ORIGINAL ARTICLE

Clinical Effect of Percutaneous Radiofrequency Ablation for Residual Lung Metastases from Breast Cancer After Systemic Chemotherapy

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ABSTRACT

Objective: To determine the clinical effect of Radiofrequency Ablation (RFA) for residual lung metastases from breast cancer after systemic chemotherapy.

Study Design: An experimental study.

Place and Duration of Study: The Second Affiliated Hospital of Soochow University, Suzhou, Fudan University Shanghai Cancer Center, Shanghai, China, from January 2008 to October 2014.

Methodology: Thirty-five breast cancer patients with 67 pulmonary metastases were involved in this study. All lesions were treated by RFA and followed by CT-scan. Primary endpoint of this clinical study was local control; secondary endpoints were overall survival and treatment-related toxicities.

Results: Complete Response (CR) was observed in 59 lesions, with Partial Response (PR) in 4 lesions, Stable Disease (SD) in 1 lesion and Progression Disease (PD) in 3 lesions. The lesion diameter > 2 cm was related to poor local control (p=0.04). The median Overall Survival (OS) was 33 months (95%CI: 21.6 - 44.4). One-, 2-, and 3-year OS rates were 88.6%, 59.3% and 42.8% respectively. The mumber of pulmonary metastases (≥ 2), the diameter of lesion (> 2 cm) and coexisting with liver metastases were significantly correlated to poor OS by multivariate analysis. Log-rank test showed statistically significant difference of OS in diameter of lesion and coexisting with other metastases.

Conclusion: RFA is a promising treatment option for patients with residual lung metastases from breast cancer after systemic chemotherapy in selected patients.

Key Words: *Lung metastases. Radiofrequency ablation. Local tumor control. Prognostic factors. Breast cancer.*

INTRODUCTION

Breast Cancer (BC) is the most common malignant tumor in women and it is the leading cause of death in women.[1] The earliest and most frequent site of BC metastasis is the lungs and bones, and no more than 5 - 20% of cases have only liver metastases.[2] Metastatic BC was mostly treated with chemotherapy or endocrine therapy according to international guideline and these therapies often are not curative, so most patients had residual lesions after these systemic therapies.[3]

Surgical resection of single lung metastases in patients with BC increased the 5-year survival rate to 54.5%.[4] However, patients with pulmonary metastases frequently required multiple surgeries because of the fact that not all the metastatic lesions were detectable at first presentation and because of the high likelihood of recurrence. Therefore, invasive therapies had explored to treat patients with oligometastatic lesions in an effort to improve long-term survival and Quality Of Life (QOL) in patients who were not able to undergo surgery. Radiofrequency Ablation (RFA) was one of such techniques that used tissue-heating to necrose tumors *in situ* and had been proved to be safe and effective in treating selected patients with some solid tumors unsuitable for surgical resection,[5] including breast cancer.

There were many literatures about RFA, but most of them focused on liver cancer or liver metastases.[6,7] Only a few clinical studies have focused on RFA for lung metastases from BC.[8]

The purpose of this study was to evaluate the clinical effect of RFA for residual lung metastases from breast cancer after systemic chemotherapy.

METHODOLOGY

The study was conducted at The Second Affiliated Hospital of Soochow University, Suzhou, Fudan University Shanghai Cancer Center, Shanghai, China, from January 2008 to October 2014. The study was

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permitted by the Ethical and Research Committee of the Second Affiliated Hospital of Soochow University and Fudan University, Shanghai Cancer Center, China.

The application of RFA was decided by a multi-disciplinary team. Selection criteria for RFA were: (a) all patients biopsy proven metastatic disease before systemic therapy; (b) patients performance status according to Eastern Cooperative Oncology Group (ECOG) was 0-1; (c) 1 - 3 lesions in unilateral lung after systemic therapy; (d) maximum tumor diameter was smaller than 4 cm after systemic therapy; (e) minimum distance was 1cm apart from the trachea, primary bronchi, esophagus, great vessels and heart; (f) medically inoperable or patients refused operation; (g) absent or controlled extra-thoracic metastases (at CT or PET-CT or MRI confirmed prior to RFA). Exclusion criteria were expected life less than 3 months; heart or lung function failure out of compensation; coagulation dysfunction and uncontrolled infection.

The equipment used for RFA of lung lesions consisted of Radiofrequency Generator (CelonLab POWER, OLYMPUS), Cold Circulation Pump (Celon Aquaflow ¢Û, OLYMPUS), Radiofrequency needle electrode (OLYMPUS CelonproSurge: T20, T30, T40, means that the electrode length is 2 cm, 3 cm, 4 cm respectively, and the maximum output power 20W, 30W, 40W respectively).

