The lung is one of the most common targets of metastases from gastrointestinal (GI) cancers. Surgical treatment (i.e., metastasectomy) is an accepted therapeutic option for pulmonary metastases from GI cancers. However, surgery may be contraindicated in advanced stages of cancer, compromised lung function, and/or comorbidities. This issue has prompted the search for innovative and less invasive ways of treating pulmonary metastases. Image-guided radiofrequency ablation (RFA) has attracted great interest as a minimally invasive approach against intrathoracic malignancies. In this technique, radiofrequency energy is applied via a needle electrode inserted into the target tissue. As the cells are agitated by the applied energy, they release heat, causing denaturation and cell death. Recently, this technique has been used on patients with pulmonary metastatic disease arising from GI cancers such as colorectal cancer, esophageal cancer, and hepatocellular carcinoma, as well as on patients with primary lung cancer. The present review updates the clinical outcomes and advances in RFA therapy of lung metastases from GI cancers.

Keywords: pulmonary metastasis, radiofrequency ablation, RFA

Introduction

The lung is commonly targeted by metastases originating from gastrointestinal (GI) cancers. The majority of lung metastatic patients have multiple lung lesions or metastatic disease at other distant organs. Such patients are typically treated with systemic therapies primarily aimed at disease control. Surgical treatment (i.e., metastasectomy) is an accepted therapeutic choice for patients with controllable primary tumors, no (unresectable) extrapulmonary lesions, long disease-free interval, and/or lack of treatment alternatives. However, pulmonary metastasectomy may be contraindicated by the patient’s condition, including respiratory disability, history of radiation treatment, or poor performance status. This limitation of surgery has prompted researchers to develop innovative and noninvasive options for treating pulmonary metastasis from GI cancers.

Image-guided percutaneous radiofrequency ablation (RFA) is a minimally invasive therapy that targets solid tumours. RFA offers the best therapeutic choice for patients...
with early-stage hepatocellular carcinoma (HCC), and for whom surgical resection or liver transplantation is unsuitable. In addition, RFA is increasingly being applied to intrathoracic malignancies. The technique yields high proportions of sustained complete responses in properly selected patients with pulmonary malignancies, and is associated with acceptable morbidity. RFA, by itself or combined with systemic therapy, is also a promising means of treating metastatic pulmonary tumors from GI cancers. This review discusses the current knowledge, available data and information regarding RFA treatment of pulmonary metastases from GI cancers such as esophageal cancer, colorectal cancer, and HCC.

RFA for Intrathoracic Malignancies

The use of computerized tomography (CT)-guided RFA for unresectable or medically inoperable liver tumors was proposed more than a decade ago. RFA is becoming accepted as a viable therapeutic choice for non-surgical patients with early stage HCC, or with limited liver metastases from colorectal cancer. This modality is now increasingly used to treat intrathoracic malignancies.

A pre-clinical study of an animal tumor model confirmed that RFA effectively destroys experimentally-induced pulmonary malignancies. Miao, et al. inoculated VX2 sarcoma into rabbit lungs and applied RFA using a cooled-tip electrode technique. They reported a 75% eradication rate following RFA treatment, and significantly higher survival benefit in the treated animals, relative to the controls. Using the same animal model, Lee, et al. achieved complete tumor ablation in 68% of VX2 sarcoma tumors treated with RFA. Clinical studies have confirmed that percutaneous CT-guided pulmonary RFA procedures are safe for human use, and that the treatment is locally controllable to a high level. A prospective study evaluating the local efficacy of RFA for lung neoplasms, with a minimum follow-up period of 1 year, reported that an 18-month estimated rate of incomplete local treatment was 7% per tumor and 12% per patient. In a retrospective study of 153 patients, with a collective total of 189 primary or metastatic medically inoperable lung cancers treated by RFA, the 1-, 2-, 3-, 4-, and 5-year local tumor progression-free rates were 83%, 64%, 57%, 47%, and 47% respectively for tumors 3 cm or smaller, and 45%, 25%, 25%, 25%, and 25% respectively for tumors exceeding 3 cm. A systematic review of RFA-treated lung cancer, compiled from observational studies, reported a median complete necrosis rate of 90% (range 38%–97%) with 1-, 2- and 3-year survival rates of 63%–85%, 55%–65% and 15%–46% respectively.

