

## Follow-Up of Cryoablated Renal Cell Carcinoma with Residual Contrast Enhancement on CT and MRI<sup>1</sup>

냉동수술을 시행한 신장세포암종의 전산화단층촬영과 자기공명영상에서 보이는 잔여 조영증강에 대한 추적검사<sup>1</sup>

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**Purpose:** To describe the characteristics of residual contrast enhancement (CE) in cryoablated renal cell carcinoma (RCC) with regard to eventual resolution and the presence of residual tumor on follow-up CT and MRI.

**Materials and Methods:** 22 patients with 24 RCCs underwent laparoscopic renal cryoablation and follow-up CT ( $n = 19$ ) and MRI ( $n = 3$ ) for a mean of 28 months. Two radiologists retrospectively assessed the CT and MRI images for the tumor size and characteristics of residual CE in the cryolesions: peripheral rim (< 10% of the maximum cryolesion diameter), focal eccentric (10-25%), and thick internal enhancement (> 25%).

**Results:** Residual CE was seen in 13 cryolesions (54%) at 3-month follow-up. Peripheral rim and focal eccentric enhancement was seen in six (25%) and four (16.7%) cryolesions, persisted for a mean follow-up of 4.5 and 6 months, and disappeared completely at a mean follow-up of 10.5 and 12 months, respectively. Three (12.5%) cryolesions showed persistent thick internal enhancement at 6-month follow-up, and were treated with radiofrequency ablation or chemotherapy. The cryolesions had decreased in size by an average of 20.2% and 39.7% at 6 and 12 months after cryoablation, respectively.

**Conclusion:** Follow-up for  $\geq 12$  months is needed to assess treatment outcomes in patients with peripheral rim or focal eccentric enhancement of cryoablated RCCs, which may persist until 12 months postoperatively without remnant viable tumor.

### Index terms

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## INTRODUCTION

Laparoscopic renal cryoablation is increasingly being used in patients with small ( $\leq 4$  cm) unilateral localized renal cell carcinoma (RCC) as a minimally invasive surgery that is alternative to open partial nephrectomy (1). In contrast to partial nephrectomy, in cryoablation there is no surgical specimen with which to identify ablative margins and therefore, recognizing the imaging characteristics of RCC after cryoablation is important.

Multiphasic CT and MRI with contrast material are usually used for postablation imaging for the detection of complica-

tions related to cryoablation and residual or recurrent tumors. In previous studies, successful ablation has been defined as the absence of contrast enhancement. Any enhancing lesion at the location of the ablated tumor suggests residual viable neoplasm or tumor recurrence (2). However, some residual contrast enhancement may persist for several months and may not be associated with any residual or recurrent tumor (3). Porter et al. (4) suggested that it may be reasonable to wait six months after technically successful renal cryoablation before performing contrast-enhanced MRI because of the resolution of enhancement at six months after cryoablation. However, we recently

encountered some cryolesions in which focal eccentric enhancement disappear at 12-month follow-up or later after cryoablation. Thus, the purpose of our study was to retrospectively evaluate the characteristics of residual contrast enhancement in cryoablated RCC with regard to eventual resolution and detection of residual tumor on follow-up CT and MRI in patients who underwent laparoscopic renal cryoablation.

## MATERIALS AND METHODS

### Patients

Our institutional review board approved the study protocol, and informed consent was obtained from all individuals. Between January 2005 and March 2011, 24 patients (20 men; 4 women; average age, 61.2) with 26 masses that had been confirmed as RCC by intraoperative needle biopsy, underwent laparoscopic renal cryoablation. Each lesion fulfilled established CT criteria without evidence of metastatic disease. Out of 24 patients, 2 patients did not undergo follow-up imaging studies, leaving 22 patients (18 men; 4 women; average age, 62 years) with 24 RCCs who were followed up with contrast-enhanced CT ( $n = 19$ ) and MRI ( $n = 3$ ) for more than 12 months (range, 12-60 months; average, 28 months). Follow-up imaging was performed 3, 6, 9, 12, 18, and 24 months after cryoablation, and then annually after 24 months.

