Received:
18 August 2017

Revised:
09 November 2017

Accepted:
16 January 2018

<https://doi.org/10.1259/bjr.20170607>

Cite this article as:

Zhou K, Pan J, Yang N, Shi H-F, Cao J, Li Y-M, et al. Effectiveness and safety of CT-guided percutaneous radiofrequency ablation of adrenal metastases. *Br J Radiol* 2018; **91**: 20170607.

FULL PAPER

Effectiveness and safety of CT-guided percutaneous radiofrequency ablation of adrenal metastases

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Objective: The imaging-guided percutaneous radiofrequency (RF) ablation of adrenal metastases is a relatively new treatment procedure, compared to the more widespread application of the technique for the treatment of liver and renal cancers. The present study aims to evaluate the safety and efficacy of the CT-guided percutaneous RF ablation of adrenal metastases in a cohort of patients.

Methods: 33 patients with 38 adrenal metastases who received percutaneous CT-guided RF ablation between 2012 to 2015 were retrospectively reviewed. The average diameter of the treated adrenal metastases was 3.0 ± 1.6 cm. The treatment outcomes, including presence of residual tumours, technical success rate, recurrence rate, and complications, were evaluated. Patients were followed up for every 3 months to monitor the progression of the disease.

Results: Postoperative CT images showed the lack of tumour enhancement in 30 tumours (30/38 tumours,

technical success rate = 78.9%), and residual disease was found in 7 tumours (7/37 tumours, 18.9%). The rate of residual disease was significantly lower in the group with tumour size <3 cm than the group with tumour size ≥ 3 cm ($p = 0.025$). The severe complication rate was 4.3%, and the mild complication rate was 48%, with intraoperative hypertensive crisis as the most frequently observed complication (27.3%). The follow-up data showed that 76.3% of patients had recurrence-free survival in 27.4 months.

Conclusion: The current study demonstrated that radiofrequency ablation is a relatively safe and effective treatment for controlling adrenal metastases, especially for patients with tumour size <3 cm.

Advances in knowledge: Surgical resection of the adrenal metastases was advocated as one of the treatment options for patients. The present study showed that radiofrequency ablation is a relatively safe and effective treatment for controlling adrenal metastases.

INTRODUCTION

Adrenal metastases accounts for 3% of all adrenal tumours. It is the most common adrenal tumour observed in patients with history of malignancy; the incidence rate was 10 to 25%. The metastases are often found in patients with lung cancer, kidney cancer, colon cancer, liver cancer, and malignant melanoma.¹⁻³ To date, there is still controversy on the treatment approach for adrenal metastases, the conventional treatment is usually the radiotherapy or chemotherapy, based on the primary malignancy type.⁴ Recently, it was suggested that surgical resection of the isolated adrenal metastases could offer survival benefits. However, a limited number of patients are eligible for surgical treatment, because of the comorbid disease, age, extra-adrenal metastases, and other reasons.³⁻⁷ Another treatment option, arterial chemoembolization, is challenging for

adrenal metastatic patients, since the catheterization of the adrenal arteries and complete embolization of the adrenal gland are anatomically difficult.⁸

Recently, image-guided ablation therapy has been applied to the treatment of adrenal metastases, including radiofrequency (RF) ablation, cryoablation, chemical ablation and microwave ablation.^{9,10} RF ablation is one of the most widely used ablation treatment. Studies have demonstrated the positive outcomes of the RF ablation.¹¹⁻¹⁵ These studies, however, had a relative small sample size. Given the imaging-guided percutaneous RF ablation of adrenal metastases is a relatively new treatment approach compared to the more widespread application of the technique for the treatment of liver and renal cancers, the present study evaluates the safety and efficacy of the CT-guided

