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INVITED REVIEW

Value of ablation therapy in the treatment of lung metastases

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Abstract

Tumor metastases are the basic biological characteristics of malignant tumors, and the lungs are the second most prominent metastatic organs in which these develop after the liver. Currently, with the rapid development of ablation technology, ablation therapy as a local treatment is playing an increasingly important role in the treatment of lung metastases. Whether alone or in combination with other treatments, ablation therapy has achieved good therapeutic effects for the treatment of partial lung metastases. This article briefly summarizes the results of current and previous ablation treatments for lung metastases, and focuses on the value of ablation therapy for different kinds of lung metastases.

Introduction

Metastasis is the basic biological characteristic of malignant tumors and the main factor leading to treatment failure or death in most tumor patients. The lungs are the second most prominent metastatic organs, after the liver, in which malignant tumors develop. Lung metastasis often occurs through the following routes: hematogenous spread, lymphatic spread, direct infiltration or overspread, and airway transcoelomic spread.[1] If patients do not receive timely and effective treatment, they may die as a result of respiratory failure.

Systemic chemotherapy is the main treatment for malignant tumors in patients with lung metastases. In recent years, with advances in chemotherapy drugs and the emergence of molecular targeted drugs, the efficacy of chemotherapy for lung metastases has significantly improved, but some patients still develop tumor progression during chemotherapy treatment.[2–5] Not all patients are tolerant to chemotherapy because of its side effects.

Surgical resection is the preferred topical treatment for lung metastases. Complete resection of lung metastases could help to prolong patient survival.[1,6] However, because of the severe trauma caused, the requirement of high patient lung function and other physical conditions, and the extent of lung metastases, many patients are not eligible for surgical treatment. Furthermore, the recurrence rate after surgical resection of lung metastases remains high, thus patients often require repeat surgical treatments.

For tumor patients with lung metastases ineligible for surgical treatment, radiotherapy and ablation therapy are currently the most commonly used local therapies. With the emergence and application of precise radiotherapy, the efficacy of radiotherapy for lung metastases has significantly improved.[7,8] However, because of radiation dose restrictions, it is not possible to apply the multiple radiation courses required to eliminate lung metastases and the patient would be intolerable to such doses. In addition, radiotherapy can cause radiation pneumonia and

pulmonary fibrosis, which in serious cases can significantly impact quality of life. Ablation therapy is increasingly used for lung metastasis treatment because of its unique characteristics, including high efficacy, minimal invasion, and strong repeatability.[9–15] The greatest advantage of ablation therapy is the ability to efficiently eliminate lung metastases and at the same time protect lung tissue. Ablation of pulmonary metastases should be performed to control the primary lesion, followed by surgery as soon as possible.

Currently, ablation therapy, whether performed alone or in combination with other treatments, has achieved good therapeutic effects for the treatment of partial lung metastases.

Ablation therapy of lung metastases from colorectal cancer

Colorectal cancer is one of the most common malignant tumors with 1.36 million new cases reported worldwide each year.[16] The liver and lung are the main sites of these metastases.[17] About 10–20% patients will develop lung metastases, with isolated lung metastases accounting for 7%.[18,19] Without treatment, the median survival duration of patients with lung metastases from colorectal cancer is eight months and the one-year survival rate is only 30%.[20]

Chemotherapy is the most important treatment for patients who develop pulmonary metastasis from colorectal cancer. Initially, systemic chemotherapy based on 5-fluorouracil increased the median survival duration to 12 months and the one-year survival rate to 50%.[21] With the continuous development of chemotherapy drugs, different combinations of oxaliplatin, irinotecan, fluorouracil, and leucovorin have effectively improved the median survival duration to 17 months.[22–24] In recent years, molecular targeted drugs, such as bevacizumab, cetuximab and panitumumab, have further increased the median survival time to 20 months.[25–28] Although chemotherapy can improve patient survival, chemotherapy is not successful in all patients because of drug resistance, side effects, poor basic patient condition, and other factors.

