

Unresectable Adrenal Metastases: Clinical Outcomes of Radiofrequency Ablation¹

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Purpose:

To retrospectively evaluate the clinical outcomes of radiofrequency (RF) ablation for the treatment of unresectable adrenal metastasis.

Materials and Methods:

The institutional review board approved this retrospective study, and informed consent to perform adrenal RF ablation was obtained from all patients. From February 2005 through May 2014, 35 patients (25 men and 10 women; mean age, 64.7 years \pm 9.6; age range, 39–82 years) underwent RF ablation to treat 41 metastatic adrenal tumors from lung cancer ($n = 15$), renal cell carcinoma ($n = 9$), colorectal cancer ($n = 5$), hepatocellular carcinoma ($n = 4$), and other tumors ($n = 2$). Tumors ranged in size from 1.2 to 8.2 cm (mean, 3.3 cm \pm 1.6). The diagnosis was established mainly on the basis of radiologic findings. Adrenal arterial embolization was combined with RF ablation in 12 of the 35 patients (34%). Technical success, safety, local tumor progression, and survival were evaluated. The Kaplan-Meier method and Cox proportional hazard model were used to evaluate prognostic factors.

Results:

There were 48 completed sessions with planned procedures and treatment protocols with no mortality and a major complication rate of 8.3% (four of 48 sessions). Tumor enhancement disappeared after initial adrenal RF ablation in 33 of the 35 patients (94%). Local tumor progression developed in eight of the 35 patients (23%); two patients received repeated RF ablation, resulting in adrenal tumor control in 27 of the 35 patients (77%) at the last follow-up (mean, 30.1 months \pm 27.5; range 1.2–96.8 months). The 1-, 3-, and 5-year overall survival rates were 75% (95% confidence interval [CI], 61%, 90%), 34% (95% CI: 17%, 52%), and 30% (95% CI: 13%, 48%), respectively, with a median survival time of 26.0 months. Existence of extra-adrenal tumors ($P = .005$) and age of 65 years or older ($P = .04$) were significant indicators of a poor prognosis.

Conclusion:

Adrenal RF ablation is a feasible and useful method for controlling adrenal metastases and offers patients opportunities for improved survival.

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Adrenal neoplasms comprise a broad spectrum of all neoplasms and are estimated to occur in 1% of the general population. Opportunities to detect adrenal tumors are increasing because of improved sensitivity of imaging techniques (1,2). Adrenal metastasis is the most common malignant tumor found in adrenal glands, particularly from lung cancer, renal cell carcinoma (RCC), colorectal cancer, hepatocellular carcinoma (HCC), and malignant melanoma. Autopsy reviews show metastases in adrenal glands in up to 27% of patients with known malignancy (2,3).

Metastatic disease to the adrenal gland is usually treated with chemotherapy or radiation therapy, depending on the primary tumor, but several investigators have emphasized the utility of surgical resection to improve patient survival in selected patients with isolated metastasis (4–16). Nevertheless, because of comorbid disease, age, previous surgery, or existence of extra-adrenal tumors, few patients are surgical candidates.

Recently, image-guided radiofrequency (RF) ablation has been used for the treatment of malignant adrenal tumors. It reportedly offers effective short-term local control of both primary and metastatic adrenal neoplasms (17–22). Given that both RF ablation and adrenalectomy are local-regional treatments, there may be a possibility that adrenal RF ablation can increase the survival of nonsurgical candidates with adrenal metastasis. However, the reported mean follow-up period was approximately 10–20 months with small

sample sizes of up to 16 cases, so the long-term results after treating adrenal metastases by using RF ablation have not been well investigated (4,21).

The purpose of our study was to retrospectively evaluate the clinical outcomes of RF ablation for the treatment of unresectable adrenal metastasis.

Materials and Methods

Study Design and Patients

This retrospective study was approved by our institutional review board. The requirement to obtain informed consent for inclusion in this study was waived. Informed consent to perform adrenal RF ablation was obtained from all patients before adrenal RF ablation.

The indication for adrenal RF ablation was determined from a multidisciplinary discussion of medical and radiation oncologists, urologists, and interventional radiologists. Adrenal RF ablation was performed in patients who were not considered surgical candidates or those who declined to undergo surgical intervention. Thirty-two of the 35 patients (91%) were not considered surgical candidates because of the existence of extra-adrenal tumors ($n = 9$), insufficient respiratory function ($n = 9$), previous multiple abdominal surgeries ($n = 7$), advanced age older than 75 years ($n = 5$), and contralateral adrenalectomy ($n = 2$). Three of the 35 patients (9%) preferred to receive adrenal RF ablation after declining surgery.

The inclusion criteria were as follows: patients who had an adrenal metastasis measuring 10 cm or less and no or controlled extra-adrenal tumor, Eastern Cooperative Oncology Group performance status of 0 or 1 (23), and a life expectancy of 2 months or longer. Patients with a coagulopathy (platelet count $<50 \times 10^9/L$ or international normalized ratio of prothrombin >1.5) despite platelet or fresh-frozen plasma

transfusion and those with Eastern Cooperative Oncology Group performance status of 2 or greater were excluded. Patients with adrenal metastasis invading the adrenal vein were also excluded.