Table 1. Clinical and demographic characteristics of patients

Characteristics	Frequency (%) <i>n</i> = 33
Gender	
Male	17 (51.5)
Female	16 (48.5)
Age (years, mean $\pm$ SD)	60 $\pm$ 9.9
Age (years, range)	43–75
Primary tumours	
Lung cancer	16 (48.5)
Liver cancer	8 (24.2)
Renal cell carcinoma	5 (15.2)
Colon cancer	3 (9.1)
Ovarian cancer	1 (3.0)
Extra-adrenal invasion	
Present	18 (54.5)
Absent	15 (45.5)
Previous chemoradiotherapy	
Yes	25
No	8
Tumour size (cm, mean $\pm$ SD)	3.0 $\pm$ 1.6
Tumour size (cm, range)	1.3–8.5
Number of adrenal tumours	
Unilateral	28 (84.8)
Bilateral	5 (15.2)

percutaneous RF ablation of adrenal metastases in a cohort of 33 patients.

PATIENTS AND METHODS

Patient characteristics

The study was approved by the institute's ethics committee, and written informed consent was collected from all of the patients. The current study included a total of 33 patients who accepted CT-guided percutaneous ablation on adrenal metastatic tumours between January 2012 and 2015. Among the patients, 17 were male and 16 were female. Their mean age was 60.4 ± 9.9 years old. 25 patients had received chemoradiation therapy previously. The total number of lesions was 38, of which 28 of them were unilateral and 5 of them were bilateral. The primary tumours were originated from lung cancer ($n = 16$), liver cancer ($n = 8$), renal cell carcinoma ($n = 5$), colon cancer ($n = 3$), and ovarian cancer ($n = 1$). The clinical and demographic characteristics of patients were listed in Table 1.

Pre-surgical assessments were performed in all patients, including physical examinations, complete blood count, urinalysis, coagulation, catecholamine test, electrocardiograms (ECGs), and chest/abdomen CT examinations. The diagnosis of adrenal metastases was mainly based on radiologic findings, in which patients with primary malignancy demonstrated new lesions of the adrenal

gland, and the lesions were enlarged during subsequent visits.¹⁶ The diagnosis of five of the patients was confirmed by pathological examination through biopsy. The recommendation of treatment with percutaneous RF ablation was made collectively by a multidisciplinary discussion of physicians from the Department of Cancer Chemotherapy, Radiology, Intervention, and Urology. The inclusion criteria include: (1) Definite diagnosis of adrenal metastases; enhanced CT scan was performed every 3–6 months, if new lesions or the adrenal gland was found increased in size, MRI (including chemical shift imaging) or PET/CT would be performed to confirm adrenal metastases. (2) No extra-adrenal invasion or the extra-adrenal metastases have been controlled; (3) Physical condition of the cancer patients with scores (performance status) <2 ; (4) Predicted survival time of more than 3 months. The exclusion criteria include: (1) rapid progression of extra adrenal metastases; (2) severe irreversible coagulation dysfunction (INR >1.5 or platelet count $<60 \times 10^9 \text{ l}^{-1}$).

RF ablation treatment

Bipolar/multipolar RF-induced thermotherapy (Olympus Winter&Ibe GmbH, Germany) was used in this study. The ranges of RF ablation probes include 20, 30, 40 mm, and the appropriate probe was selected according to the lesion areas. Each of the probes has variety of lengths (100, 150, 200 mm) and maximum output (250 W and 470 kHz). During the course of operation, the water pump was used to cool the RF needle (CelonAquaflow, Olympus-Celon, Germany). CT imaging (Somatom Perspective, Siemens Healthcare, Forchheim, Germany) was used as real-time monitoring of the insertion position of needle and the progress of the ablation therapy.

The RF treatment was performed by three interventional radiologists with 25, 20, and 10 years of experience, respectively. All patients were fasted for 8 h before operation. No medication was used before operation. The general anaesthesia of a patient was performed by the anaesthesiologist. Vascular access was established and the routine ECGs, non-invasive blood pressure, and oxygen saturation were monitored. Propofol $3\text{--}4 \mu\text{g ml}^{-1}$ was administered as target controlled infusion; fentanyl $1\text{--}2 \mu\text{g kg}^{-1}$ and rocuronium bromide 0.7 mg kg^{-1} were administered as induction. Propofol and remifentanyl were continuously administrated during the operation. Invasive blood pressure monitoring and central venous catheterization were established after tracheal intubation.

