

# Percutaneous CT-guided Radiofrequency Ablation for Renal Cell Carcinoma in von Hippel-Lindau Disease: Midterm Results

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## Abstract

**Purpose:** To evaluate the safety and midterm results of radiofrequency (RF) ablation for the treatment of renal cell carcinoma (RCC) in patients with von Hippel-Lindau (VHL) disease. **Materials and methods:** This study included 13 patients with VHL (8 women and 5 men; mean age: 35.5 years) and RCC. Each patient presented with 1-6 RCCs (mean:  $2.4 \pm 1.7$ ) without extrarenal metastasis. The mean tumor diameter was  $18.0 \pm 5.0$  mm. Transcatheter arterial embolization was performed for 5 (16.7%) of 31 tumors. All RF ablation procedures involved the percutaneous use of internally cooled RF electrodes under computed tomography fluoroscopic guidance. Adverse events were evaluated using the Common Terminology Criteria for Adverse Events, version 4.0, and pre- and post-treatment estimated glomerular filtration rates (eGFRs) were compared using paired t-tests. Local tumor progression, distant metastasis, and survival were also evaluated. **Results:** Twenty-three RF ablation sessions were technically successful. A grade 3 adverse event (hydronephrosis due to blood clotting, thus requiring ureteral stent placement) occurred in 1 (4%) of 23 sessions. The mean eGFR measured at  $\geq 1$  month after ablation was significantly lower than the mean eGFR before ablation ( $70.2 \pm 21.9$  versus  $78.8 \pm 23.0$ ,  $p < 0.001$ ). Local tumor progression was seen in 1 (3%) of 31 tumors. No patients died, required dialysis, or developed extra-renal metastases during a median 40-month follow-up. **Conclusions:** RF ablation for RCC is a safe, highly effective, and promising treatment option for patients with VHL disease.

**Key words:** radiofrequency ablation, von Hippel-Lindau disease, renal cell carcinoma

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## Introduction

Von Hippel-Lindau (VHL) disease is an autosomal-dominant, inherited multisystem disorder characterized by the development of various benign and malignant tumors, including retinal and central nervous system (CNS) hemangioblastomas, clear cell renal cell carcinomas (RCCs), pancreatic neuroendocrine tumors, pheochromocytomas, and endolymphatic sac tumors[1-3]. In addition, renal, pancreatic, and epididymal cysts are also observed in patients with

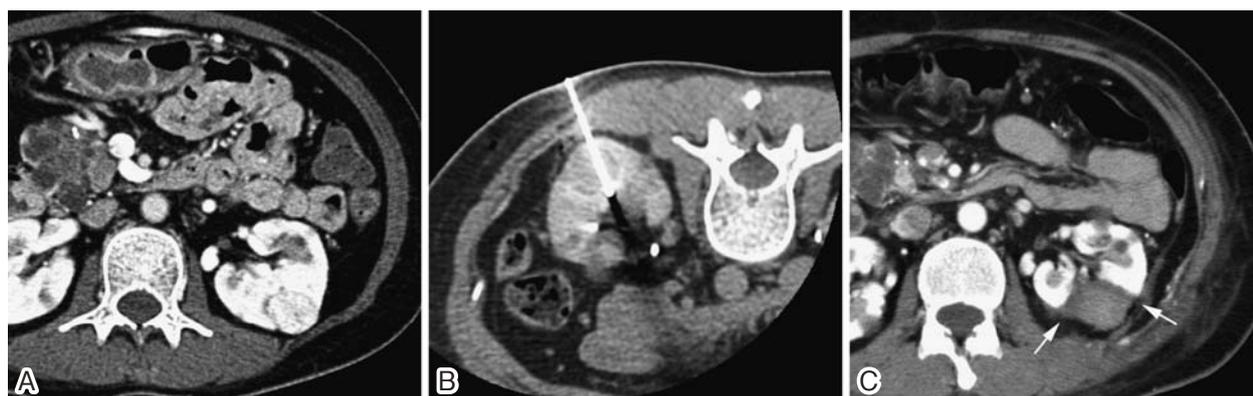
VHL. In particular, RCC occurs in 3-53% of patients with VHL[2, 4, 5]; these RCCs are often multiple or bilateral[6, 7] and arise at a relatively young age[3, 6].