### Imaging

CT scans were performed with two scanners, the 64-multi-detector computed tomography (MDCT) Brilliance 64 (Philips Medical Systems, Cleveland, OH, USA) and the 4-MDCT Volume Zoom (Siemens Medical Systems, Forchheim, Germany). Contrast-enhanced CT scans were performed in all patients from the level above the diaphragm to the symphysis pubis during a single breath hold with patients in the supine position. Triphasic (unenhanced, corticomedullary, and excretory phase) CT scans were obtained. The scan delay time ranged from 30 to 40 seconds for the corticomedullary phase and was 5 minutes for the excretory phase after contrast injection. All patients received 120-150 mL of iopromide (Ultravist 300; Bayer Healthcare, Berlin, Germany) administered at a rate of 3 mL/s through an 18 or 20 gauge angiographic catheter inserted into a forearm vein using an automatic power injector. The scanning parameters

for 4-MDCT were as follows:  $4 \times 2.5$  mm detector collimation, 120 kVp, 130 mAs, and 5-mm slice thickness. The parameters for 64-channel MDCT were as follows:  $64 \times 0.625$  mm detector collimation, 120 kVp, 300 mAs, and 5-mm slice thickness. Images were acquired with a section thickness of 5 mm.

MRI was performed with a 3-T MR imager (Magnetom Tim Trio; Siemens, Erlangen, Germany) using a body phased-array coil. Routine kidney MR imaging consisted of a coronal single-shot fast spin-echo sequence (repetition time msec/echo time msec, 600/97; section thickness, 5 mm; interslice gap, 0.5 mm; matrix,  $320 \times 320$ ; flip angle,  $150^\circ$ ; field of view,  $16 \text{ cm}^2$ ), an axial half-Fourier acquired single-shot turbo spin echo sequence (500/148; 4 mm; 0.4 mm;  $320 \times 340$ ;  $150^\circ$ ;  $8.1 \text{ cm}^2$ ), axial in-phase and out-of-phase spoiled gradient-echo images (142/1-3; 5.5 mm; 1 mm;  $256 \times 192$ ;  $65^\circ$ ;  $8.1 \text{ cm}^2$ ), and dynamic fat-suppressed three-dimensional fast spoiled gradient-echo images before and after contrast administration (3/1; 5 mm; no interslice gap;  $352 \times 224$ ;  $10.4^\circ$ ;  $11.8 \text{ cm}^2$ ). Gadoterate meglumine (Dotarem; Guerbet, Aulnays sous Bois, France) was administered at a rate of 2 mL/s using a power injector. Contrast-enhanced sequences were performed in the corticomedullary, nephrographic, and excretory phases.

### Surgical Techniques

An oncologic urologist with eight years of experience performed laparoscopic renal cryoablation using a third-generation cryotechnology (Galil Medical Inc., Plymouth Meeting, PA, USA) with three to nine cryoprobes, depending on the size of the renal tumor. Under the guidance provided by intraoperative ultrasonography (Aloka Dynaview II; Americanlab, Miami, FL, USA), the lesion was identified and the degree of the ice ball extension was determined. Following renal mass biopsy, three to nine cryoprobes (IceRod; Oncura, Plymouth Meeting, PA, USA), depending on the size of the renal tumor, were advanced into the mass with real-time sonographic guidance, and a double freeze-thaw cycle was performed. A rapid freeze made isothermal lesion with  $-40^\circ\text{C}$  and the edge of the ice ball was circumferentially extended 1 cm beyond the tumor margin on ultrasonography.

### Image Interpretation and Statistical Analysis

All imaging studies were retrospectively reviewed by two radiologists (one radiologist with 14 years of experience in body

