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Percutaneous thermal ablation for renal cell carcinoma in patients with Birt—Hogg—Dubé syndrome

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KEYWORDS
Birt—Hogg—Dubé syndrome;
Renal cell carcinoma;
Percutaneous thermal ablation;
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Cryoablation

Abstract
Purpose: The purpose of this study was to analyze the outcome of patients with Birt—Hogg—Dubé (BHD) syndrome who underwent percutaneous thermal ablation of renal cell carcinoma (RCC).
Materials and methods: Six patients with genetically proven BHD syndrome who underwent one or more sessions of percutaneous thermal ablation for the treatment of RCC were included. There were 4 men and 2 women, with a mean age of 57.3 ± 7.5 [SD] years (range: 44—67 years). A total of 29 RCCs (1—16 tumors per patient) were treated during 20 thermal ablation sessions (7 with radiofrequency ablation and 13 with cryoablation). Outcomes of thermal ablation therapy were assessed, including technical success, adverse events, local tumor progression, development of metastases, survival after thermal ablation, and changes in renal function.
Results: Technical success was achieved in all ablation sessions (success rate, 100%). No grade 4 or 5 adverse events were observed. All patients were alive with no distant metastasis during a median follow-up period of 54 months (range: 6—173 months). No local tumor progression was found. The mean decrease in estimated glomerular filtration rate during follow-up was 10.7 mL/min/1.73 m^2. No patients required dialysis or renal transplantation.
Conclusion: Radiofrequency ablation and cryoablation show promising results for the treatment of RCCs associated with BHD syndrome. Percutaneous thermal ablation may be a useful treatment option for this rare hereditary condition.

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Birt—Hogg—Dubé (BHD) syndrome is a rare autosomal dominant disorder characterized by cutaneous fibrofolliculomas, pulmonary cysts, spontaneous pneumothorax, and renal neoplasia [1]. Since the identification of the responsible germline mutation in the *folliculin* (*FLCN*) gene in 2002, this syndrome has increasingly gained attention [2]. Renal cell carcinoma (RCC) in patients with BHD tends to be bilateral and multifocal and is the most severe complication [3,4]. Although partial or radical nephrectomy is generally indicated for BHD-associated RCC, maintaining a balance between oncological radicality and preservation of renal function needs to be considered in its management because of the high risk of multiple synchronous and metachronous tumors [5]. Percutaneous thermal ablation such as radiofrequency ablation (RFA) and cryoablation is now an effective treatment for RCC [6,7]. Because of minimal invasiveness and repeatability, thermal ablation may be theoretically advantageous in patients with hereditary RCC who require repeated treatment for multiple lesions. In fact, previous reports have suggested the usefulness of RFA for RCC in patients with von Hipple—Lindau disease [8—10]. On the other hand, the efficacy of percutaneous thermal ablation for RCC associated with BHD syndrome has not been well studied.

The purpose of this study was to analyze the outcome of patients with BHD syndrome who underwent percutaneous thermal ablation for the treatment of RCC.

Materials and methods

Written informed consent for ablation therapy was obtained from all patients before the initiation of any procedure. This study was approved by the authors' institutional review board. Because of its retrospective design, the requirement for written informed consent was waived for this study.

Patients

The present study included six patients (4 men and 2 women) with BHD syndrome who had a proven germline *FLCN* gene mutation and underwent RFA and/or cryoablation for RCC from June 2003 to July 2017. The mean age of the patients at RCC onset was 56.3 ± 8.0 (standard deviation [SD]) years (median 57.5; first—third quartile [Q1—Q3]: 54.0—62.5; range: 41—65 years) and the mean age at referral for ablation was 57.3 ± 7.5 (SD) years (median 58; Q1—Q3: 54.3—62.5; range: 44—67 years). Two patients had a history of total nephrectomy and another had partial nephrectomy because of RCC. The other three patients had no history of nephrectomy.