Percutaneous image-guided radiofrequency (RF) ablation has been recently accepted as a treatment option for RCC[8-10] and has been described by many authors as a safe and effective procedure that is expected to preserve renal function[11, 12]. Given the multifocal nature of VHL, affected patients with RCC often require repeated treatments. Thus, RF ablation is considered a good potential treatment option that would spare the renal parenchyma to

**Table 1. Characteristics of 13 patients**

Case	Age/Sex	family history	VHL gene	previous treatment for RCC	hemangioblastoma	neuroendocrine tumor	cyst
1	23/F	yes	yes	RN	CNS	no	renal/pancreatic
2	26/F	yes	NE	no	CNS	no	renal
3	25/M	no	yes	no	CNS	no	pancreatic
4	37/M	yes	yes	RN	CNS/retinal	pancreatic	renal/pancreatic/epididymal
5	42/F	no	NE	no	CNS	no	renal/pancreatic
6	35/F	no	NE	PN	CNS	no	renal/pancreatic
7	35/M	no	yes	PN, TE	CNS	no	renal/pancreatic
8	44/M	yes	yes	RN	CNS	pancreatic	renal/pancreatic
9	47/F	no	yes	no	CNS	no	renal/pancreatic
10	35/M	yes	yes	no	no	pancreatic/adrenal	pancreatic
11	40/F	yes	yes	PN	retinal	no	renal/pancreatic
12	37/F	yes	yes	no	CNS/retinal	no	renal/pancreatic
13	36/F	yes	yes	RN	no	pancreatic	pancreatic

VHL: Von Hippel–Landau, RCC: renal cell carcinoma, NE: not evaluated, RN: radical nephrectomy, PN: partial nephrectomy, TE: tumor enucleation, CNS: central nervous system



**Figure 1. Imaging findings from a 41-year-old woman with renal cell carcinoma. A hypervascular tumor was observed in the left kidney (A). An internally cooled electrode was placed in the tumor (B). Computed tomography imaging after radiofrequency ablation revealed the ablation zone as an area of perfusion defect with an adequate ablative margin (C).**

the greatest possible extent. Several authors have reported the preliminary results of RF ablation for RCC in patients with VHL[13, 14]. The purpose of this study was to evaluate the safety and midterm results of RF ablation for the treatment of RCC in patients with VHL disease.

## Materials and Methods

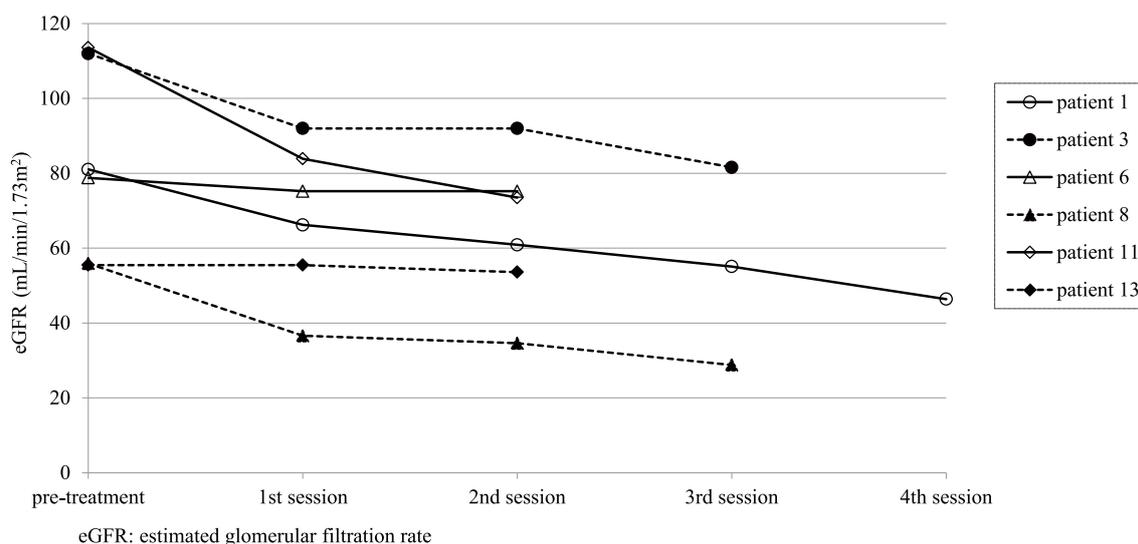
Our institutional review board approved this retrospective study and waived the requirement for informed consent to use the patients' medical data.