A positioner was pasted on the surface of the body (as showed in Figure 1a). The number of probes, and the angle/depth of probe insertion was determined according to the scanned image; and the puncture point was marked accordingly. After disinfection of the area, probes were inserted, and scanning was performed again to confirm the position of probes. In case of uncertainty of the image, such as the presence of important blood vessels, an enhanced CT would be performed (Figure 2). For lesions with diameter less than 2 cm, a single probe ablation was used; for lesions with diameter larger than 2 cm, double probe was used, as the interactions of the two probes appeared to provide a better ablation effect.¹⁷ The accumulated power output was used as an end point of the ablation procedure: (1) 20 mm probe: 9 and 14 kJ were used for single and double probe, respectively; (2) 30 mm probe: 15 and 25 kJ for

Figure 1. A 75-year-old male, appearance of right adrenal metastasis after surgical treatment of the primary hepatic cell carcinoma. (a) An enhanced CT showed the right adrenal metastatic tumour (2.56 × 2.09 cm). (b) The use of CT-guided RF ablation (with two 30-mm probes). (c, d) MRI images indicate a recurrence on the right side and the presence of new metastases on the left side at 9 months after the first treatment. (e–g) The recurrence on the right side and the new metastases on the left side, with each treated with double probes (30 mm). (h) Minimal pneumothorax was found during the treatment. (i, j) No recurrence was found 9 months after the second treatment. RF, radiofrequency.

single and double probe; (3) 40 mm probe: 29 and 39 kJ for probe and double probe. Based on the experiences of the surgeon, the accumulated power output could be adjusted appropriately. For example, if the tumour was located in proximity of a main blood vessel, the power output would need to be increased due to the “heat sink” effect. The blood pressure was monitored closely during the procedure. When the blood pressure was increased to more than 20% of baseline level, intermittent injection of sodium nitroprusside/nitroglycerin, 5 mg urapidil, or 1 mg phenotolamine, 5–10 mg Esmolol was performed by anaesthetist to control the heart rate to less than 100 beats min^{-1} . Enhanced CT images were taken to

Figure 2. A 50-year-old female, appearance of left adrenal metastasis 2 years after surgical treatment of the primary renal cell carcinoma. (a) An enhanced CT showed the left adrenal metastatic tumour (arrow). (b) The use of CT-guided RF ablation (with a 20-mm probe), the enhanced CT image provided the location of the artery. (c) No enhancement of the tumour was found 3 years after the treatment, and the tumour was significantly smaller than before (arrow). RF, radiofrequency.

confirm the successful ablation procedures. 12 h ECG monitoring was performed after treatment, and any post-treatment complications were recorded using Clavien-Dindo classification.¹⁸ Grade 1 and Grade 2 complications were defined as mild complications; and Grade 3 or above were defined as severe complications.

Efficacy assessments and follow-up

Efficacy evaluation was performed based on images of the lesions. Contrast-enhanced CT scans or MRI were taken every 3 months after treatment. The latest follow-up time was January 2017. Technical success was defined as the completion of adrenal RF ablation according to a planned treatment protocol, as well as the disappearance of tumour enhancement when compared to the initial contrast-enhanced CT or MRI images. Local tumour recurrence is defined as the observation of emerging tumour lesions in the ablation area after confirmed successful ablation procedure. For the residual tumour or local tumour recurrence, ablation procedure could be repeated as appropriate.

