Renal tumor ablation: beyond limitations of biopsy and follow-up
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Chapter 9

Contrast-enhanced ultrasound for the evaluation of the cryolesion after laparoscopic renal cryoablation: an initial report

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ABSTRACT

Purpose: Stringent radiological follow-up is essential after renal tumor ablation. Drawbacks of post-ablation follow-up (FU) by contrast-enhanced Computed Tomography (CECT) are the associated ionizing radiation and nephrotoxic contrast-agent. Contrast-enhanced ultrasound (CEUS) has shown potential to demonstrate microvasculature without using neither ionizing radiation nor toxic contrast-agent.

We assessed the concordance of enhancement patterns of CEUS and CECT/MRI in cryolesion assessment after laparoscopic renal cryoablation (LCA).

Methods: From 01/2006-01/2009 a CEUS was performed before and after LCA (3 and 12 months) in addition to regular CECT/MRI. Using an enhancement-score (0=no enhancement, 1=rim enhancement, 2=diffuse enhancement, 3=localized enhancement, 4=no enhancement defect) the cryolesion was assessed by both modalities and concordance of enhancement-score was assessed.

Results: In total 45 tumors were included (29 biopsy proven RCC, mean size 2.66 cm). One cryoablation failed resulting in a non-enhancing cryolesion apart from the persisting renal tumor. There were no post-ablation recurrences during the study period.

Pre-LRC: Both modalities were available in 26 cases. In 20/26 there was concordance of enhancement-score (77%, all cases score 3 or 4).

3m: Both modalities were available in 32 cases. Enhancement-score corresponded in 23/32 cases (72%). 7 cases showed enhancement on CECT/MRI (‘1’in six cases, ‘4’in one case) with enhancement-score ‘0’on CEUS. 2 cases showed enhancement on CEUS without enhancement on CECT/MRI (specificity 92%, NPV 77%). Except one case all enhancement resolved on subsequent imaging.

12m: Both modalities available in 21 tumors. Enhancement-score corresponded in 19/21 cases (91%). 2 cases showed enhancement on CEUS without enhancement on CECT/MRI (specificity 90%, NPV 100%).

Conclusion: This pilot study shows that CEUS is a safe imaging technique with high concordance of enhancement-score between CEUS and CECT/MRI. While cross-sectional imaging seems sensible to demonstrate successful ablation at first FU, CEUS might be used to diminish the burden of contrast-enhanced cross-sectional imaging in the long-term FU.
INTRODUCTION

Due to its minimal invasive nature combined with good intermediate- and long-term oncological results[1], cryoablation (CA) has gained a role as a treatment option in selected small renal masses[2;3]. As the tumor is eliminated rather than extirpated, there is at least hypothetically a chance that a recurrent tumor evolves from as little as one single malignant cell that survived the thermal ablation. Therefore a thorough follow-up is of capital importance to evaluate the success and to trace any potential recurrence as early as possible to simplify eventual re-treatment. Currently this follow-up relies on contrast enhanced imaging with CT-scans as the modality of choice and MRI as an alternative in case of iodine based contrast allergy or renal function impairment[4]. The cornerstone of radiological follow up is the absence of contrast enhancement in the ablated lesion, a premise that seems to exclude the presence of vital tissue after cryoablation[5].

Unfortunately, the routine use of CT-scans in the follow-up has several major drawbacks, including the unavoidable ionizing radiation and the nephrotoxicity of the iodine-based contrast agent. This potential toxicity will have higher impact in younger patients and those with an already impaired renal function. MRI as follow-up alternative is costly and requires use of a nephrotoxic contrast-agent as well, albeit less toxic than iodine-based contrast[6-8].

Recently contrast-enhanced ultrasound (CEUS) has emerged as a diagnostic tool in several fields in medicine, in cardiology and liver tumor-diagnostics in particular[9]. CEUS is based on ultrasonography and uses stabilized microbubbles to improve the echogenicity of blood flow. CEUS can provide real-time information on the enhancement properties of tissue under study without using ionizing radiation or nephrotoxic contrast agent. This represents a major advantage over contrast CT/MRI-scans.

