# Clinical outcomes of percutaneous radiofrequency ablation for small renal cancer

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**Abstract.** Partial nephrectomy is the treatment of choice for small renal cell carcinoma (RCC) from the perspective of cancer management and renal function. However, when patients with RCC are of advanced age, exhibit severe comorbidities, including cardiovascular and pulmonary diseases, or have hereditary RCC, ablative therapies, including radiofrequency ablation (RFA) and cryoablation are useful treatment options. In the present study, the clinical outcomes of percutaneous RFA for treating small RCC were evaluated. Between December 2005 and March 2015, 40 patients (41 renal tumors in total) underwent RFA and a total of 50 sessions of RFA were performed. The average tumor size was 2.5 cm. A total of 18 tumors were exophytic and 23 were parenchymal. Of the 41 tumors, 85.4% were completely ablated by initial RFA and the rate of complete ablation following reablation for residual viable lesions was 95.1%. Local recurrence-free survival following complete ablation was 84.2% at 3 years. A patient with a 4.7 cm RCC tumor rapidly progressed following four RFA treatments until complete ablation was achieved. The metastasis-free survival rate following initial RFA was 95.7% at 3 years. The RCC-specific survival was 100% (mean follow-up, 38 months). Adverse events occurred in five sessions (10%); however, only 1 patient with arteriovenous fistula required intervention (transarterial embolization). The mean hospital stay following RFA was 3.2 days. The mean decrease in estimated glomerular filtration rate following RFA was 2.7%. The results of the present study indicate that percutaneous RFA was an effective treatment for small RCCs with respect to management of cancer, minimal invasiveness and minimal loss of renal function, particularly in patients for whom surgery would be a high risk and those at increased risk of deterioration of renal function.

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## Introduction

Partial nephrectomy (PN) has been a standard treatment for small renal cell carcinoma (RCC) (1-3). The loss of renal function is decreased following PN compared with that following radical nephrectomy (RN), and oncological management is reportedly equivalent between PN and RN (1,4). Although patients following RN are not likely to exhibit severe renal dysfunction requiring hemodialysis (5,6), 65% of patients develop grade 3 chronic kidney disease, defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 $m^3$, 3 years after nephrectomy (7) and the decrease in eGFR may lead to an increased risk of cardiovascular-related death in the future (8,9). Therefore, the preservation of renal function as well as cancer management should be considered in the treatment of RCC. Although PN appeared to be the best treatment for patients with small RCC in good general condition (10), patients with RCC are typically elderly and exhibit comorbidities that increase operative risks (11). In particular, for patients of advanced age (>80 years) and those with high-risk comorbidities, including cardiovascular and severe pulmonary diseases, major operations requiring general anesthesia should be avoided. Furthermore, for patients with hereditary RCCs, including RCCs due to von Hippel-Lindau (VHL) or Birt-Hogg-Dubé diseases, renal function gradually decreases if the patients undergo repeated partial resection (12,13). Furthermore, the difficulty of a surgical procedure increases following multiple surgeries (12). For small RCCs in high-risk patients or patients with hereditary diseases, less invasive treatments with good cancer management and minimal loss of renal function are ideal.

The efficacies of ablative therapies, including radiofrequency (RF) ablation (RFA) and cryoablation, have been reported previously: A number of authors have reported long-term results following RFA for RCC and demonstrated excellent oncological outcomes (14-20). In our institute, percutaneous RFA for renal cancer was initiated in 2005. In the present study, patients undergoing percutaneous RFA for renal cancer were evaluated with respect to oncological management, invasiveness and renal function.