In patients with primary non-small-cell lung cancer (NSCLC), RFA is becoming a valid tool in specific clinical scenarios. It is applied either singly or in combination with other treatments such as radiotherapy; although surgical resection remains the standard care. RFA is usually indicated for patients with early stage I or II NSCLC, for whom surgical resection is contraindicated. A study of 75 primary NSCLC (75% stage IA and 25% stage IB) patients reported a median survival of 29 months with 1-, 2-, 3-, 4-, and 5-year overall survival rates of 78%, 57%, 36%, 27%, and 27%, respectively. RFA may also be suitable for patients with advanced disease who respond to chemo/radio-therapies, but whose peripheral focus of disease persists. RFA has been administered to post-surgical patients with isolated recurrence of NSCLC, who would not benefit from further surgery. In an undefined subset of patients, RFA warrants evaluation versus surgery for treatment of primary NSCLC; however, this hypothesis is difficult to test in a randomized trial because of the anticipated difficulties of patients consenting to randomization among very different treatments.

Complications

RFA treatment of lung tumors is relatively safe, with low mortality and excellent tolerance in terms of respiratory function. However, RFA of lung lesions can lead to some complications; most commonly, pneumothorax. Pneumothoraces appear in the CT scans in approximately 60% of just-completed ablation sessions. However, in most cases, they are sufficiently small to self-resolve. Approximately 20% must be expelled manually with a small needle catheter immediately during or after RFA, and before the patient is removed from the CT table. Chest tube drainage is necessary in 4% to 12% of patients. In our experience, a pneumothorax needing drainage occurred in two out of ten cases. In one patient the chest tube was maintained until air leakage had ceased; in the other, degassing with a single puncture was performed under CT fluoroscopic guidance. Therefore, pneumothorax does not prevent completion of the planned RFA protocol. Risk factors for pneumothorax include previous pulmonary...
surgery, emphysema, increased length of the aerated lung traversed by the electrode, high mean number of ablated tumors and many electrode insertions.\textsuperscript{19–21} Refractory pneumothorax induced by bronchopleural fistula has been reported in about 0.6% of cases.\textsuperscript{22} The second most frequent complication of RFA is reactive pleural effusion, which usually resolves spontaneously. Pleural effusion requiring chest tube drainage is a rare event.\textsuperscript{20} Other reported complications are subcutaneous emphysema, hemorrhage, infection and pulmonary abscesses. In one reported case, a patient administered RFA developed acute interstitial pneumonia, which deteriorated to a fatal outcome.\textsuperscript{23} Tumor seeding after RFA is a very rare complication, reduced further by maintaining RFA during the electrode extraction.\textsuperscript{24}

The RFA procedure is well tolerated. The Visual Analogue Scale rates patients’ discomfort on a scale from 0 (no pain) to 10 (worst pain possible). In our experience, RFA patients reported a mean Visual Analogue Scale score of 1, suggesting that the RFA procedure is relatively painless.\textsuperscript{18} However, many patients report mild to moderate periprocedural and postprocedural pain, lasting up to 7 days and requiring oral analgesics. Mild dyspnea is a common symptom that may warrant nasal or mask administration of oxygen. Fever also frequently develops in the periprocedural period.

**RFA for Metastases from Colorectal Cancer**

Most studies on RFA treatment for lung metastases from GI cancers have focused on colorectal cancer. Disease recurrence is expected in more than half of the patients undergoing curative resection for colorectal cancer. Approximately 10%–15% of all colorectal cancer metastases appear in the lung. As systemic therapy has advanced through combined oxaliplatin and irinotecan to fluorouracil and leucovorin-based therapies, progression-free survival has become significantly extended. Under modern treatments, the overall median survival for patients with metastatic colorectal cancer reaches up to 17 months. Incorporation of molecularly-targeted therapies (e.g., bev-acizumab, cetuximab, and panitumumab) into the treatment regime has further extended the median survival up to 20 months.\textsuperscript{25} However, responses to these systemic therapies are not definitive, and residual tumor cells remain in the resolving tumor lesions after chemotherapy.\textsuperscript{26} Pulmonary metastasectomy may remain the only definitive curative treatment; the median overall 5 year survival of patients undergoing pulmonary metastasis resection is reportedly 48%.\textsuperscript{27} Recurrence rates of 36%–58% have been documented after initial pulmonary resection.\textsuperscript{28} Survival can be further improved by repeated thoracotomy, but the effect is counteracted by increased morbidity as more functional lung tissue is resected. Importantly, patients who are selected for surgical resection constitute only a small proportion of patients whose disease progression, response to systemic treatments, and lesion characteristics are favorable. In addition, pulmonary metastasectomy may be nonviable in patients with certain comorbidities, such as severe chronic obstructive pulmonary disease. Thus, in recent years, RFA has become increasingly considered as an alternative to surgical resection of metastatic pulmonary lesions arising from colorectal cancers.