### Patient population

Between June 2002 and March 2012, we treated 154

RCCs in 86 patients at our institution through 134 consecutive percutaneous RF ablation sessions. Among these, 23 RF sessions were performed for 13 patients with VHL (8 women and 5 men; mean age: 35.5 years; range: 23-47 years). The patients' characteristics are listed in **Table 1**. VHL was genetically diagnosed in 10 of 13 patients and was clinically diagnosed from family histories and various associated neoplasms in 3 patients.

RCC diagnoses were based on computed tomography (CT) or magnetic resonance imaging (MRI) findings (**Fig. 1 A**). RCC was histologically confirmed in 4 patients (all clear cell RCCs). RF ablation was the initial treatment for RCC in 6 of 13 patients and the secondary treatment after surgery in the remaining 7 patients; the mean interval be-



**Figure 2.** Sequential change in the estimated glomerular filtration rate (eGFR) after each radio-frequency (RF) ablation session in 6 patients who underwent multiple RF ablation sessions.

tween surgery and RF ablation in these 7 patients was  $4.8 \pm 4.2$  years (range: 1-10 years). Surgeries for RCC treatment before RF ablation (1 patient required two procedures) included radical nephrectomy (n = 4), partial nephrectomy (n = 3), or tumor enucleation (n = 1).

### Indications

Eleven patients were not surgical candidates because of at least one of the following conditions: solitary kidney (n = 4), number of tumors (n = 8), or bilateral tumors (n = 3). The remaining 2 patients were surgical candidates but refused to undergo surgical resection. A tumor was considered an indication for RF ablation treatment when the tumor measured  $\geq 1$  cm in diameter and was located in an area where percutaneous needle placement was possible and the estimated placement route would not penetrate a critical organ such as the colon, pancreas, or renal hilum. Coagulopathy was considered a contraindicating factor. Therefore, RF ablation was indicated for a total of 31 tumors. The mean maximum diameter of these 31 tumors was  $18.0 \pm 5.0$  mm (range: 11-28 mm). Regarding tumor location, 17 (55%) were exophytic, 10 (32%) were central, and 4 (13%) were parenchymal.

### Radiofrequency ablation

All ablation procedures were performed percutaneously under CT fluoroscopic guidance (Asteon and Aquillion 16; Toshiba, Otawara, Japan). The patient's position during the procedure was determined according to the tumor location. Intraprocedural pain was treated with a combination of local anesthesia and intravenously administered fentanyl in 22 sessions, or epidural anesthesia in 1 session.

We used an RF ablation system comprising a 17-gauge internally cooled electrode (Cool-tip; Covidien, Boulder, CO, USA) and a generator (CC-1; Covidien). The active tip length of the electrode was selected to exceed the tumor di-

ameter. The electrode was introduced into the tumor (**Fig. 1 B**) and connected to the generator. If the estimated ablation zone did not surround the tumor, ablation was repeated after repositioning the electrode; for example, we typically treated RCCs with diameters  $\geq 1.5$  cm using multiple overlapping ablations to obtain an adequate ablative margin. At each site, RF energy was applied for 10-12 minutes using an impedance control algorithm during internal electrode cooling. Technical success was defined as successful placement of the electrode at the planned site and completion of the planned ablation protocol[15]. To evaluate the initial efficacy, contrast-enhanced CT or MRI was conducted immediately or within 1 month after the procedures (**Fig. 1C**). If the imaging exams showed residual tumor enhancement, additional RF ablation was performed.