## Patients and methods

*Patients*. Between December 2005 and March 2015, percutaneous RFA for renal tumors had been performed in 40 patients (30 male; 10 female) at the National Defense Medical College (Tokorozawa, Japan). Written informed consent was obtained from all patients who participated in the present study. In the 40 patients (41 tumors), a total of 50 sessions of RFA were performed. The mean age was 69.7 years (range, between 23 and 88 years; median, 73 years). The mean follow-up was 38 months (range, between 5.8 and 89.3 months). RFA was indicated only for tumor 1 (T1) stage renal cancer. A total of 39 tumors were T1a (≤4 cm) and 2 tumors were T1b (4.6 and 4.7 cm). For patients in good general condition for whom the use of general anesthesia was possible, surgical resection was recommended. RFA was indicated mainly for patients with high-risk comorbidities, patients of advanced age and patients with hereditary RCC. Although surgical resection was recommended even for patients with a solitary kidney or renal dysfunction, RFA was indicated for certain patients according to the wishes of the patient. The reasons for indicating RFA are presented in Table I. The mean diameter of ablated tumors was 2.5 cm (range, 1-4.7 cm; median, 2.4 cm). A total of 18 tumors were exophytic and 23 tumors were parenchymal. A total of 31 tumors had a Radius (tumor size as maximal diameter), Exophytic/endophytic properties of the tumor, Nearness of tumor deepest portion to the collecting system or sinus, Anterior (a)/posterior (p) descriptor and the Location relative to the polar line (R.E.N.A.L.) nephrometry score (21), of ≤7, and 10 tumors were scored as ≥8. A total of 16 tumors were located anteriorly and 25 were located posteriorly. The present study was approved by the Institutional Review Board of the National Medical Defense College, Tokorozawa, Japan (no. 549).

*RFA procedure*. Percutaneous RFA was performed using an internally cooled electrode (Cool-tip™ RF electrode; Radionics, Burlington, MA, USA) or a multitined expandable electrode (LeVeen™ needle electrode with an RF 3000 generator; Boston Scientific, Boston, MA, USA). The type of electrode used was determined mainly by tumor location, size, shape and the physician's preference. For the Cool-tip™ electrode, RF energy was applied for 12 min under an impedance control algorithm. For the LeVeen™ electrode, the tines were expanded step-by-step in four steps, and RF energy was applied at each step until a drastic increase in impedance (roll-off) was achieved. Lidocaine (Xylocaine®; AstraZeneca plc., London, UK) was used for local anesthesia and fentanyl citrate (0.1-0.2 mg; Daiichi Sankyo Co., Ltd., Tokyo, Japan) was used for analgesia. For the majority of patients, the prone position was used during RFA. All ablations were guided and monitored using ultrasound (US; EUB7500; Hitachi Medical Systems, Tokyo, Japan) and computed tomography (CT; Aquillion; Toshiba Medical Systems, Tochigi-ken, Japan). On the basis of the size and shape, overlapping ablations were applied by repositioning the electrode to ablate the entire tumor. In certain cases, hydrodissection was used to prevent thermal injury of neighboring organs by displacing the tumor away from adjacent structures (Fig. 1). A maximum of 1,000 ml 5% dextrose was infused into the space between the tumor and tissue to be protected through a 19-guage needle placed under US or CT guidance. In certain cases, transarterial embolization was also performed a number of days prior to RFA to decrease the vascular cooling effect and to increase the complete ablation rate at initial RFA (Fig. 2). Lipiodol (Guerbet Japan, Tokyo, Japan) was used for the transarterial embolization.

Since 2011, a biopsy of renal tumors was essentially performed using RFA procedures. Prior to 2011, biopsy for renal tumors was not performed in the majority of patients and RFAs were performed for renal tumors for which RCC was strongly suspected by imaging studies. Biopsy was performed for 12 tumors. In total, 8 tumors were diagnosed as clear-cell RCC, one as chromophobe RCC, one as oncocytoma and pathological diagnosis could not be determined in 2 tumors because of insufficient amounts of tissue samples for pathological evaluation. These 2 tumors were enhanced renal tumors and suggestive of RCC. A total of 8 tumors did not undergo renal biopsies for the following reasons: Biopsy was not performed for 3 renal tumors in patients with VHL disease because these tumors were evidently enhanced by imaging studies. In addition, biopsy was not performed for 3 renal tumors in 3 patients who had bilateral renal tumors and whose contralateral tumors were pathologically diagnosed as RCC. In total, 2 patients had a history of RCC in contralateral kidneys and did not undergo renal biopsy for renal tumors that were diagnosed as RCC by CT and magnetic resonance imaging (MRI). For the remaining 21 tumors, biopsy was not performed because RCC was suspected using CT and/or MRI.