For patients with pulmonary metastasis from colorectal cancer, surgical resection is a positive effective treatment. Accurate and complete resection of all lung metastases is the main surgical treatment principle. Several studies have shown that patients with pulmonary metastasis from colorectal cancer who have undergone surgical resection had median survival duration of 35–50 months and five-year survival of 36–67.8%.[11,29–35] However, Inoue *et al.* reported a recurrence rate after the first surgical resection of 68% and that the lung was the most common site of recurrence.[36] The five-year survival rate after reoperation was 25–58%. However, not all patients are eligible for surgical treatment.

For patients with lung metastases from colorectal cancer that cannot be surgically resected, ablation therapy as a local treatment can effectively control and inactivate pulmonary lesions (Fig 1). The median survival duration of patients with pulmonary metastasis from colorectal cancer treated with radiofrequency ablation (RFA) is 33–67 months, the one, three, and five-year survival rates are 83.9–95%, 46–76.1% and 35–56%, respectively, and the local recurrence rate is 13–38%.[11,29,33,34,37] Therefore, ablation therapy can achieve similar efficacy as surgical resection. Meanwhile, RFA and surgery provide similar survival predictors, including the number of lung metastases, whether to perform R0 resection, preoperative ACE levels, and whether thoracic lymph node metastasis has developed.[29,33] However, it is noteworthy that pulmonary metastasis from colorectal carcinoma treated with RFA usually cannot be removed by surgery. Compared to surgery, RFA does less harm to the normal lung tissue, which does not cause changes to lung function and RFA can be repeatedly performed on the same or different lung metastases.

Inoue *et al.* conducted a study of 17 patients with colorectal carcinoma with pulmonary metastasis treated with RFA combined with systemic chemotherapy (n = 10) and systemic chemotherapy alone (n = 7).[38] The median survival duration of RFA combined with systemic chemotherapy versus systemic chemotherapy alone was 44.2 vs. 24.7, and the three-year survival rates were 87.5% vs. 33.3% (P = 0.0041), respectively. Ablation therapy combined with systemic chemotherapy was superior to chemotherapy alone for the treatment of pulmonary metastasis in colorectal carcinoma. Ablation therapy can efficiently inactivate a tumor and reduce the tumor burden in a minimally invasive way; combined with chemotherapy, it can significantly stimulate the chemotherapy effect and help to extend patient survival.

Ablation treatment, whether alone or in combination with systemic chemotherapy, can effectively eliminate lung metastases and prolong patient survival.

Ablation therapy of lung metastases from bone and soft tissue sarcoma

Bone and soft tissue sarcoma in malignant tumors originate from mesenchymal and ectodermal nerve tissue, which mostly occur at the trunk, limbs, and retroperitoneal space. Morbidity and mortality account for 1% and 2% among adult malignancies, respectively.[16]

Ten to 15% of osteosarcoma and 20% of soft tissue sarcoma patients have developed distant metastases by the time they are diagnosed, and lung metastases account for 85%.[39–41] Once metastasis occurs, treatment has a poor