Statistical analyses

SPSS (SPSS v. 16, New York, NY) was used for statistical analyses. Patient groups with or without residual disease after treatment were compared with various parameters. Qualitative data were expressed in frequency (%), and Fisher's exact test was used to compare differences between groups. Quantitative data were expressed in mean $\pm$ standard deviation (SD), and *t*-test was used to compare differences between groups. Kaplan–Meier method

Table 2. Comparison of tumour size between cases of post-operative residual disease vs non-residual disease

Parameters	Present of residual tumour after treatment		<i>p</i>
	No <i>n</i> = 30 (81.1%)	Yes <i>n</i> = 7 (18.9%)	
Pre-procedure tumour diameter (cm), mean $\pm$ sd	2.5 $\pm$ 0.7	5.3 $\pm$ 2.3	0.018
Pre-procedure tumour diameter (cm), <i>n</i> (%)			0.025
<3	23 (76.7)	2 (28.6)	
≥ 3	7 (23.3)	5 (71.4)	

was used for analyses of survival time of patients. A *p*-value of less than 0.05 was regarded as statistically significant.

RESULTS

Outcomes of the treatment

A total of 46 RF ablation treatments were performed in 38 lesions between January 2012 to 2015, with 8 of the lesions received 2 RF ablation treatments. The electrode was punctured through the liver in four of the patients, and five of the patients underwent thoracic puncture. All of the patients had completed the ablation treatment as planned, except one. This patient had intraoperative hypertension crisis and ECG abnormalities (ST segment) was observed; the ablation procedure was, therefore, terminated. This patient has unilateral tumour, and the data were not used for further analyses, such as the presence of residual disease.

Post-operative CT images showed the lack of tumour enhancement in 30 cases (30/38, 78.9%), suggesting the successful treatment. This group of patients had average pre-procedure tumour diameter of 2.5 $\pm$ 0.7 cm. Residual disease was found in 7 cases (7/37, 18.9%), the average pre-procedure diameter was 5.3 $\pm$ 2.3 cm, with 5 of the cases > 3 cm. Statistical analyses showed that patients with residual disease had significantly larger tumour size (*p* = 0.018), and the residual rate was significantly different between the groups with tumour size <3 and ≥ 3 cm (*p* = 0.025) (Table 2). Other parameters, such as age, gender, primary tumours, extra-adrenal invasion, number of adrenal tumours, were not statistically associated with the presence of residual disease. For the seven cases of residual disease, four of them received RF ablation again 2 weeks after the first treatment. Three of the patients showed successful treatment after the second ablation, and one of the patients still showed residual tumour. CT and MRI images that illustrated the clinical course of the disease were shown from two representative cases (Figures 1 and 2).

ADVERSE EVENTS AND COMPLICATIONS

2 cases of severe complications, and 16 cases of mild complications were observed (Table 3) with intraoperative hypertension crisis (*n* = 9) as the most frequently reported complication. Hypertension crisis was defined as blood pressure increased to >180/120 mmHg and heart rate to >120 beats min⁻¹ during the procedure. There was one case of ECG ST segment changes

Table 3. Reported complications of the ablation treatment

Grading of complications	Description	Frequency <i>n</i> = 33 (%)
Severe complications (Grade 3 or above)	Hypertensive crisis combined with acute myocardial injury	1 (3.0)
	Massive pneumothorax	1 (3.0)
Mild complications (Grade 1 or Grade 2)	Hypertension crisis during operation	9 (27.3)
	Local bleeding	3 (9.1)
	Minimal pneumothorax	2 (6.1)
	Reduced adrenal function after treatment	2 (6.1)

during the treatment, and the procedure was terminated immediately. Also, a transient increase of cTnI (Cardiac Troponin I) was observed post-operatively. Considering the patient had acute myocardial injury, he was discharged without further ablation treatment after 1-week stay in intensive care unit. Another severe complication of dyspnoea occurred in a patient 3 h post-operatively. X-ray examination showed the severe pneumothorax on the treatment side. Closed chest drainage was performed, and the symptom was improved. The tube was removed 3 days after, and the patient was discharged 5 day post-treatment. For the rest of the patients with high hypertension crisis during treatment, the condition was controlled with the use of medications. For patients who underwent the second RF ablation, none of them had high blood pressure crises.

