors per patient	Tumor size (cm)	Follow-up period (mo)	Mortality and morbidity	Local efficacy	Survival	Prognostic factors
Steinke *et al*[18]	St. George Hospital	2003	20	62 (mean)	2.1	1.4 (mean)	14 (median)	Mortality: 0%, Overall PTX: 50%, PTX requiring chest tube placement: 25%, Self-limiting intrapulmonary hemorrhage: 7.5%	NA	NA	NA
Yan *et al*[26]	St. George Hospital	2007	55	62 (mean)	NA	2.1 (mean)	24 (median)	Mortality: 0%, Overall morbidity rate: 42%, PTX: 29%, Pleural effusion: 7%, PTX requiring chest tube placement: 16%, Self-limiting intrapulmonary hemorrhage: 9%	Proportion of local tumor progression: 38%	1-/2-/3-year OS rate: 85%/64%/46%, respectively, Median OS: 33 mo, 1-/2-year local PFS rate: 74%/56%, respectively, 1-/2-year overall PFS rate: 61%/34%, respectively, Median overall PFS: 15 mo	Tumor size and CEA level at 1 month after RFA for local PFS by multivariate analyses, Tumor size for overall PFS by multivariate analyses
Lencioni *et al*[15]	Multicenter in the United States, United kingdom, Italy, Germany, and Australia	2008	53	63 (mean)	2.2	1.4 (mean)	NA	Mortality: 0%	Proportion of local tumor progression: 9%	OS 1-/2-year: 89%/66%, Cancer-specific survival 1-/2-year: 91%/68%	NA
Hiraki *et al*[30]	Okayama University	2007	27	62 (mean)	1.8	1.5 (mean)	20 (median)	Mortality: 0%, Overall PTX: 49%, PTX requiring chest tube placement: 7.3%, Pleural effusion: 15%,	Primary and secondary proportion of local tumor progression: 31% and 20%, respectively 1-/2-/3-year primary and secondary local control rate: 72% and 85%/56% and 62%/56% and 62%, respectively	1-/2-/3-year OS rate: 96%/54%/48%, respectively, Mean OS: 33 mo	Extrapulmonary metastasis for OS by univariate analyses
Yamakado *et al*[31]	Multicenter in Japan	2007	71	64 (mean)	2.2	2.4 (mean)	19 (mean)	Mortality: 0%, Overall PTX: 37%, PTX requiring chest tube placement: 20%, Pleural effusion: 14%, > 38 ℃ fever: 20%, Empyema requiring chest tube placement: 1.4%	Proportion of local tumor progression: 17%	1-/2-/3-year OS rate: 84%/62%/46%, respectively, Median OS: 31 mo	Extrapulmonary metastasis and tumor size for OS by multivariate analyses
Yamakado *et al*[32]	Mie University	2009	78	66 (mean)	2.5	2.0 (mean)	25 (mean)	Mortality: 0%, Overall PTX: 22%, PTX requiring chest tube placement: 13%, Pleural effusion requiring chest tube placement: 1.4%	Proportion of local tumor progression: 14%, 1-/3-/5-year local control rate: 90%/79%/79%	1-/3-/5-year OS rate: 84%/56%/35%, respectively, Median OS: 38 mo	Extrapulmonary metastasis and CEA level for OS by multivariate analyses
Petre *et al*[33]	Memorial Sloan-Kettering Cancer Center	2013	45	63 (mean)	1.5	0.4–3.5	18 (median)	Mortality: 0%, Overall PTX: 33%, PTX requiring chest tube placement: 19%, Overall pleural effusion: 5%, Pleural effusion requiring chest tube placement: 1.7%, Pneumonia: 1.7%	Primary and secondary proportion of local tumor progression: 13% and 7.2%, respectively	1-/2-/3-year OS rate: 95%/72%/50%, respectively, Median OS: 46 mo, 1-/2-/3-year primary and secondary local PFS rate: 92% and 95%/77% and 89%/77% and 89%, respectively	Number of pulmonary metastasis for OS by univariate analyses

Gillams *et al*[34]	University College London Medical School	2013	122	68 (median)	3.3	1.7 (mean)	NA	Mortality: 0%, Late procedure-related death: 0.4%, Major complication: 3.9%, PTX requiring chest tube placement: 15%, Pleural effusion requiring chest tube placement: 1.2%, Infection: 2.0%, Nerve injury: 0.8%	Proportion of local tumor progression: 19%	OS 3-year rate: 57%, Median OS: 41 mo	None

NA: Not available; PTX: Pneumothorax; OS: Overall survival; PFS: Progression-free survival; CEA: Carcinoembryonic antigen; RFA: Radiofrequency ablation.