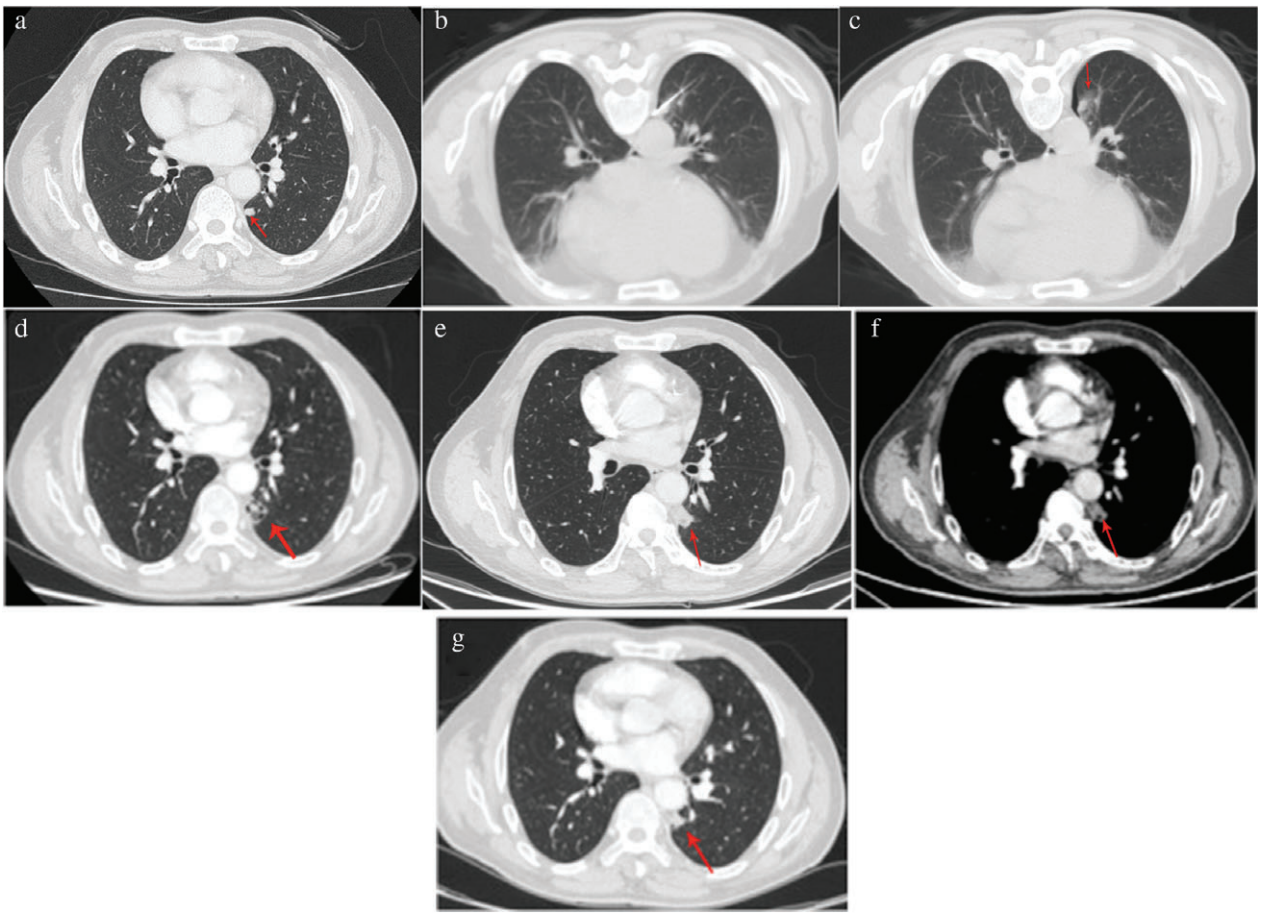

Figure 1 Ablation treatment of lung metastases from colorectal cancer. A 62-year-old man displayed left lung metastasis on computed tomography (CT) scans, after rectal adenocarcinoma surgery and seven-course systemic chemotherapy. The patient received microwave ablation for the lung metastasis under CT-guidance. No tumor recurrence was found during 11 months of follow-up. (**a**) Chest CT scans: lung metastases (red arrows) were found in the superior segment of left lower lobe near the pleural. (**b**) CT-guided microwave ablation of lung metastases. (**c**) Immediate chest CT scans after ablation: the periphery of the ablation lesion showed ground glass changes (red arrow). (**d**) Chest CT reviews one month after ablation: the ablation lesions showed mixed density changes (red arrow). (**e,f**) Chest CT reviews three months after ablation: ablation lesions showed substantial alteration without enhancement (red arrow; [**e**]: pulmonary window; [**f**]: mediastinal window). (**g**) Chest CT reviews 11 months after ablation: ablation lesions had significantly shrunk and no tumor recurrence was found.