All puncturing was guided by CT. When the needle was at the right place, connected the Radiofrequency generator and began Radiofrequency ablation. Ablation finished when ground-glass opacity was 0.5 - 1 cm away from the tumor boundary. Then needles were withdrawn and CT scan performed again to observe the occurrence of pneumothorax, hemorrhage and other complications.

All patients had CT scan carried out 1 month after RFA and served as a new basis for comparison of future scans, then CT scans were obtained within approximately 3, 6, 9, 12 months after RFA and every 6 months after 1 year. PET-CT was recommended when physician could not judge the clinical effect by CT scan. The assessment criteria of local lesion was based on the modified Response Evaluation Criteria In Solid Tumors (mRECIST).[9] Local control was defined that target lesion had not progressed during follow-up period and each lesion was observed and judged.

Primary endpoint of this clinical study was local control; secondary endpoints were overall survival and treatment-related toxicities. Local control was calculated by Chi-square test and OS curves were calculated by Kaplan-Meier analysis from the time of RFA completion. Cox proportional hazards were used to calculate the Hazard Ratios (HRs) and their 95% confidence interval (CI) in multivariate analysis and the Log-rank test was used to test for survival differences of each factor. All p-value were two-sided and < 0.05 was considered as statistical significance. Statistical analyses were carried out with the Statistical Package for the Social Sciences version 19.0 (SPSS, IBM).

RESULTS

From January 2008 to October 2014, 35 patients with 67 lung metastases were enrolled in the study. Patient characteristics are listed in Table I.

All punctures were successful. According to mRECIST, with our follow-up, 59 in 67 (88.0%) lesions were confirmed Complete Response (CR), 4 (6.0%) lesions Partial Response (PR), 1 (1.5%) lesions Stable Disease (SD), 3 (4.5%) lesions Progression Disease (PD). All the 3 lesions of PD received radiotherapy, and reached PR. Among the 8 NOT CR lesions, the number of lesion diameter ≤ 2 cm was 2, the number of lesion diameter > 2 cm was 6 ($\chi^2 = 4.119$, $p = 0.04$).

Table I: Patient characteristics.

Patient characteristics	Number
Number of patients	35
Number of lesions	67
ER/PR status	
+	23
-	12
Age	
> 65	6
≤ 65	29
Number of pulmonary metastases	
1	18
2	8
≥ 3	9
Diameter of the largest lesion	
≤ 2 cm	20 (39 lesions)
> 2 cm	15 (28 lesions)
Presence of extrathoracic metastases	
Liver (liver and bone)	12 (9)
Bone (without liver metastases)	7
Lung only	16

Table II: Outcome of multivariate analysis by Cox-regression and comparison by Log-rank*.

Factor	Age	ER/PR	Other MT	No. lesion	Diameter
HR	2.301	2.483	2.844	2.270	4.907
95%CI lower	0.581	0.947	1.471	1.323	1.634
95%CI upper	9.117	6.510	5.497	3.895	14.733
p-value	0.236	0.064	0.002	0.003	0.005
* χ^2	2.196	2.433	29.576	3.870	7.848
* p-value	0.138	0.119	0.000	0.144	0.005

Table III: Main complications and treatment.

Complications	N (%)	Treatments
Pneumothorax	3 (8.6)	Two patients percutaneous chest tube
Pneumorrhagia	3 (8.6)	Intravenous injection thrombin
Pleural effusion	2 (5.7)	Combined by infection,antibiotics and percutaneous chest tube
Fever	4 (11.4)	Indomethacin Suppositories
Thoracalgia	4 (11.4)	Self-healing
Aerodermectasia	1 (2.9)	Self-healing

On follow-up, 25 patients died of disease progression in lung (other sites of lung) and/or extrapulmonary sites and 10 patients were alive.

The median Overall Survival (OS) from RFA was 33 months (95%CI: 21.6 - 44.4). One-, 2-, and 3-year OS rates were 88.6%, 59.3% and 42.8% respectively. The mumber of pulmonary metastases was ≥ 2, the diameter of lesion > 2 cm and coexisting with liver metastases were significantly related to poor OS by multivariate analysis, other variates showed no statistic significance.

The Log-rank test showed that there was statistical significant difference of OS in diameter of lesion and coexisting with other metastases. The diameter of lesion > 2 cm and coexisting with liver metastases related to poor suivival (Figure 1, Table II).

There was no periprocedural mortality in this study. Main complications and their treatments are listed in Table III.