Reports on CEUS as a potential diagnostic method for evaluation of radiofrequency ablation (RFA) of kidney tumors showed promising results[10;11]. However very little is known on the value of CEUS to evaluate the cryoablated kidney tumors[12]. The primary objective of this study was to assess the concordance of enhancement patterns of CEUS-scans and CT/MRI-scans (gold standard) in the follow-up after CA.
METHODS

Patients

From January 2006 to March 2009, a prospective study on CEUS on patients treated by laparoscopic CA (LCA) of a renal tumor was conducted in our centre. The local Institutional Review Board (IRB) approved the study. Patient selection, the interventional procedure and follow-up protocol have been described earlier[13]. After obtaining informed consent, CEUS was performed in addition to the clinical protocol at three points in time (before LCA and at 3 and 12 months after ablation). Interval between CT/MRI-scan and CEUS-imaging was maximally 10 days. In the frame of an investigational study patients were able to refuse participation in the study at any point in time and to join the study after LCA.

Collection of imaging studies: CT/MRI-scan

Pre-ablation CT- and MRI-scans were performed either in the radiology department of our institution or in case of referrals (48%) the images were integrated in our hospital computer system. CT-scans in our institution were performed using a Philips 4-slice MX8000 or 64-slice Brilliance CT-scanner (Philips Healthcare, Best, the Netherlands). For contrast enhancement Ultravist 300 (Bayer Pharma AG, Leverkusen, Germany) was injected at a rate of 4ml/s and a total maximum of 120 ml. Pre-operative CT-scans consisted of a four-phase abdominal 3 mm CT-scan (unenhanced, arterial scan at 45 seconds, venous phase at 115 seconds, delayed phase at 10 minutes after injection of contrast) and follow-up scans were performed according to a predefined scanning protocol developed in collaboration with the department of Radiology of our institution consisting of a triple-phase 3 mm scan (unenhanced, arterial and venous phase). In case of a contra-indication for contrast-enhanced CT-scanning (e.g. intolerance of iodine-based contrast or a serum creatinine >130 µmol/L), a contrast-enhanced MRI was performed using a Siemens Avanto 1.5 Tesla MRI-scanner (Siemens AG Healthcare Sector, Erlangen, Germany) with 16-channel body array coils. Standard protocol consisted of T2-trufi coronal and transversal series with fat suppression, a contrast-enhanced T1-fl2d sequence in and out of phase, T2-haste (transversal and coronal), T1 vibe transversal with both unenhanced and dynamic series (at 30 seconds, 60 seconds and 15 minutes with 3 mm slices). Images were acquired during breath
hold in inspiration and using Gadovist® 1.0 (Bayer Pharma AG, Leverkusen, Germany) for contrast enhancement.

Collection of imaging studies: CEUS

For all CEUS imaging a Siemens ‘ACUSON Sequoia’ ultrasonography device with Contrast Pulse Sequence (CPS) imaging was used[14]. CEUS was carried out in an out-patient setting by a urologist or urology researcher with experience in performing renal ultrasonography.

After preparation of the patient including placement of a venous cannula in the antecubital vein, grayscale ultrasonography was used to localize the renal mass or cryolesion. After slow intravenous injection of 2.4 ml of CEUS contrast agent SonoVue® (Bracco, Milan, Italy), the contrast-enhanced images showing the renal mass or cryolesion were recorded using CPS imaging. When necessary, an additional injection of 2.4 ml of SonoVue® was administered to extend the time available for CEUS investigation. All recorded cineloops were stored for offline evaluation. All cineloops and on-screen display functions were encrypted to enable blinded evaluation of the images after censoring the study.

Assessment of images

In order to assess the images we utilized the descriptive enhancement-score previously developed at our institution (see discussion) [12]. The score consists of a scale from 0 to 4 were “0” represents no enhancement at all, “1” represents presence of a tiny peripheral rim enhancement, “2” represents weak diffuse enhancement, “3” represents nodular enhancement and “4” represents absence of an enhancement defect in the lesion. All CEUS-scans were assessed by an investigator blinded for the CT/MRI-scans and the clinical results.

For the reference test the original clinical radiological report was retrieved and converted to a enhancement-score. After determination of the degree of enhancement using the score, the data were subsequently entered in a Predictive Analytics SoftWare (PASW) 18.0.2. database and merged with clinical and procedural data of the corresponding patients.