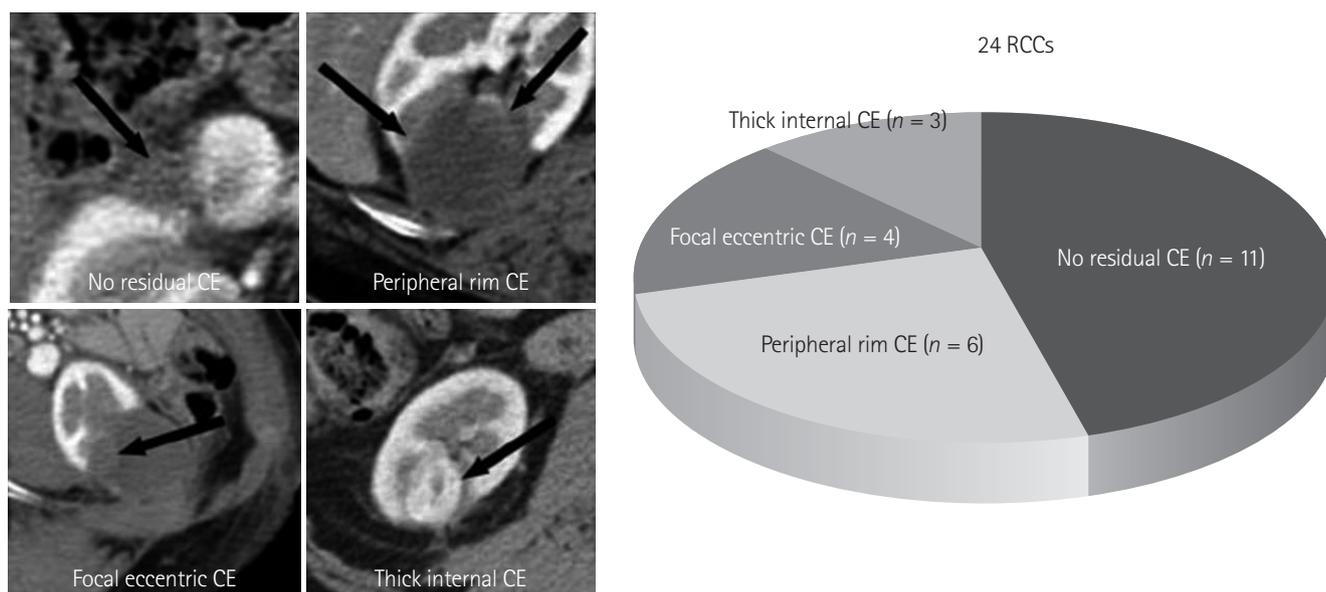
imaging and a fourth-year radiology resident), in consensus. The sizes of the initial tumors and cryolesions after laparoscopic renal cryoablation were measured as the maximal diameter. To compare the size change after cryoablation, the diameter of the initial tumor, measured on preoperative CT or MRI, was considered the reference, and the relative change in diameter measured on subsequent imaging was calculated as a percentage of the reference lesion. The characteristics of residual contrast enhancement in the cryolesions were classified as A) absence of residual contrast enhancement, B) peripheral rim enhancement (circumferential, thickness, less than 10% of the maximum cryolesion diameter), C) focal eccentric enhancement (noncircumferential, thickness between 10% and 25% of the maximum cryolesion diameter), and D) thick internal enhancement (noncircumferential, thickness greater than 25% of the maximum cryolesion diameter). Contrast enhancement for CT was defined as a contrast increase in the region of interest of more than 10 Hounsfield units (5). For MRI, the signal intensity of the ablation site was subjectively determined after the subtraction of unenhanced T1-weighted gradient-echo sequences from contrast-enhanced T1-weighted gradient-echo sequences, and contrast enhancement was defined as an increase of more than 15% in signal intensity.

Paired *t*-tests were used to compare the initial tumor size be-

fore cryoablation between the cryolesions with and without residual contrast enhancement. Initial tumor size was also compared between cryolesions with peripheral rim or focal eccentric enhancement and those that showed thick internal enhancement after the procedure. A *p*-value less than 0.05 was considered indicative of a significant difference.