From February 2005 through May 2014, 38 patients with adrenal metastases were referred to our department for adrenal RF ablation. Two patients were excluded because of poor performance status (Eastern Cooperative Oncology Group grade 3), and one patient was excluded because of adrenal venous invasion. Therefore, 35 of the 38 patients (92%) underwent adrenal RF ablation.

Patient demographics are presented in Table 1. The 35 patients ranged in age from 39 to 82 years (mean age \pm standard deviation, 64.7 years \pm 9.6). There were 25 men (mean age, 64.2 years \pm 9.8; age range, 39–82 years) and 10 women (mean age, 65.6 years \pm 8.6; age range, 57–82 years). The primary sites of disease were NSCLC in 15 patients, RCC in nine patients, colorectal cancer in five patients, HCC in four patients, and breast cancer and thymic cancer in one patient each. At the time of initial adrenal RF ablation, 16 of the 35 patients (46%) had extra-adrenal tumors. Primary tumors remained in five patients (HCC in four patients and



Advances in Knowledge

- The 5-year overall survival rate after adrenal radiofrequency (RF) ablation was 30.2% (95% confidence interval: 12.7%, 47.6%); the median survival time was 26.0 months.
- Advanced age and existence of extra-adrenal tumors were poor prognostic factors in patients with adrenal metastases who underwent adrenal RF ablation.

Implication for Patient Care

- RF ablation can contribute to prolongation of survival of patients with adrenal metastasis.

Published online before print

10.1148/radiol.2015142029 Content codes:  

Radiology 2015; 277:584–593

Abbreviations:

CI = confidence interval
HCC = hepatocellular carcinoma
NSCLC = non-small cell lung cancer
RCC = renal cell carcinoma
RF = radiofrequency

Author contributions:

Guarantors of integrity of entire study, T.H., K.Y., Y.S.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, T.H., K.Y., H.S., Y.S.; clinical studies, T.H., K.Y., A.N., J.U., T.Y., M.F., M.M., T.S., Y.S.; statistical analysis, T.H., Y.S.; and manuscript editing, T.H., K.Y., J.U., H.S., Y.S.

Conflicts of interest are listed at the end of this article.

Table 1

Patient and Tumor Demographics

Variable	Value
Patient characteristics	
No. of patients	35
F	10
M	25
Mean age (y)	64.7 ± 9.6
Age group	
<65 y	17
≥65 y	18
Extra-adrenal tumor	
Yes	16
No	19
Previous adrenalectomy	
Yes	3
No	32
Previous chemotherapy	
Yes	23
No	12
Tumor number	
Single	29
Double	6
Ipsilateral	2
Contralateral	4
Combination with embolization	
Yes	12
No	23
Tumor origin	
NSCLC	15
RCC	9
Colorectal cancer	5
HCC	4
Other	2
Tumor characteristics	
No. of tumors	41
Maximum tumor size (cm)	
Mean	3.3 ± 1.6
Range	1.2–8.2
No. of tumors <3 cm	21
No. of tumors ≥3 cm	20
Location	
Right	21
Left	20

Note.—Except where indicated, data are numbers of patients or tumors. NSCLC = non-small cell lung cancer.

RF ablation. Two adrenal tumors were present in one adrenal gland in two patients and in bilateral adrenal glands in three patients at the time of initial RF ablation. One new tumor developed in the contralateral adrenal gland 7 months after initial adrenal RF ablation in one patient, and the new tumor was also treated with RF ablation. Therefore, RF ablation was performed to treat 41 adrenal tumors.

Adrenalectomy had been performed in three patients before adrenal RF ablation: one patient with local recurrent tumors in the resected area and two patients with newly developed metastasis in the contralateral adrenal gland.

Systematic chemotherapy had been performed in 23 of the 35 patients (66%) before adrenal RF ablation. The regimen of paclitaxel and carboplatin (Taxol [Bristol-Meyers Squibb, Tokyo, Japan] and Carboplatin [Sandoz, Tokyo, Japan]), docetaxel (Onetaxotere; Sanofi, Tokyo, Japan), docetaxel and cisplatin (Onetaxotere and Cisplatin Maruko; Yakult Pharmaceutical Industry, Tokyo, Japan), tegafur, gimeracil, and uteracil potassium (TS-1; Taiho Pharmaceutical, Tokyo, Japan), TS-1 and carboplatin (TS-1 and Carboplatin), tegafur-uracil (UFT combination capsule T100, Taiho Pharmaceutical), iressa (Iressa; Astra Zeneca, Osaka, Japan), or pemetrexed (Alimta; Eli Lilly Japan, Kobe, Japan) was used in all 15 patients with NSCLC (100%). Interferon- α (Sumiferon; Sumitomo Dainippon Pharma, Osaka, Japan) was used in two of the nine patients with RCC (22%). Fluorouracil, leucovorin, and irinotecan (5-FU [Kyowa Pharmaceutical Industry, Tokyo, Japan], Leucovorin [Pfizer Japan, Tokyo, Japan], and Campto [Yakult Pharmaceutical Industry]), fluorouracil, leucovorin, and oxaliplatin (5-FU, Leucovorin, and Elplat; Yakult Pharmaceutical Industry), fluorouracil and leucovorin (5-FU, Leucovorin), xeloda (Xeloda; Chugai Pharmaceutical, Tokyo, Japan), TS-1 (TS-1), and cetuximab (Erbix; Merck Serono, Tokyo, Japan) were used in four of the five patients with colorectal cancer (80%). Anastrozole (Arimidex, Astra Zeneca) was used in the patient with

