ORIGINAL ARTICLE

Contrast-enhanced ultrasound for assessment of therapeutic response after percutaneous radiofrequency ablation of small renal tumors

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Summary

Purpose: The purpose of this study was to evaluate the efficacy of contrast-enhanced ultrasound (CEUS) in the assessment of therapeutic response, after percutaneous radiofrequency ablation (RFA) of small renal tumors.

Methods: Twenty patients (12 men, 8 women; median age, 77.4 years; median tumor size, 2.7 cm) were treated with RFA. All patients were examined by contrast-enhanced computed tomography (CECT), followed by CEUS one week later. Tumor enhancement characteristics and thickness of the enhancing area in viable lesions were evaluated.

Results: Median time from RFA to diagnostic imaging was 16.8 months. All 20 patients underwent CT. CEUS was finally performed in only 14 out of 20 patients (70%), since 2 out of 6 had contraindications for the application of a US contrast agent. Also, one patient refused the application and a further 3 had tumors that were impossible to differentiate adequately on the conventional B-mode US, in order to satisfactorily

monitor the contrast enhancement. CEUS showed a complete response in 9 out of 14 (64.3%) patients, residual tumor in 4 (28.6%) and tumor progression in 1 patient (7.1%). Median thickness of the enhancing area on CECT and CEUS was 20 mm vs 17 mm, respectively, with no statistically significant difference in the thickness (t = -0.816, p=0.461) between both modalities. The concordance between CECT and CEUS in the assessment of tumor response and detection of residual vascular enhancement was 100%.

Conclusions: CEUS is an effective and safe imaging modality in assessing the therapeutic response, after percutaneous radiofrequency ablation of small renal tumors. Disadvantages can be overcome with improved CEUS technology.

Key words: computed tomography, contrast-enhanced ultrasound, percutaneous radiofrequency ablation, small renal tumors

Introduction

Renal cell carcinoma (RCC) is the most common malignancy of the kidney and the ninth most common type of cancer in Europe [1]. Cases of this cancer type have been on the rise in the last decades because of the expanded use of cross-sectional imaging methods [1,2]. Partial nephrectomy remains the "gold standard" of treating small renal masses (T1 stage). Recently, minimally invasive nephron-sparing techniques, such as percutaneous RFA, are increasingly being used in the treatment of these patients [3-7]. Based on the updated European Guidelines on RCC from 2010, thermal ablation is intended for patients with tumors <3cm, who are not surgical candidates because of significant co-morbidities [2].

Accurate evaluation of the therapeutic effect and recognition of recurrent tumor, is of great importance for proper treatment of these patients. Generally, CECT, or, rarely, magnetic resonance imaging (MRI), is used for post-ablation surveil-

Correspondence to: Peter Popovic, MD, PhD. University Medical Centre Ljubljana, Clinical Institute of Radiology, Zaloska cesta 7, 1525 Ljubljana, Slovenia. Tel: +38615223415, E-mail: peter.popovic@kclj.si Received: 04/11/2015; Accepted: 21/11/2015 lance [8]. In patients with intermediate or high risk for relapse, routine CT scans should be carried out [2]. However, CECT is nephrotoxic, exposes the patient to ionising radiation and is contraindicated in allergy to contrast media [9].

CEUS, with a second generation contrast agent (CA), offers a useful, non-expensive and diagnostically reliable alternative, also lacking radiation exposure and nephrotoxicity. This is especially suitable for patients with impaired renal function [10,11]. Recently, CEUS is being widely used for assessment of the ablation efficacy and, in many institutions, as a follow-up for recurrence of liver tumors [12]. Although promising results are reported on the application of CEUS in treatment evaluation and follow-up of RCC after RFA [12], the data is still scarce [13-15].

The aim of this prospective study was to investigate the efficacy of CEUS in the evaluation of the therapeutic effect of RFA on patients with small renal tumors, using CECT as the reference standard.

Methods

Patients

This prospective study included 20 patients who were treated with RFA at our institution, between February 2006 and June 2012. A written informed consent was obtained from all patients before imaging was performed. Patient and tumor characteristics are listed in Table 1. In all 20 patients, regardless of the time after the treatment, imaging with CEUS was performed in order to evaluate its diagnostic effectiveness in detecting tumor response. Additionally, tumor characteristics of successfully ablated tumors were assessed. The CEUS results were then compared to CECT, as the reference standard.

Imaging methods

CECT was performed with a 64-row multidetector CT scanner (Siemens Medical Systems[®], Erlangen, Germany) or a 16-row multidetector CT scanner (Siemens Medical Systems[®], Erlangen, Germany) with a threephase protocol. A hundred to 130 ml of non-ionic CA (Ultravist 370[®], Bayer Healthcare, Germany; Visipague 320[®], GE Healthcare) were administered at a rate of 3-4 ml/s via a power injector, by using a bolus tracking algorithm. Images were reconstructed at 5- and 2-mm thickness in axial and coronal planes.

