A prospective clinical trial of radiofrequency ablation for pulmonary metastases

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Abstract. Pulmonary oligometastases can be treated by local treatment options, such as resection, radiofrequency ablation (RFA), and radiotherapy, in selected patients. In the present study, 67 patients with 115 pulmonary metastases were treated, and all the lesions were treated by RFA and followed with a computed tomography scan. The local control, overall survival (OS), progression-free survival (PFS) and treatment-related toxicity were observed. Median follow-up duration after the initial RFA was 24 months (range, 3-39 months). The median PFS from RFA was 14 months [95% confidence interval (CI), 11.6-16.4]. The 6-, 12- and 18-month PFS rates were 82.1, 55.7 and 27.5%, respectively. The median OS rate from RFA was 24 months (95% CI, 18.2-29.8). The 1-, 2- and 3-year OS rates were 83.6, 46.3 and 14.3%, respectively. Primary tumor was significantly correlated to PFS and OS on multivariate analysis, and other variates showed no significance. Therefore, RFA is safe for patient treatment and can be considered as a promising treatment option for patients with pulmonary metastases.

Introduction

The lung is a main site of metastatic disease for the majority of solid tumors and local treatments have been playing an emerging role in combination with systemic therapies. In oligometastatic (1-3 pulmonary nodules) and clinically selected patients (good performance status and absent or stable extra-thoracic disease), surgery can be considered as the standard option, with good results in terms of local control and survival rate (1).

Patients with pulmonary metastases often receive multiple surgeries due to the fact that not all the metastatic disease is Wdetectable at first presentation and the high likelihood of recurrence. Therefore, invasive therapies have been explored to treat patients with oligometastatic disease in an effort to improve the long-term survival rate and quality of life in patients who are not able to undergo surgery. Radiofrequency ablation (RFA) is one such technique that generates tissue heating to necrose tumors *in situ* and has been proved to be safe and effective in treating selected patients with certain solid tumors unsuitable for surgical resection (2).

In addition, several studies have shown that RFA was as effective as surgical resection in selected patients with primary pulmonary tumors (3-5).

Patients and methods

Patient characteristics. Between January 2011 and September 2014, 67 patients with 115 lung metastases were enrolled in the prospective trial. Patient characteristics are listed in Table I. The decision to perform RFA was made by a multidisciplinary team and approved by the Ethics Committee of the Fudan University Shanghai Cancer Center and the patients.

The selection criteria for RFA were: i) 1-3 lung metastases at the treatment time, with a maximum tumor diameter <50 mm; ii) minimum distance was 10 mm apart from the big trachea, primary bronchi, esophagus, great vessels and heart; iii) medically inoperable or patients refused surgery; iv) absent or controlled extra-thoracic disease [at computed tomography (CT) or positron emission tomography (PET)-CT or magnetic resonance imaging confirmed prior to RFA].

All the patients had biopsies of their metastatic lung lesions proving metastatic disease prior to RFA and their grade of Eastern Cooperative Oncology Group were grade 0-1. Patients who had coagulation disorders, severe heart or pulmonary failure, or uncontrolled infection were excluded from the trial.

RFA. The equipment used for RFA of lung lesions consisted of the radiofrequency generator (CelonLab POWER), cold circulation pump (Celon Aquaflow III), radiofrequency needle electrode (Celon proSurge: T20, T30 and T40 is an electrode length of 20, 30 and 40 mm respectively, and maximum output power of 20, 30 and 40 W; Olympus Surgical Technologies Europe, Hamburg, Germany).

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Key words: pulmonary metastases, radiofrequency ablation, local tumor control, prognostic factors

Table I. Patient characteristics.

Patient characteristics	n
Patients	67
Lesions	115
Gender	
Male	38
Female	29
Age, years	
>65	15
≤65	52
Pulmonary metastases	
1	36
2	14
3	17
Prior chemotherapy for metastatases	
Yes	47
No	20
Presence of extrathoracic disease	
Yes	33
No	34
Primary tumor	
CRC	26
HCC	5
NSCLC	13
GCC	3
STC	7
RCC	2
EC	7
GC	1
BC	3

CRC, colorectal cancer; HCC, hepatocarcinoma; NSCLC, non-small cell lung cancer; GCC, gynecologic cancer; STC, soft tissue sarcoma; RCC, renal cellcarcinoma; EC, esophagus carcinoma; GC, gastric carcinoma; BC, breast cancer.