Analysis of results

For the comparative analyses, cases with a missing study at a given time point (pre-
Table 1 Characteristics of patients and tumors

<table>
<thead>
<tr>
<th>Cases (tumors)</th>
<th>N</th>
<th>45 (45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at treatment</td>
<td>Mean (SD)</td>
<td>67.4 (11.4)</td>
</tr>
<tr>
<td>Male gender</td>
<td>N (%)</td>
<td>34 (76%)</td>
</tr>
<tr>
<td>Tumor size in cm</td>
<td>Mean (SD)</td>
<td>2.66 (0.78)</td>
</tr>
<tr>
<td>Tumor side</td>
<td>L:R</td>
<td>16:29</td>
</tr>
<tr>
<td>Charlsong-index</td>
<td>Median</td>
<td>1</td>
</tr>
<tr>
<td>Charlsong age-adjusted</td>
<td>Median</td>
<td>3</td>
</tr>
<tr>
<td>eGFR (by CKD-EPI)</td>
<td>Median (range)</td>
<td>85 (37-108)</td>
</tr>
<tr>
<td>Biopsy results</td>
<td>N (%)</td>
<td>29 RCC (64%) 4 oncocytoma (9%) 1 AML (2%) 11 non-diagnostic* (24%)</td>
</tr>
</tbody>
</table>

*Biopsies without tumor cells or with insufficient tumor cells hindering differentiation between a benign and malignant tumor were classified as non-diagnostic.

Ablation and at 3- or 12 months after ablation) were excluded for analysis at that particular time point.

Concordance of enhancement-score between cross-sectional imaging and CEUS was assessed. Furthermore accuracy of CEUS with respect to the regular follow up cross-sectional imaging was calculated using contingency tables. For the latter purpose we dichotomized the enhancement-scores with “0” being considered as negative and ≥ 1 being considered as positive.

The statistical setup of the analysis and the analysis itself were performed in close collaboration with the Department of Biostatistics of our centre. Quantification was based on percentage agreement without correction for chance agreement and specificity, sensitivity, negative predictive value (NPV) and positive predictive value (PPV) were calculated. Data were reported in adherence to the STROBE guidelines (STrengthening the Reporting of OBservational studies in Epidemiology)[15].

Table 2 Contingency table at 3 months follow-up

<table>
<thead>
<tr>
<th>CT/MRI scan</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enhancement</td>
</tr>
<tr>
<td><strong>CEUS</strong></td>
<td></td>
</tr>
<tr>
<td>Enhancement</td>
<td>0</td>
</tr>
<tr>
<td>No enhancement</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>7</td>
</tr>
</tbody>
</table>
**Figure 1a:** Contrast-enhanced ultrasound (CEUS) image (left) using Contrast Pulse Sequence (CPS) for a contrast-only image of a 3.2 cm renal cell carcinoma. This tumor was scored 4 on the P/E score. Right shows the corresponding greyscale ultrasound image.

**Figure 1b:** Pre-cryoablation CT-scan (venous phase) of the tumor showing a 3 cm enhancing tumor in the right kidney. This tumor was scored as 4 on the P/E score.

**Figure 2a:** Contrast-enhanced ultrasound image (left) 3 months after cryoablation of the tumor showed in figure 1. The perfusion defect (arrow) shows a cryolesion without signs of residual enhancement (P/E score 0).

**Figure 2b:** Three months post-ablation CT-scan (venous phase) of the same patient showing the non-enhancing cryolesion (arrow) in the right kidney (P/E score 0).
RESULTS

In total 45 cases (45 tumors) were included in the study with the characteristics being described in table 1. In one patient the ablation missed the tumor resulting in one unsuccessful cryoablation, all other patients underwent treatment successfully with no persistent or recurrent disease at 3 or 12 months follow-up. There were no procedure related complications or adverse reactions due to administration of the SonoVue®.

In total 129 conventional cross sectional scans (121 CT; 95%) and 115 CEUS-scans were collected.

Figure 3: Unenhanced (a) and arterial phase (b) of a CT-scan performed three-months after cryoablation showing the cryolesion in the left kidney with an enhancing area (arrow). This was considered P/E score 1.

