



Radiofrequency ablation using real-time ultrasonography–computed tomography fusion imaging improves treatment outcomes for T1a renal cell carcinoma: Comparison with laparoscopic partial nephrectomy

Dong Jin Chung¹ , Hyun Hwang¹ , Dong Wan Sohn²

Departments of ¹Radiology and ²Urology, The Catholic University of Korea, Yeouido St. Mary's Hospital, Seoul, Korea

Purpose: To determine whether real-time ultrasonography–computed tomography (US-CT) fusion imaging can improve technical feasibility versus B-mode US and provide comparable outcomes of radiofrequency ablation (RFA) for T1a renal cell carcinoma (RCC) compared with laparoscopic partial nephrectomy (LPN).

Materials and Methods: Between June 2013 and August 2016, biopsy- or pathologically confirmed stage T1a RCCs were retrospectively reviewed. Of these, 39 cases were included in the RFA group, and 46 cases were included in the LPN group. In the RFA group, we evaluated tumor visibility and technical feasibility before RFA on a four-point scale on B-mode US and US-CT fusion images. After RFA, hospital days, creatinine value, complications, and disease-free survival rate were compared between the two groups. All results were analyzed by use of the Mann–Whitney U-test and Kaplan–Meier method.

Results: Compared with B-mode US alone, real-time US-CT fusion significantly improved the tumor visibility score and overall mean technical feasibility grade ($p < 0.001$). The 5-year disease-free survival rate was 97.4% and 97.8% in the RFA and LPN groups, respectively, and there was no statistically significant difference between groups ($p = 0.1$). Mean perioperative creatinine levels were significantly lower in the RFA group than in the LPN group. The number of hospital days was shorter in the RFA group. Minor complications were present in 5.1% of the RFA group and 13.0% of the LPN group, with no major complications.

Conclusions: US-CT fusion-image-guided RFA improved tumor visibility scores and overall mean technical validity and resulted in a comparable disease-free survival rate to LPN.

Keywords: Radiofrequency; Renal cell carcinoma; Survival rate; Ultrasound

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INTRODUCTION

Recently, the detection of renal cell carcinoma (RCC) has

been increasing owing to the frequent use of cross-sectional images for other reasons, and most of these incidental RCCs are less than 4 cm and are classified as stage T1a RCC [1].

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Corresponding Author: Dong Jin Chung <https://orcid.org/0000-0002-3250-142X>

Department of Radiology, The Catholic University of Korea, Yeouido St. Mary's Hospital, 10, 63-ro, Yeongdeungpo-gu, Seoul 07345, Korea
TEL: +82-2-3779-1327, FAX: +82-2-783-5288, E-mail: bookdoo7@catholic.ac.kr

Partial nephrectomy is still considered the standard treatment for stage T1a RCC. However, given a patient's general condition, minimally invasive techniques including radiofrequency ablation (RFA) have emerged as alternative treatment options for stage T1a RCC [2]. RFA can be performed under the guidance of computed tomography (CT) or ultrasonography (US). In addition to CT and US guidance, imaging guidance methods such as CT and the combination of CT and US guidance (not fusion) have been reported [3,4]. Each procedure has advantages and disadvantages. CT has advantages such as no artifacts generated from intestinal gas and bone, early detection of complications such as bowel perforation, and detection of incomplete ablation [5]. Therefore, most operators prefer CT-guided RFA over US guidance. However, RFA is not always possible by CT guidance alone and is sometimes considered infeasible because of the inadequacy of electrode paths. Real-time US-CT fusion imaging provides more flexibility than CT-guided RFA for the direction of needle placement, lacks radiation exposure, and offers portability, a shorter procedure time, and ease of access to equipment and cost [6]. Many previous studies have reported that RFA is an effective, minimally invasive therapy for stage T1a RCC compared with laparoscopic partial nephrectomy (LPN) [7,8]. The purpose of this study was to prove two hypotheses about whether real-time US-CT fusion images can improve technical feasibility compared with B-mode US and whether RFA using this technique shows clinical results equivalent to LPN.