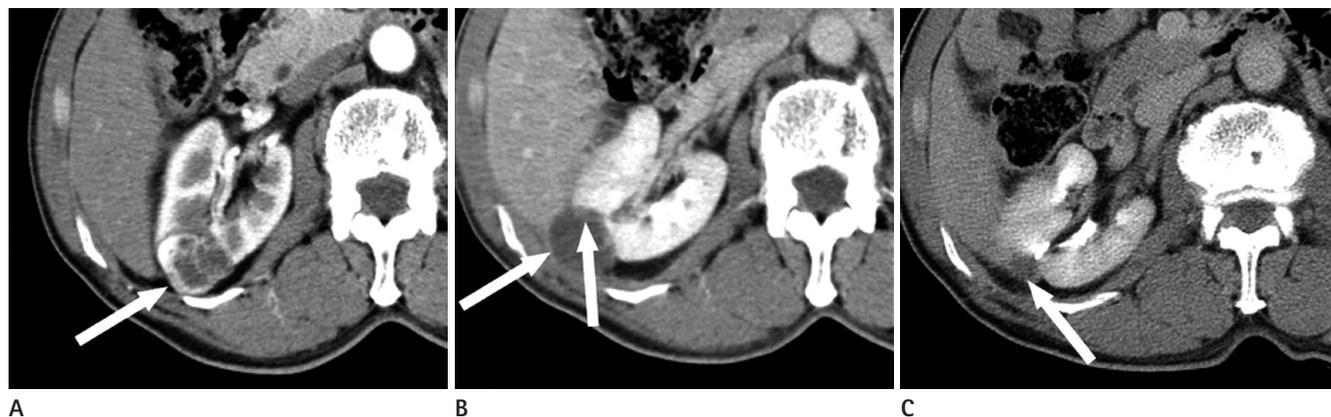
## RESULTS

Residual contrast enhancement was seen in 13 (54%) of the 24 cryolesions (Fig. 1), and 11 (46%) cryolesions showed no residual contrast enhancement at 3-month follow-up. Table 1 summarizes the characteristics of cryolesions showing residual contrast enhancement. Of the 13 cryolesions with residual contrast enhancement at 3-month follow-up, peripheral rim enhancement was seen in six (25%) cryolesions. Peripheral rim enhancement persisted for a mean follow-up of 4.5 months and disappeared completely at a mean follow-up of 10.5 months (Fig. 2). Focal eccentric enhancement was seen in four (16.7%) cryolesions at 3-month follow-up. In one cryolesion with focal eccentric enhancement, residual contrast enhancement persisted for 12 months. Focal eccentric enhancement persisted for a mean follow-up of 6 months and disappeared completely at a mean follow-up of 12 months (Fig. 3). Three cryolesions (12.5%)



**Fig. 1.** The chart shows 24 renal cell carcinomas in 22 patients who underwent contrast-enhanced CT and MRI after laparoscopic renal cryoablation. At 3 month follow-up, 13 cryolesions showed residual contrast enhancement. CT images show characteristic examples of residual contrast enhancement (arrows).

Note.—CE = contrast enhancement, RCC = renal cell carcinoma



**Fig. 2.** Peripheral rim enhancement after cryoablation in a 73-year-old man with renal cell carcinoma.  
**A.** Contrast-enhanced CT before cryoablation shows 3.2 cm enhancing renal cell carcinoma (arrow) in the right kidney.  
**B.** Contrast-enhanced CT obtained 3 months after cryoablation shows peripheral rim enhancement (arrows) in the cryolesion.  
**C.** Contrast-enhanced CT obtained 12 months after cryoablation shows complete resolution of the peripheral rim enhancement and a reduction in the size of the cryolesion (arrow).

**Table 1. Characteristics of Cryoablated Renal Cell Carcinomas Showing Residual Contrast Enhancement in 13 Patients**

Case	Age	Sex	Initial Tumor Size (cm)	Size Decrease (%)		Disappearance of CE at Follow-Up (Months)	Total Follow-Up (Months)
				6 Month	12 Month		
Peripheral rim enhancement							
1	24	M	1.9	-32.6	-42.1	6	36
2	64	F	3.5	-24.3	-28.6	12	38
3	56	M	2.6	+19.2	-23.1	12	38
4	62	M	2.2	+4.5	-13.7	12	34
5	73	M	2.1	-23.9	-28.6	9	12
6	54	M	2.3	-31.5	-69.5	12	28
Focal eccentric enhancement							
7	44	F	7.5	+2.7	-20.0	6	45
8	33	F	3.7	-29.7	-35.1	18	24
9	76	F	2.7	-44.5	-71.4	12	24
10	52	M	4.5	-33.4	-35.6	12	60
Thick internal enhancement							
11	70	M	2.3	-17.4	-8.9	-	26
12	59	M	4.3	-24.3	-34.9	-	24
13	61	M	3.4	-17.7	-21.6	-	24

Note.—CE = contrast enhancement

showed thick internal enhancement at 3-month follow-up. In all cryolesions with thick internal enhancement, residual contrast enhancement persisted for more than 12 months and these were considered viable tumors (Fig. 4). One cryolesion was treated with systemic chemotherapy, and two cryolesions were treated with radiofrequency ablation.