Figure 4: CEUS-image 3 months after cryoablation showing rim enhancement in the cryolesion (arrow). This was considered P/E score 1.
Table 3 Contingency table at 12 months follow-up

<table>
<thead>
<tr>
<th></th>
<th>CT/MRI scan</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enhancement</td>
<td>No enhancement</td>
</tr>
<tr>
<td>CEUS</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>21</td>
</tr>
</tbody>
</table>

**Pre LRC:**
In 26 tumors pre-ablation scans on both modalities were present. All cases presented with a enhancement-score 3 or 4 on both the CT/MRI and CEUS; in 20 of 26 cases (77%) these scores were concordant (see figure 1).

**3m FU:**
At 3 months after treatment both CT/MRI and CEUS scans were available in 32 cases. There was a concordance of enhancement-score in 23 cases (72%) (see figure 2). In 7 of 32 (22%) cases there was enhancement on CT/MRI without enhancement on the corresponding CEUS. In the single tumor where the cryoablation missed the tumor there was enhancement of the tumor on CT/MRI (score 4) with a CEUS interpreted as score 0 (see discussion). In the 6 other cases the enhancement on the CT/MRI-scan concerned slight rim enhancement (score 1). These 7 cases were considered false negatives (see figure 3).
In 2 cases (6%) there were signs of enhancement on the CEUS (all score 1) without enhancement on the corresponding CT-scan. These cases were considered as false positives (figure 4). The contingency table (table 2) shows a specificity and negative predictive value (NPV) of 92% and 77% respectively.

**12m FU:**
In 21 tumors both modalities were present at twelve months after ablation. The enhancement-scores of CT/MRI and CEUS were concordant in 19 cases (91%). All CT/MRI-scans were negative for enhancement resulting in no false negative CEUS. In 2 cases (10%) there were signs of enhancement on the CEUS (all enhancement-score 1) without enhancement on CT. These cases were considered as false positives. The contingency table (table 3) shows a specificity and NPV of 90% and 100% respectively.
DISCUSSION

Our study compares in a prospective longitudinal manner CEUS enhancement scores with conventional contrast enhanced cross-sectional imaging in a cohort of renal masses treated by laparoscopic cryoablation. At diagnosis all renal masses showed enhancement on both the CT/MRI and CEUS with an absolute concordance in terms of enhancement-score in 77% of cases. During follow up absolute concordance in terms of enhancement-score was 72% and 91% at 3 and 12 months respectively. There were no adverse reactions due to the SonoVue® or other aspects of the CEUS demonstrating that CEUS is feasible, safe and well tolerated.

The need for regular follow-up with contrast enhanced CT or MRI represents a major disadvantage of renal ablation. A multiphase scan of the abdomen delivers a median radiation dose of 31 (range: 6-90) mSv resulting in one radiation-induced malignancy for every 660-700 of such scans in a 60-year old patient[7]. Furthermore most of them are older and have co-morbidities, including an impaired renal function. In this setting iodine contrast is potentially toxic and may worsen the impaired renal function and potentially even lead to contrast-induced acute kidney injury[16]. Therefore, CT-scanning is far from ideal to perform long-term follow-up after cryoablation. However several aspects prevent MRI from being the ultimate alternative for CT-scanning, such as the high costs and lower availability. Furthermore, since the MRI contrast-agent gadolinium may cause nephrogenic systemic fibrosis (NSF) in patients with a GFR < 30 ml/min/1.73 m², performing an MRI in patients with severe renal impairment is also contra-indicated[17]. CEUS-imaging requires an intravenous injection of microscopic gas bubbles and availability of an ultrasound device equipped with specific software. The contrast images provide real-time information of the enhancement pattern of the tissue while it is harmless for the kidney regardless of the renal function. The technique has shown its power in the detection and evaluation of tumors in other organs such as the liver and it is possible that CEUS will replace the CT-angiogram to evaluate the function and endoleakage of vascular endoprostheses[18]. Recently several reports have been published showing promising results of CEUS in the follow-up after RFA of renal tumors[11]. While extrapolation of these studies to cases ablated by cryotherapy is likely, no studies have explored the subject apart from a feasibility study[12].

Using an enhancement score previously described[12] CEUS replicated the results of
the CT during follow-up of small renal masses after cryoablation. At three months (first control in our setting) CEUS had a specificity of 92% and a NPV of 77% when compared with CT/MRI which increased to 90% and 100% respectively at 12 months.

