Characterization of Renal Cell Carcinoma Using Agent Detection Imaging: Comparison with Gray-Scale US

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Objective: We wanted to compare the imaging features of renal cell carcinoma (RCC) and their diagnostic accuracy on agent detection imaging (ADI) and gray-scale ultrasonography (US).

Materials and Methods: Thirty non-consecutive patients (age range; 32-80 years, mean age; 53.7 years) with 30 RCCs were examined with gray-scale US and with ADI in conjunction with using SH U 508A. We described the imaging features of the renal tumors obtained from ADI according to their enhancement pattern, the intratumoral anechoic areas and the presence of any pseudocapsule. The imaging features and diagnostic accuracy of ADI and gray-scale US were then compared.

Results: On the ADI exam, the RCCs were shown as being heterogeneous in 87% of the cases (26/30), homogeneous in 7% of the cases (2/30), and there was peripheral irregular enhancement in 7% of the cases (2/30). Intratumoral anechoic areas and pseudocapsule were seen in 87% and 77% of the RCCs on the ADI exam, whereas these features were seen in 53% and 17% of the cases on the gray-scale US, respectively. The diagnostic sensitivity, specificity, and accuracy for RCC with ADI were 97%, 93%, and 95%, respectively. However, those for RCC with using gray-scale US were 70%, 86%, and 78%, respectively. There was a significant difference for the diagnostic accuracy of RCC between ADI and gray-scale US ($p < 0.05$).

Conclusion: Agent detection imaging can help visualize the enhancement pattern of RCC and improve the diagnostic accuracy of this tumor by better displaying the intratumoral anechoic areas and the pseudocapsule than does the gray-scale US.

Index terms:
Contrast media
Ultrasound (US)

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The development of ultrasonography (US) has increased the physician's ability to detect asymptomatic renal masses. The early detection and characterization of solid renal masses are of great clinical importance for their accurate diagnosis, treatment planning and prognosis (1). So far, the role for US has been mainly centered on the differentiation of renal cell carcinoma (RCC) and angiomyolipoma (AML), which are the most common malignant and benign solid renal tumors, respectively (2–6). Although US is considered to be a useful imaging modality for solid renal masses, its capability for detecting or characterizing lesions is somewhat limited. A low incidence of specific features or the considerable overlap of vascular signals still exists between RCC and the other solid renal masses.

Several recent studies have reported that contrast-enhanced harmonic US can provide a better assessment of vascular morphology and enhancing patterns, and this can improve the detection and characterization of focal liver lesions (7–9). To the best

of our knowledge, a few studies have reported on the imaging characterization of RCCs with using contrast-enhanced harmonic US, but the studies did not completely evaluate the enhancement patterns and the morphologic features of RCC as compared with those of the gray-scale US exam and the pathologic exam (10−12).

Agent detection imaging (ADI) is a contrast-enhanced harmonic mode that uses a high mechanical index, and this can provide high spatial resolution and the segmental display of contrast and tissue images. The purpose of this study is to compare the imaging features of RCC and their diagnostic accuracy on ADI and gray-scale US.

MATERIALS AND METHODS

Patients

During a 10-month period, 30 non-consecutive patients (6 males and 24 females [age range; 32−80 years, mean age; 53.7 years]) with 30 RCCs that were detected on CT scan were referred to us for performing US before the masses were histologically confirmed. All of the patients underwent a gray-scale US and an ADI scan that were performed by one radiologist (B.K.P.). All the patients gave us an informed written consent for the ADI, and this study was approved by the institutional review board of the Seoul National University Hospital, Korea.

The RCCs measured from 1.5 cm to 10 cm in size (mean ±standard deviation; 4.9 ±2.7 cm) and they consisted of 27 clear cell, two papillary and one chromophobe type masses. Partial (n=1) or total nephrectomies (n=29) were performed on all the patients. On the pathologic exams, pseudocapsule and intratumoral cyst or necrosis were found in 93% (28/30) and 90% (27/30) of all the RCCs.