Tumour progression after treatment

The follow-up time of the cases was from 3 to 48 months, with the mean follow-up time at 22.8 $\pm$ 8.5 months. There were 30 cases with no local residual after the first ablation treatment, and 3 cases achieved complete removal of the lesions after the second ablation treatment. Recurrence was observed in eight cases (24.2%) in between 3 and 24 months after treatment (mean 10.5 $\pm$ 6.2 months). Four of these eight patients received secondary ablation treatment, no recurrence was observed during the follow-up period. The Kaplan-Meier analysis showed that the mean recurrence-free time was 27.4 months [95% confidence interval at (22.5–32.3)] (Figure 3). The representative images of the residual tumours were shown in Figure 4. Overall, 29 cases (76.3%, 29/38) with no local recurrence as of the last follow up of the study. Further analysis was performed to evaluate the associations between different clinical parameters and recurrence, but no significant correlation was found (Table 4).

DISCUSSION

The present study showed the positive outcomes of RF ablation treatment for patients with unresectable adrenal metastases. Approximately 76% of the patients had no recurrence observed after treatment in 27.4 months. The procedure was safe, with low incidence rate (4.3%) of severe complications reported. This RF ablation treatment appeared to provide better outcomes for patients with lesions <3 cm, these patients had higher chance to achieve complete control of tumours after treatment.

Figure 3. Kaplan–Meier analysis of recurrence-free survival of patients. The mean recurrence-free time was 27.4 months [95% confidence interval at (22.5–32.3 months)].

Surgical resection of the adrenal metastases was advocated as one of the treatment options for patients. Studies showed that 77–84% of the patients had no local recurrence after surgical resection;^{4, 5} the rate was similar to the results observed in the present study (76.3%). Patients who are eligible for surgical treatment were usually those who had isolated or limited metastatic lesions. In the present study, 18/33 of the patients had extra-adrenal invasion, and some of the patients were not suitable for surgery or had local recurrence after surgery. We believe the RF ablation has clinical significance in providing additional treatment option for patients. It is worth to note that the RF ablation could be repeated in case of local recurrence. In the present study, of the eight patients who had local recurrence, four had received the second RF treatment; and none of the four patients had recurrence occurred after the second RF treatment. Patients who received ablation procedure should be followed up closely, so the repeated ablation treatment could be performed timely.

The present study had follow up visits every 3 months, and we found it reasonable. The comparison of residual tumours and complications between surgery and RF is difficult, since studies have used different definitions of residual tumour and severity of complications. For example, positive margins might be used for surgical treatment. Strong et al reported that the incidence of positive margins in surgery was 28%, with a severe complication rate of 8%, which are higher than our study (18.9% residual disease and 4.3% severe complication rate).¹⁹ Another study reported the mortality rate of surgical treatment was 0.75% (6/793); while no deaths were reported so for the RF treatment of adrenal tumour.

The local recurrence rate was low in our study, 76.3% of patients had recurrence-free survival in 27.4 months, which is similar to other reports: Yamakado et al showed that the treatment of RF ablation combined with adrenal arterial chemoembolization in eight patients with adrenal metastasis of hepatocellular carcinoma had a local recurrence rate of 25% in a follow-up period of 37.7 months.¹² Another study demonstrated that 88% of patients received adrenal ablation had recurrence-free survival in 36 months.¹⁵ Hasegawa et al reported that the RF ablation provided tumour control in 77% of patients in 30 months.²⁰ In addition to RF ablation, a report showed that the non-surgical treatment—stereotactic body radiotherapy (SABR)—had a 2-year control rate of local recurrence at 63%,⁴ while another study showed that the 2-year control rate was 90% after stereotactic body radiotherapy treatment.²¹ This inconsistency may be attributed to the differences in inclusion criteria.

To date, whether surgical treatment, RF ablation, or other local treatments could improve overall survival remained controversial. Several studies showed the improvement of survival,^{11–15} but some showed the negative results.²² Currently, there is no large sample size randomized controlled trial to showed the efficacy of the treatments. The current study has small sample size, and bias might happen during patient selection; also no proper case control was included in this study. As such, the present study focussed on assessing the effectiveness of local treatment, such as the local residual rate and recurrence rate.