Transcatheter arterial embolization (TAE) was performed prior to RF ablation when we wished to reduce the perfusion-mediated heat sink effect (4 tumors in 3 patients), thus enlarging the ablation zone, or if we expected that the tumor had not been identified via CT fluoroscopy, thereby hindering accurate RF ablation (1 tumor in 1 patient). TAE was performed by placing a catheter as selectively as possible to reduce the deterioration of renal function, using a mixture of absolute ethanol and iodized oil (Lipiodol; Guerbet, Villepinte, France) at a ratio of 7:3.

### Follow-up and assessment of local progression

The follow-up protocol included CT or MR scans at 1, 3, and 6 months after the procedure and at 6-12 month intervals thereafter. Local tumor progression was defined as the appearance of a nodular focus within or adjacent to the ablation zone. This focus typically exhibited some degree of contrast enhancement and was thus distinguished from the unenhanced necrotic tumor tissue[15, 16].

**Table 2. Renal function before and after RF ablation**

	eGFR (mL/min/1.73 m <sup>2</sup> )		<i>p</i> *
	before RF ablation	≥1 month after RF ablation	
Total (n = 21)	78.8 ± 23.0	70.2 ± 21.9	<0.001
number of tumors treated in a single session			
single (n = 15)	79.5 ± 24.2	69.2 ± 23.1	<0.001
multiple (n = 6)	76.7 ± 21.5	73.1 ± 20.0	0.36
Previous TAE			
without previous TAE (n = 18)	78.5 ± 23.7	70.2 ± 22.3	<0.001
with previous TAE (n = 3)	87.1 ± 29.1	80.6 ± 28.7	0.43

eGFR: estimated glomerular filtration rate, TAE: transcatheter arterial embolization, \*: paired Student's *t*-test

### Data collection

The medical charts of the 13 patients were carefully reviewed. The serum creatinine (SCr) concentrations before and ≥ 1 month after RF ablation were recorded. The estimated glomerular filtration rate (eGFR) was calculated using the following formula:  $eGFR (mL/min/1.73 m^2) = 194 * SCr^{-1.094} \times age^{-0.287} \times 0.739$  (if female)[17]. The maximum tumor diameter and tumor location were determined according to the classification proposed by Gervais et al.[18] and recorded. Adverse events that occurred during and after the procedure, local tumor progression, distant metastases, and survival were also evaluated. Each adverse event was evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0[19].

### Statistical analyses

Renal function data (SCr and eGFR) before and ≥ 1 month after the procedure were compared using a paired Student's *t*-test. We also evaluated changes in eGFR in groups classified according to the number of tumors treated in a single session or to a previous history of TAE. Additionally, the eGFR values calculated at the latest follow-up and before the first session were compared. A *p*-value of < 0.05 was considered to indicate a significant difference. SPSS version 22 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis.

### Results

A total of 23 sessions were needed to treat RCCs in 13 patients. In each patient, 1-6 (mean:  $2.4 \pm 1.7$ ) RCCs were treated with 1-4 RF ablation sessions; 1-3 tumors (mean:  $1.5 \pm 0.7$  tumors) were treated per session. RF ablation was performed using a single electrode position in 12 tumors and using multiple overlapping ablations in 19. Two of the 31 tumors (6.7%) were located anterolateral to the right kidney, and the electrode was therefore placed in the tumors via a transhepatic approach; details of these cases have been previously reported in the literature[20]. The maximum

power output was  $80 \pm 25$  W (range: 20-150 W), and the total ablation time was  $36 \pm 23$  minutes (range: 12-121 minutes) per tumor. Technical success was achieved in all RF ablation sessions.