effusion was encountered after 15% of the sessions. Local progression after RFA was observed in 31% (15/49) of the tumors; 5 of these locally progressing tumors were completely treated by repeating the procedure. Thus, local progression was observed in 20% of the tumors at the time of study. The primary local control rates were 72% at 1 year, 56% at 2 years, and 56% at 3 years. By repeating the procedure for local progression, the local control rates were improved to 85% at 1 year, 62% at 2 years, and 62% at 3 years. The 1-, 2-, and 3-year survival rates were 96%, 54%, and 48%, respectively. The mean survival time was 33 mo. Univariate analysis revealed that the presence of extrapulmonary metastasis at the time of RFA was the only significant factor associated with survival.

Yamakado *et al*[31] reported the results of a multicenter study in Japan comprising 71 nonsurgical candidates. No mortality was observed. Fever (> 38 ℃) developed in 14 patients (20%), and asymptomatic pleural effusion was observed in 10 (14%) patients. Pneumothorax developed in 26 (37%) patients, 14 (20%) of whom required a chest tube. Empyema developed in 1 (1.4%) patient. Local tumor progression was observed in 12 (17%) of the 71 patients during the mean follow-up period of 19 mo. The proportion of patients with local tumor progression was 11% (7/61) in those with tumors ≤ 3 cm and 50% (5/10) in those with tumors > 3 cm. This difference was statistically significant. The 1-, 2-, and 3-year overall survival rates were 84%, 62%, and 46%, respectively. The median survival time was 31 mo. Univariate analyses revealed that extrapulmonary metastasis, tumor size, and CEA level were significant prognostic factors. The first 2 factors were also significant according to multivariate analysis. Subsequently, Yamakado *et al*[32] reported a single-center study involving 78 patients with pulmonary metastases from colorectal cancer. The mean follow-up period was 24.6 mo. Pneumothorax developed in 22% (31/140) of the sessions, and pneumothorax and pleural effusion requiring chest tube placement occurred in 13% (18/140) and 1.4% (2/140) of the sessions, respectively. Local tumor progression was observed in 11 patients (14%). The 1-, 3-, and 5-year local tumor progression rates were 10%, 21%, and 21%, respectively. The 1-, 3-, and 5-year local tumor progression rates were 5%, 14%, and 14% in patients with tumors ≤ 3 cm and 53%, 69%, and 69% in patients with tumors > 3 cm. This difference was statistically significant. The 1-, 3-, and 5-year survival rates were 84%, 56%, and 35%, respectively, and the median survival time was 38 mo. Univariate analyses identified maximum tumor diameter of ≤ 3 cm, single-lung metastasis, absence of extrapulmonary metastasis, and normal CEA levels as prognostic factors. Multivariate analysis also indicated that the latter 2 variables were significantly independent prognostic factors. The 1-, 3-, and 5-year survival rates were 98%, 83%, and 57%, respectively, in the 54 patients with no extrapulmonary metastases and 97%, 86%, and 63%, respectively, in the 33 patients with negative CEA levels.

Petre *et al*[33] studied 45 nonsurgical candidates with 69 pulmonary metastases (< 3.5 cm) from colorectal cancer. The median hospital stay was 1 d. There was no periprocedural mortality. Pneumothorax occurred in 33% of the sessions, with 12 (19%) patients requiring a percutaneous chest tube. There were 3 cases of pleural effusion, one of which required catheter drainage. One patient developed bacterial pneumonia. The median follow-up period was 18 mo after RFA. Of the 69 lesions, local tumor progression occurred in 9 lesions (13%) at a median of 11.1 mo after RFA. Lesions > 1.5 cm had a tendency toward a higher risk of local progression compared with lesions ≤ 1.5 cm (HR = 7.03). Among the lesions that progressed, 4 were re-treated with RFA, and the secondary (after repeat ablations) effectiveness rate was 93% (64/69 lesions). The primary and secondary local tumor progression-free survival rates were 92% and 95%, respectively, at 1 year, 77% and 89%, respectively, at 2 years, and 77% and 89%, respectively, at 3 years. The median overall survival time after the RFA procedure was 46 mo. The 1-, 2-, and 3-year overall survival rates from the time of RFA were 95%, 72%, and 50%, respectively. Univariate analyses using various variables revealed that the only significant prognostic factor was the number of pulmonary metastasis at the time of RFA.