breast cancer (100%). Adriamycin and doxorubicin and cisplatin and vincristine and cyclophosphamide (Adriacin [Kyowa Pharmaceutical Industry]; Cisplatin Maruko; Oncovin [Nippon Kayaku, Tokyo, Japan], and Endoxan [Shionogi, Osaka, Japan]) were used in the one patient with thymic cancer (100%). Three patients underwent adrenal RF ablation after chemotherapy failure, and 20 underwent adrenal RF ablation owing to the appearance of adrenal metastases during chemotherapy.

The mean maximum tumor diameter of treated adrenal metastasis was 3.3 cm ± 1.6 (range, 1.2–8.2 cm). Twenty-one metastases were in the right adrenal gland and 20 were in the left. All but one patient with back pain were asymptomatic at the time of RF ablation.

Pretreatment Work-up

Routine physical examination, laboratory tests, including determination of hormone levels, chest radiography, and chest, abdominal, and pelvic computed tomography (CT) with and without contrast material were performed before RF ablation in all patients.

The diagnosis of adrenal metastasis was established mainly on the basis of radiologic findings. Emerging adrenal tumors in patients with malignant neoplasms that increased in size twice or more in a row on serial CT scans obtained every 3–6 months were diagnosed as adrenal metastases (24) (Fig 1a). CT scans were obtained with intravenous contrast material in the early and delayed phases. The diagnosis was confirmed with percutaneous biopsy in seven of the 35 patients (20%) in whom radiologic findings were atypical for adrenal metastasis. To exclude adenoma and confirm malignancy, magnetic resonance (MR) imaging, including chemical shift imaging, and positron emission tomography/CT were performed in 19 (54%) and 13 (37%) of the 35 patients, respectively (24). Pheochromocytoma was ruled out by means of serum hormone levels before the procedure.

Adrenal RF Ablation

Adrenal RF ablation was performed by three interventional radiologists (K.Y.,

NSCLC in one patient) and extra-adrenal metastases were observed in 11 (bone in five patients, lymph node in four patients, and lung in two patients).

Five of the 35 patients (14%) had two adrenal tumors at the time of initial

Figure 1



Figure 1: Images in 61-year-old man who developed adrenal metastasis 2 years after right upper lobectomy for lung squamous cell carcinoma. **(a)** Contrast-enhanced CT scan shows tumor (arrow) in right adrenal gland. **(b)** RF electrode was placed in tumor under real-time CT fluoroscopic guidance. **(c)** Contrast-enhanced CT scan obtained 4 years after RF ablation shows disappearance of tumor enhancement (arrow).

A.N., and J.U., with approximately 23, 21, and 10 years of experience in oncologic interventional radiology, respectively) under moderate sedation and local anesthesia on an inpatient basis. Fentanyl citrate (Fentanyl; Daiichi Sankyo, Tokyo, Japan) was used for analgesia. Lidocaine (Xylocaine; Astellas Pharma, Tokyo, Japan) was used as a local anesthesia. Antibiotics (Cefazolin, Astellas Pharma) were administered prophylactically before and for 2–3 days after RF ablation. No patient received premedication such as α -blocker before RF ablation.

Real-time CT fluoroscopy (Aquilion; Toshiba, Otawara, Japan) was used to place the internally cooled electrodes (Cool-Tip RF Ablation System; Covidien, Boulder, Colo) into the tumor. The electrode was placed in the center of the tumor, and additional electrodes were used depending on the tumor size and shape (Fig 1b). After the electrode was connected with the generator (Cool-tip RF generator or Cool-tip RF ablation system E-series, Covidien), RF energy was applied for 12 minutes by using an impedance control algorithm. During the procedure, the heart rate was monitored continuously. Blood pressure was monitored every minute. When systolic blood pressure increased higher than 180 mm Hg, a calcium blocker (Nifedipine; Sawai Pharmaceutical, Osaka,

Japan) was administered immediately via an intravenous route (21). When an adrenal tumor was located adjacent to a critical organ such as bowel or pancreas, RF ablation was performed after injecting distilled water via an 18-gauge needle to displace such adjacent organs (ie, hydrodissection) (25).

Selective adrenal arterial embolization was performed before RF ablation in patients who had hypervascular or large tumors—except for the initial two patients with RCC adrenal metastases. After selecting the supra, middle, or inferior adrenal artery by using a 4-F catheter and 2.1-F microcatheter (Progreat; Terumo, Tokyo, Japan), embolization was performed with iodized oil (Lipiodol Ultra Fluid; Guerbet Japan, Tokyo, Japan) and gelatin sponge particles (Spongel; Nihon Kayaku, Tokyo, Japan). The mean interval between arterial embolization and RF ablation was 6.8 days \pm 9.7 (range, 0–37 days).