Figure 4. A 75-year-old liver cancer male patient, who had received TACE treatment previously. (a) A pre-operative enhanced CT image showing the right adrenal giant metastatic cancer. (b, c) The use of two 4-mm probes in combination provided four ablations. Shown are the pictures taken from two RF treatments. (d) Enhanced CT taken immediately after the RF treatment, showing a striped enhancement at the edge of the tumour, suggesting the residual disease.

Table 4. Associations between clinical characteristics and recurrence

Characteristics		Recurrence		Total	p
		Absent n (%)	Present n (%)		
Tumour diameters	<3 cm	15 (68.18)	5 (62.50)	20	1.000
	≥3 cm	7 (31.82)	3 (37.50)	10	
Gender	Male	13 (59.09)	3 (37.50)	16	0.417
	Female	9 (40.91)	5 (62.50)	14	
Primary tumours	Lung	11 (50.00)	3 (37.50)	14	0.689
	Others	11 (50.00)	5 (62.50)	16	
Extra-adrenal metastases	Absent	9 (40.91)	6 (75.00)	15	0.215
	Present	13 (59.09)	2 (25.00)	15	
Number of adrenal tumours	Unilateral	18 (81.82)	7 (87.50)	25	1.000
	Bilateral	4 (18.18)	1 (12.50)	5	
Residual disease	Absent	17 (77.27)	8 (100.0)	25	0.287
	Present	5 (22.73)	0 (0.00)	5	
Number of operations	1	17 (77.27)	3 (37.50)	20	0.078
	2	5 (22.73)	5 (62.50)	10	

The present study showed a satisfactory safety of the ablation procedure. The severe complication rate was 4.3%, and the mild complication rate was 48% with the most frequently observed mild complication of intraoperative hypertension (27.3%). Hypertensive crises caused by heating of the adrenal gland during RF ablation of the adrenal area was first reported by Onik et al.²³ Subsequently, several studies reported cases of hypertensive crises during RF ablation.^{13–15,20} Some reported the occurrence rate was 45% or above,^{15,20} while others reported 0–9%.^{13,14} It was suggested that the hypertension crisis was attributed to the catecholamine surge during operation, and this risk was associated with the tumour diameter of less than or equal to 4.5 cm.²⁴ To prevent the occurrence of hypertension crisis, the use of pre-ablation α -blockade was suggested.²⁵ From our experiences, we recognized the importance of establishing invasive blood pressure monitoring during operation. The blood pressure often increased to the level of 180/120 mmHg or above in a short period of time (within half a minute). Thus, the use of intermittent non-invasive blood pressure monitoring may not provide timely alert for administration of medication. The use of pre-ablation α -blockade may not be needed, as most of the hypertension crises in the present study were well-controlled after administration of medication. It is worth noting that the hypertension crisis was not observed in patients who underwent the second ablation treatment,

which was in consistence with the observation from Fintemann et al.²⁴

There are limitations of the current study, e.g. it is a single-centre retrospective study with small sample size, appropriate case control was lacking, and no surgery control for comparison. Also, there were some patients concurrently received chemoradiation therapy while of the RF treatment. There were only five cases pathologically confirmed through biopsy, although the adrenal biopsy may only provide limited information for diagnosis. High specificity was found for the biopsy examination, but the sensitivity was low (57–80%). Also, there is a concern of the occurrence of complications after biopsy procedure, therefore, the use of biopsy as diagnosis of adrenal lesions will need to weight carefully. The criteria for the imaging diagnosis include enhanced CT scan performed in every 3–6 months, if new lesions or increased size of adrenal gland was found, MRI (including chemical shift imaging) or PET/CT would be performed to examine adrenal metastases. Several studies suggested that biopsy examination has high specificity closed to 100% and sensitivity up to 80–90%.^{16,26,27}

In conclusion, the current study demonstrated that CT-guided percutaneous RF ablation is a relatively safe and effective treatment for use in the control of adrenal metastases, especially for patients with tumour size <3 cm.

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