MATERIALS AND METHODS

1. Characteristics of patients and tumors

This single-center, retrospective study was approved by the Institutional Review Board of the ethics committee of Yeouido St. Mary's Hospital (approval number: SC19RE-SI0105 on September 3, 2019). The need for informed consent was waived by the Institutional Review Board of our hospital owing to the retrospective design of the study. This was a retrospective review of pathologically confirmed T1a RCC cases from June 2013 to August 2016. The main selection criteria for RFA included coexisting morbidity, the location of the tumor, endophytic tumors, old age (>80 y), and a single kidney. Exclusion criteria were bilateral RCC, biopsy-proven stage T3a RCC smaller than 4 cm, two or more RCCs, metastatic RCC, and hereditary RCC. A multidisciplinary team of interventional radiologists, urologists, and oncologists determined indications for RFA versus partial nephrectomy. A total of 98 patients with stage T1a RCC were included. Among them, seven patients who were lost during follow-up, five patients who underwent CT-guided RFA, and one patient with T3a RCC smaller than 4 cm were excluded. Of the remaining 85 candidates, 39 patients underwent US-CT fusion imaging-guided RFA, and 46 patients underwent LPN (Fig. 1).

The demographics of the patients and their tumor characteristics are shown in Table 1. Thirty-nine patients were included in the RFA group and 46 patients were included in the LPN group. The tumor locations were classified into three categories: exophytic ($\geq 50\%$), partially exophytic ($< 50\%$),

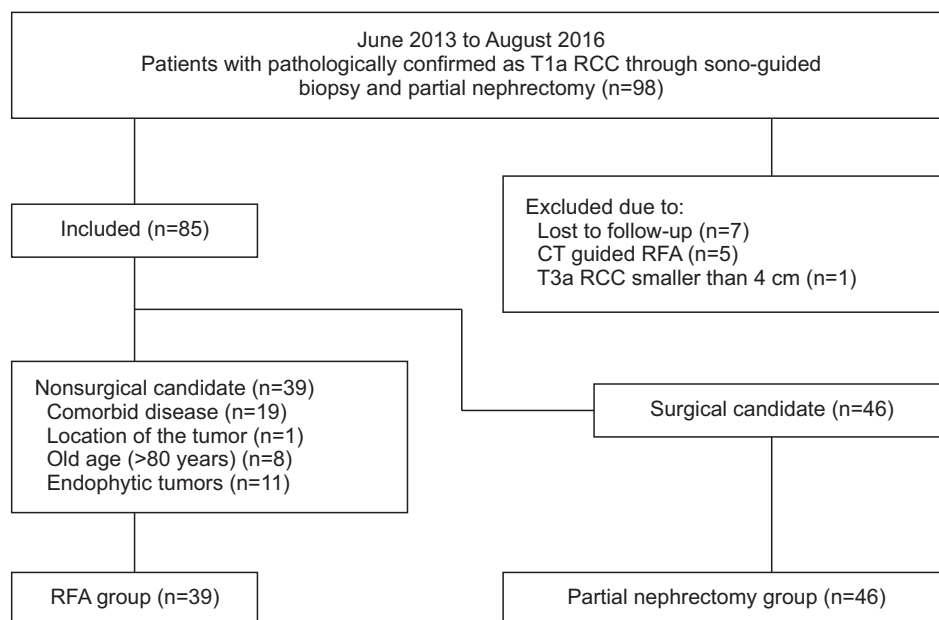


Fig. 1. Flow diagram of study population. RCC, renal cell carcinoma; CT, computed tomography; RFA, radiofrequency ablation.

Table 1. Patient demographics and renal cell carcinoma characteristics

Characteristic	RFA (n=39)	LPN (n=46)	p-value
Age (y)	61.59	59.42	0.539
Preoperative Cr value (mg/dL)	1.24±0.43	1.02±0.23	0.686
Comorbid diseases			
Hypertension	13 (33.3)	10 (21.7)	0.380
Diabetes mellitus	8 (20.5)	7 (15.2)	0.450
CKD	5 (12.8)	3 (6.5)	0.180
Tumor histology			0.725
Clear cell	28 (71.8)	36 (78.3)	
Papillary	6 (15.4)	4 (8.7)	
Chromophobe	5 (12.8)	6 (13.0)	
Tumor size (cm)	2.2±0.2	2.4±0.3	0.675
PADUA score	7.68	8.24	0.791
≥50% exophytic	15 (38.5)	26 (56.5)	
<50% exophytic	13 (33.3)	15 (32.6)	
Entirely endophytic	11 (28.2)	5 (10.9)	0.01
Hilar	2 (5.1)	3 (6.5)	0.78

Values are presented as mean only, mean±standard deviation, or number (%).