US Exams

The US contrast agent used in this study was SH U 508A (Levovist; Schering AG, Berlin, Germany); it consists of galactose microparticles (99.9%) and palmitic acid (0.1%). Four grams of SH U 508 A at a concentration of 300 mg/ml were intravenously administered by a manual bolus injection via an 18-gauge cannula inserted into an antecubital vein.

The US exams were performed with a high-resolution US unit (Sequoia; Siemens Medical Solutions, Mountainview, CA, USA) that was equipped with ADI software. The acoustic power of the ADI was adjusted to the default maximal setting (mechanical index, 1.9). The dynamic range was set to 50−55 dB. The line density and frame rate were lowered to 9 Hz without frame averaging. A 4C1 convex-array probe only was used for the ADI scan. Before the ADI scan, the gray-scale exam was conducted (a) in order to determine the optimal imaging plane to display the renal masses because the shorter the distance between the probe and the renal masses, the stronger the signal, (b) to compare the diagnostic accuracy between the gray-scale US and the ADI.

Real-time scanning commenced immediately after the intravenous injection of the contrast agent, and the scan time was measured when the contrast agent passed the intravenous cannula. When the first signal of contrast agent appeared in the kidney, we rapidly moved the probe to cover the region including the lesions. Rapid sweeping was repeated every 10−15 seconds (interval delay scan). For each sweep, we used clip store that can record the continuous images displayed on the monitor during a 6-second period, in a manner similar to video recording, and we also captured still images by employing cine loops. All of the scanned images were automatically stored in the picture archiving communication system (Marotech, Seoul, Korea). The scan time used for ADI was usually about 5 minutes.

Imaging Analysis

Two radiologists (S.H.K. and H.J.C) working in consensus retrospectively analyzed all of the US images for the enhancement patterns and the presence or absence of intratumoral anechoic areas and pseudocapsule. The enhancement patterns of the tumor were classified as homogeneous, heterogeneous, stippled and peripheral irregular enhancement. Homogeneous enhancement was defined as an even signal intensity over the whole tumor with no signal defects. Heterogeneous enhancement was defined as an uneven signal intensity over the whole lesion. Stippled enhancement was defined as tiny enhancing foci distributed throughout the entire lesion. Peripheral irregular enhancement was defined as a discontinuous ring of contrast-enhanced peripheral nodules.

Intratumoral anechoic areas were classified as intratumoral cysts and necrosis. Intratumoral cysts or necrosis were noted depending on whether the contour of the signal defect was smooth or irregular.

Pseudocapsule was defined as a hypoechoic halo on the gray-scale US and as a peritumoral rim that showed no enhancement in the early phase and delay enhancement in the late phase of ADI.