therapeutic effect. Lung metastasis is the main cause of death in bone and soft tissue sarcoma patients.[42,43]

Despite improvements in chemotherapeutic drugs and schedules, chemotherapy continues to have poor efficacy (25%) in patients with bone or soft tissue sarcoma with metastases.[44] Chemotherapy can effectively prolong survival in patients without local or distant metastasis, but fails to improve overall survival.[45] Unfortunately, few developments have been made in systemic chemotherapy for bone and soft tissue sarcoma in recent years.

Bone and soft tissue tumors are not sensitive to conventional radiotherapy. Because of limitations to the radiation dose, radiotherapy is not effective for lung metastases in bone and soft tissue tumors. With developments in radiotherapy, stereotactic body radiotherapy (SBRT) is increasingly used in patients with bone and soft tissue tumors with lung metastasis and has achieved a promising effect.[10,46] Dhakal *et al.* found that in patients with soft tissue sarcoma with lung metastases treated with SBRT, the three-year local control rate was 82% and the median survival duration was significantly longer than in patients not treated with SBRT (2.1 vs. 0.6, respectively; $P = 0.006$).[8] Baumann *et al.* treated 39 lung metastases in 30 sarcoma patients with SBRT.[47] The one and two-year local control rates were 94% and 86% and the one and two-year survival rates were 76% and 43%, respectively.

Surgical resection is the main treatment method for patients with lung metastases from bone and soft tissue tumors. The three and five-year survival rates of surgical resection range from 25–54% and 14–25%, respectively,

but only 25–30% of patients are operable[47–50] and 40–80% patients will develop recurrence.[51] Although reoperation has been proven effective for controlling tumor recurrence, not all patients are able to tolerate reoperation.

For patients with lung metastases that cannot be surgically removed, ablation therapy is an effective supplemental treatment (Fig 2). Nakamura *et al.* performed RFA in 20 patients with lung metastases from osteosarcoma.[52] The one and three-year survival rates were 88.9% and 59%, respectively. Palussiere *et al.* conducted RFA in 29 patients with lung metastases from sarcoma.[53] The one and three-year survival rates were 92% and 63%, respectively. Koelblinger *et al.* also reported on 21 patients with lung metastases from sarcoma that underwent RFA.[12] The two and three-year survival rates were 94% and 85%, respectively. Thus, RFA can achieve a similar therapeutic effect to surgical resection for patients with lung metastases from bone and soft tissue sarcoma.

The use of surgical resection for elderly patients with lung metastases from bone and soft tissue sarcoma has long been contentious. Ginsberg *et al.* and Deslauriers *et al.* reported high rates of perioperative mortality in elderly patients after surgery.[54,55] Because it is minimally invasive, ablation treatment is an effective method for patients with lung metastases from bone and soft tissue tumors. Nakamura *et al.* performed RFA in 12 elderly patients with lung metastases from osteosarcoma.[52] The one and three-year survival rates were 81.8% and 38.4%, respectively, and the median survival time was 19 months.

Ablation therapy of lung metastases from renal cancer

Renal cancer accounts for 2–3% of adult malignancies, and is the second most common urinary system tumor after bladder cancer.[17] Twenty-five to 30% of patients have distant metastases at the time of diagnosis, and lung is the most common site of metastasis.[56]

Lung metastases from renal cancer are not sensitive to traditional radiotherapy and chemotherapy. The median survival duration is only 8–12 months and the five-year survival rate is only 2–3%.[57] Treatment with IL-2 and IFN-a based immunotherapy is effective in < 20% of patients, the overall median survival duration is only 13.3 months, and such treatment is accompanied by significant adverse reactions.[58]