*Post-RFA assessment*. Primary technical success of RF ablation was evaluated using contrast-enhanced three-phase CT examinations, immediately following or within 1 week of the procedure. Patients were scheduled for follow-up imaging at 1, 3, 6 and 12 months and semi-annually thereafter. In cases of impaired renal function, unenhanced MRI was performed. Primary technical success was defined as an absence of enhancement in the target tumor on the initial post-RFA CT. Complete ablation was defined as an absence of enhancement in the tumor determined using CT >3 months after RFA. Residual tumor was defined as persistent enhancement in the ablated tumor on the 3-month follow-up study. Local tumor progression was defined as the appearance of enhancement around the ablated tumor. Regarding unenhanced MRI, a high signal intensity area on the T1 weighted image was considered an ablative zone, according to a previous study in the liver (22). The treatment was considered to be successful when the targeted lesion was covered by the hyperintense area. If a residual or recurrent tumor was detected on imaging, repeat ablation sessions were scheduled as required and as appropriate.

*Factors evaluated*. The factors evaluated were age, sex, tumor size, location (exophytic/parenchymal/central), R.E.N.A.L. nephrometry score (21), and reasons for indicating RFA. The oncological outcomes were evaluated by the rate of complete ablation at initial RFA, rate of complete ablation (including reablation of residual viable lesion), local recurrence-free survival (LRFS) following complete ablation, metastasis-free survival (MFS) following initial ablation, RCC-specific survival (RCC-SS) and overall survival (OS). LRFS, MFS,

Table I. Reasons for selecting RFA.

| Reason | Number of patients (n=29) |
|---|---|
| Comorbidities+advanced age | 8 |
| Comorbidities | 5 |
| Advanced age | 4 |
| Solitary kidney | 3 |
| Severe cirrhosis of the liver | 3 |
| Comorbidities+renal dysfunction | 2 |
| VHL disease | 2 |
| Wishes of the patient[a] | 2 |

[a]One patient had a history of undergoing radical prostatectomy. Another patient had a history of surgery for lung cancer. These patients desired less invasive treatment for small renal cancer. RFA, radiofrequency ablation; VHL, von Hippel-Lindau.

RCC-SS and OS were evaluated in 39 patients, excluding a patient with oncocytoma. Invasiveness was evaluated by complication and duration of hospital stay. Post-ablative renal function was evaluated by the percentage decrease in eGFR between 1 and 6 months after complete ablation. The eGFR was calculated using an equation [eGFR ml/min/1.73 $m^2$ = 194 (x 0.739 if female) x $SCr^{-1.094}$ x $age^{-0.287}$].

*Statistical analysis*. The results are expressed as the mean ± standard deviation. The independence of the fit of the categorical data was analyzed using the $\chi^2$ test. Survival curves were constructed using the Kaplan-Meier estimator method. $P<0.05$ was considered to indicate a statistically significant difference.

## Results

*Oncological outcome*. The rate of complete ablation by single ablation was 85.4% (35/41 tumors). The rate of complete ablation at initial RFA was increased (although not significantly) in exophytic tumors compared with in parenchymal tumors (94.4 vs. 78.3%; P=0.1457; Table II). The rate of complete ablation at initial RFA was increased in tumors ≤3 cm compared with in tumors >3 cm (90 vs. 72.7%; P=0.1656; Table II). In addition, complete ablation at initial RFA was increased in tumors of R.E.N.A.L. nephrometry score ≤7 compared with in tumors of R.E.N.A.L. score ≥8 (90.3 vs. 70%; P=0.1139; Table II). No significant difference in the rate of complete ablation at initial RFA was identified between anterior tumors and posterior tumors (76.9 vs. 88.0%; P=0.5508; Table II). However, percutaneous RFA tended to be avoided for tumors with anterior locations because of the risk of bowel injury.