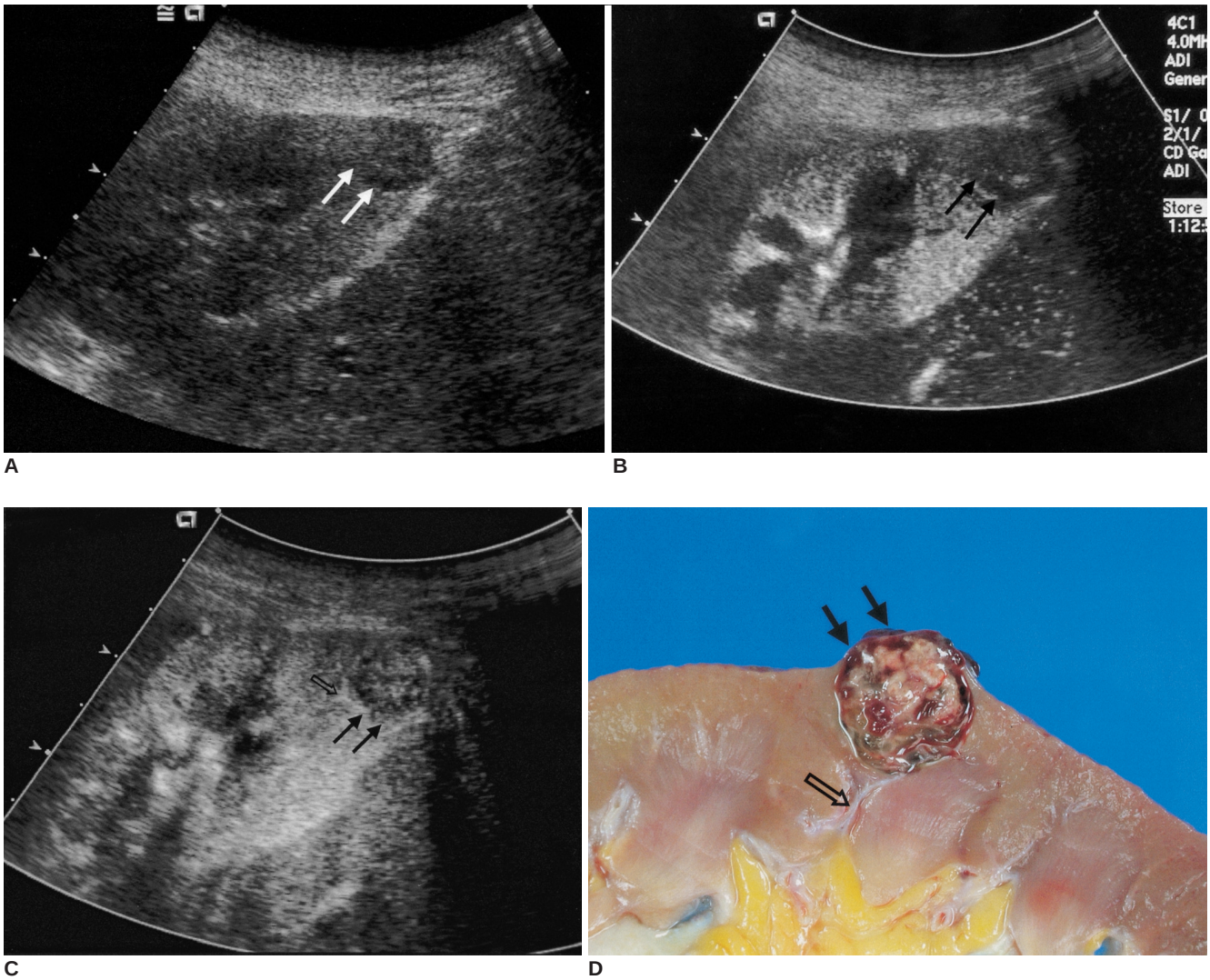
Comparison of the Diagnostic Accuracy between Gray-scale US and ADI

We retrospectively compared the diagnostic accuracy for RCC between the gray-scale US and the ADI. On the gray-scale US examination, when the lesion had more than two imaging features among intratumoral anechoic areas,

pseudocapsule and hyperechogenicity relative to that of the normal renal parenchyma, then we made a diagnosis of RCC. On the ADI exam, when the lesion had more than two imaging features among the most common enhancement patterns of RCC, intratumoral anechoic areas and pseudocapsule, then we made a diagnosis of RCC. We then compared the diagnostic accuracy for RCC between the gray-scale US and the ADI exam.

Statistical Analysis

Fisher's exact test was used to compare the imaging features of RCC that were seen on gray-scale US and ADI. The diagnostic accuracy, which included the sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy for RCC on the ADI exam, was calculated and then compared with those of the gray-scale US by using the McNemar test. A p value of less than 0.05 was considered statistically significant.



A B C D

Fig. 1. Small renal cell carcinoma in a 64-year-old man.
A. Transverse image on gray-scale US shows an ill-defined isoechoic mass (arrows) containing suspicious anechoic cysts. Any pseudocapsule is not seen around the tumor.
B. The transverse image of agent detection imaging that was obtained 17 seconds after the administration of SH U 508A shows a thick pseudocapsule (arrows) around the tumor.
C. The transverse image of agent detection imaging that was obtained 34 seconds after the administration of SH U 508A shows heterogeneous enhancement of the tumor with multiple anechoic cysts, and these are better depicted here than on gray-scale US. The pseudocapsule as well as the tumor is also enhanced (arrows). A feeding vessel (blank arrow) is clearly seen on the agent detection imaging exam.
D. The cut surface of the gross specimen shows small cysts, necrosis and hemorrhage within the renal cell carcinoma (arrows). A feeding vessel (blank arrow) is demonstrated on the pathologic exam, and this correlated very well with the findings on the agent detection imaging exam.