With the emergence of molecular targeted therapy, sorafenib has now become one of the preferred treatments for advanced renal cell carcinoma. In a phase III clinical study conducted by Escudier *et al.*, 903 patients with advanced renal cell carcinoma who were treated with radical nephrectomy and/or cytokine but experienced disease progression were randomly assigned to sorafenib and placebo groups.[59] Overall survival in the sorafenib group was

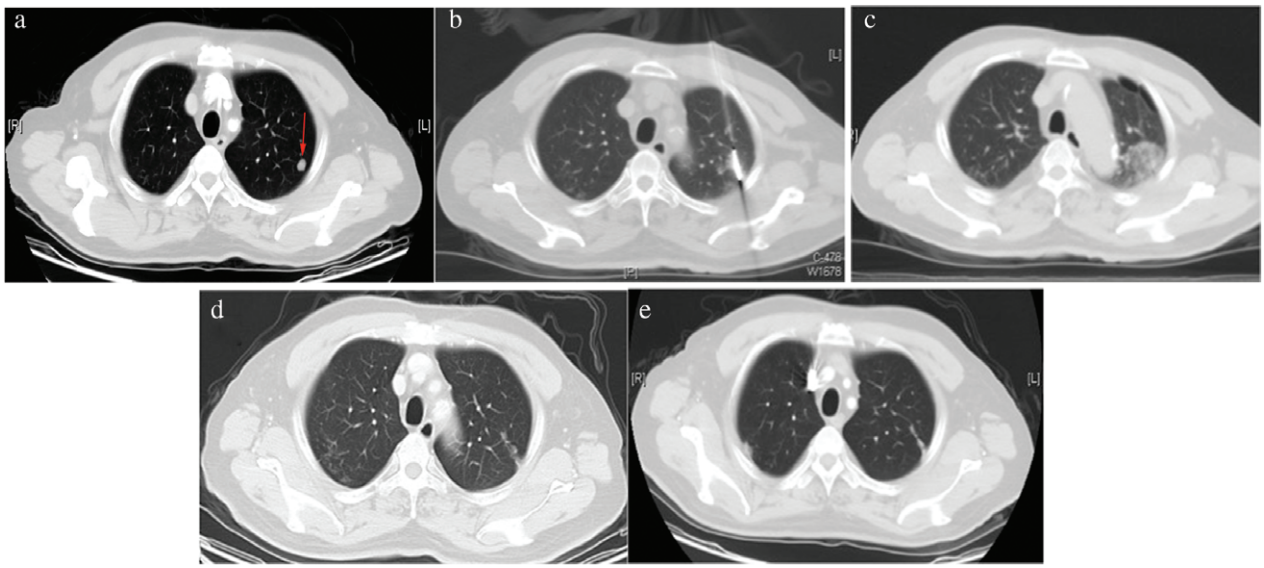

Figure 2 Ablation of lung metastases from sarcoma. A 56-year-old man displayed lung metastases on computed tomography (CT) scan four years after left nasal sarcoma resection. The patient received microwave ablation for the lung metastasis under CT-guidance. No tumor recurrence was found during five months of follow-up. (**a**). Chest CT scans shows lung metastases (red arrows) in left lung. (**b**) CT-guided microwave ablation of lung metastases. (**c**) Immediate chest CT scans after first ablation: the ablation lesion showed patchy changes. (**d**) Chest CT reviews three months after ablation: the ablation lesion became a fibrotic streak. (**e**) Chest CT reviews five months after ablation: the fibrotic streak had significantly shrunk and no tumor recurrence was found.

significantly higher than in the placebo group (17.8 vs. 14.3 months, hazard ratio 0.78; $P = 0.0287$). Although targeted therapy is more tolerable than cytokine therapy, the side effects cannot be ignored, and most patients will experience disease progression or drug resistance after a period of medication.