A grade 3 or higher adverse event occurred in only 1 (4%) session; this patient developed anuria and abdominal pain 1 week after the procedure, and CT revealed hydronephrosis caused by a ureteral blood clot at his single kidney. A double-J ureteral stent was inserted and removed 6 months later, after the disappearance of the blood clot. Peri-procedural pain (grade 1) occurred in 9 (39%) of 23 sessions, and nausea (grade 1) and fever (grade 1) each occurred in 2 (9%) sessions. Hemorrhagic adverse events (subcapsular or perirenal hematoma; grade 1) occurred in 5 (24%) sessions. The only other adverse event was a urinary fistula that required no treatment in 1 (4%) session.

For these 13 patients, the median follow-up period after the first ablation session was 40 months (mean:  $49 \pm 24$  months; range: 22-105 months). The median follow-up period for the 31 tumors was 40 months (mean:  $42 \pm 24$  months; range: 0.2-105 months). One tumor exhibited a small enhancing focus in the ablation zone on contrast-enhanced CT images; therefore, an additional RF ablation was performed 7 days after the initial procedure, which was not included in the 23 sessions. One (3%) of the 31 tumors exhibited local tumor progression more than 12 months after the procedure. This locally progressed tumor retreated during an RF ablation session for another tumor, and was included in the 23 sessions. For the remaining tumors, RF ablation was deemed technically effective according to the latest follow-up images. No patients developed distant metastasis or died during the follow-up period. Four (33%) of the 12 patients had RCCs smaller than 1 cm and are being carefully followed up.

Pre-ablation SCr values were available for 23 sessions, and values measured at ≥ 1 month after ablation (median: 2 months; range: 1-12 months) were available for 21 sessions. Therefore, the SCr values associated with those 21 sessions were used to evaluate changes in renal function. The SCr values before and ≥ 1 month after the procedure were 0.82

$\pm 0.20$  mg/dL and  $0.89 \pm 0.29$  mg/dL, respectively ( $p = 0.03$ ). In addition, the eGFR values before and  $\geq 1$  month after the procedure were  $78.8 \pm 23.0$  mL/min/1.73 m<sup>2</sup> and  $70.2 \pm 21.9$  mL/min/1.73 m<sup>2</sup>, respectively ( $p < 0.001$ ; **Table 2**). In addition, changes in eGFR according to the number of tumors treated in a single session or to a previous history of TAE are shown in **Table 2**. Statistically significant differences were not observed among those with multiple tumors treated during the same session or those with a previous history of TAE.

At the patients' last follow-up examination, the mean eGFR value was  $69.5 \pm 18.5$  mL/min/1.73 m<sup>2</sup>, which was significantly lower than the value determined before the first RF ablation (mean:  $87.0 \pm 23.9$  mL/min/1.73 m<sup>2</sup>;  $p = 0.002$ ). Six (46%) of 13 patients underwent multiple RF ablation sessions (2 sessions,  $n = 3$ ; 3 sessions,  $n = 2$ ; 4 sessions,  $n = 1$ ). The eGFR values of the 6 patients gradually decreased after each treatment session (**Fig. 2**). In one patient, the eGFR decreased to  $< 30$  mL/min/1.73m<sup>2</sup>; however, this value had recovered to  $\geq 30$  mL/min/1.73m<sup>2</sup> at the last follow-up examination. However, no patients developed renal failure requiring hemodialysis or renal transplantation.

## Discussion

Currently, RCC is the cause of death of 15-50% of patients with VHL[1, 2, 4], in spite of the fact that RCCs in these patients tend to have a low histological grade and slower growth, compared with sporadic RCCs[21]. Although the mean growth rate of RCC in patients with VHL was found to be between 0.3 and 0.5 cm/year[22, 23], the median life expectancy of affected patients has been reduced to 49 years[21].

Given its favorable preliminary results, percutaneous RF ablation has been designated as a treatment option for RCC in patients with VHL disease[13, 14]. Regarding local efficacy, Park et al.[13] reported that 88% of tumors were successfully managed by RF ablation (mean follow-up:  $23 \pm 13$  months), and Iwamoto et al.[14] reported a lack of local tumor progression (mean follow-up:  $22 \pm 11$  months). The mean tumor diameter in the present series was 1.8 cm, which was smaller than the diameters listed in previous reports. This smaller tumor size is likely due to the slower growth of RCCs in patients with VHL, as well as good surveillance of these patients. Our favorable local efficacy rate (3% local tumor progression during a median follow-up of 40 months) might therefore be attributable to the small size of the treated tumors.