RESULTS

On the ADI exam, the RCCs showed as being heterogeneous in 87% of the patients (26/30), homogeneous in 7% of the patients (2/30), and peripheral irregular enhancement in 7% of the patients (2/30). Heterogeneous enhancement was the most common enhancement pattern of the RCCs, and thus, it was included into the diagnostic criteria for RCC on the ADI exams (Figs. 1, 2). The RCCs revealed intratumoral anechoic areas in 87% of the cases (26/30), and intratumoral cysts (n=25), necrosis (n=21) or both (n=20) were also noted (Figs. 1, 2). On the gray-scale US, the intratumoral anechoic areas were seen in 53% of the cases (16/30), of which ten of the RCCs were not able to be classified into cysts or necrosis. The intratumoral anechoic areas were more commonly detected on the ADI exam than on the gray-scale US ($p < 0.05$). Pseudocapsule was seen in 77% of the cases (23/30) of RCC on the ADI exam, whereas it was seen only in 17% of the cases (5/30) of RCC on the gray-scale US ($p < 0.05$) (Figs. 1, 2). RCCs appeared as hyperechoic in 90% of the cases (27/30), and as iso or hypoechoic in 10% of the cases (3/30), relative to the normal renal parenchyma (Figs. 1, 2).

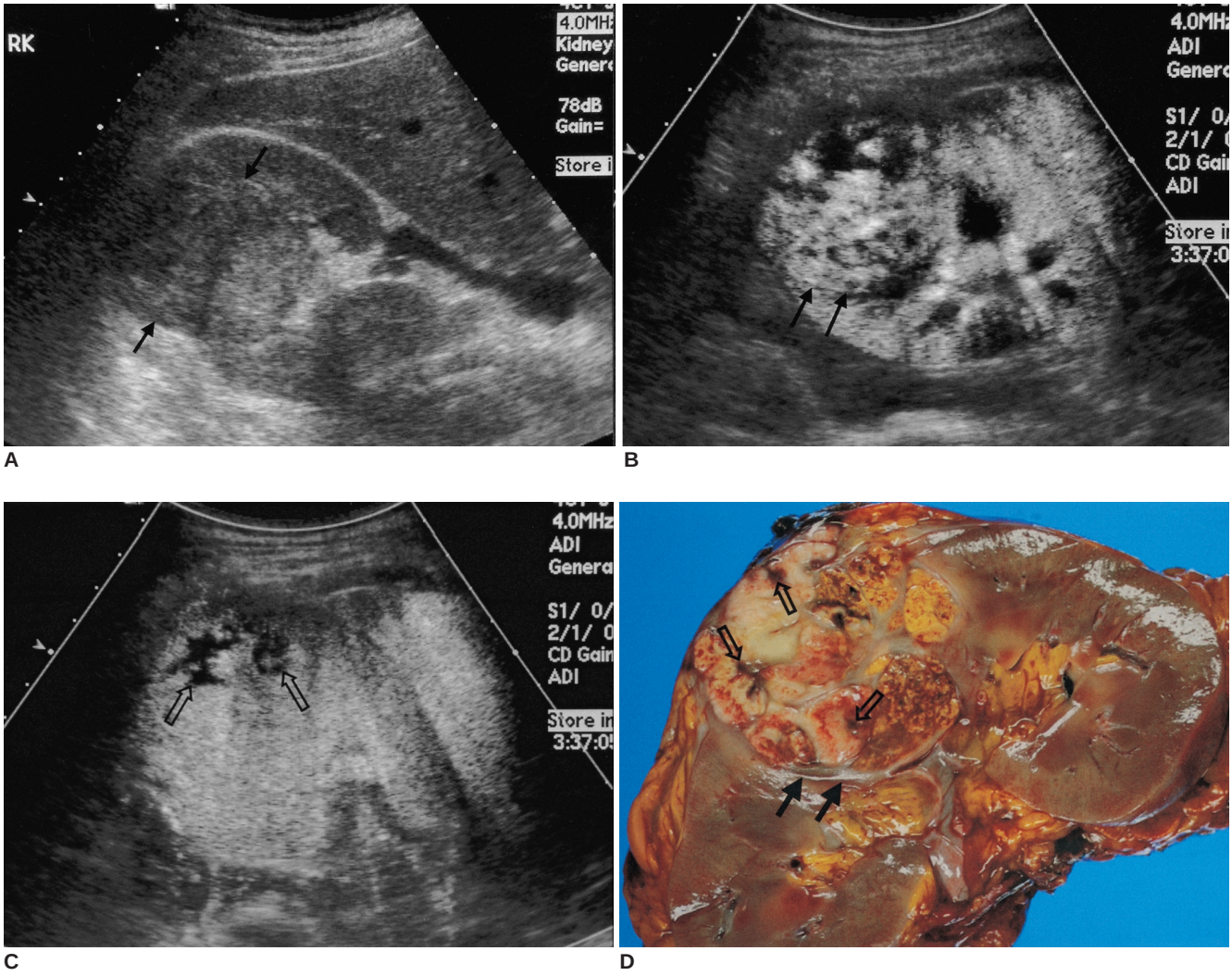


Fig. 2. Renal cell carcinoma in a 60-year-old man.
A. Transverse image of the gray-scale US shows a slightly hyperechoic solid mass (arrows) with no intratumoral anechoic areas and a pseudocapsule in the right kidney.
B. Transverse image of agent detection imaging that was obtained 15 seconds after the administration of SH U 508A shows heterogeneous enhancement of the tumor with a thin pseudocapsule (arrows).
C. Transverse image of agent detection imaging that was obtained 1 minute after the administration of SH U 508A shows heterogeneous enhancement of the tumor with multiple intratumoral anechoic areas (blank arrows). The pseudocapsule is not clearly seen due to the delayed enhancement.
D. The cut surface of the gross specimen shows multiple small cystic and necrotic portions (blank arrows) in the renal cell carcinoma with a pseudocapsule (arrows).