A total of 29 RCCs (mean, 4.8 tumors per patient; range: 1—16) were treated in 20 ablation sessions including 7 RFA for 14 RCCs and 13 cryoablations for 15 RCCs. The mean RCC size was 13.9 ± 4.6 (SD) mm (median, 13; Q1—Q3: 10—16; range: 7—26 mm). Sixteen RCCs were located in the right kidney and 13 RCCS in the left kidney, with 19 exophytic, 6 parenchymal, and 4 intracystic RCCs. The diagnosis of RCC was established based on the findings on dynamic computed tomography (CT) images when they were consistent with that of previous pathologically proven RCC. Needle biopsy was performed for five RCCs in three patients who did not have a history of nephrectomy before ablation, using an 18-Gauge semi-automatic cutting biopsy needle. The pathological diagnosis according to biopsy examination included two clear cell RCCs and a hybrid oncocytic/chromophobe tumor (HOCT) in one patient, a chromophobe RCC in another patient, and a chromophobe RCC in the third patient. The clinicopathologic and genetic information of patients is summarized in Table 1.

Thermal ablation procedures

Either RFA or cryoablation was performed to treat between one and three RCCs in each ablation session. RFA had been performed for all tumors until 2011. Cryoablation was introduced in the authors' Institution in April 2012; thereafter, all tumors have been treated with cryoablation. All procedures were performed percutaneously under CT fluoroscopy guidance in an inpatient setting by interventional radiologists with 1—15 years of experience in renal thermal ablation. For both RFA and cryoablation sessions, procedural pain was controlled with local anesthesia and intravenous administration of fentanyl, except in one session. General anesthesia was used in one cryoablation session in which a balloon catheter was placed between the tumor and gallbladder using laparotomy, to protect the gallbladder from cryoinjury. Artificial pneumothorax was created in one cryoablation session to avoid transpulmonary probe insertion. Hydrodissection or pneumodissection was used in 8 thermal ablation sessions to prevent injury of adjacent critical organs. Hydrodissection was performed in 5 cryoablation sessions by injecting mixture of saline and contrast medium through an 18- to 21-Gauge needle inserted between the target tumor and the organ at risk. Pneumodissection was performed in 2 RFA and 1 cryoablation sessions by injecting carbon dioxide with a similar technique.

RFA was performed using a 17-Gauge internally cooled electrode (Cool-tip; Medtronic) and a generator (CC-1; Medtronic). An electrode with an active tip length of 1 or 2 cm was used, depending on the tumor size. After the electrode was inserted into the tumor, 10—12 min of ablation was performed with internal cooling of the electrode using an impedance control algorithm. If necessary, multiple overlapping ablations were performed to secure adequate ablation margins.

Cryoablation was conducted using an argon-based cryoablation system (CryoHit; Galil Medical). One to three cryoprobes (IceRod or IceSeed; Galil Medical) were introduced into the target depending on the tumor size. The standard ablation protocol included two 10- to 15-min freezing cycles separated by ≥ 2 min of passive thawing. CT was performed to assess the ablation zone (i.e., ice ball) at the end of each freezing cycle. The ablation procedure aimed to cover the target lesion with an ice ball margin larger than 6 mm, according to Georgiades et al. [11].

Technical success was defined as completion of the planned ablation protocol and complete coverage of the tumor by the ablation zone [12]. After ablation, CT was performed to assess adverse events.

Table 1 Clinicopathologic and genetic information of six patients with renal cell carcinoma and Birt–Hogg–Dubé syndrome.

Patient #	Age at referral for ablation (year)	Sex	*FLCN* germline mutation		Lung cysts	History of pneumothorax	History of nephrectomy	Histological type of RCC
			Location	Mutation				
1	64	Female	Exon 5	c.327_328delCC	Yes	Yes	No	Clear cell RCC[a] HOCT[a]
2	53	Male	Exon 11	c.1285dupC	Yes	Yes	Partial	HOCT[b]
3	44	Female	Exon 12	c.1347_1353dupCCACCCT	Yes	No	Total	HOCT[b]
4	58	Male	Exon 11	c.1285dupC	Yes	Yes	Total	Clear cell RCC[b] HOCT[b]
5	58	Male	Exon 13	c.1533_1536delGATG	Yes	Yes	No	Chromophobe RCC[a]
6	67	Male	Intron 9	c.1062+1G>A	Yes	No	No	Chromophobe RCC[a]

RCC: renal cell carcinoma; HOCT: hybrid oncocytic/chromophobe tumor.
[a] Diagnosis by needle biopsy before ablation.
[b] Diagnosis based on surgical specimen.