The puncture point, direction, depth and the needle electrode type and number were confirmed by the CT scan (120 kV, 100 mA, 3 mm thickness) and 3-dimentional reconstruction prior to treatment. Puncturing was subsequently performed, and the CT scan confirmed whether the needle was at the right place, prior to connecting the radiofrequency generator and commencing RFA. Ablation finished when ground-glass opacity was 5-10 mm away from the tumor boundary. Subsequently, the needles were withdrawn and the CT scan was performed again to observe the occurrence of pneumothorax, hemorrhage and other complications.

Follow-up and assessment. All the patients on the trial had a CT carried out 1 month after RFA and this served as a new basis for the comparison of future scans. Subsequently, CT scans were obtained within ~3, 6, 9 and 12 months after RFA and every 6 months after 1 year. PET-CT was recommended at the physician's discretion. The criteria of the assessment of local lesion were abiding by the modified Response Evaluation Criteria in Solid Tumors (mRECIST) (6). Local control defined that the target lesion had not progressed during the follow-up period and was analyzed by every lesion.

Table II. Multivariate analysis.

	PFS		OS	
Factors	HR	P-value	HR	P-value
Gender	0.596	0.092	0.632	0.186
Age, years	1.133	0.743	1.591	0.269
Mets, n	1.361	0.091	1.279	0.213
Prior chemo	0.835	0.586	1.341	0.401
Extra D	0.967	0.916	0.758	0.463
Primary	1.213	0.002	1.290	0.001

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; mets, metastases; chemo, chemotherapy; Extra D, extrathoracic disease.

Statistical methods. Primary endpoint of the clinical study was local control, and the secondary endpoints were overall survival (OS), progression-free survival (PFS) and treatment-related toxicity.

Local control was calculated by χ^2 test, and PFS and OS were calculated using the Kaplan-Meier method. Cox proportional hazards was used to calculate the hazard ratios (HRs) and 95% confidence interval (CI) in multivariate analysis. All P-values are two-sided and $P<0.05$ was considered to indicate a statistically significant difference. Statistical analyses were carried out with the Statistical Package for the Social Sciences v19 (SPSS; IBM Corp, Armonk, NY, USA).

Results

Local tumor control. In the study, all the punctures were successful. According to mRECIST, 101 in 115 (87.8%) lesions were confirmed as complete response (CR) in the follow-up, 3 (2.6%) were partial response (PR), 5 (4.3%) were stable disease, 6 (5.2%) were progression disease and 4 of these 6 patients received radiotherapy, with the other 2 receiving RFA again and obtaining CR.

PFS and OS. Median follow-up after RFA was 24 months (range, 3-39). A total of 41 patients succumbed to disease progression in the lung (other sites of lung) and extrapulmonary sites and 2 were lost during follow-up. In total, 24 patients were remained.

The median PFS from RFA was 14 months (95% CI, 1.6-16.4). The 6-, 12- and 18-month PFS rates were 82.1, 55.7 and 27.5%, respectively. The median OS from RFA was 24 months (95% CI, 18.2-29.8). The 1-, 2- and 3-year OS rates were 83.6, 46.3 and 14.3%, respectively. Primary tumor was significantly correlated to PFS and OS on multivariate analysis, and the other variates showed no significance difference (Figs. 1 and 2, and Tables II and III).

Complications. There was no periprocedural mortality in the trial. The main complications and relative treatments are listed in Table IV.

Table III. PFS and OS of different primary tumors.