The primary technical success was defined as completion of adrenal RF ablation with a planned treatment protocol and disappearance of tumor enhancement on the initial contrast-enhanced CT or MR images obtained 2–5 days after RF ablation as ablation zone in surrounding fat tissue was difficult to detect on CT or MR images (26). CT scans were obtained by using the same protocol as

that used for the images obtained before treatment and read by two interventional radiologists (K.Y. and A.N.). When the tumor enhancement remained, repeat RF ablation was performed 1 week later if the patient agreed to treatment.

Secondary success was defined as technical success determined on CT or MR images obtained 2–5 days after initial and second adrenal RF ablation for residual tumor.

Complications

Complications were evaluated according to Common Terminology Criteria for Adverse Events version 4.03 (27). Any patient death occurring within 30 days of imaging-guided tumor ablation was designated as a grade 5 adverse event. Grades 3 and 4 adverse events were defined as major complications. Grade 2 adverse events were defined as minor complications.

Follow-up

Follow-up ended at the time of death or the last visit of the patient until June 30, 2014. Patients were followed up by five interventional radiologists (K.Y., A.N., J.U., T.Y., and M.F., with approximately 23, 21, 10, 6, and 3 years of experience in oncologic interventional radiology, respectively) and two urologists (M.M. and T.S., both with approximately 6

Figure 2



Figure 2: Images in 64-year-old man who developed adrenal metastasis 12 years after right nephrectomy for RCC. **(a)** Angiogram shows hypervascular tumor from right inferior phrenic artery (black arrow). Adrenal arterial embolization was performed via supra-adrenal artery (white arrows). **(b)** RF electrode was placed in tumor under real-time CT fluoroscopic guidance. RF electrode was placed through lung and liver. **(c)** Contrast-enhanced CT scan obtained 7 years after RF ablation shows that tumor (arrow) is well controlled.

years of experience in urology). Routine physical examinations and laboratory tests, including determination of blood count, adrenal hormone levels, and tumor markers on the basis of primary tumor histologic findings, were performed every month. Chest, abdominal, and pelvic CT studies with and without contrast material enhancement were obtained 1 month later and then every 3–4 months for 3 years after RF ablation, and then every 6 months after that.

Local tumor progression was defined as the appearance of tumor foci at the edge of the ablated zone after confirming adequate ablation and an absence of viable tissue in the target tumor on follow-up CT images (Fig 1c) (26). Recurrent tumors were treated again with RF ablation when they satisfied the indication criteria of RF ablation.

Assessment and Statistical Analysis

Technical success and complications were evaluated on a per-session basis. Local tumor progression rates were evaluated on a per-patient basis. Survival was calculated from the time of initial adrenal RF ablation. Cumulative overall survival curves were generated by using the Kaplan-Meier method. The local tumor progression and survival rates were compared by using the log-rank

test between subgroups categorized according to patient backgrounds. Multivariate analysis was performed by using the Cox proportional hazard model. The frequencies of respective causes of death between patients aged 65 years or older and those younger than 65 years were compared by using the Fisher exact test. Survival was also evaluated on the basis of primary tumors and the presence or absence of extra-adrenal tumors. Data are expressed as means \pm standard deviations. $P < .05$ was considered to indicate a statistically significant difference. Statistical analyses were performed by using software (SPSS for Windows, version 21; SPSS, New York, NY).

Results

Adrenal RF Ablation

A total of 48 RF ablation sessions were performed for 41 tumors. Adrenal arterial embolization was performed before RF ablation in 12 of the 35 patients (34%) with adrenal metastasis from RCC ($n = 7$), HCC ($n = 4$), and NSCLC ($n = 1$), with a maximum tumor diameter of 1.9–8.2 cm (mean, 3.7 cm \pm 2.2) (Fig 2a).

RF ablation electrodes were placed into planned sites. The ablation was

completed with the planned protocol in all tumors (100%, 48 of 48 tumors). According to the tumor location, the electrode was punctured through the liver in five of the 48 sessions (10%) and through the lung in five (10%) (Fig 2b). Hydrodissection was performed in 10 of the 48 RF ablation sessions (21%).

Tumor enhancement disappeared in 29 patients after initial adrenal RF ablation, so the primary technical success rate was 83% (29 of 35 patients). Tumor enhancement remained at the tumor peripheries in six patients with tumors larger than 3 cm (17%, six of 35 patients). Four patients received RF ablation for residual tumor within 1 week, so tumor was ablated in 33 of the 35 patients (94%) after the second RF ablation. Two patients declined repeated RF ablation because lung metastases were found in one patient and mandible bone metastasis was found in the other. Therefore, the secondary technical success rate was 94% (33 of 35 patients). Symptomatic relief was achieved in a patient with back pain after RF ablation.