In total, 5 patients with initially incomplete ablation underwent reablation. Furthermore, 1 patient of advanced age (>85 years) opted not to undergo reablation. The rate of complete ablation following reablation for residual viable lesions was 95.1%. The LRFS rates following complete ablation were 97.3, 89.8, 84.2 and 84.2% at 1, 2, 3 and 5 years, respectively (Fig. 3). Furthermore, 2 patients succumbed to heart failure or cerebellar hemangioblastoma due to VHL disease. The 3- and 5-year OS rates were 96.9 and 90%, respectively, and the RCC-specific survival was 100%. Metastases developed following RFA in 2 patients. A patient with a 4.7 cm RCC underwent RFA four times until complete radiological ablation was achieved. Multiple lung metastases and lymph node metastases, and local progression with renal vein tumor thrombus were identified 7 months after the final ablation (see the next section). In another patient with RCC (3 cm), the tumor once demonstrated complete ablation, but local recurrence with small renal vein tumor thrombus was revealed 6 months after the RFA. The patient of advanced age was observed without reablation as was his preference; however, repeated gross hematuria occurred for 31 months after the RFA. Subsequently, laparoscopic radical nephrectomy was performed 37 months after RFA. However, multiple lung metastases developed 3 months after the nephrectomy. MFS rates following complete ablation were 100, 95.7, 95.7 and 83.7 at 1, 2, 3 and 5 years, respectively.

*Rapid progression following repeated percutaneous RFA*. A 61-year-old male patient was diagnosed as left RCC (4.7 cm) in August 2011 (Fig. 4A). As the patient had chronic renal dysfunction, severe diabetes mellitus, hypertension, hyperlipidemia and a history of myocardial infarction, percutaneous RFA was performed in December 2011 (Fig. 4B). However, complete ablation could not be achieved and an enhanced lesion remained near the collecting system. Pathological diagnosis by needle biopsy was clear-cell RCC (Fuhrman nucleolar grade 2). A second RFA was performed in April 2012; however, complete ablation was also not achieved. Growth of the remaining lesion was identified using CT 4 months after the second ablation, and a third ablation was performed in December 2012. However, complete ablation could not be achieved at that time (Fig. 4C). The fourth ablation was performed in March 2013 and radiological complete ablation was achieved. Although complete ablation was confirmed 3 months after the final ablation (Fig. 4D), lymph node metastases in the mediastinum, multiple lung metastases (Fig. 4E) and local progression with renal vein tumor thrombus (Fig. 4F) were presented 7 months after the final ablation. Subsequently, interferon-α treatment was initiated for this patient.

*Complication and post-operative course*. In a total of 50 sessions of RFA, complications were observed in five sessions (10%). These were an arteriovenous fistula, a perirenal hematoma, a high fever, a pneumothorax and a temporal hypotension due to a sedative drug (midazolam). A patient with arteriovenous fistula was embolized by transarterial approach 2 days after RFA. In 4 other patients, the complications were all improved by conservative therapies. The average hospital stay was 3.2 days (range, between 1 and 20 days). The majority of patients were able to resume dietary intake on the day of percutaneous RFA a number of hours later.

*Renal function*. Postoperative eGFR was evaluated between 1 and 6 months after complete ablation in each patient. Compared with eGFR prior to RFA, the average decrease in eGFR following complete ablation was 2.7±9.0% (range: between -19.6 and 18.9%; median, 1%).

Table II. Association between factors and initial successful ablation.

| Factor (tumor conditions) | Success rate (%) (successful/not successful) | P-value[a] |
|---|---|---|
| Exophytic vs. parenchymal | 94.4 (17/1) vs. 78.3 (18/5) | 0.1457 |
| ≤3 cm vs. >3 cm | 90 (27/3) vs. 72.7 (8/3) | 0.1656 |
| R.E.N.A.L. score ≤7 vs. ≥8 | 90.3 (28/3) vs. 70 (7/3) | 0.1139 |
| Anterior location vs. posterior | 76.9 (13/3) vs. 88 (22/3) | 0.5508 |

[a]$\chi^2$ test.