	PFS, months				OS, months			
Primary	Median	6	12	18	Median	1	2	3
CRC	18	100.0	72.9	48.6	38	92.0	75.3	28.8
HCC	6	20.0	-	-	9	20.0	-	-
LC	16	83.9	71.9	24.0	33	91.7	66.7	-
GCC	7	33.3	-	-	12	33.3	-	-
STC	8	42.9	-	-	15	57.1	-	-
RCC	5	-	-	-	13	50.0	-	-
EC	8	57.1	-	-	12	42.9	-	-
GC	17	-	-	-	17	-	-	-
BC	15	100.0	66.7	-	26	50.0	-	-
All patients	14	82.1	55.7	27.5	24	83.6	46.3	14.3

PFS, progression-free survival; OS, overall survival; CRC, colorectal cancer; HCC, hepatocarcinoma; LC, local control; GCC, gynecological cancer; STC, soft tissue sarcoma; RCC, renal cellcarcinoma; EC, esophagus carcinoma; GC, gastric carcinoma; BC, breast cancer.

Table IV. Main complications and treatment.

Complications	n (%)	Treatment
Pneumothorax	8 (11.9)	2 patients percutaneous chest tube
Pneumorrhagia	6 (9.0)	Intravenous injection thrombin
Pleural effussion	7 (10.4)	Combined by infection, antibiotics and percutaneous chest tube
Fever	7 (10.4)	Indometacin suppositories anal plug
Thoracalgia	6 (9.0)	Self-healing
Aerodermectasia	2 (3.0)	Self-healing
Emesia	1 (1.5)	Self-healing

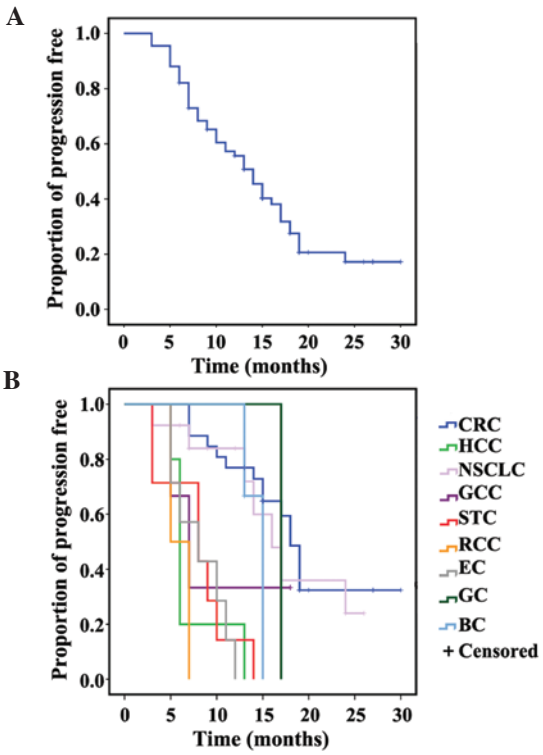

Figure 1. PFS of (A) all patients and (B) different primary tumors. PFS, progression-free survival.

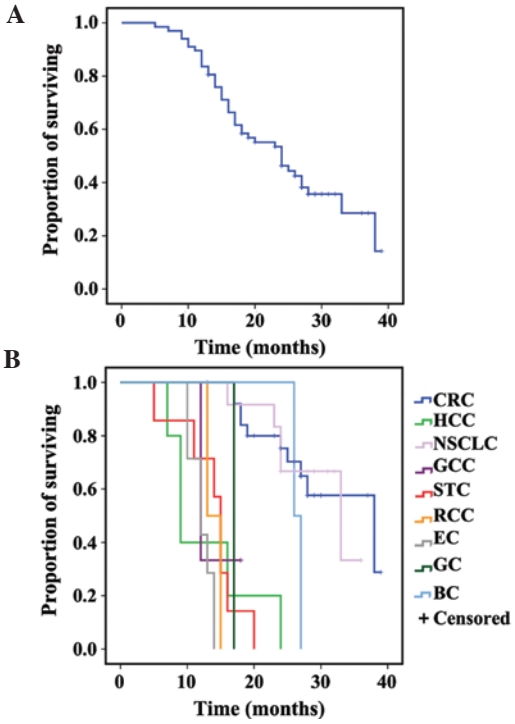

Figure 2. OS of (A) all patients and (B) different primary tumors. OS, overall survival.