Tumor Progression

The mean follow-up period was 30.1 months \pm 27.5 (range, 1.2–96.8 months). In addition to two patients

with residual adrenal tumors after RF ablation, eight of the 35 patients (23%) experienced local tumor progression in the treated tumor 2.2–24.0 months after RF ablation (mean, 8.6 months \pm 8.5). The primary local tumor progression rates were, respectively, 29.5% (95% confidence interval [CI]: 11.5%, 47.4%) at 1 year and 43.6% (95% CI: 20.9%, 66.1%) at 3 and 5 years. A tumor size of 3 cm or more at the time of adrenal RF ablation was determined to be a significant factor affecting local tumor progression (Table 2).

Repeated RF ablation was performed for two of eight patients with locally progressed tumors. Both tumors were controlled until the last follow-up. RF ablation was not applied for the other six patients with locally progressed tumors because of the appearance of extra-adrenal metastases. Therefore, RF ablation ended up controlling adrenal metastases at the last follow-up in 27 of the 35 patients (77%) (Fig 2c), with secondary local tumor progression rates of 22.3% (95% CI: 5.9%, 38.7%) at 1 year and 36.4% (95% CI: 14.2%, 58.6%) at 3 and 5 years.

Disease-free status was achieved at least once during the follow-up in 18 of 19 patients without extra-adrenal metastases at the time of initial adrenal RF ablation (51%, 18 of 35 patients). Disease-free status could not be achieved in a patient because of residual tumor. However, extra-adrenal metastases or local tumor progression developed in 14 of the 18 patients in whom disease-free status was achieved (78%) 2.2–66.2 months (mean, 14.5 months \pm 15.8) after initial follow-up examination. The mean disease-free time in 18 patients in whom a tumor-free condition was achieved was 21.2 months \pm 25.0 (range, 2.2–98.5 months). The extra-adrenal tumor progression rates were 56.8% (95% CI: 31.0%, 76.1%) at 1 year and 81.5% (95% CI: 53.3%, 93.6%) at 3 and 5 years, and the mean disease-free time was 21.2 months \pm 25.0 (range, 2.2–98.5 months) in 18 patients who achieved disease-free status. RF ablation was performed for liver metastases in two patients and renal metastasis in one patient. The

Table 2

Local Tumor Progression Rate according to Variable

Variable	No. of Patients	Local Tumor Progression Rate (%)			P Value
		1 Year	3 Years	5 Years	
Age					
<65 y	17	18.7 (9)	32.3 (5)	32.3 (4)	.37
≥65 y	18	30.2 (6)	56.4 (2)	56.4 (0)	
Sex					
M	25	30.4 (9)	30.4 (4)	30.4 (2)	.67
F	10	25.0 (5)	55.0 (3)	55.0 (2)	
Tumor size					
<3 cm	18	14.1 (11)	33.2 (6)	33.2 (3)	.04
≥3 cm	17	50.6 (3)	50.6 (1)	50.6 (1)	
Primary tumor					
NSCLC	15	58.2 (3)	58.2 (2)	58.2 (1)	.09
Other	20	10.9 (11)	33.2 (5)	33.2 (3)	
Combination with embolization					
No	23	38.9 (8)	38.9 (4)	38.9 (2)	.54
Yes	12	10.0 (6)	46.0 (3)	46.0 (2)	
Previous chemotherapy					
No	12	8.3 (5)	31.3 (3)	31.3 (1)	.35
Yes	23	37.8 (9)	48.1 (4)	48.1 (3)	
Total	35	29.5 (14)	43.6 (7)	43.6 (4)	

Note.—Numbers in parentheses are the frequency count (number of patients).

remaining 11 patients received systemic chemotherapy. No patient having extra-adrenal disease at the time of initial adrenal RF ablation reached disease-free status during the follow-up.

Survival

Twenty-two of the 35 patients died (63%) (Fig 3). The cause of death were tumor progression ($n = 16$), gastrointestinal bleeding ($n = 3$), pneumonia ($n = 2$), and liver failure ($n = 1$). Of the 17 patients younger than 65 years, seven (41%) died of tumor progression. Of 18 patients aged 65 years or older, nine (50%) died of tumor progression and six (33.3%) died of a cause other than tumor progression. Although no difference was found in the frequency of death due to tumor progression between the two patient groups ($P = .74$), the frequency of death due to causes other than tumor progression was significantly greater in older patients (≥ 65 years) than in younger patients (< 65 years) (33% vs 0%, respectively; $P = .019$).

The 1-, 3-, and 5-year overall survival rates were, respectively, 75.4%

(95% CI: 60.6%, 90.2%), 34.5% (95% CI: 16.7%, 52.3%), and 30.2% (95% CI: 12.7%, 47.6%). The median survival time was 26.0 months (Fig 4).

Age of 65 years or more ($P = .01$), male sex ($P = .03$), metastasis from NSCLC ($P = .04$), and existence of extra-adrenal tumor ($P = .04$) were significant indicators of a worse prognosis at univariate analysis (Table 3). Age of 65 years or more ($P = .04$; hazard ratio: 3.0; 95% CI: 1.1, 8.8) and existence of extra-adrenal tumor ($P = .005$; hazard ratio: 4.9; 95% CI: 1.6, 14.7) remained significant in the Cox proportional hazard model. Although a tendency was apparent by which patients with small adrenal metastases (< 3 cm) survive longer than those with large metastases (≥ 3 cm), the difference was not significant ($P = .06$).

