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● *Original Contribution*

IMPACT OF ACQUISITION METHOD AND REGION OF INTEREST PLACEMENT ON INTER-OBSERVER AGREEMENT AND MEASUREMENT OF TUMOR RESPONSE TO TARGETED THERAPY USING DYNAMIC CONTRAST-ENHANCED ULTRASOUND

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Abstract—This study evaluated the impact of different acquisition methods, user-directed region of interest placement and post-processing steps on the quantification of dynamic contrast-enhanced ultrasound measurements of blood volume in 29 patients with renal cancer, pre- and post-treatment. Specifically, we compared tumor quantification using multiple planes versus a single plane, breathhold versus free breathing and large region of interest versus a region targeting the area of highest vascularity. Performance was evaluated using area under the receiver operating characteristic curves to identify the method that best predicts progression-free survival. The intra-class correlation coefficient was also used to investigate how the same parameters affect inter-observer agreement. Of the different methods used to quantify blood volume in this study, the combination that had the highest level of inter-observer agreement (intra-class correlation coefficient = 0.8–0.97) and was the best predictor of progression-free survival was the change in blood volume measured (area under receiver operating characteristic curve = 0.77, p = 0.04) by a multiplane average, acquired during quiet breathing, quantified using a region of interest that encompassed the entire tumor. (E-mail: Mostafa.atri@uhn.ca) © **2016 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Ultrasound contrast, Tumor blood flow, Inter-observer agreement, Treatment evaluation.**

INTRODUCTION

The introduction of anti-angiogenic therapy has dramatically improved the therapeutic response and progression-free survival (PFS) of patients with renal cell carcinoma (RCC) (Motzer et al. 2009). Traditionally, the effectiveness of cancer drugs is evaluated according to the RECIST guidelines, which relate the change in the anatomic size of a tumor to a categorized treatment response (Therasse et al. 2000). However, changes to the tumor microvasculature, the intended target of anti-angiogenic therapy, occur as early as a few days after the start of treatment (Mancuso et al. 2006), long before any subsequent effect on tumor volume. This time lag between anti-angiogenic activity and clinical response has led to the development of potential RECIST alternatives. One strategy has been to leverage the capabilities of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), computed tomography (DCE-CT) and ultrasound (DCE-US) to monitor the tumor microvasculature during the course of therapy (Choi et al. 2007; Hahn et al. 2008; Nathan et al. 2010; Williams et al. 2011). Although studies to date show promise, establishing the sensitivity and specificity of these methods to evaluate treatment response has been an ongoing effort with promising results (Lassau et al. 2014; Mains et al. 2014; Panebianco et al. 2013). Equally important is developing an understanding of the variables that affect the reproducibility of these methods.

With respect to DCE-US, reproducibility is influenced by many factors including aspects of the individual patient, tumor, ultrasound operator, measurement

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protocol and ultrasound technology (Tang et al. 2011). Notably, tumor response assessment requires repeated evaluation over the course of treatment. In this context, it may be difficult to reproduce identical imaging locations, which is particularly important during follow-up studies in lesions with a large vascular heterogeneity (Gerlinger et al. 2012). The interplay between the acquisition parameters and the operator-dependent demarcation of the tumor boundary during post-processing, and their impact on the reproducibility and significance of DCE-US as a therapy monitoring tool is currently unexplored. Here, we hypothesized that a volumetric assessment of tumor vascularity, made by averaging multiple perfusion measurements across the tumor volume, would minimize the impact of the operator during post-processing quantification compared with a single plane assessment. In addition, we evaluated the robustness of an alternative post-processing strategy to overcome tumor heterogeneity that focuses the measurement on the areas of maximum enhancement to reduce the impact of necrosis, which may lead to underestimation of the local angiogenic activity. Furthermore, we investigated how motion of the target lesion caused by breathing affects DCE-US data quantification (Averkiou et al. 2010) and whether a breathhold for the duration of the measurement improves reproducibility. Finally, we evaluated how these same variables affect the predictive potential of DCE-US measurements to identify patients that would progress early versus late compared with the median PFS of the population using receiver operator characteristics.

METHODS

The institutional research ethics board approved the study, and written informed consent was obtained from all patients.

Study population

The study population consisted of 29 consecutive patients with metastatic RCC who were enrolled in a separate prospective phase II trial to evaluate the response to sunitinib treatment between May 2007 and October 2009. There were 17 men and 12 women ranging from 42 to 81 y (median = 60) of age. Patients received sunitinib 50 mg orally daily for 4 wk, followed by a 2-wk break. DCE-US data for the present study were drawn from patient scans recorded at baseline (day 0) and on day 14, which are the time points reflective of the best predictor of response according to previously published literature (Lassau et al. 2007; 2012a; 2012b; Lavisse et al. 2008). Two baseline studies were not included because of data corruption, and some patients did not complete the study because of sunitinib toxicity or progression of disease. The data from post-treatment studies of patients with missing baseline or those who could not continue with all sessions were used only for the inter-observer portion of the study. DCE-US was performed on the primary renal tumor (N = 27), liver metastasis (N = 1) or lymph node metastasis (N = 1). The study endpoint, reflective of treatment outcome, was PFS as determined by RECIST (Version 1.1) measurements (Eisenhauer et al. 2009) on CT by one of the authors (M.A.) blinded to DCE-US results, comparing baseline CT with 6-wk follow-up CT.

DCE-US examination

Dynamic contrast-enhanced US imaging was performed using the contrast-specific mode (PMPI) of a Philips iU22 machine (Philips Ultrasound, Bothell, WA, USA) with a C5-1 curvilinear probe at low mechanical index (MI) (<0.06). Patients received an infusion of 0.9 mL of Definity microspheres (Lantheus Medical Imaging, Billerica, MA, USA) that was diluted in 54 mL of saline and injected over 12 min using a Medfusion 3500 injection pump (Smiths Medical, Dublin, OH, USA). Disruption–replenishment measurements were performed 2 min after the onset of the infusion to allow the contrast agent to reach a steady state within the blood pool. Receive gain, dynamic range and the image depth and focus were optimized for each patient during the baseline scan. The same machine parameters were used for all follow-up examinations. Under steady-state conditions, the tumor was sampled in seven parallel planes spanning the anatomic volume of the lesion as evenly as possible. The planes would be closer with smaller lesions and farther apart with larger lesions. Disruption–replenishment data were collected for approximately 30 s after an eight-frame flash at a maximum MI of 1.3. Frame rates ranged from 7 to 12 Hz. Considering measurements were made during perfusion, flow velocity is expected to be similar as long as contrast is running. Data were stored in a compressed "native" format to allow subsequent linearization using an algorithm provided by the ultrasound manufacturer (Philips Ultrasound). All examinations were performed by one of the two radiologists (M.A., L.M.) with 25 and 9 y of experience in US examination.

When possible, the scan plan was oriented in line with the respiratory motion to minimize out-of-plane target motion that cannot be corrected using off-line compensation. The patients were instructed to maintain quiet gentle breathing during the acquisitions. The impact of breathing was investigated with a second series of scans acquired during a breathhold while imaging the largest tumor plane showing enhancing components. Eighteen of the 27 patients were able to maintain a steady breathhold for the 30-s scan.