Gillams *et al*[34] performed 256 RFA procedures in 122 patients with a total of 398 metastases. The major complication rate was 3.9%. There were no cases of prolonged air leak. The 30-d mortality rate was 0%. There were 10 major complications (3.9%): 3 pleural effusions requiring drain insertion; 5 infections, including 1 delayed infection that resulted in fatal hemoptysis; and 2 nerve injuries (1 recurrent laryngeal nerve injury and 1 brachial plexus injury). Pneumothorax requiring drainage occurred in 39 (15%) of the

procedures. The local progression analysis included 268 tumors with > 6 mo of imaging follow-up data available for review. On a tumor-by-tumor basis, 52 (19%) of 268 tumors progressed locally. The mean and median times to local progression were 9 and 8 mo (range 2-27 mo), respectively. The median overall survival and 3-year survival rate were 41 mo and 57%, respectively. No significant prognostic factors were identified, although survival tended to be better in patients with smaller tumors.

In summary, RFA for colorectal pulmonary metastasis is a safe procedure that rarely results in death. The most common complication is pneumothorax, which occurs in up to 50% of procedures. Chest tube placement for pneumothorax is required after up to 25% of procedures. Other severe complications, such as pleural effusion requiring chest tube placement, infection, and nerve injury, are rare. Local tumor progression after RFA is not rare (10% or more) and is particularly common for tumors > 3 cm. Short- to mid-term survival after RFA appears promising, with survival rates of approximately 85%-95% at 1 year and 45%-55% at 3 years. Long-term (5 years or more) survival data are sparse. Significant prognostic factors include number and size of pulmonary metastases, CEA levels, and extrapulmonary metastasis.

The ultimate application of RFA may be to replace metastasectomy. Accordingly, survival data after surgical resection of pulmonary metastases from colorectal cancer should be assessed. Pfannschmidt *et al*[35] systematically reviewed 20 published series of surgical resection of pulmonary metastases from colorectal cancer. The postoperative mortality ranged from 0% to 2.4%, and approximately 40% of patients remained alive 5 years after resection. Fiorentino *et al*[36] also performed a systematic review of 51 articles on pulmonary metastasectomy in colorectal cancer. Most pulmonary metastasectomies were performed for a single metastasis. The 5-year survival rate after single metastasectomy was approximately 50%, whereas the rate after multiple metastasectomy was 30%. Recently, Gonzalez *et al*[37] performed a systematic review of 25 studies involving a total of 2925 patients and found that the median 5-year survival rate was 43.5%. At present, data for long-term survival after RFA are too sparse to compare with surgical data, although the short- to mid-term survival data are promising. In our opinion, given the high local progression rate for tumors > 3 cm after RFA, patients with such tumors should undergo surgery whenever operable. As a therapy for small tumors, RFA may be competitive with metastasectomy, which must be validated in future trials.

ADVANTAGES AND DISADVANTAGES OF LUNG RFA

RFA has various notable advantages. The procedure is simple and can be performed percutaneously using local anesthesia. The procedure is also safe and minimally invasive. Thus, RFA may enable long-term survival or even a cure for patients with pulmonary metastases who are considered nonsurgical candidates because of comorbidities and/or refusal to undergo surgery. Given that pulmonary metastases are usually of a multifocal nature and, consequently, pose a high risk of intrapulmonary *de novo* recurrence after therapy, the treatment for pulmonary metastases must be repeatable and should preserve as much of the parenchyma as possible to preserve pulmonary function. The repeatability of the procedure may also be a great advantage of RFA. Repeat procedures may also be used to effectively treat local tumor progression[38]. The influence of RFA on pulmonary function was found to be minimal[39-41], and RFA may be applied regardless of previous treatments. Consequently, this method can be used as a second salvage treatment for recurrence after surgery, radiation therapy, or chemotherapy and in combination with other treatments to eradicate multiple cancers.

There are also disadvantages of the use of RFA. CT is used for the procedure, which is associated with radiation exposure to both the patient and the physician. Thus, the use of CT fluoroscopy, although useful, should be minimized. The procedure is also accompanied by a high risk of pneumothorax. The most substantial disadvantage of RFA may be its limited local efficacy.

CONCLUSION

RFA for pulmonary metastasis of colorectal cancer is safe and minimally invasive. The most common complication, which occurs in up to 50% of cases, is pneumothorax. However, in most cases, this can be treated conservatively. The local efficacy of RFA depends on the tumor size, and local progression after RFA is not rare, occurring in 10% or more of cases. The local progression rate is particularly high for tumors > 3 cm. The short- to mid-term survival data after RFA are promising, with 1- and 3-year survival rates of approximately 85%-95% and 45%-55%, respectively. Long-term survival data remain sparse. Better survival may be expected for patients with small metastasis, low carcinoembryonic antigen levels, and/or no extrapulmonary metastasis. The ultimate application of RFA may be to replace metastasectomy for small metastases. Future studies should include randomized trials comparing RFA with surgery.

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