Recent studies have shown the clinical significance of RFA for non-surgical lung metastases from colorectal cancer, with 66% to 72% overall survival at 2 years (Table 1).\textsuperscript{13,28–31} The prospective intention-to-treat multicenter clinical trial (RAPTURE study) assessed the feasibility, safety, and effectiveness of percutaneous RFA in treating malignant lung tumors. The RAPTURE study reported an overall survival rate of 89% at 1 year and 66% at 2 years in colorectal metastatic patients; cancer-specific survival was 91% at 1 year and 68% at 2 years.\textsuperscript{8} In a Japanese multicenter study of 71 patients with (collectively) 155 unresectable colorectal lung metastases, the estimated 3-year survival rate was 46% for all patients.\textsuperscript{30} Extra-pulmonary metastasis and tumor size (greater than 3 cm) were independent prognostic factors in the multivariate analysis. Yan, et al.\textsuperscript{31} investigated 55 colorectal cancer patients with lung metastases. They found an independent association between the largest lung metastases (>3 cm) and reduced overall survival. They also identified the independent survivor predictors as response to RFA treatment, repeated RFA treatment, presence of extrapulmonary metastases, and use of adjunct systemic chemotherapy. Yamakado et al.\textsuperscript{32} reported single center outcomes of RFA treatment for pulmonary metastases from colorectal cancer. Among 78 patients, the 1-, 3-, and 5-year survival rates were 84%, 56%, and 35%, respectively. The mean follow-up period was 25 months. Lack of extrapulmonary metastasis and normal carcinoembryonic antigen (CEA) level were independently associated with favorable prognosis. The 1-, 3-, and 5-year survival rates were 98%, 83%, and 57% in 54 patients with no extrapulmonary metastases and 97%, 86%, and 63% in 33 patients with negative CEA levels. Chua, et al., who monitored 100 patients with colorectal
Baba Y, et al.

Table 1 RFA for lung metastases from colorectal cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Country</th>
<th>Number or patients</th>
<th>Median survival (months)</th>
<th>2-year overall survival (%)</th>
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<td>Petre, et al.</td>
<td>2013</td>
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<td>von Meyenfeldt, et al.</td>
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<td>Yamakado, et al.</td>
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<td>Japan</td>
<td>198 tumors in 78 patients</td>
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<td>56 *</td>
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<tr>
<td>Yamakado, et al.</td>
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<td>Japan</td>
<td>155 tumors in 71 patients</td>
<td>-</td>
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<td>UK</td>
<td>24 tumors -</td>
<td>-</td>
<td>-</td>
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<tr>
<td>de Baère, et al.</td>
<td>2006</td>
<td>France</td>
<td>23 patients -</td>
<td>-</td>
<td>32 **, ***</td>
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*: 3-year overall survival; **: the data including other types of tumors; ***: 1.5-year overall survival. RFA: radiofrequency ablation

pulmonary metastases, reported a 36-month median overall survival following RFA treatment, and a 5-year overall survival rate of 30%.10) More recently, the research group from the Memorial Sloan-Kettering Cancer Center reported post-RFA 1-, 2- and 3-year overall survival rates of 95%, 72%, and 50%, respectively.33) Within the setting of nonoperable colorectal lung metastases, these studies suggest an association between RFA and favorable outcome; namely, relatively high survival rates and good local tumor control.

Stereotactic Body Radiation Therapy (SBRT) offers an alternative non-invasive therapeutic option for nonoperable lung metastases from colorectal cancer. In a multi-institutional phase I/II trial of SBRT, the actuarial local control at 1 and 2 years following treatment was 100% and 96%, respectively.34) Schlijper, et al.35) conducted a systematic review to identify the most effective radical local treatment for lung metastases from colorectal cancer (i.e., surgery, RFA, or SBRT). However, since no randomized controlled study was implemented, they could not reach a definitive conclusion, although the evidence supported surgery as the most effective treatment option. High-quality trials comparing currently used treatment modalities such as surgery, RFA, and SBRT are necessary to inform treatment decisions.