Discussion

The lung is a main site of metastatic disease for the majority of solid tumors, and local ablation techniques, such as radiofrequency, cryotherapy (7) and microwave (8), were widely used for patients who were not candidates for surgery.

Hiraki *et al* (3) applied RFA to non-small cell lung cancer (NSCLC) and evaluated the role of RFA in the treatment of early-stage NSCLC and concluded that RFA may currently be reserved for early-stage NSCLC patients who are unfit for sublobar resection or stereotactic body radiotherapy (SBRT). Schlijper *et al* (1) reviewed 27 studies and identified that the treatment-related mortality rates for RFA

and surgery were 0 and 1.4-2.4%, respectively, whereas morbidity rates were reported inconsistently but appeared to be the lower for surgery. The study by Ochiai *et al* (9) was conducted to compare the clinical outcomes of RFA with those of SBRT. The RFA and SBRT groups showed a similar 3-year local tumor progression (9.6 vs. 7.0%, p=0.746) and OS rates (86.4 vs. 79.6%, p=0.738).

In recent studies, RFA was certificated with efficacy and safety to lung metastases. The Matsui *et al* (10) retrospective study showed that RFA was a promising treatment option for patients with pulmonary metastases from esophageal cancer. Baba *et al* (11,12) applied RFA to pulmonary metastases from gastrointestinal cancers and esophageal squamous cell carcinoma. Nakamura *et al* (13) and Koelblinger *et al* (14) applied RFA in elderly patients with lung metastases from musculoskeletal sarcomas and concluded that elderly sarcoma patients with lung metastases should always be considered for either metastasectomy or RFA. In particular, Petre *et al* (15) and Hiraki *et al* (16) studied the OS of patients with lung metastases treated by RFA and identified that short- to mid-term survival after RFA appears to be promising and is 85-95% in 1 year and 45-55% in 3 years.

RFA as a radical means can destroy all tumor or normal cells in its ablation extent and no tumors reoccur theoretically. Due to the special site and shape of tumors, the ablation was not complete in certain patients. In the present study, the local control rate was that 87.8% (101/115) of lesions were confirmed CR, 3 (2.6%) were PR, and only 6 (5.2%) progressed. During the observational period, no periprocedural mortality occurred. The median follow-up of PFS was 14 months and the progression reasons were outside the RFA site, including distant intrapulmonary, and intra- and extrapulmonary progression. Therefore, we can conclude that the local lesions were well controlled by RFA.

In the present study, primary tumor was significantly correlated to PFS and OS on multivariate analysis. It is well known that each tumor has its own biological characteristics and its prognosis is different from other tumors. PFS or OS in the study was in accordance with the biological characteristics; the patients of colorectal cancer survived longer.

However, the outcome of the 1-, 2- and 3-year OS was 83.6, 46.3 and 14.3%, respectively. The outcome was not as good as other similar studies. The selection criteria of the patients was not the same as others, the ratio of ≥2 pulmonary metastases and having extrathoracic diseases was higher compared to other studies, and the two factors were risk factors in uinvariate analysis although they had no statistical significance in multivariate analysis. Petre *et al* (15) found that lesions >1.5 cm in size had a higher risk of local progression compared to those ≤1.5 cm. Baschnagel *et al* (17) identified that the 3-year survival rate of patients with the lung as the only known site of metastatic disease treated with SBRT was 71 vs. 58% in patients who had extrathoracic disease treated prior or subsequent to SBRT. Therefore, more patients should be enrolled to confirm that ≥2 pulmonary metastases and having extrathoracic disease were the risk factors. Another possible reason was the different treatment following progression, as there was no treatment guideline in this stage and the majority inclined to adopt systematic chemotherapy. In the study, 70.1% (47/67) patients have received chemotherapy to lung metastases and the lesions were residual disease following chemotherapy, the sensitivity of next line chemotherapy to progression following RFA was lower than first line chemotherapy. These were possibly the reasons for the low survival rate.

In conclusion, RFA is safe for patients and can be considered as a promising treatment option for patients with pulmonary metastases.

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