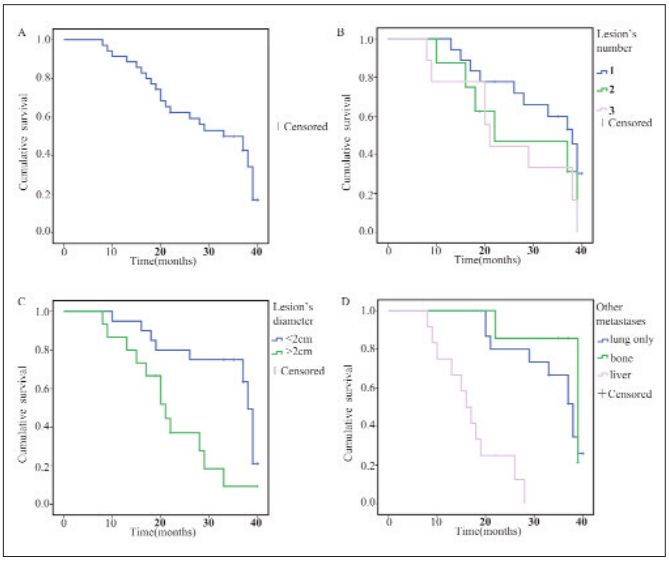

Figure 1: (A) OS of all patients; **(B)** OS of different number of lesions in lung; **(C)** OS of different diameter of lesion; **(D)** OS of extrathoracic metastases. *Graphed by Kaplan-Meier for univariate analysis.

DISCUSSION

The lung is a main site of metastatic disease for most solid tumors. Local ablation techniques like radio-frequency, cryotherapy, microwave were widely used for patients with lung metastases who were not the candidates for surgery.[10,11]

Hiraki applied RFA to non small cell lung cancer and discussed the role of RFA in treatment of early-stage non small cell lung cancer and reached the conclusion that RFA may currently be reserved for these patients who are unfit for sublobar resection or SBRT.[12] Schlijper reviewed 27 studies and found treatment-related mortality rates for RFA and surgery were 0% and 1.4%-2.4% respectively, whereas morbidity rates were reported inconsistently but seemed to be the lowest for surgery.[13] Tramontano had built a microsimulation model and the results suggest that RFA and stereotactic body radiotherapy could provide life expectancy gains to patients with stage IA or IB NSCLC who are ineligible for resection.[14]

In recent studies, RFA was certificated efficacy and safety to lung metastases. Matsui did a retrospective study that showed RFA was a promising treatment option for patients with pulmonary metastases from esophageal cancer.[15] Baba applied RFA to pulmonary metastases from gastrointestinal cancers and esophageal squamous cell carcinoma and the outcome was positive.[16,17] Nakamura and Koelblinger 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.[18,19] Particularly, Elena and Hiraki studied the OS of patients with lung metastases treated by RFA and found that short- to mid-term survival after RFA appears to be promising and is approximately 85-95% in 1 year and 45 - 55% in 3 years.[20,21]

As radical means, RFA can destroy all tumor or normal cells in its ablation extent and no tumors could recur theoretically. Because of the special site and shape of tumors, the ablation was not complete in some patients. In this study, 59 in 67 (88.0%) lesions were confirmed CR, 8 lesions were not confirmed CR. The local control was related to the diameter of the lesions. The diameter of the lesion > 2 cm was risk factor of local control. During the observation period, no periprocedural mortality happened and RFA could be regarded as safety to patients.

In this study, the median OS from RFA was 33 months (95% CI: 21.6 - 44.4), One-, 2-, and 3-year OS rates were 88.6%, 59.3% and 42.8% respectively. In Bortolotto's report, disease free and overall median survival patients with lung metastases from breast cancer were 13.4 and 34.8 months respectively after CT-guided RFA,[8] the result was almost similar to this study. On multivariate analysis, the more pulmonary metastases, the larger diameter of lesion and coexisting with liver metastases were significantly correlated to poor OS, other variates showed no significance to OS. It is easy to know that the more pulmonary metastases, the larger diameter of lesion and coexisting with liver mean the more advanced and severe condition, the function of organ has more probability to be harmed which could follow with cachexia. By Log-rank test, there was no significant difference in number of pulmonary metastases. But one can see the trend that the survival rate was higher in patients with 1 lesion than patients with ≥ 2 lesions. Therefore, more patients should be observed to confirm the trend.

CONCLUSION

RFA is a safe alternative technique for selected patients with residual lung metastases from breast cancer after systemic chemotherapy. The local control rate in this study was satisfactory. Breast cancer patients whose diameter of lung metastases are ≤ 2 cm and who do not have coexistent liver metastases benefit more from RFA.

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