There was one persistent tumor at 3 months in our series which was not detected on CEUS. This tumor was a small 1.2 cm tumor that was missed during the cryoablation resulting in a cryolesion located caudal of the tumor with the tumor being untouched. As the CEUS-investigator was blinded for clinical results while assessing the CEUS-scans, the cryolesion caudal of the tumor was interpreted as a cryolesion without signs of residual enhancement and the small tumor more cranially was overlooked.

Tumor persistence and recurrence occur in a low percentage of cases in all cryoablation series, however a long-term follow-up is of capital importance after cryoablation since recurrences may occur as late as after 58 months[1;13]. Based on our results, CEUS might substitute some of the repetitive cross-sectional imaging tests performed during this long-term regimen of follow-up. However being focused on absence of enhancement in the cryolesion, other abnormalities in the kidney or the abdomen might be overlooked which was also the case in our series with a persistent tumor located completely outside of the cryolesion. In a similar study comparing CT/MRI with CEUS after RFA, CEUS failed to detect a persistent tumor at 6 weeks in 3 of 14 cases compared to 0 with CT/MRI[11]. Therefore it seems sensible to perform a cross-sectional study as first follow-up study after ablation to demonstrate successful ablation. For the subsequent long-term follow-up CEUS might be used to show absence of enhancement in the successfully ablated tumor, alternated by regular CT/MRI to detect abnormalities in other abdominal structures including the contralateral kidney.

At least two points deserve further comments, with the first one being related to the lack of radiological and clinical recurrences in our series. In fair strictness we considered as positives those cases with enhancement-score ≥ 1 at three and twelve months in both the index and the investigational test. However clinical studies demonstrate that a tiny peripheral (rim) enhancement in cross sectional imaging is present at the first evaluation in up to 26% of the cases and resolves later on[19;20]. Clinically the cases with rim enhancement on cross sectional imaging were not considered as a radiological persistence but as a finding deserving further cross sectional evaluation. In our series as well the rim enhancement disappeared later on.
in all cases when assessed by cross sectional imaging. Negative cross sectional imaging has proven to correctly demonstrate the absence of tumor persistence or recurrence after cryoablation when verified by tumor biopsy[5].

The second issue is the appropriateness of the enhancement-score used. There are no standardized scores to assess enhancement patterns in renal tumors and even less for post-ablation assessment. We therefore used a home-designed visual and easy to use enhancement score with rather grades patterns of enhancement instead of intensity[12] and applied it retrospectively to CT and MRI. The absence of other scores precludes any comparison at the present time.

We acknowledge that technological developments currently enable raw CEUS-data to be used for the calculation of Time Intensity Curves (TIC) and several quantitative perfusion parameters[21]. We did not perform such calculations in this pilot-study since for our clinical question assessment of the entire cryolesion on CEUS is required rather than a TIC which is based on a single-plane CEUS-image. Secondly similar calculations cannot be performed for CT/MRI-images, which was considered the gold standard for comparison in this study.

To our best knowledge no reports on cost-effectiveness of CEUS after cryoablation of small renal masses have been published which is natural given the premature status of CEUS in this field. Although such economical assessments are highly setting-dependent, one report showed a significant saving of costs when CEUS was used for the characterization of focal liver tumors compared to CT/MRI and comparable results might be expected in the case of the long-term follow-up after renal cryoablation[22].

While limitations inherent to ultrasound such as operator dependency and patient dependent factors cannot be overcome by CEUS and its use in renal masses is not yet approved by the FDA[23] we postulate that CEUS might have a role in decreasing the cross-sectional imaging burden of the follow-up schemes after cryoablation, although a study showing its ability to detect recurrences would further validate this.

**CONCLUSION**

Contrast-enhanced ultrasound (CEUS) is a safe imaging modality with a high specificity and NPV in the follow-up of cryoablated renal masses. The absence of recurrent tumors in this series hinders firm conclusions on sensitivity and PPV. While cross-sectional
imaging should be used to demonstrate a successful cryoablation at first follow-up after ablation, clinical implementation of CEUS for further follow-up of the cryolesion can decrease the number of CT/MRI-scans performed during follow-up.

Acknowledgements

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REFERENCES