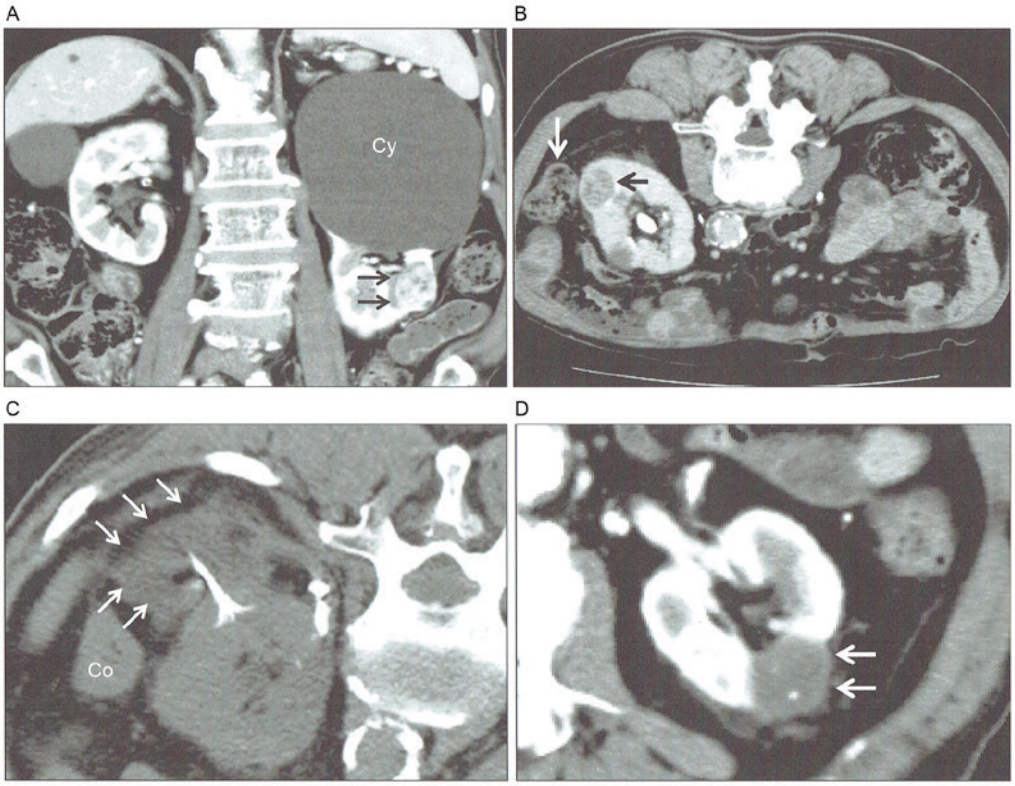


Figure 1. (A) CT identified enhanced renal tumor (black arrows) and increased renal cyst (labeled Cy) in the upper side of the left kidney. The descending colon was located near the renal tumor and there was a risk of bowel injury at percutaneous RFA. (B) CT following the cyst puncture. It was hoped that the cyst puncture would enlarge the distance between the renal tumor and the descending colon; however, the descending colon (white arrow) remained located near the tumor (black arrow). (C) Hydrodissection was performed. White arrows indicate 5% dextrose which was infused into the space between the tumor and the descending colon (labeled Co). RFA was safely performed. (D) CT 9 months after percutaneous RFA. The renal tumor was completely ablated and no residual enhanced lesion was identified (white arrows). CT, computed tomography; RFA, radiofrequency ablation.

## Discussion

Percutaneous RFA has become a viable option for the treatment of small RCC. Excellent cancer management with rigorous follow-up periods has been reported previously in hospitals with a high volume of RFA (14-20). RFA appears to be an effective treatment, particularly for patients of advanced age, patients exhibiting comorbidities and patients with hereditary RCC. The indications for RFA were considered to be comorbidity, age, hereditary disease, solitary kidney and decreased renal function. Although many patients who underwent RFA were at high risk for surgery, the complication rates were low and oncological outcome was acceptable. The RCC-SS rate was 100% (mean follow-up, 38 months) and the 3-year OS rate was 96.3%. Furthermore, the decrease in eGFR was low following RFA. Percutaneous RFA appeared to be beneficial for the majority of the patients in the present study.