Surgical resection is an effective method for the treatment of lung metastasis from renal carcinoma, with the five-year survival rate ranging from 31% to 40%.[60–62] Kanzaki *et al.* performed surgical resection in 48 patients with lung metastases from renal cancer, yielding three, five, and 10-year survival rates of 60%, 47%, and 18%, respectively.[63] Alt *et al.* also performed surgical resection in 224 patients with lung metastases from renal cancer.[64] The five-year tumor-specific survival rates of the complete resection ($n = 49$) and palliative resection ($n = 175$) groups were 73.6% and 19%, respectively. However, only a small portion of patients is eligible for surgery as the extent of metastasis is too great in most patients.

In recent years, ablation therapy has been attempted as a method to treat lung metastasis from renal cancer (Fig 3). de Baère *et al.* reported a five-year survival rate of 53.8% in 68 patients with lung metastases from renal cancer.[33] Soga *et al.* used RFA to treat 39 patients with lung metastases from renal cancer.[13] There were significant differences in the overall survival rates between the curative and palliative groups at one (100% vs. 90%), three (100% vs. 52%) and five (100% vs. 52%) years ($P < 0.05$). Whether the tumor was completely eliminated was an important prognostic factor.

Ablation therapy for lung metastasis from primary liver cancer

Primary liver cancer is one of the most common malignant tumors. The number of new cases reported annually in China accounts for 50% of global liver cancer incidence. The mortality rate of primary liver cancer is the second highest after lung cancer.[17] Because there are usually no obvious symptoms in the early stage, most patients have already reached advanced stage when this disease is diagnosed, and thus, have an extremely poor prognosis. The incidence of lung metastases from primary liver cancer is as high as 20% or more, and reaches 40–73% in autopsy.[65]