RFA, radiofrequency ablation; LPN, laparoscopic partial nephrectomy; Cr, creatinine; CKD, chronic kidney disease; PADUA score, preoperative aspects and dimensions used for an anatomic classification score.

and entirely endophytic. In addition, preoperative aspects and dimensions used for an anatomic classification (PADUA) nephrometry scores were calculated to quantify the complexities of the renal tumors [9].

2. Real-time US-CT fusion imaging

We used three-phase dynamic CT performed within 1 month of fusion imaging. The cortical, parenchymal, and excretory phases were obtained after intravenous injection of Iohexol (Iobrix 300; Taejoon Pharm, Seoul, Korea) at 40, 70, and 200 seconds. Among the three-phase images, the image showing the tumor best was selected for fusion imaging. Axial CT images were reconstructed to a section thickness of 3 mm without gaps. The CT images stored in the Picture Archiving and Communication System (PACS) were transferred to a US-CT fusion system (LOGIQ E9 ultrasound fusion; GE Healthcare, Chicago, IL, USA).

3. Evaluation of tumor visibility and technical feasibility

The day before each RFA procedure, planning B-mode US was performed to evaluate tumor visibility and technical feasibility. The next day, immediately before the procedure, US-CT fusion imaging was performed to evaluate tumor visibility and technical feasibility in the same manner, and the RFA procedure was performed. A urologist (DWS) developed the scoring criteria for visibility and technical feasibility by referring to the study by Ahn et al. [10]. The visibility of the

index tumor was scored by the operator according to the following four-point scale: invisible, poor, fair, or good. Invisible and poor were classified into the “not visible” categories, and fair and good were classified into the “visible” categories. The operator evaluated technical feasibility on a four-point scale using a combination of the tumor visibility and the safe approach pathways as follows: not feasible, equivocally feasible, fairly feasible, and definitely feasible. The criteria for the technical feasibility of percutaneous RFA determined not only visibility but also the safety of the procedure, approach pathway, avoidance of collateral organ damage, and likelihood of complete ablation of the target tumors. The evaluation was performed by an experienced ablation specialist (DJC with 15 years of clinical experience performing RFA) and one abdominal radiologist (HH) with consensus. Detailed criteria regarding the evaluation of tumor visibility and technical feasibility for RFA are described in Table 2.

4. RFA procedures

Percutaneous RFA was performed by one interventional radiologist (DJC) with 15 years of experience. Depending on the location of the tumor, the patients were placed in a supine, prone, or decubitus position. Except for three patients with severe comorbidity, all patients underwent general anesthesia under the supervision of an anesthesiologist. A 17-gauge internally cooled monopolar electrode with a 3-cm exposed tip (RF Medical, Seoul, Korea) was used for all patients. After application of the fusion imaging technique,

Table 2. Scoring criteria for evaluation of tumor visibility and technical feasibility for radiofrequency ablation

Criteria	Category
Visibility	
Invisible	Not visible
Poor: partially visible tumor with unclear boundary or poor conspicuity	Not visible
Fair: visible tumor with unclear boundary or an indistinct margin	Visible
Good: clearly visible tumor with clear boundary or a distinct margin	Visible
Technical feasibility	
Not feasible: invisible tumor with a poor safe access route	
Equivocally feasible: poorly visible tumor with a fair safe access route	
Fairly feasible: fairly visible tumor with a fair safe access route	
Definitely feasible: good visible tumor with a good safe access route	

the B-mode US and CT images were displayed side-by-side on the US monitor. As a result, the fusion CT demonstrated the same plane and rotated simultaneously with the real-time US. Radiologists identified targets on the US-CT fusion images and determined the optimal path to avoid damage to nearby vital organs.