Percutaneous RF ablation has been accepted as a minimally invasive treatment for patients with RCC. This is supported by the finding that in the present study, grade 3 or higher adverse events occurred in only 1 (4%) session. All other reported adverse events (e.g., pain, nausea, fever, hemorrhage) were grade 1. The adverse events in this series were therefore comparable to those reported in previous larger series[8, 9], in which the complication rates ranged

from 8% to 13%. Although a transhepatic approach, which was reported to be safe for selected tumors[20], was selected for two sessions in the present study, it was not associated with adverse events.

The preservation of renal function is an important issue in the treatment of RCCs associated with VHL. Limited therapeutic options are available for multiple and bilateral RCCs. For such cases, renal transplantation or hemodialysis is required after bilateral radical nephrectomy; however, both worsen the patient's prognosis and quality of life[21, 22, 24]. Recently, nephron-sparing surgery has been considered a "gold standard" treatment for small renal masses and is considered a favorable treatment for RCCs in patients with VHL. Following a 10-year investigation, Walther et al.[24] reported that VHL patients ( $n = 52$ ) who underwent nephron-sparing surgery for the treatment of tumors  $\leq 3$  cm did not require renal transplantation or hemodialysis. Pavlovich et al.[25] similarly reported initial results following the application of percutaneous RF ablation for patients with VHL. Additionally, many authors mentioned that the multiplicity and newly emerging nature of RCC associated with VHL rendered it a good indication for RF ablation[9, 12, 18]. Indeed, in the present series, 3 patients with VHL had a solitary kidney, 4 had bilateral RCCs, and 7 had multiple RCCs.

Duffey et al.[26] investigated the correlation between tumor size and metastasis and found that solid RCCs with diameters  $< 3$  cm did not metastasize. Additionally, these authors demonstrated that none of the 108 investigated patients with tumors  $\leq 3$  cm developed metastatic disease during a median follow-up of 41 months, whereas 20 of the 73 patients with tumors  $> 3$  cm developed metastases during a median follow-up of 59 months. Accordingly, some groups recommended an observational strategy for tumors  $\leq 3$  cm[24, 26]. In contrast, in this study, we treated tumors  $< 3$  cm in diameter. All of the tumors were progressive and were therefore expected to exceed a diameter of 3 cm in the future, especially when the young age of the patients (mean: 35.5 years) was considered. Additionally, once a tumor exceeds 3 cm in diameter, local control via RF ablation might become more challenging[8, 9]. Therefore, we treated the tumors before they reached 3 cm in diameter.

Deterioration in renal function might be unavoidable after local treatment for RCC (e.g., surgical resection and ablation). Accordingly, eGFR is a more accurate measurement of true renal function than SCr. We noted that in this series, both the eGFR and SCr values were significantly worse after RF ablation. After a single RF ablation session, the change in renal function was minimal. However, as shown in **Fig. 2**, the repeated procedures required for patients with VHL might worsen their renal function. When managing such patients, physicians will need to achieve the optimal balance between renal function and renal tumor control. We believe that RF ablation could contribute to this balance.

Our study had several limitations. First, this was a retrospective study. In addition, the study population was small

(13 patients), and the follow-up period was not very long (median: 40 months). Furthermore, TAE was performed prior to RF ablation in some cases, making it difficult to evaluate the efficacy of RF ablation alone.

In conclusion, RF ablation of VHL-associated RCC was safe and yielded an extremely high technique effectiveness rate. Therefore, it may be a promising treatment option for RCC in patients with VHL.

**Conflict of interest:** This study was not supported financially by any organization with a financial interest in the subject matter. There are no potential conflicts of interest with regard to this study.

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