In the present study, the rate of complete ablation at initial RFA was 85.4%. As the rate of complete ablation at initial RFA was reportedly between 87 and 100% in a high-volume hospital (14,15,17,18,20), further improvement is required. In the present study the rate of complete ablation at initial RFA tended to be decreased in patients with parenchymal tumor, tumors >3 cm and tumors with R.E.N.A.L. nephrometry scores ≥8, compared with their respective counterparts. Schmit *et al* (23) reported a significant association between R.E.N.A.L. nephrometry score and local treatment failure. To improve oncological outcomes, we recently performed transarterial embolization prior to ablation in certain patients whose RCC was located near large vessels (Soga *et al*, unpublished

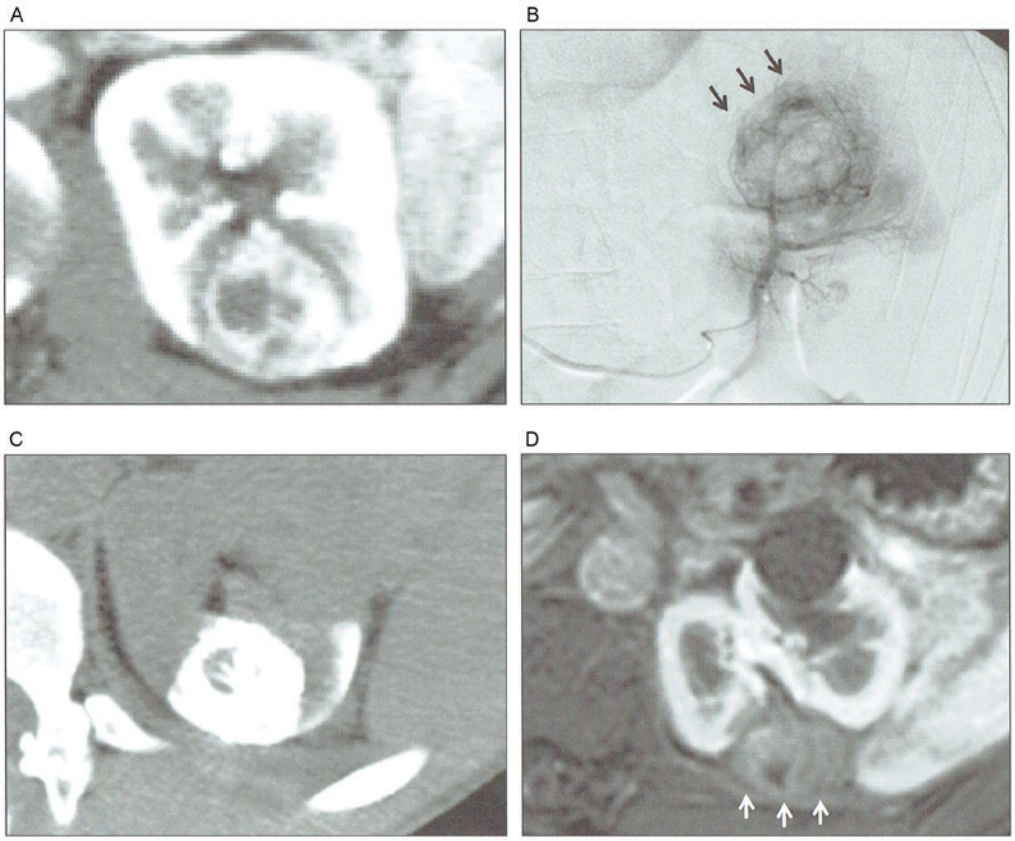


Figure 2. (A) CT demonstrated a parenchymal type renal tumor in the upper side of the left kidney. (B) Transarterial embolization was performed 1 day before percutaneous RFA to achieve successful ablation. Transarterial embolization theoretically decreases a vascular cooling effect and possibly improves the rate of complete ablation. (C) CT at the day of RFA. The presence of lipiodol remained at the renal tumor and the surrounding renal tissue. Owing to the presence of lipiodol, the tumor was easily targeted at percutaneous RFA. (D) Dynamic MRI 1 year after RFA. No enhancement was observed in the ablated tumor (complete ablation). CT, computed tomography; RFA, radiofrequency ablation; MRI, magnetic resonance imaging.