In the US-CT fusion imaging, we chose a path that passed minimally through the renal parenchyma and directly through the tumor. When the index tumor was not visible even after image fusion, the radiologist inserted the electrode needle into the tumor by correlating the location of anatomical landmarks around the tumor. When the electrode reached the main region of the tumor, 60 to 200 W of power was generated from the electrode, and the RCC was ablated for 6 to 12 minutes according to the automatic impedance control method. Hydrodissection was done in two patients. After ablation, we cauterized the electrode path while withdrawing the electrode to minimize bleeding and tract seeding. A US-guided biopsy was performed concurrently with RFA in all patients under US-CT fusion image guidance before ablation.

5. Surgical technique

All laparoscopic kidney surgeries were performed by a single surgeon (DWS) with 16 years of experience. All LPNs were performed via the peritoneal approach. Briefly, mannitol was administered during hilar vascular control in LPN and the renal artery was immobilized. Renal veins were not routinely tightened. The kidney mass was dissected using cold 10-mm Metzenbaum scissors with a safety margin of 5 mm. After tumor resection, the calyx, bleeders, and tumor bed were closed.

6. Assessment of RFA treatment response and complications

Immediately after the RFA procedures, 38 patients underwent three-phase contrast-enhanced kidney CT to

evaluate the technical success of the procedure and the development of complications such as bleeding. At 1 month after treatment, contrast-enhanced CT of the kidneys was performed in all patients. Follow-up checkups of the serum creatinine level were performed every 3 months for the first year and every 6 months for the second year. Follow-up kidney CT was performed every 6 months for the first year. For 2 to 5 years, CT was performed once a year. Technique effectiveness was determined based on the 1-month follow-up CT. Recurrence, defined as local tumor progression, was assessed during the follow-up period. Technical success was defined as treatment completion according to protocol with complete coverage and adequate safety margins on CT performed within 48 hours of RFA. Technical effectiveness was defined as complete ablation of the tumor as shown on CT 1 month after RFA. Local tumor progression was defined as nodular or irregular enhancement at the follow-up assessment performed 1 month after RFA. To compare treatment outcomes between the RFA and LPN groups, parameters including the primary technical success, technical effectiveness, length of hospital stay, creatinine levels, and hemoglobin were measured before and after the procedure, within 48 hours and 3 months, and acute kidney injury, complications, and disease-free survival rate were assessed. Complications were classified as major or minor according to Clavien–Dindo classification.

7. Statistical analysis

The two patient groups were compared using the Mann–Whitney U-test for continuous variables and the chi-square test for categorical variables. Fisher's exact test was used to compare tumor location and local tumor recurrence rates in the RFA and LPN groups. An unpaired t-test was used to compare serum creatinine levels, complication rates, and hospital stay in the two groups. Visibility and technical feasibility between B-mode US and fusion imaging were compared using the chi-square test. Disease-free survival interval was

defined from the time of each treatment to RCC recurrence or death related to RCC. The Kaplan–Meier method was used to estimate disease-free survival and the results compared to the Cox proportional hazard model. Statistical analyses were performed by using the StatView statistics package (SAS Institute, Cary, NC, USA). A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

1. Comparison between RFA and LPN patients

All procedures were performed by using US-CT fusion guidance. In the RFA group (n=39), the histological subtypes were clear-cell RCC (n=28), papillary RCC (n=6), and chromophobe RCC (n=5), and in the LPN group (n=46), clear-cell RCC (n=36), papillary RCC (n=4), and chromophobe RCC (n=6). The average tumor size in the RFA patient group was 2.2±0.2 cm, and the average value in the LPN patient group was 2.4±0.3 cm. The difference in tumor size between the two groups was not statistically significant (p=0.675), nor did tumor histology show a statistically significant difference. The PADUA nephrotomy score was 7.68 in the RFA group and 8.24 in the LPN group without a statistically significant difference (p=0.791). However, the number of patients with endophytic masses was higher in the RFA group than in the LPN group (p=0.01). In the RFA group, the percentage of patients with more than 50% exophytic lesions, partially exophytic lesions (<50%), and entirely endophytic RCC locations

was 38.5% (15/39), 33.3% (13/39), and 28.2% (11/39), respectively, and in LPN group, was 56.5% (26/46), 32.6% (15/46), and 10.9% (5/46), respectively (Table 1). The percentage of hilar tumors was 5.1% and 6.5% in the RFA and LPN groups, respectively, with no statistically significant difference between groups (p=0.78).