The prognosis according to tumor origin was summarized in Table 4. The median survival time of patients with NSCLC, RCC, colorectal cancer, and HCC was 18.9 months, 62.6 months, 26.2 months, and 9.3 months, respectively.

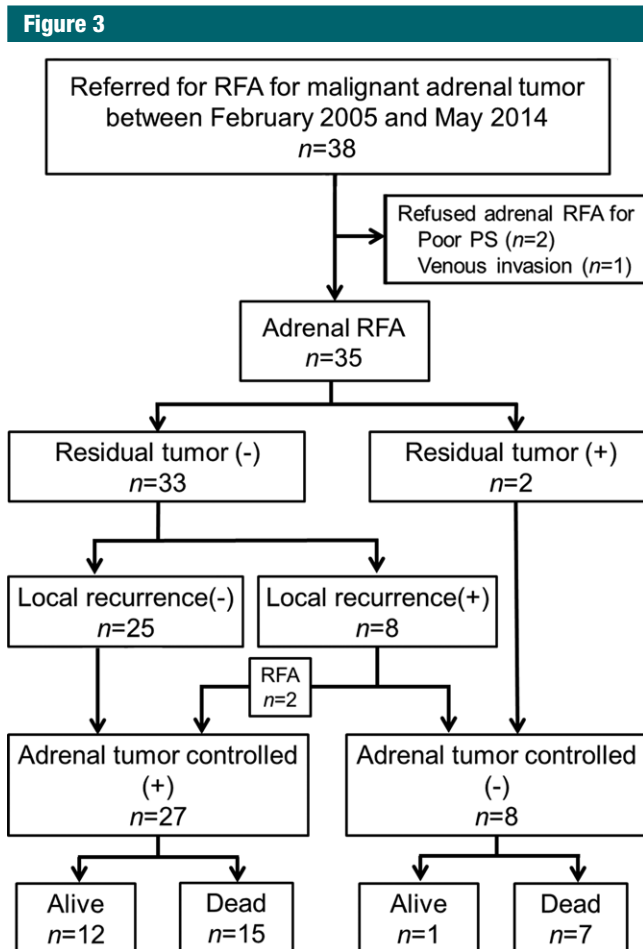


Figure 3: Outcomes of patients who received RF ablation (RFA) for malignant tumor. PS = performance status.

Complications

Complications are presented in Table 5. No death (grade 5 adverse event) was related to RF procedures (0%, 0 of 48 sessions). Grade 4 acute renal failure and grade 3 hemorrhage, heart failure, and stroke occurred in one session each, so the major complication rate was 8.3% (four of 48 sessions). Acute renal failure developed 2 days after RF ablation and recovered after temporary dialysis. Subcapsular liver hemorrhage occurred immediately after RF ablation and was controlled after embolization of the posterior segment branch of the hepatic artery. Acute stroke and heart failure occurred 3 and 5 days after RF ablation. These patients were treated with medication.

Minor complications (grade 2 adverse events) developed in 21 of the 48 RF sessions (44%) (Table 2). Hypertension of 180 mm Hg or more occurred in 22 of the 48 sessions (46%), but blood pressure normalized soon after administration of calcium blocker in all cases. No sequelae related to hypertension were found in any patient. Supplementation of steroid was required in two patients who received RF ablation after adrenalectomy of the contralateral side. Adrenal failure did not occur in patients who received RF ablation for both sides of adrenal tumor.

Discussion

Our study showed that adrenal RF ablation is a feasible therapeutic option

for patients with unresectable adrenal metastases. Given that most patients in our study were not surgical candidates, and two-thirds of the patients had adrenal metastasis resistant to chemotherapy, adrenal RF ablation seems to improve survival in selected patients. The median survival times after chemotherapy or molecular target drug treatment have been reported to be 7–12 months in patients with NSCLC (28), 7–16 months in patients with RCC (29), 8–24 months in patients with colorectal cancer (30), and 7–19 months in patients with HCC (31). Although a maximum tumor diameter was not described in most of the previous studies featuring chemotherapy, the mean patient age (57–70 years) was almost similar to that in our study (64.7 years). Prolonged survival has been reported if patients are initially considered surgical candidates. The median survival time after adrenalectomy has been reported to be 8–30 months in patients with adrenal metastasis from various types of primary tumors (3–11), 11–29 months in patients with NSCLC (5,11,12), 20–89 months in patients with RCC (11,13), 23–29 months in patients with colorectal cancer (11,14), and 12–21 months in patients with HCC (15,16). Both the mean age (55–65 years) and the maximum tumor diameter (2.0–6.0 cm) in patients undergoing adrenalectomy were almost similar to the mean age and the mean maximum tumor diameter (3.3 cm \pm 1.6; range, 1.2–8.2 cm) in our study (3–6,10–16). Results obtained in our study were almost similar to those obtained after adrenalectomy—except in patients with HCC. However, Yamakado et al (17) performed combination therapy of adrenal artery chemoembolization and RF ablation in six patients with HCC adrenal metastases and reported a median survival time of 24.9 months, which is almost similar to that obtained after adrenalectomy.