Table 1. Comparison of the Diagnostic Accuracy for Renal Cell Carcinoma with Using Agent Detection Imaging and Gray-Scale US ($p < 0.05$)

	Agent Detection Imaging	Gray-Scale US
Sensitivity	97%	70%
Specificity	93%	86%
Positive predictive value	94%	84%
Negative predictive value	96%	74%
Overall accuracy	95%	78%

Table summarizes the diagnostic accuracy of RCC with using ADI and gray-scale US. When the presence of two or more ADI features was noted out of heterogeneous enhancement, intratumoral anechoic areas and pseudocapsule, then this was regarded as positive findings for RCC, and the sensitivity, specificity, and accuracy for RCC were 97%, 93%, and 95%, respectively. However, those for the RCC on the gray-scale US were 70%, 86%, and 78%, respectively and its diagnostic accuracy were significantly different from that of the ADI ($p < 0.05$).

DISCUSSION

Agent detection imaging is a microbubble-specific harmonic US modality that is designed for the optimal detection of signals from SH U 508A with using high mechanical index technique (8, 9). It can produce signals from stationary microbubbles as easily as from those that are moving in the vessels, and this unlike conventional US that relies on Doppler shift signals. Other techniques of the gray-scale contrast-enhanced harmonic imagings such as pulse inversion harmonic imaging (PIHI) and coded harmonic imaging (CHA), have been developed by various US equipment manufacturers (7, 10, 11). Pulse inversion harmonic imaging uses a pair of pulses with opposite polarity, and the nonlinear echoes of the tissue harmonic and the contrast agent responses are detected, while the linear echoes of the fundamental tissue are canceled. Coded harmonic imaging uses digital encoding and decoding of the transmitted pulses, and it can separate the contrast from the tissue and reduce the unwanted echoes from the fundamental frequency and the tissue harmonic signals. Agent detection imaging uses two pulses with the same polarity and it subtracts the signals from the two pulses.