Follow-up examination

Dynamic contrast-enhanced CT was performed at 1-, 3-, and 6-months after the procedure and at 6- to 12-month intervals thereafter. The follow-up CT protocol consisted of unenhanced and triphasic contrast-enhanced CT examinations at 36-, 53-, and 240-s delays. Axial and coronal images of each phase were reconstructed with a slice thickness of 5 mm. The appearance of a nodular focus exhibiting contrast enhancement within or adjacent to the ablation zone indicated local tumor progression [12,13]. On follow-up imaging, if a new enhancing nodule was identified outside the ablated zone that was increased in size, it was diagnosed as a new RCC. Once a new RCC developed, it was carefully observed and ablation was typically considered when it became larger than 1—2 cm. However, the actual timing of treatment varied depending on the patient's clinical condition.

Data collection

The medical records of the six patients were retrospectively reviewed, and demographic and procedural data were recorded. Outcomes of thermal ablation were assessed, including technical success, adverse events, local tumor progression, development of metastases, survival after ablation, and change of renal function. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. To evaluate the change of renal function, serum creatinine value (sCr) (mg/dL) and estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2) before the initial ablation and at last follow-up were recorded. The increase in serum creatinine value ([sCr at the last follow-up] − [sCr before initial treatment] mg/dL) and decrease in eGFR ([eGFR before initial treatment] − [eGFR at the last follow-up] mL/min/1.73 m^2) were calculated.

Statistical analysis

Categorical data were expressed as raw numbers, proportions and percentages. Quantitative variables were expressed as means, standard deviations (SD), medians, Q1—Q3, and ranges. Microsoft Excel for Mac version 16 (Microsoft) was used for descriptive statistics.

Results

Technical success was achieved in all thermal ablation sessions (20/20, 100%). The most frequent adverse event was hematuria (grade 1), which was found after all sessions in which postprocedural urinalysis data were available (16/16 [100%] sessions, 6/6 [100%] patients). The other grade 1 adverse events included post-treatment fever (3/20 [15%] sessions, 1/6 [17%] patients), nausea (3/20 [15%] sessions, 2/6 [33%] patients), thermal injury at the skin puncture site (1/20 [5%] sessions, 1/6 [17%] patients), cutaneous sensory disorder in the inguinal region (1/20 [5%] sessions, 1/6 [17%] patients), and pneumothorax (1/20 [5%] sessions, 1/6 [17%] patients). Vasovagal reflex requiring injection of atropine sulfate (grade 3) was observed in 2/20 (10%) sessions (2/6 [33%] patients). Asymptomatic pulmonary embolism (grade 3) was found after 1/20 (5%) sessions (1/6 [17%] patients). No grade 4 or 5 adverse events were observed.

Treatment outcomes of the six patients are presented in Table 2. Multiple tumors were treated in four patients (Fig. 1). No local tumor progression was observed during a median follow-up period of 60 months (range: 5—173 months). All patients were alive with no distant metastasis during a median follow-up period of 54 months (range: 6—173 months). At the time of last follow-up, three patients had no residual RCC whereas the remaining patients had 1, 3, or more than 10 residual RCCs upon observation. Values of sCr and eGFR before the initial thermal ablation session and at the last follow-up are reported in Table 3. The mean increase in sCr values during follow-up was 0.13 ± 0.11 (SD) mg/dL (median, 0.09; Q1—Q3: 0.07—0.12; range: 0.04—0.36 mg/dL). The mean decrease in eGFR during follow-up was 10.7 ± 6.5 (SD) mL/min/1.73 m^2 (median: 9.2; Q1—Q3: 6.6—11.6; range: 3.7—23.9 mL/min/1.73 m^2). No patients required dialysis or renal transplantation during the follow-up period.

Discussion

The present study demonstrates favorable local control and safety of percutaneous thermal ablation for RCC associated with BHD syndrome. All patients were alive with no distant metastasis at the last follow-up. Furthermore, the decrease

Table 2 Outcomes of six patients with renal cell carcinoma and Birt—Hogg—Dubé syndrome who underwent thermal ablation.