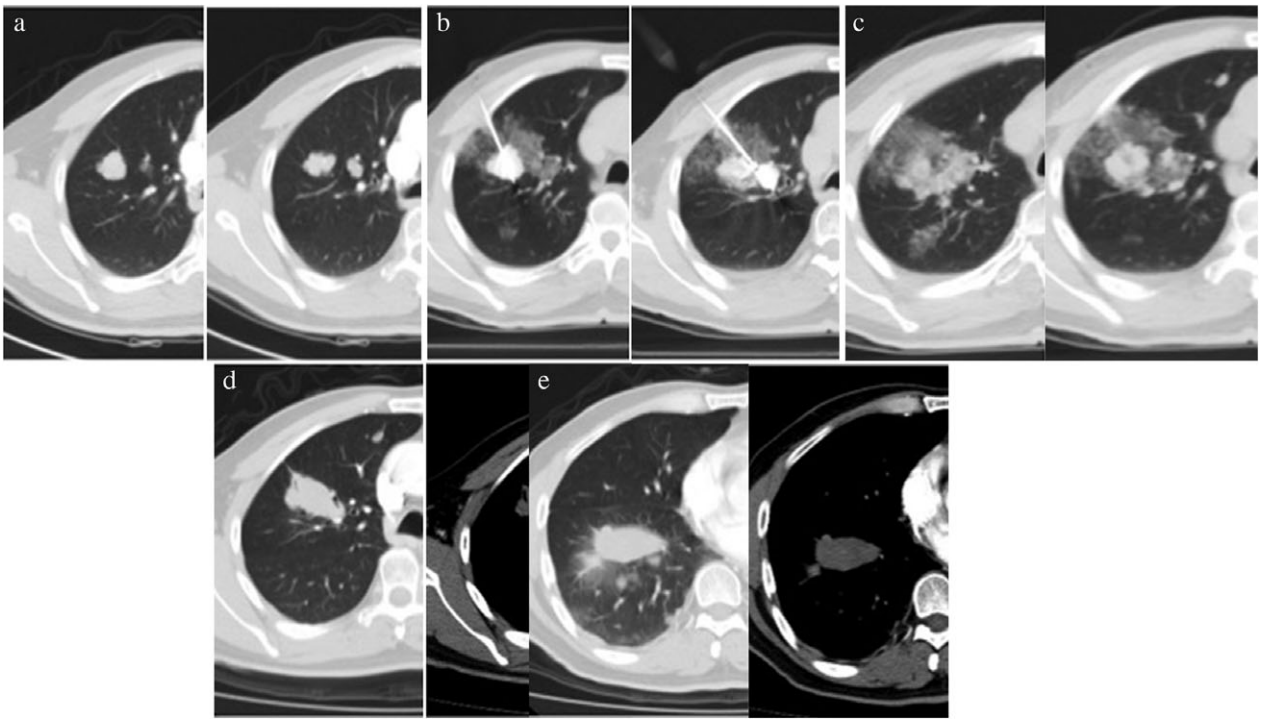

Figure 3 Ablation of lung metastases from renal cancer. A 51-year-old man with lung metastases from renal cancer received laparoscopic resection of left renal cell carcinoma in April 2010. The patient was administered sorafenib after surgery, but the lung metastases progressed. He received microwave ablation for the lung metastasis under CT-guidance. No tumor recurrence was found during two months of follow-up. (**a**) Chest computed tomography (CT) scans showed multiple metastases in the left superior lung. (**b**) CT-guided microwave ablation of lung metastases. (**c**) Immediate chest CT scans after ablation: the periphery of the ablation lesion showed ground glass changes. (**d,e**) Chest CT reviews two months after ablation: ablation lesions showed substantial alteration without enhancement and no tumor recurrence was found.

Sorafenib is the preferred treatment for lung metastases from primary liver cancer.[66] However, the low response rate, severe adverse reactions, and high cost restrict its application in patients with lung metastases from primary liver cancer.

Surgical resection of lung metastases from liver cancer can significantly improve patient survival. A study of 280 patients with lung metastases from liver cancer in Hong Kong indicated that resection of lung metastases can significantly improve patient survival.[67] The median survival duration was 40.36 and 7.46 months, and the one, three, five, and 10-year survival rates were 86.7%, 53.9%, 31.8%, and 26.9% and 34.1%, 8.1%, 3.5%, and 2.1% in resected and unresectable groups, respectively. However, because chronic hepatitis B cirrhosis is often associated with liver cancer, the patient's liver reserve function is so poor that they cannot tolerate surgical treatment for lung metastases.

If the primary lesion is well controlled, RFA could benefit patients with lung metastases from liver cancer (Fig 4). Baba *et al.* treated 83 lung metastases in 32 liver cancer patients with RFA, and the one, two, and three-year survival rates were 83%, 57%, and 57%, respectively.[14] Li *et al.* performed RFA for 68 lung metastases in 29 liver cancer patients, and the one, two, and three-year survival rates were 73.1%, 41.1%, and 30%, respectively.[68] Therefore, when good control of primary liver lesions is possible, ablation therapy is playing an increasingly important role in treatment for patients with lung metastases from primary liver cancer who cannot tolerate surgical treatment.

Ablation therapy for lung metastasis from nasopharyngeal cancer

Qi *et al.* performed microwave ablation of 29 lung metastases in 17 patients with nasopharyngeal cancer. The lung metastases were completely ablated in 27 patients and new lung metastases only occurred in five patients within the one-year follow-up period.[69] A pairing study conducted by Pan *et al.* indicated that the median survival duration of patients with lung metastases from nasopharyngeal cancer (10 cases) treated with RFA combined with chemotherapy was significantly longer than those who received chemotherapy alone (77.1 vs. 32.4 months, respectively; $P = 0.009$).[15] Although the number of cases is limited, ablation therapy has achieved good results for the treatment of lung metastasis from nasopharyngeal cancer.