Local tumor control by means of surgical intervention has been reported as 77%–83% (4–6). In our study, adrenal tumors were controlled to 77% (27 of 35 patients) by using repeated RF ablation at the last follow-up, which is almost equal to that after adrenalectomy. Tumor

Figure 4

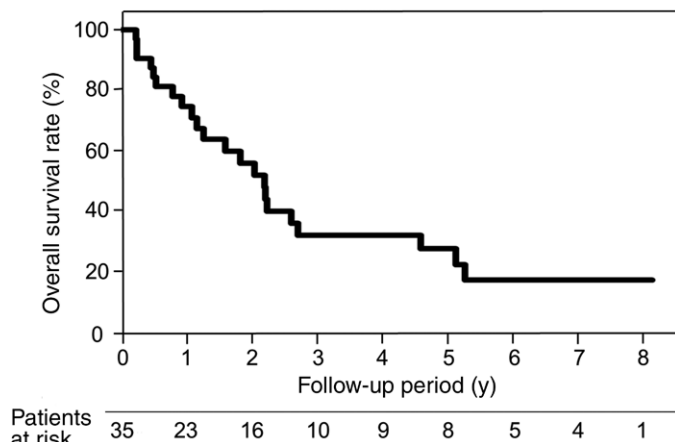


Figure 4: Overall survival curve after RF ablation for adrenal tumor. Median survival was 26.0 months.

Table 3

Overall Survival Rate according to Variable

Variable	No. of Patients	Survival Rate (%)			Median Survival Time (mo)	P Value
		1 Year	3 Years	5 Years		
Age						
<65 y	17	87.4 (12)	48.6 (6)	48.6 (5)	26.6	.01
≥65 y	18	62.5 (10)	21.1 (3)	14.1 (2)	19.0	
Sex						
M	25	71.3 (16)	21.1 (4)	15.8 (3)	24.3	.03
F	10	87.5 (6)	72.9 (5)	72.9 (4)	NA	
Tumor size						
<3 cm	18	82.4 (13)	55.4 (8)	47.4 (6)	54.5	.06
≥3 cm	17	67.7 (9)	8.8 (1)	8.8 (1)	24.3	
Multiple adrenal metastasis						
No	29	78.4 (20)	39.7 (9)	34.7 (7)	26.2	.11
Yes	6	53.3 (2)	0.0 (0)	0.0 (0)	14.9	
Primary tumor						
NSCLC	15	58.7 (7)	20.1 (2)	10.1 (1)	19.0	.04
Other	20	88.9 (15)	44.9 (7)	44.9 (6)	31.0	
Combination with embolization						
No	23	71.9 (13)	26.5 (4)	17.7 (2)	24.3	.34
Yes	12	81.8 (9)	45.5 (5)	45.5 (5)	32.2	
Extra-adrenal tumor						
No	19	83.3 (14)	44.9 (7)	37.4 (5)	32.2	.04
Yes	16	66.7 (8)	20.8 (2)	20.8 (2)	13.8	
Previous chemotherapy						
No	12	80.0 (8)	40.0 (4)	40.0 (3)	26.0	.95
Yes	23	73.1 (14)	30.9 (5)	24.7 (4)	24.3	
Total	35	75.4 (22)	34.5 (9)	30.2 (7)	26.0	

Note.—Numbers in parentheses are the frequency count (number of patients). NA = not applicable.

size affected local tumor progression after adrenal RF ablation in our study, as previous studies have described (17,18). Because repeatability is a clear benefit of RF ablation, close follow-up must be done to detect local tumor progression early and treat it quickly, especially 2 years after RF ablation as most of local tumor progression was found within these periods. Our study also demonstrated that extra-adrenal metastases develop frequently after adrenal RF ablation (more than three-fourths of patients who had once been considered free of tumor after adrenal RF ablation), even in patients with isolated adrenal metastases. Given that RF ablation is applicable for extra-adrenal tumors such as the liver and kidney as shown in our study and previous studies, the importance of close follow-up should be re-emphasized to find extra-adrenal tumors (19,20).

Age of 65 years or older and the existence of extra-adrenal tumors were determined to be worse prognostic factors. Age was a prognostic factor because the frequency of death due to a cause other than tumor progression was significantly higher in older patients (≥65 years) than in younger patients. Absence of extra-adrenal tumors has also been reported as an important prognostic factor in previous reports featuring adrenalectomy (8,9). Probably because the disease stage is higher even after RF ablation in patients with extra-adrenal tumors, the prognosis of these patients is not good.

In addition, metastasis from NSCLC was detected as a worse prognostic factor in the univariate analysis, probably because of the progression of primary tumors (7,8). However, survival of patients with NSCLC adrenal metastases achieved in this study (median survival time, 19.0 months) is apparently higher than that after systemic chemotherapy in such patients (median survival time, 7–12 months) (28). This finding is expected to be validated in the near future.