Patient #	Number of ablated RCCs	Maximum size of ablated RCCs (mm)	Number of ablation sessions	Follow-up (month)	Local progression after ablation	Number of residual RCCs	Distant metastasis	Survival
1	16	23	10	173	No	> 10	No	Alive
2	5	15	3	124	No	0	No	Alive
3	2	15	1	48	No	0	No	Alive
4	1	11	1	60	No	1	No	Alive
5	4	15	4	11	No	0	No	Alive
6	1	26	1	6	No	3	No	Alive

RCC: renal cell carcinoma.

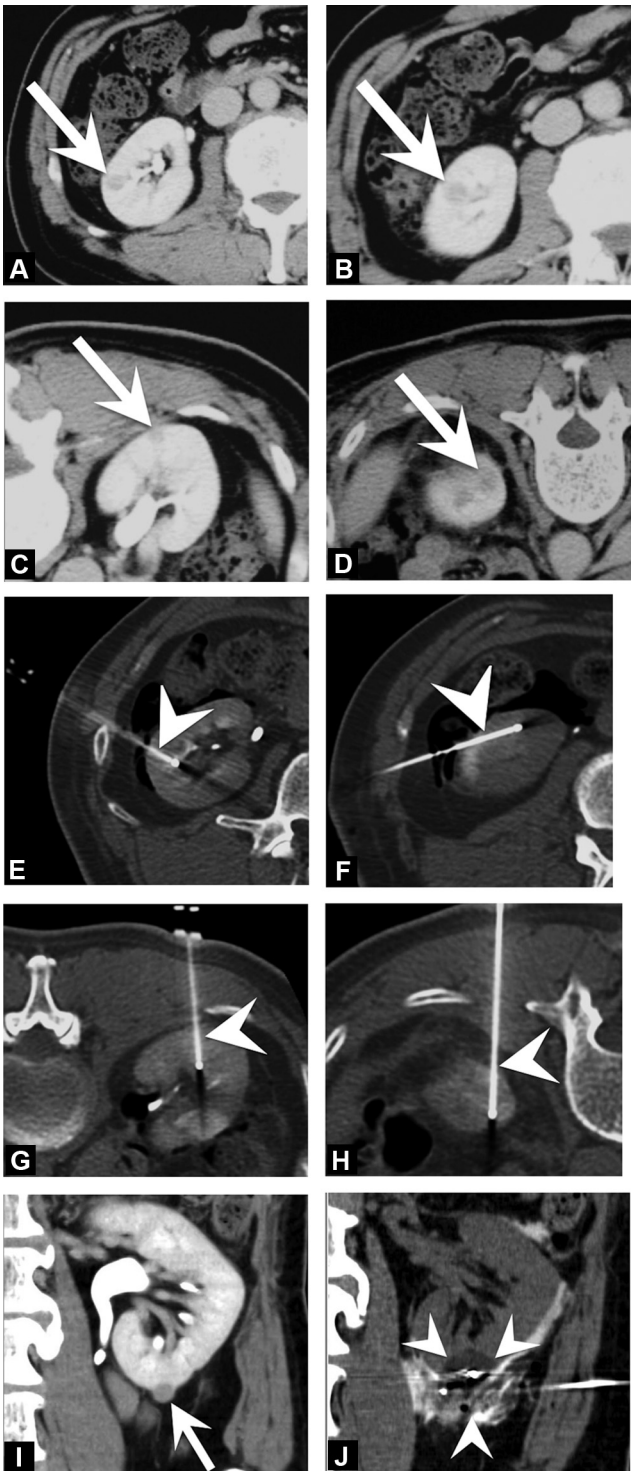

Figure 1. A 53-year-old man with Birt—Hogg—Dubé syndrome who had a history of partial nephrectomy and underwent ablation therapy repeatedly for synchronous and metachronous multiple renal cell carcinomas (RCCs). A—D. Computed tomography (CT) images in the axial plane show four RCCs (arrows) that were initially identified and treated in two separate sessions of radiofrequency ablation (RFA). E & F. CT images in the axial plane obtained during the first sessions of RFA show RFA probes (arrowheads) into two of the four RCCs. G & H. CT images in the axial plane obtained during the 2nd sessions of RFA show RFA probes (arrowheads) into two of the four RCCs. I. CT image in the coronal plane shows a new RCC (arrow) developed in the left kidney 64 months after the initial RFA session. J. The newly developed RCC was treated with cryoablation. CT image in the coronal plane shows ice ball (arrowheads) during the procedure. The patient was alive with no local progression or distant metastasis 124 months after the initial thermal ablation.

in renal function remained at an acceptable level even in patients who underwent multiple thermal ablation sessions.