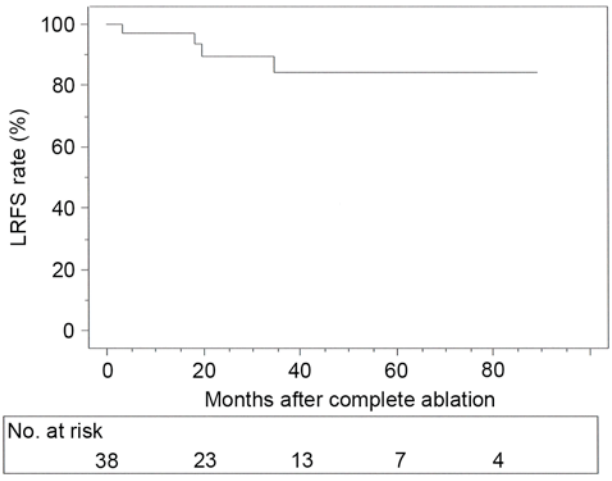


Figure 3. Kaplan-Meier estimator curve of LRFS following complete ablation. The LRFS rate was evaluated using 38 tumors that did not include an oncocytoma and was able to be completely ablated. LRFS rates following complete ablation were 97.3, 89.8, 84.2 and 84.2 at 1, 2, 3 and 5 years, respectively. LRFS, local recurrence-free survival.

data). In addition, multiple RFA needles were used for relatively large tumors. With these efforts, the rate of complete ablation at initial ablation has gradually improved. One of the merits of percutaneous RFA of residual lesions is that reablation is possible. The rate of complete ablation following reablation was 95.1%.

Multiple repeated ablation should be avoided because of the possibility of rapid progression. In the present study, a patient with T1b RCC (4.7 cm) was rapidly progressed following four RFA treatments. Although rapid progression following RFA appears to be a rare event in RCC, complete ablation should be achieved within a minimal number of sessions (two sessions). Although rapid progression in RCC has been rarely reported (24), rapid progression following RFA has been reported in hepatocellular carcinoma (HCC) (25,26). Obara *et al* (27) reported that insufficient RFA may induce further malignant transformation of HCC. Furthermore, Dong *et al* (28) demonstrated that insufficient RFA promoted epithelial-mesenchymal transition of HCC cells through protein kinase B and extracellular-signal-regulated kinase signaling pathways. In contrast with rapid progression in HCC, there are few reports regarding that in RCC. Kroeze *et al* (29) reported that incomplete thermal ablation stimulated proliferation of residual RCC cells in a murine model. To the best of our knowledge, only one study has previously demonstrated rapid progression following laparoscopic RFA for T1b RCC (4.5 cm) (24). Rapid progression appeared to be unlikely to occur in RCC compared with HCC.

The oncological outcomes of RFA with durable follow-up periods have previously been reported (14-20).