CEUS was performed one week later with Aplio XV (Toshiba Medical Systems[®]; the Netherlands) or a more modern scanner, Aplio 500 (Toshiba Medical Systems[®]; the Netherlands), using an abdominal curved array transducer. Imaging was performed with contrast harmonic imaging software with a low mechanical index (MI<0.2). A bolus injection of 2.4-4.8 ml of sulphur hexafluoride-filled microbubble CA (Sonovue[®]; Bracco SpA; Milan, Italy) was administered through an 18-gauge antecubital cannula. The injection was followed by a flush of 10 ml 0.9% sodium chloride solution. The entire examination was stored as a dynamic digital video file on the hard disk of the US scanner and recorded on a digital video recorder for further analysis.

Imaging analysis

All contrast-enhanced sonographic studies were correlated with CT studies. Tumor size, location (central or exophytic) and enhancement characteristics were evaluated.

According to contrast enhancement in the ablated area, tumor response to treatment was evaluated on both imaging modalities.

A similar pattern of peripheral nodular or crescent enhancement in the ablated area, seen on CEUS and CECT, was determined as a residual tumor. Complete necrosis – a well defined non-enhancing area – was defined as a successfully ablated tumor.

Progressive disease was defined as increase in viable tumor size. The thickness of the enhancing area in viable lesions was measured in CEUS and CECT studies. In addition, characteristic imaging features of the successfully ablated tumors (perinephric stranding, halo sign and fat invagination) were assessed.

Statistics

All calculations were performed with SPSS statistical package, version 19.0 (SPSS Inc, Chicago, IL). The baseline quantitative characteristics of patients and tumors were expressed as median and range, as well as categorical in counts and proportions. A paired Student's t-test was used to evaluate the statistical significance of difference in the thickness of the enhancing area between the viable tumors on both modalities (p<0.05).

Results

Median time from the completed treatment

Table 1. Patient	and tumor	characteristics
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Characteristics	Results	
Patients		
Male (%)/female (%)	12(60)/8(40)	
Age (years)*	77.4 (58.4–89.3)	
Tumors		
Size, cm (range)*	2.7 (1.0-5.4)	
Kidney (left (%)/right (%)	13(65)/ 7(35)	
Location (exophytic, %/other, %)	14(70)/ 6(30)	

*Quantitative variables expressed as median and range

Table 2. Tu	mor response	e to treatment
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Type of tumor response	N (%)
Complete necrosis	9 (64.3)
Residual tumor	4 (28.6)
Progressive disease	1 (7.1)

with RFA to the time of imaging control was 16.8 months (range 1.9–77.5). Three out of 20 (15%) patients underwent CEUS immediately after the treatment (2–3 months), while the remaining 17 (85%) were part of post-ablation imaging surveillance.

CECT was performed in all 20 patients. Primarily, 13 out of 20 (65%) patients underwent CEUS. Of the remaining 7 patients, 2 (10%) had contraindications for the application of US CA, 1 (5%) refused the application of US CA and in the remaining 4 (20%) patients the ablated tumors were insufficiently differentiated from the surrounding parenchyma on the conventional B-mode US in order to successfully monitor the contrast enhancement. After a more modern US scanner, with split-screen display, had been purchased at our institution, CEUS was additionally and successfully performed on one of these 4 patients. Overall, a total of 14 (70%) patients underwent CEUS.

Regarding the ablation success, both imaging techniques showed 9 out of 14 (64.3%) tumors with complete necrosis (Figure 1), 4 (28.6%) tumors with peripheral or nodular enhancement in the ablated area, suggesting residual tumor (Figure 2), and one (7.1%) with progressive disease (Table 2). One of 4 patients with residual disease underwent successful additional RFA, and the remaining 3 patients declined the procedure due to their older age. In the tumor where progressive disease was noted, successful ablation was not possible at the beginning of treatment, due to the unfavorable tumor location. In the tumors that had already shown complete necrosis no recurrent disease was found. In summary, there was a complete concordance between CEUS and CECT for the assessment of therapeutic response in all 14 tumors (100%).

Additionally, thickness of the enhancing area of residual tumors and progressive disease was evaluated. Median thickness of the enhancing area was 17 mm (range 5–36 mm) on CECT and 20 mm (range 6–31 mm) on CEUS (Table 3). Howev-

Table 3. Thicknesses of the enhancing area (EA) of viable tumors on CECT and CEUS

Tumor response	Patient and tumor characteristics (sex, age, location)	Tumor size (mm)	Thickness of EA on CECT (mm)	Thickness of EA on CEUS (mm)
RT	ho, 79 yrs, left kidney	54	17	30
RT	♂, 58 yrs, left kidney	40	18	20
RT	\bigcirc , 85 yrs, right kidney	33	6	6
RT	♂, 74 yrs, left kidney	27	5	7
PD	്, 83 yrs, right kidney	36	33	30

RT:residual tumor, PD:progressive disease, ♀:female, ♂:male; yrs:years, EA: enhancing agent



Figure 1. A 74-year old male with ischemic heart disease and thrombocytopenia, with exophytic tumor in the left kidney. **a)** Follow up imaging, 4 years after successful tumor ablation showed absence of contrast enhancement (arrow) in the ablated region on CECT in axial plane. **b)** Absence of enhancement with microbubbles on real time imaging, with one-split screen display on CEUS (arrow).