RFA for Metastases from Esophageal Cancer

The predominant histological types of esophageal cancer are squamous cell carcinoma and adenocarcinoma.36) Of these two types, esophageal squamous cell carcinoma (ESCC) predominates in East Asian countries, and ranks among the most aggressive malignant tumors.36) Despite remarkable advances in multimodal therapies involving surgery, chemotherapy, radiotherapy and chemoradiotherapy, the prognosis remains poor, even among patients whose carcinomas have been completely resected.37–40) The disease recurs in 27%–53% of patients undergoing radical esophagectomy, with a median post-recurrence survival time of 2.7–9.0 months.41–47) Among the major recurrence patterns of ESCC is metachronous pulmonary metastasis, which accounts for 18%–41% of hematogenous recurrences.41–43) Since pulmonary metastases are often detected as multiple lesions or in combination with extrapulmonary metastases, all such recurrences are initially treated by systemic chemotherapy. Surgical resection of pulmonary metastasis has also been validated in selected ESCC patients,48) suggesting that both systemic therapy and local treatment are important in managing pulmonary recurrence.

Our previous retrospective study showed that RFA is clinically significant in treating pulmonary metastasis from ESCC.18) We performed CT-guided RFA on 10 ESCC patients (collectively, 17 pulmonary tumors). The ablation device could be correctly inserted into all of the target tumors (Fig. 1). The procedure was well-tolerated, as evidenced by the mean Visual Analogue Scale score of 1 reported by patients. Two patients developed a major complication, namely, pneumothorax requiring drainage. Among the 12 ablated tumors that could be later assessed, 10 (83%) were locally controlled for at least 1 year. The locoregional recurrences that developed in two of these tumors were re-controlled by repeat RFA treatment. The predicted 1- and 2-year overall survival rates following lung RFA were 78% and 62%, respectively. The effectiveness of RFA in treating recurrent ESCC and pulmonary ESCC metastases has also been reported.49,50)
HCC is the fifth most prevalent and the third most deadly type of cancer worldwide. Early-stage HCC can be treated by surgical resection and liver transplantation. Recently, RFA has become globally recognized as a curative and minimally invasive treatment for removing small HCCs. However, regardless of treatment (resection, transplantation, or RFA), HCC recurrences, which will likely spread to the lung, are of major concern. Extrahepatic metastases are rarely controlled by invasive treatments, mainly because of the multifocal nature of the disease and the poor hepatic reserve. However, metastasectomy may benefit pulmonary metastatic patients if the intrahepatic tumor is controllable and if no extrathoracic metastasis develops, justifying local therapeutic treatment of pulmonary metastasis from HCC. Hiraki, et al. demonstrated that pulmonary metastases from HCC are locally controllable by RFA, as are other lung cancers such as primary lung cancer, and pulmonary metastases from colorectal and renal-cell carcinomas. The retrospective multicenter study conducted in Japan evaluated the technical success and effectiveness of percutaneous RFA in treating pulmonary metastases from HCC. Thirty-two patients with no other metastases, and in whom intrahepatic recurrence was absent or treatable, participated in the study. These 32 patients collectively presented 83 HCC-induced pulmonary metastases. During a median follow-up period of 20.5 months, the overall post-RFA survival rates were reported as 87% at 1 year and 57% at both 2 and 3 years. Median and mean survival times were 37.7 months and 43.2 months, respectively. Survival rates were significantly increased in patients with no viable intrahepatic recurrence, Child-Pugh class A disease, liver cirrhosis, or hepatic C virus infection, and whose α-fetoprotein level (AFP) was 10 ng/mL or lower at the time of RFA. All 13 patients without liver cirrhosis, and all 11 patients whose AFP level remained within 10 ng/mL, were alive 3 years after treatment. Conversely, all five patients with Child-Pugh class B disease, and all 11 patients with viable intrahepatic recurrence, had died within 2 years. These results suggest that pulmonary metastases arising from HCC may be suitably treated by RFA, provided that the primary tumor is well controlled.

Conclusions

In conclusion, RFA treatment of lung metastases from GI cancers may exert a significant therapeutic effect on nonsurgical candidates. Thus, RFA may be incorporated into the management of lung metastases to improve cure rates, stabilize the tumor and inhibit recurrence. In future, the usefulness and viability of RFA for treating pulmonary metastases from GI cancers must be clarified in prospective, preferably randomized, studies.

Disclosure Statement

No conflicts of interest exist.
References


31) Yan TD, King J, Sjarif A, et al. Percutaneous