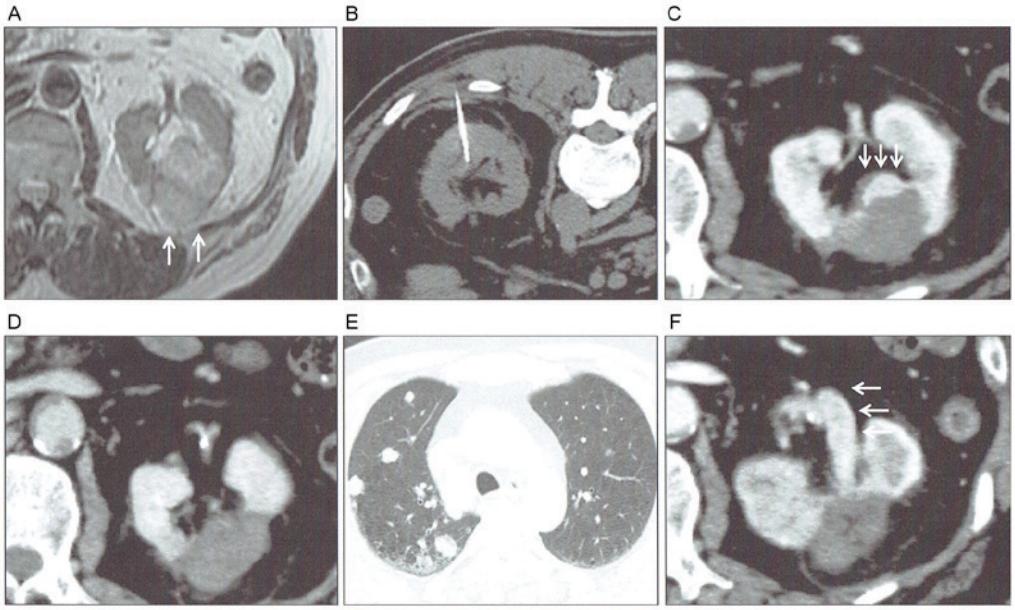


Figure 4. (A) Renal tumor (4.7 cm) located in the lower side of the left kidney. (B) Percutaneous RFA was performed because the patients exhibited multiple comorbidities. (C) CT following three RFA treatments. The residual enhanced lesion (white arrows) remained in the inner side of the kidney. (D) CT 3 months after the fourth ablation. Radiological complete ablation was achieved. (E) Multiple lung metastases and (F) local progression with renal vein tumor thrombus (white arrows) identified by CT 7 months after the final ablation. RFA, radiofrequency ablation; CT, computed tomography.

Ferakis *et al* (14) reported the outcome with an average follow up of 61.2 months. In that study, RFA was performed in 31 patients (39 tumors) and the rates of initial complete ablation, complete ablation, 5-year LRFS and RCC-SS were 90, 97, 89 and 100%, respectively. Psutka *et al* (17) reported the results of biopsy-proven RCC (median follow-up, 6.43 years; T1a, 143 tumors; T1b, 42 tumors). In that study, when T1a tumors were focused, local recurrence was observed in 6 patients (4.2%) and metastasis was observed in 1 patient (0.7%). The 5-year RCC-SS was 100%. In contrast, the 5-year OS was 74%, suggesting that many high-risk patients were included in that study. Furthermore, Olweny *et al* (16) compared the clinical results of RFA with those of PN in patients who were followed up for >5 years after treatment. They reported that the 5-year MFS, 5-year RCC-SS and 5-year OS were all comparable. Moreover, Ma *et al* (18) reported results of RFA for RCC in 52 healthy adults (average size, 2.2 cm; median follow-up, 60 months) and local recurrence was observed in 3 tumors (5.1%). The 10-year disease-free survival, 10-year RCC-SS and 10-year OS were 94.2, 100 and 91.1%, respectively. On the basis of these results, the rate of local recurrence following complete ablation appears to be low in T1a RCC and RCC-specific survival is excellent. RFA may be one of the first choices for small RCC in patients for whom surgery would be a high risk.

Although various complications have been reported, the majority of those were minor and the complication rates were low (30,31). In the present study, complications were observed in five sessions following RFA (10%). However, only 1 patient required intervention (TAE). As that case was treated because arteriovenous fistula occurred 2 days after RFA, enhanced CT was routinely performed immediately following RFA (between 1 and 3 days after RFA). The average hospital stay following RFA was 3.2 days, and hospital stay may be reduced if the CT was performed in an outpatient clinic. General patient condition was usually excellent the day following RFA and dietary intake was usually able to be resumed on the day of RFA. These results reflected the minimal invasiveness of RFA. Early resumption of dietary intake and maintaining daily activities appear to be advantageous for patients of advanced age and patients exhibiting comorbidities.

One attractive advantage of RFA is the minimal decrease in eGFR. In the present study, the mean decrease in eGFR was only 2.7% following RFA. Lucas *et al* (32) reported a significantly decreased rate of eGFR <60 following RFA, compared with those following RN or PN. The decrease in eGFR following RFA was <10% in patients with a solitary kidney (33,34). In view of renal function, RFA also appears to be a viable option for patients with a solitary kidney, renal dysfunction and hereditary disease, which carry a lifelong risk for multiple RCC.

Although further improvements in oncological outcomes and complication rates are required, RCC-SS and renal function following RFA were excellent. Percutaneous RFA is a viable option as a treatment for small RCC, especially in patients exhibiting comorbidities, patients of advanced age, patients with hereditary RCC and certain patients with decreased renal function.

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