The introduction of US has led to improving the detection of renal tumors in asymptomatic patients. Renal cell carcinoma seen on gray-scale US has specific features including intratumoral cyst and pseudocapsule, and AML characteristically shows posterior shadowing (2−4). These features are important findings that may help distinguish RCC from AML, but the presence of these features is not sufficient to differentiate RCCs from the other solid renal masses that are incidentally detected on gray-scale US. On the power Doppler US, the analysis of the vascular distribution has not increased the diagnostic accuracy for small solid renal tumors (4). Contrast-enhanced Doppler US can increase the detection of intratumoral vascularity compared to color/power Doppler US (5, 6). However, its signal intensity hasn't been found to be sufficiently intense for tumor characterization, and it contains artifacts or noises that prevent a correct diagnosis. Recently, the development of contrast-enhanced harmonic US imaging has provided for a better assessment of the vascular morphology and the enhancing patterns; thus, it has improved the detection and characterization of focal liver lesions (7−9). To the best of our knowledge, there have been a few reports about the differentiation of RCC with employing contrast-enhanced harmonic US imaging using SH U 508A (10−12). However, these studies did not completely evaluate the various enhancement patterns and the intratumoral or peritumoral features of RCC on the ADI exam as compared with those features on the gray-scale US and pathologic exams.

On the ADI exam, heterogeneous enhancement was most commonly seen in the RCC because most of the lesions contain intratumoral signal defects that pathologically corresponded to cystic change, necrosis or both. Homogeneous enhancement was shown for the small RCCs, and cystic change or necrosis was not found in these tumors on the pathologic exam. Peripheral irregular enhancement was seen in those RCCs with a large necrosis.

Intratumoral anechoic areas have been reported to be pathologically cystic change, degeneration or necrosis. On gray-scale US, these were specific for RCC, but their frequency was previously reported as being 12−31% (2−4). The number of intratumoral cysts in the RCCs was larger on the AD scan than on the gray-scale US because the signal of the contrast agent on the ADI can be seen in almost all the tissue with vessels, except for the avascular areas such as cysts or necrosis.

The pseudocapsule pathologically corresponds to fibrous tissue and renal parenchyma that is compressed by the RCC (13, 14). The preoperative identification of the pseudocapsule was one of the criteria that allow nephron-sparing surgery (15). Ascenti et al., reported that the pseudocapsule appeared as a nonenhancing peritumoral rim in the early phase and as a well-enhancing rim in the late phase on the contrast-enhanced harmonic US (12). In their study, the contrast-enhanced second-harmonic US

showed a higher sensitivity for the peritumoral pseudocapsule of RCC than did the gray-scale US (12). Similarly, the gray-scale US and ADI detected the encapsulated RCCs in 18% (5/28) and 82% (23/28) of all the cases, respectively.

This study has a few limitations. First, only a small number of patients with RCC were included in the study. A larger scale of study will be necessary to support our results for the ADI exam. Second, it was nearly impossible for us to detect the contrast signals of the RCC situated 10 cm or deeper from the US probe. Body habitus, lung or bowel gas, ribs and the location of the lesions also affected the signal intensity of the renal tumors. Third, color/power Doppler US, which can provide more information on intratumoral vascular distribution, was not performed to evaluate the RCC in this study. It is necessary to compare the diagnostic accuracy between the ADI scan and the combination of gray-scale US with power Doppler US for the diagnostic accuracy of the solid renal masses. Fourth, the diagnostic criteria for RCC with using gray-scale US and ADI exams have not been established. We made a diagnosis of RCC when the tumor showed two out of the three most common imaging features on the gray-scale US and ADI exams.

In conclusion, ADI can describe the enhancement patterns of RCC. It can improve the diagnostic accuracy of RCC as compared with gray-scale US by allowing better visualization of the intratumoral anechoic areas and the pseudocapsule than can the gray-scale US.

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