The mean size  $\{3.31 \pm 1.52$  [standard deviation (SD)] cm} of initial tumors with residual contrast enhancement after cryoablation was larger than that  $[2.56 \pm 0.67$  (SD) cm] of initial tumors showing no residual enhancement. In addition, the mean size  $[3.33 \pm 1.0$  (SD) cm] of initial tumors showing thick internal

enhancement after cryoablation was larger than that  $[3.30 \pm 1.69$  (SD) cm] of initial tumors showing only peripheral rim or focal eccentric residual contrast enhancement. However, there was no significant size difference between the cryolesions with and without residual contrast enhancement ( $p = 0.11$ ), or between the cryolesions with thick internal enhancement and those with peripheral rim or focal eccentric enhancement ( $p = 0.97$ ).

The cryolesions decreased in size by an average of 6.7% at 3 months, 20.2% at 6 months and 39.7% at 12 months after cryoablation, while the cryolesions showing thick internal enhance-

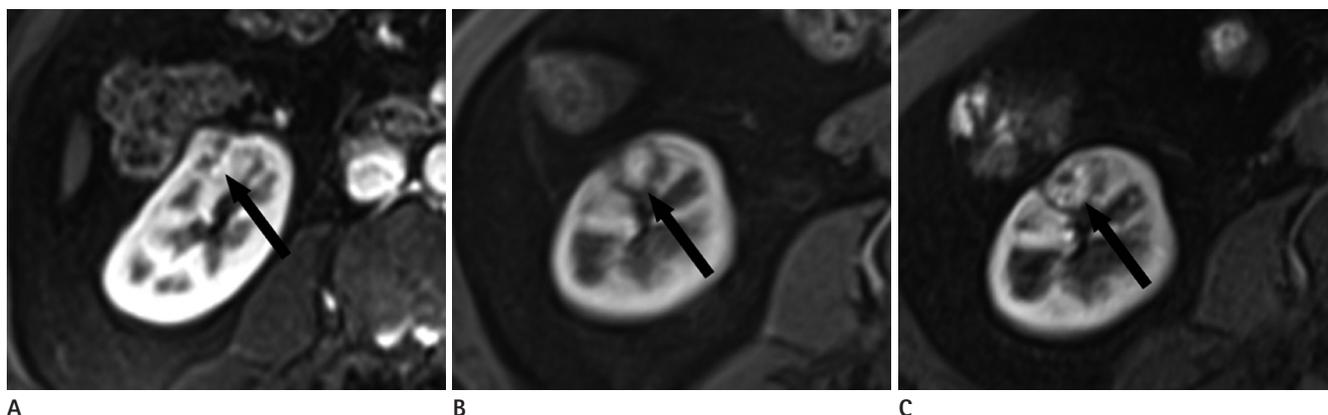


**Fig. 3.** Focal eccentric enhancement after cryoablation in a 52-year-old man with renal cell carcinoma.

**A.** Contrast-enhanced CT before cryoablation shows 4.5 cm enhancing renal cell carcinoma (arrow) in the right kidney.

**B.** Contrast-enhanced CT obtained 3 months after cryoablation shows residual focal eccentric enhancement (arrows) in the cryolesion.

**C.** Contrast-enhanced CT obtained 18 months after cryoablation shows complete resolution of focus enhancement and a size reduction of the cryolesion (arrow).



**Fig. 4.** Persistent thick internal enhancement after cryoablation in a 59-year-old man with renal cell carcinoma.

**A.** Contrast-enhanced MRI before cryoablation shows 2 cm enhancing renal cell carcinoma (arrow) in the right kidney.

**B.** Contrast-enhanced MRI obtained 3 months after cryoablation shows thick internal enhancement (arrow) in the cryolesion.

**C.** Contrast-enhanced MRI obtained 12 months after cryoablation shows interval enlargement of the enhancing focus (arrow), representing residual viable tumor in the cryolesion.

ment decreased in size by an average of 19.8% at 6 months and 21.8% at 12 months. Furthermore, the thick internal enhancement in the cryolesions gradually increased in size after 6 months of follow-up.

## DISCUSSION

Incidental detection of early stage renal tumors has increased due to the widespread use of ultrasonography and CT. The discovery of small tumors and the desire to preserve renal function in patients with comorbid conditions or with multiple renal cell carcinomas has stimulated advances in minimally invasive treatment options (6, 7). Therefore, cryoablation and radiofrequency ablation are being widely used for the treatment of small re-

nal tumors.