Although most renal tumors are sporadic, some are associated with heritable diseases such as von Hipple—Lindau disease, tuberous sclerosis, or hereditary papillary RCC. BHD syndrome is one such hereditary condition, which causes renal tumors [14]. In this regard, approximately one-third of patients with BHD develop RCC [14]. Histological subtypes of BHD-associated renal tumors include HOCT, chromophobe RCC, clear cell RCC, oncocytoma, and papillary RCC [15]. The diagnosis of BHD syndrome may not always be established during management because of the rarity of this syndrome. In fact, BHD syndrome was not suspected until referral for thermal ablation in any patients in the present study, including those who had a history of nephrectomy for previous RCC. Physicians who are in charge of patients with renal tumors should become acquainted with this rare but important syndrome, for its proper management.

Although specific reports on the application of thermal ablation to BHD-associated RCC are lacking, some authors have discussed the theoretical usefulness of such thermal ablation therapies as a treatment option for BHD-associated RCC, especially for tumors smaller than 3 cm [3,16]. The advantages of percutaneous thermal ablation therapy include its minimal invasiveness and repeatability. On the other hand, as a drawback of thermal ablation, a previous article pointed out a concern that ablation might complicate subsequent surgical procedures in patients with new tumor development or local tumor progression [4]. Regardless of the treatment modality, the timing of intervention for multifocal hereditary RCC should be carefully determined by considering both preservation of renal function and prevention of metastatic disease. Walther et al. advocated a tumor size of 3 cm as a threshold for renal parenchymal sparing surgery in von Hipple—Lindau disease or hereditary papillary RCC [17]. On the other hand, Gobara et al. reported earlier application of RFA for von Hipple—Lindau disease-associated RCC because local control with ablation becomes more challenging for tumors larger than 3 cm [10]. Regarding BHD syndrome, there is a paucity of data for discussing the appropriate timing of intervention; therefore, further accumulation of experience is warranted.

The present study has some limitations. This is a retrospective study including a small number of patients. The treatment included two types of procedures (i.e., RFA and cryoablation) and the therapeutic strategy varied on a case-by-case basis. Although this study included some patients with a relatively long follow-up period, the true effect of thermal ablation on survival could not be determined because of the indolent nature of BHD-associated RCC [4]. Finally, the theoretical advantages of thermal ablation over surgery could not be confirmed in this single-arm study.

In conclusion, the present study shows promising outcomes of RFA and cryoablation for RCC associated with BHD syndrome. Because of its minimal invasiveness and

Table 3 Changes in serum creatinine values and estimated glomerular filtration rate after thermal ablation of renal cell carcinoma.

Patient #	sCr before initial ablation session (mg/dL)	sCr at last follow-up (mg/dL)	eGFR before initial ablation session (mL/min/1.73 m^2)	eGFR at last follow-up (mL/min/1.73 m^2)
1	0.73	1.09	61.3	37.4
2	0.88	0.98	71.4	60.4
3	0.67	0.71	75.0	68.7
4	1.28	1.35	46.2	42.5
5	0.62	0.69	102.1	90.3
6	1.01	1.14	57.4	50.1

sCr: serum creatinine level; eGFR: estimated glomerular filtration rate.

repeatability, percutaneous thermal ablation may be a useful treatment option for this rare hereditary condition.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans..

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

Because of its retrospective design, the requirement for written informed consent was waived for this study. The authors also confirm that the personal details of the patients and/or volunteers have been removed.

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Authors' contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

Yusuke Matsui: conceptualization, formal analysis, investigation, data curation, writing — original draft, project administration. Takao Hiraki: conceptualization, investigation, writing — review & editing, supervision. Hideo Gobara: conceptualization, investigation, writing — review & editing. Toshihiro Iguchi: investigation, writing — review & editing. Koji Tomita: validation, writing — review & editing. Mayu Uka: validation, writing — review & editing. Motoo Araki, Yasutomo Nasu, Mitsuko Furuya: writing — review & editing. Susumu Kanazawa: writing — review & editing, supervision.

Disclosure of interest

The authors declare that they have no competing interest.

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