2. Comparison between fusion imaging and B-mode US for tumor visibility and technical feasibility

Compared with B-mode US alone, real-time US-CT fusion significantly improved the tumor visibility score from 2.02±0.72 to 2.56±1.02 (p<0.001). In B-mode US, there were 12 tumors in the not visible category (12/39, 30.8%). However, with real-time fusion imaging, 5 of those 12 lesions (41.7%) were classified in the visible category. The overall mean technical feasibility grade for the RFA group increased from 2.41±0.52 to 3.59±0.38 after the fusion system was applied (p<0.001) (Table 3). Among the 39 RCCs, 27 lesions (69.2%) were detected on B-mode US, whereas 12 RCCs (30.8%) were not well visualized on B-mode US because of overlapping ribs or colonic gas (n=7), small kidney (n=3), or obesity (n=2). The mean size of the RCC in the not visible category (1.50±0.34 cm) was significantly smaller than that in the visible category (2.43±0.64 cm) (p<0.001). In the not visible category, technical feasibility increased from 1.40±0.60 to 3.12±0.38 after the fusion system was applied (p<0.001) (Table 4). Three of 39 total tumors were scored as not treatable owing to invisible tumors on B-mode US alone. After applying US-CT fusion imaging, the operator’s confidence in feasibility in all three tumors was upgraded from not feasible to equivocally feasible (n=3). Although the tumor was invisible on B-mode US, the electrode could be placed in the tumor region via real-time US-CT fusion imaging by use of anatomical landmarks, and the tumor could be safely and completely ablated without complications (Fig. 2). Interobserver agreement (κ) was good for all parameters of the fusion system as

Table 3. Comparison of tumor visibility and technical feasibility score between B-mode US and US-CT fusion imaging

	B-mode	Fusion imaging	p-value
Tumor visibility	2.02±0.72	2.56±1.02	<0.001
Technique efficacy	2.41±0.52	3.59±0.38	<0.001

Values are presented as mean±standard deviation. US, ultrasonography; CT, computed tomography.

Table 4. Comparison of tumor characteristics, technical feasibility, and technical efficacy according to visibility on B-mode ultrasound

	Visible category (n=27)	Not visible category (n=12)	p-value
Tumor location (right/left)	12/15	5/7	0.876
Hydrodissection (not used/used)	25/2	12/0	0.753
Size of tumor (cm)	2.43±0.64	1.50±0.34	<0.001
Technical feasibility			
B-mode	2.79±0.63	1.40±0.60	<0.001
Fusion imaging	3.84±0.39	3.12±0.38	<0.001
Technical efficacy (success/fail)	27/0	12/0	-

Values are presented as number only or mean±standard deviation. -, not available.



Fig. 2. Endophytic renal cell carcinoma (RCC), clear-cell type, which was poorly visible on B-mode ultrasonography (US). (A) Endophytic RCC at the mid pole of the left kidney (arrow) on axial contrast-enhanced computed tomography (CECT) before the procedure. (B) The US-CT fusion image displays the US and CECT side-by-side on the monitor in real time. Note an unclear RCC region in the ultrasound image and accurate RCC localization in the CECT image (arrows). (C) Visualization of the inserted electrode (small arrows) placed on the RCC (large arrows) using US-CT fusion imaging. (D) CECT shows ablation of the RCC region after radiofrequency ablation (arrow).

well as B-mode (range, 0.65–0.78).

3. Comparison of treatment outcomes between LPN and real-time US-CT fusion imaging-guided RFA

The two groups were compared over 5 years. The primary technical success was 100% for RFA groups (39/39). One-month follow-up CT of the RFA group showed that 39 tumors were completely ablated, yielding a technical effectiveness rate of 100% (39/39). The 5-year disease-free survival rates were 97.4% and 97.8% in the RFA and LPN groups, respectively, and there was no statistically significant difference ($p=0.1$). During the 5-year follow-up CT scan, no patients in either group showed local tumor progression. Changes in the parameters before and after the procedure are shown in Table 5. Serum creatinine levels measured within 48 hours of treatment increased to 0.021 mg/dL in the RFA group and 0.215 mg/dL in the LPN group ($p=0.001$). Postprocedural acute kidney injury occurred more frequently in the LPN group (39.1%) than in the RFA group (5.1%) ($p=0.001$). However, there was no statistically significant difference in serum creatinine levels between the two groups after 3 months ($p=0.735$). Hospital days were shorter in the RFA group than in the LPN group (mean values of 3.00 days vs. 9.77 days; $p=0.001$). The changes in hemoglobin level were not statistically significant ($p=0.220$). Minor complications occurred in 5.1% of patients (2/39) in the RFA group, which included perirenal hematomas ($n=2$) that did not require any treatment. Six patients in the LPN group