Cryoablation is an effective technique that is used to freeze and ablate tumor tissue with small probes and circulating liquid nitrogen or argon gas. During cryoablation, the direct cytotoxic effect of intracellular and extracellular ice crystals leads to cell dehydration and rupture, and indirect ischemic injury by microvascular occlusion causes cell hypoxia (8). Liquid gas rapidly cools the cryoprobe inserted into the target renal mass. Then, an ice ball forms along the cryoprobe shaft and enlarges over time. Cryoprobes were arranged to make overlapping ice balls, and the ice balls formed by the cryoprobes were extended to the tumor margin to sufficiently target the lesion. Renal cryoablation can be performed using an open, laparoscopic, or percutaneous surgical approach.

Following cryoablation, thorough follow-up imaging surveillance is required to screen for residual or recurrent tumors because renal tumors can remain *in situ*. Either CT or MRI can be used in the assessment of treatment efficacy, but there are no prospective clinical studies to validate a particular imaging schedule, and controversies exist concerning how often and for how long follow-up imaging should be performed (9). However, many radiologists recommend follow-up CT or MRI at 1-3 months after ablation (5, 10, 11), and we evaluated patients at 3, 6, 9, 12, 18, and 24 months, and annually thereafter. The initial cryoablated lesions on follow-up CT or MRI within the first 3 months are subsequently used as a baseline postablation measurement to which future measurements can be compared, because the cryoablated area will contract and scar with time (12, 13).

Renal tumors treated successfully with cryoablation or radiofrequency ablation manifest as low attenuation areas on CT and, relative to the renal parenchyma, are generally hypointense on T2-weighted MRI images and iso- to hyperintense on T1-weighted images, without evidence of contrast enhancement (14). However, residual or recurrent tumors appear as abnormal foci of contrast enhancement on follow-up CT or MRI (14). Nevertheless, peripheral rim enhancement often persists for several months following cryoablation (2). Peripheral rim enhancement could be demonstrated on follow-up CT in 16-20% of cryolesions in the first 6 months (3, 15). In our study, peripheral rim enhancement in the cryolesions was relatively common and persisted for a longer time, sometimes up to 12 months.

The nature of persistent contrast enhancement after cryoablation may most likely be caused by one of several factors including inflammation, persistent tumor, or volume averaging (3). The interface between the normal parenchyma adjacent to the ablated area and the outer edge of the ice balls constitute a watershed zone, in which the inflammatory response after cryoablation may cause peripheral rim enhancement or small focal enhancement (3). In animal models, peripheral enhancement in the cryolesion after 45 days was histopathologically characterized by abnormal tubules and congestive vessels immediately outside the lesion, and after 90 days by vascular granulation tissue and dilatation of small vessels and capillaries (16).

The pattern of residual or recurrent tumors often manifests as a focus of nodular or crescentic enhancement on follow-up CT scans and MRI (10, 17). However, Schwartz et al. (18) re-

ported a cryolesion with residual atypical enhancement that was subsequently treated by nephrectomy and demonstrated no evidence of tumor. Beemster et al. (15) reported that both peripheral rim and focal enhancement observed in one cryolesion at 3-month follow-up decreased in size at 6-month follow-up, and remained as a small area of enhancement for up to 18 months without interval change. In our study, focal eccentric enhancement in four cryolesions, which disappeared at a mean follow-up of 12 months, did not represent residual tumor. This observation is in agreement with that of Stein et al. (3), who reported that persistent contrast enhancement several months after cryoablation may not be due to malignancy. However, thick internal enhancement, demonstrated in three cryolesions in our study, was found to increase in size relative to that on subsequent follow-up imaging and represented residual tumor caused by incomplete treatment.

Zagoria et al. (19) reported that larger tumor size correlated with a higher risk of residual tumor at follow-up after the initial radiofrequency ablation of RCC. One would need to have an increased suspicion of incomplete cryoablation for tumors larger than 3.5 cm (3). However, in our study, the mean initial tumor size of cryolesions showing thick internal enhancement was not significantly larger than that of cryolesions showing peripheral rim or focal eccentric enhancement. Therefore, insufficient overlap of the individual ice balls and the technically challenging nature of the procedure can lead to thick residual enhancement, even in smaller tumors.