Our study also demonstrated that adrenal RF ablation is a safe procedure. The major and minor complication rates in our study were 8.3% and 43.8%, respectively. An increase in blood pressure (>180 mm Hg) was seen in 46% (22 of

Table 4**Prognosis according to Tumor Origin**

Tumor Origin and Variable	Value	Extra-Adrenal Tumor		PValue
		Yes	No	
NSCLC				
No. of patients	15	6	9	
Mean 3-year survival rate (%)	20.1	0	31.1	
Mean MST (mo)	18.9	5.3	24.3	.002
RCC				
No. of patients	9	4	5	
Mean 3-year survival rate (%)	75.0	33.3	100	
Mean MST (mo)	62.6	26.6	NR	.15
Colorectal cancer				
No. of patients	5	1	4	
Mean 3-year survival rate (%)	0	0	NA	
Mean MST (mo)	26.2	26.2	NR	NA
HCC				
No. of patients	4	3	1	
Mean 3-year survival rate (%)	0	0	0	
Mean MST (mo)	9.3	12.8	5.8	.6

Note.—MST = median survival time, NA = not applicable, NR = not reached to survival rate of 50%.

Table 5**Adverse Events**

Adverse Event Grade	No. of Events*	Description
4	1 (2.1)	Acute renal failure (grade 4) and adrenal failure (grade 2)
3	3 (6.3)	Heart failure (grade 3) (<i>n</i> = 1); stroke (grade 3) and hypertensive crisis (grade 2) (<i>n</i> = 1); hepatic subcapsular hematoma (grade 3) and hypertensive crisis (grade 2) (<i>n</i> = 1)
2	21 (44)	Hypertensive crisis (grade 2) (<i>n</i> = 17); hypertensive crisis (grade 2) and adrenal failure (grade 2) (<i>n</i> = 1); hypertensive crisis (grade 2) and hemothorax (grade 2) (<i>n</i> = 1); hypertensive crisis (grade 2) and pneumothorax (grade 2) (<i>n</i> = 1); adrenal failure (grade 2) (<i>n</i> = 1)

Note.—There were no grade 5 adverse events.

* Numbers in parentheses are percentages based on 48 procedures.

48) of sessions in our study. Although some authors have reported that adrenal RF ablation should be performed under general anesthesia or after administration of an α -blocker (18,20,22), adrenal RF ablation was performed while the patient was under local anesthesia. Blood pressure was also well controlled. A major complication occurred in four sessions. A transient acute renal failure developed in a patient who had undergone both adrenalectomy and nephrectomy, probably owing to dehydration.

Although renal function recovered after temporary dialysis, we have to take care when treating patients with a single kidney. Subcapsular liver hemorrhage occurred in a session in which the liver was punctured with an electrode. Kuehl et al (32) reported that adrenal RF ablation could be performed safely with a transhepatic approach, but this approach apparently has a risk of bleeding, so it is important that the system for emergent embolization be maintained. Acute stroke occurred 3 days after adrenal RF

ablation, and heart failure occurred 5 days later. The relationship between the procedure and these complications is unclear as these patients have a history of old cerebral infarction and old myocardial infarction, but adrenal RF ablation seems to be a tough procedure as adrenal gland is very sensitive organ producing several hormones. So, we think that we have to observe patients carefully after adrenal RF ablation for several days. Steroid cover was required in two patients who received RF ablation after adrenalectomy of the contralateral side. Conversely, adrenal failure did not occur in four patients who received RF ablation for both sides of adrenal tumors. Adrenal function is impaired when more than 90% of adrenal tissue is destroyed (19). An advantage of adrenal RF ablation is that adrenal tissue remains to some extent after RF ablation. The risk to cause adrenal failure seems to be lower after RF ablation than after adrenalectomy. Although we did not perform bilateral RF ablation in a single session to keep safety, Lo et al (33) reported that bilateral adrenal RF ablation could be achieved in a single session without complications or endocrine disorder.

Adrenal embolization was combined with RF ablation in one-third of patients with large and hypervascular tumors in our study. Arterial embolization itself has an anticancer effect (34). It is useful for expanding the ablative zone size created by RF ablation because of blocked arterial blood flow (heat-sink effect) (35). In addition to increasing anticancer effects, adrenal embolization is apparently useful for preventing hemorrhagic complications at the time of RF ablation (17).

Our study has some limitations. First, this is a retrospective, single-center study. The small number of patient series is another limitation. Third, the tissue type was proved with biopsy or previous surgery in only 28.6% of patients. Fourth, there was no control study. Last, an inhomogeneous patient population makes it difficult to compare our results with those in previous studies featuring adrenalectomy.

In conclusion, adrenal RF ablation is a feasible and useful treatment to

control adrenal metastases and could potentially give patients with unresectable adrenal metastases an opportunity for improved survival.

Disclosures of Conflicts of Interest: T.H. disclosed no relevant relationships. K.Y. disclosed no relevant relationships. A.N. disclosed no relevant relationships. J.U. disclosed no relevant relationships. T.Y. disclosed no relevant relationships. M.F. disclosed no relevant relationships. M.M. disclosed no relevant relationships. T.S. disclosed no relevant relationships. H.S. Activities related to the present article: disclosed no relevant relationships, none to disclose. Activities not related to the present article: has grants/grants pending with Bayer and Siemens. Other relationships: disclosed no relevant relationships. Y.S. disclosed no relevant relationships.

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