(6/46, 13.0%) had minor complications including three perirenal hematomas, one renal infarction, and two pleural effusions. Not all these complications required treatment. One patient in the RFA group had RCC in the upper pole of the right kidney. It was difficult to ablate the tumor with only B-mode US, and US-CT fusion imaging improved technical feasibility (Fig. 3). In the case of an endophytic RCC, especially one abutting the renal pelvis, US-CT fusion imaging improved technical feasibility, and treatment was possible without causing pelvicalyceal injury. US-CT fusion imaging could accurately determine the distance between the tumor and the pelvicalyceal system. The distance between the electrode and the dangerous anatomic structure can be accurately maintained at 5 to 10 mm. We can avoid pelvicalyceal injury using fusion images that clearly show the pelvicalyceal system and the tip of the electrode in real time (Fig. 4).

DISCUSSION

According to the 2019 European Association of Urology RCC guidelines, the recommended primary treatment for stage T1a RCC is partial nephrectomy. This is because patients undergoing LPN have a significantly lower mortality rate than do non-surgical-management groups [11]. However, the recommendation for therapeutic approaches as an alternative to surgery is to “offer active surveillance or thermal ablation to frail and/or comorbid patients with small renal masses” [12]. Among the various alternative treatments, the effectiveness of RFA compared with LPN has been

Table 5. Postprocedural changes in parameters and complications

Variable	RFA (n=39)	LPN (n=46)	p-value
Hb change within 48 h (g/dL)	-0.393	-1.294	0.220
Serum Cr change (mg/dL)			
Baseline	1.24±0.43	1.02±0.23	0.686
Within 48 h	0.021	0.215	0.001
Postprocedural AKI	2 (5.1)	18 (39.1)	0.001
Postoperative (3 mo)	1.29±0.21	1.38±0.38	0.735
Length of hospital stay (day)	3.00	9.77	0.001
Minor complications (Clavien I and II)	2 (5.1)	6 (13.0)	0.030
Perirenal hematoma	2 (5.1)	3 (6.5)	
Renal infarction	0 (0.0)	1 (2.1)	
Pleural effusion	0 (0.0)	2 (4.3)	
Major complication (Clavien III and IV)	0 (0.0)	0 (0.0)	
5-year disease-free survival rates (%)	97.4	97.8	0.1

Values are presented as mean only, mean±standard deviation, or number (%).

RFA, radiofrequency ablation; LPN, laparoscopic partial nephrectomy; Hb, hemoglobin; Cr, creatinine; AKI, acute kidney injury.