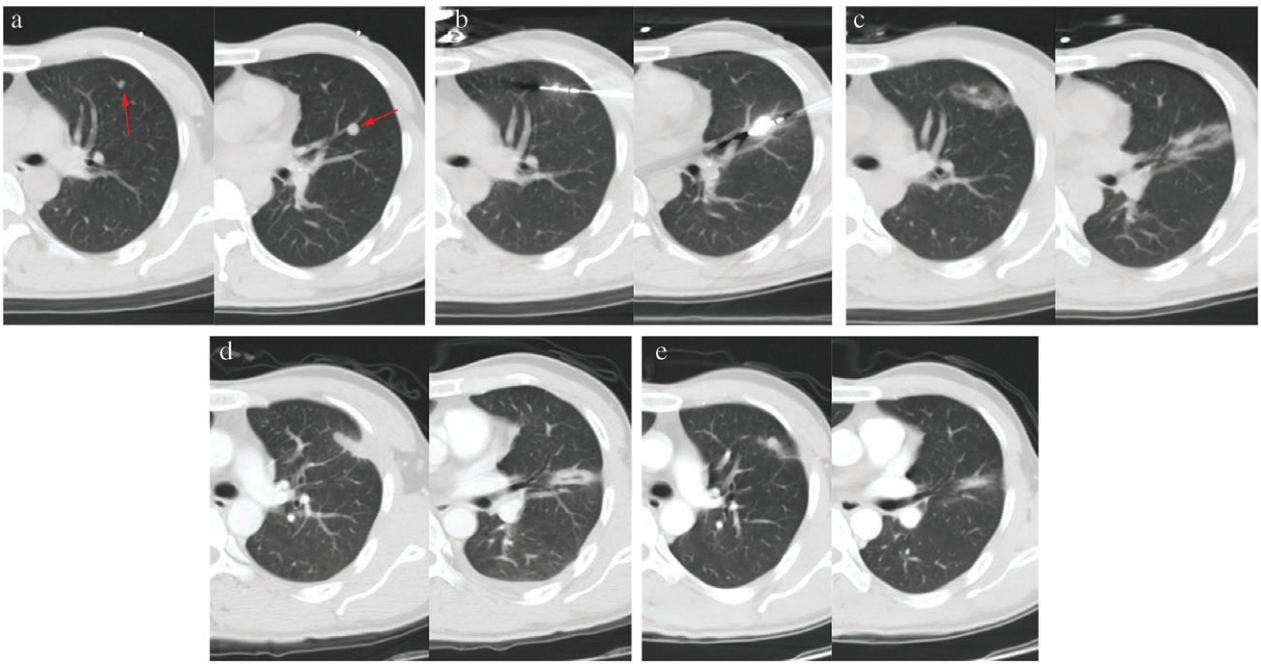

Figure 4 Ablation of lung metastasis from primary liver cancer. A 38-year-old man displayed two left lung metastases on chest computed tomography (CT) review one year after resection of primary liver cancer. The patient received microwave ablation for the lung metastasis under CT-guidance. No tumor recurrence was found during five months of follow-up. (**a**) Chest CT scans: lung metastases in the left superior and inferior lobes (red arrow). (**b**) CT-guided microwave ablation of lung metastases. (**c**) Immediate CT scans after ablation: the periphery of the ablation lesion showed ground glass changes. (**d**) Chest CT reviews one month after ablation: the ablation lesion became fibrotic streaks. (**e**) Chest CT reviews five months after ablation: fibrotic streaks in the inferior lobe significantly shrank and the ablation lesion in superior lobe changed into a consolidation nodule. No tumor recurrence was found.

Ablation therapy, as a local treatment method, is playing an increasingly important role in the comprehensive treatment of lung metastases. Particularly in patients with lung metastases from colorectal cancer, ablation therapy has been demonstrated to achieve the same effect as surgical resection. Evidence of the therapeutic effect of ablation treatment for lung metastases from other cancers continues to accumulate. However, ablation therapy should only be performed in cases where the primary tumor is well controlled. Individualized ablation is increasingly used but should be adapted according to patient characteristics, combined with different treatment methods, and in a multi-disciplinary comprehensive treatment model in order to eliminate the tumor, protect the normal lung tissue, and avoid any occurrence of serious complications.

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Disclosure

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