Figure 2. A 74-year old male, with end-stage renal failure and exophytic tumor in the left kidney. **a)** Control imaging, 2 months after RFA showed peripheral crescent enhancement (arrow) on CECT in coronal plane. **b)** CEUS showed the same enhancing pattern as CECT (arrow).

er, no statistically significant difference was noted in the thickness of the enhancing area (t=-0.816, p=0.461) between CECT and CEUS.

CECT detected CT characteristic imaging features of the successfully ablated tumors, in 8 out of 9 patients with complete necrosis. Halo sign was detected in 5 out of 8 patients, fat invagination in 6 and perinephric stranding in 2 patients. CEUS did not detect any of these features.

None of the patients suffered from adverse reactions, neither to US CA nor to non-ionic CA, used for CECT.

Discussion

Image-guided radiofrequency ablation has been used extensively for the treatment of small renal tumors on patients that are not ideal candidates for surgery [3-7]. In addition to proper patient selection, the accurate evaluation of the therapeutic effect is of great importance, as to properly treat these patients [8]. Currently, the evaluation of the ablation effect is performed with CECT (or rarely MRI) [8]. Due to certain limitations to these methods, CEUS offers a potential alternative as it is fast, non-expensive, widely used, not nephrotoxic and does not expose the patient to ionising radiation [11]. To our knowledge, there are only a few studies describing the role of CEUS in evaluating tumor response and in the follow-up of renal tumors after RFA [13-15].

Our study investigated the performance of CEUS in assessing the therapeutic response of small renal tumors to ablation treatment, compared to CECT results as the gold standard. CEUS showed the same treatment responses as CECT in all tumors, regardless of whether the tumor was assessed on the first imaging control after the ablation or as part of a long-term follow-up. The results strongly correlate with other studies, where the concordance between both techniques, in a study by Meloni et al., was 96.4% [14] and 100% in a study by Kong et al. [15].

The enhancement pattern of residual tumor and progressive disease was the same on both imaging modalities. In addition, differences in contrast enhancement on CEUS, between hypervascular viable tissue and normal renal parenchyma, occurred early (approximately 15–25 seconds after a CA injection) and were observed only for a few seconds. This is probably due to the fact that ultrasound contrast is an exclusively real blood pool agent, enabling peripheral capillary pass [10,12].

There was no statistically significant difference between the thickness of the enhanced tumor residue between the two methods, suggesting that CEUS shows vital parts of the tumor with the same accuracy as the CECT. There was a complete concordance for detecting residual vascular enhancement between CEUS and CT.

Four completely ablated tumors, that had all been followed for a long period of time (more than three years), showed complete necrosis on CECT but were impossible to differentiate from the capsula adiposa on a conventional B-mode scan. Therefore, successful monitoring of contrast enhancement in contrast harmonic imaging was inaccessible. This feature is probably due to the shrinking of successfully ablated tumors over time [16,17]. The difficulty was overcome by the usage of a state-of-the-art US scanner, with split-screen display, which enabled satisfactory contrast enhancement visualisation. Considering both the fact that the usage of modern technology enabled evaluation of necrotic tumors on long-term follow-up and that tumor response results were equivalent for both methods regardless of the time passed after the ablation procedure, CEUS could become a potential method for assessing therapeutic responses.

It is important to be familiar with the characteristic changes of successfully ablated tumors (tumor shrinkage over time, halo sign, fat invagination and perinephric stranding) in order to not mistake them for residual or recurrent tumors [16,17]. CECT in our study readily depicted the aforementioned changes in all successfully ablated tumors apart from one, where CEUS, as expected, showed none of the changes. These changes do not represent viable tissue and can therefore not be demonstrated by contrast enhancement.

There are some limitations in our study. First,

histopathologic assessment of residual tumor tissue after RFA was not performed. Therefore, the correlation with CECT or CEUS results was not possible. However, previous reports already showed that post-ablation biopsies with proper tissue staining confirmed evident necrosis, as seen on imaging studies [18,19]. Furthermore, needle biopsy after RFA showed sampling errors [20]. Also, patients were not monitored at fixed intervals for prolonged periods of time. Instead, all suitable patients were summoned at the same time, regardless of the time passed from the conclusion of RFA.

In conclusion, CEUS is an effective, low-cost and safe alternative to CECT in the assessment of short and long-term tumor response, especially in patients with impaired kidney function. Disadvantages can be overcome with improved CEUS technology.

Conflict of interests

The authors declare no confict of interests.

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