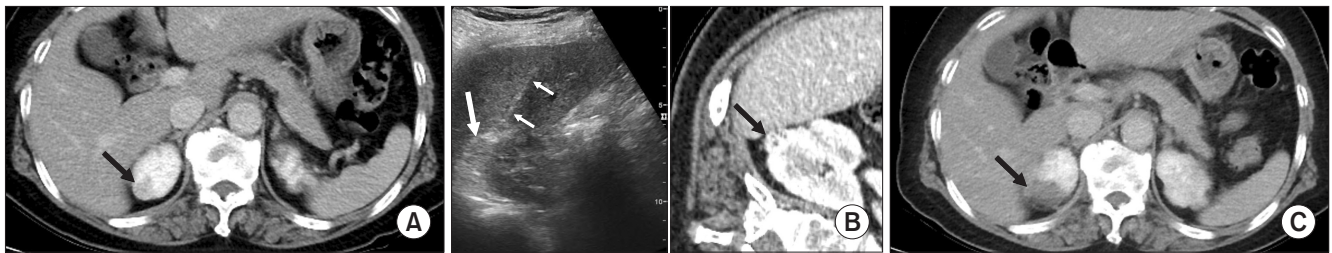


Fig. 3. Clear-cell renal cell carcinoma (RCC) of the right kidney treated with fusion-imaging-guided radiofrequency ablation using a transhepatic approach. (A) Preprocedural contrast-enhanced computed tomography (CT) demonstrated RCC at the upper pole of the right kidney (arrow). (B) Ultrasonography (US)-CT fusion image shows partially exophytic RCC (large arrows). The radiofrequency ablation electrode traversed the right hepatic lobe in the US-CT fusion image (small arrows) with improved technical feasibility. (C) After 5 months, the ablation defect was observed in the right kidney without tumor recurrence or residual tumor (arrow).



Fig. 4. A clear-cell renal cell carcinoma (RCC) of the right kidney treated with fusion-imaging-guided radiofrequency ablation (RFA) performed without calyceal injury. (A) Preprocedural contrast-enhanced computed tomography (CT) shows an endophytic RCC (large arrow) abutted on the renal pelvis at the right kidney (small arrow). (B) Visualization of the non-abutted region (large arrow) of the RCC to avoid pelvicalyceal injury during RFA. Echogenic bubbles are noted at tip of electrode (small arrow). (C) In the post-RFA CT, the ablated RCC (large arrow) was visible in the right kidney without any pelvicalyceal injury (small arrow).

described in previous studies that reported equivalent outcomes [13,14]. However, some other studies showed higher rates of local tumor recurrence or progression in the RFA group [15]. Therefore, to improve the outcome of RFA, we attempted fusion-imaging-guided RFA.

We reported here that creatinine levels and lengths of

hospital stay were significantly lower in the RFA group. A lesser increase in creatinine and less postprocedural acute kidney injury in the RFA group can be interpreted as less kidney damage as a result of the procedure.

In general, when an RCC is in the upper pole of the right kidney, LPN and CT-guided RFA are difficult approaches.

In this case, US-CT fusion-imaging-guided RFA is considered a better option than B-mode US or CT-guided RFA alone to avoid injury to the hepatic vessels and to safely access the kidney. It is possible that US-CT fusion imaging guidance could reduce procedure time and avoid unnecessary multiple needle insertions compared with CT guidance. Accuracy is particularly important in nephron-preserving procedures. For these reasons, US-CT fusion imaging can be used for guidance during ablation of RCC [16]. For example, Mauri et al. [17,18] reported that US-CT image fusion guidance allows for correct tumor targeting of renal tumors that are poorly visible, inconspicuous, or invisible with US alone. However, in that study, the RFA procedure did not use only US-CT fusion imaging guidance, and CT scans were simultaneously performed to confirm the position of the inserted electrode needle. In our study, all procedures were performed only with US-CT fusion imaging guidance.

Some limitations of the present study should be considered. First, selection bias occurred because of different criteria for patient selection for LPN and RFA. In our situation where LPN is a standalone treatment, this was an inevitable choice. Therefore, additional randomized controlled trials may be needed to prove the comparison of outcomes between RFA and LPN. Second, this was a retrospective single-center study, where RFA was performed only with US-CT imaging guidance, and there were no controls with CT guidance techniques. Third, some criteria for tumor visibility and technical feasibility included subjective factors. To date, there is no objective grading system for use when evaluating the visibility and technical feasibility of ultrasound-guided RFA. Therefore, we tried to make an objective estimate of the grading system by referring to previous studies, but further verification is required [10].

CONCLUSIONS

Real-time US-CT fusion imaging can be a useful imaging guidance tool for the treatment of stage T1a RCC because it improves tumor visibility and technical feasibility and provides disease-free survival rates equivalent to those of LPN.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Dong Jin Chung and Dong Wan Sohn. Data acquisition: Dong Jin Chung and Hyun Hwang. Statistical analysis: Dong Jin Chung and Hyun Hwang. Data analysis and interpretation: Dong Jin Chung and Hyun Hwang. Drafting of the manuscript: Dong Jin Chung and Hyun Hwang. Critical revision of the manuscript: Dong Wan Sohn. Obtaining funding: None. Supervision: Dong Jin Chung and Dong Wan Sohn. Approval of the final manuscript: Dong Jin Chung and Dong Wan Sohn.

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