The cryolesions in our study showed average decreases in diameter of 20.2% and 39.7% at 6 and 12 months, respectively, after treatment. In the study by Weld et al. (20), the mean diameter of the cryolesions decreased by 0% and 19% in 6 and 12 months, respectively. Possible explanations for this variation in size reduction after cryoablation are the difference of the mean sizes of the initially treated tumors and/or of the ablated margin (15). At the time of follow-up examinations, renal tumors that have been successfully treated with cryoablation demonstrate a reduction in size (14). However, in our study, the cryolesions with thick internal enhancement showed a mean size reduction of 19.8% at 6 months and 21.8% at 12 months. Therefore, the reduction in tumor size after cryoablation cannot adequately predict treatment outcome. To ensure a successful outcome, serial follow-up CT or MRI is warranted to confirm the eventual resolution of rim or

focal residual contrast enhancement in the cryolesions.

Our study had some limitations. First, there was no pathologic confirmation to explain residual contrast enhancement in cryolesions and their characteristics on CT or MRI. In several studies, postablative surveillance biopsy was performed to confirm treatment success after cryoablation or radiofrequency ablation of RCC (21, 22). However, the best way to assess viability versus necrosis and the appropriate time point at which to perform the surveillance biopsy are ongoing controversies (9). Moreover, radiologic findings in cryolesions were adequately correlated with histopathologic findings, in contrast with the poor correlation between post-RFA imaging and pathologic results (21). Second, this was a retrospective study from a single institution with a relatively small number of patients. Previous studies dealing with residual contrast enhancement include Porter et al. (4) described 3 of 23 patients with persistent tumor enhancement 3 months after cryoablation, and Bolte et al. (23) reported 7 of 18 patients with peripheral rim enhancement at 3-month follow-up. In comparison, in our study of 24 tumors, 6 cryolesions had imaging findings of peripheral rim enhancement and 7 cryolesions had focal enhancement at 3-month follow-up. Third, because all images were interpreted in consensus by two radiologists, interobserver agreement for the residual contrast enhancement was not assessed.

In conclusion, serial radiologic surveillance is necessary to confirm the eventual resolution of rim or focal residual contrast enhancement in cryolesions. Follow-up CT or MRI for more than 12 months after cryoablation is needed to assess treatment outcomes in patients with cryoablated RCCs showing peripheral rim or focal eccentric contrast enhancement, which may persist until 12 months after cryoablation without remnant viable tumor.

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## 냉동수술을 시행한 신장세포암종의 전산화단층촬영과 자기공명영상에서 보이는 잔여 조영증강에 대한 추적검사<sup>1</sup>

박은경<sup>1</sup> · 성득제<sup>1</sup> · 박범진<sup>1</sup> · 김민주<sup>1</sup> · 한나연<sup>1</sup> · 조성범<sup>1</sup> · 강석호<sup>2</sup>

**목적:** 냉동수술을 시행한 신장세포암종의 추적 전산화단층촬영과 자기공명영상에서 치료된 병변에서 관찰되는 잔여 조영증강의 특성에 대하여 기술하고자 한다.

**대상과 방법:** 22명의 환자에서 24개의 신세포암종에 대해 복강경하 신냉동수술과 전산화단층촬영(19명), 자기공명영상(3명)을 이용한 추적검사가 평균 28개월 동안 시행되었다. 두 명의 영상의학과 의사가 종양의 크기 변화와 잔여 조영증강의 특성에 대해 후향적으로 평가하였다. 잔여 조영증강의 특성은 테두리 띠 조영증강(두꺼운 띠, 종양의 최대직경의 10% 미만), 국소 편심성 조영증강(10% 이상 25% 이하), 두꺼운 내부 조영증강(25% 초과)으로 나누었다.

**결과:** 3개월 추적검사에서 13개(54%)의 병변에서 잔여 조영증강을 보였다. 테두리 띠 조영증강과 국소 편심성 조영증강이 각각 6개(25%), 4개(16.7%)의 병변에서 나타났고, 평균 4.5개월과 6개월까지 지속되다가 평균 10.5개월과 12개월에 사라졌다. 3개(12.5%)의 병변은 6개월 추적검사에서 지속적인 두꺼운 내부 조영증강을 보였고, 이후 고주파절제와 항암치료요법으로 치료하였다. 냉동병변(cryolesion)은 냉동수술 후 6개월에 평균 20.2%, 12개월에 평균 39.7% 크기가 감소하였다.

**결론:** 냉동수술을 시행한 신장세포암종에서 테두리 띠 조영증강이나 국소 편심성 조영증강은 잔여 생종양 없이도 수술 후 12개월까지 지속될 수 있으므로, 치료결과의 평가를 위해서는 12개월 이상의 추적검사가 필요할 것으로 판단된다.

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