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Short Communication

Evaluation of two-dimensional ultrasonography and computed tomography in the mapping and measuring of canine urinary bladder tumors

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ABSTRACT

Determining the dimensions of transitional cell carcinomas (TCCs) of the urinary bladder in dogs is important in assessing tumor progression and the response to treatment. The primary aim of this study was to evaluate the reliability of a standardized two-dimensional (2-D) ultrasound (US) protocol performed by a single experienced operator. Secondary aims were to compare World Health Organization (WHO) and Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, and to compare measurements by two operators following these guidelines. These were evaluated by inter-operator and intra-operator reliability using the concordance correlation coefficient (CCC) and Cohen's κ statistics, which demonstrated substantial to better agreement by an experienced operator using either set of guidelines. It was demonstrated that 2-D US provides a reliable means to determine the dimensions of urinary bladder TCC when an experienced operator used a standardized protocol. In a subset of dogs, urinary bladder distension was varied, which resulted in differences in measurement with 2-D US and computed tomography.

In dogs with transitional cell carcinoma (TCC) of the urinary bladder, it is important to be able to obtain reliable measurements of tumor size, in order to monitor and adjust treatment in individual animals, and to assess drug activity in clinical trials (Knapp et al., 2014; Rippy et al., 2016). The primary aim of this study was to determine the reliability of a standardized two-dimensional (2D) ultrasound (US) protocol for determining the dimensions of TCCs of the canine urinary bladder when performed by a single experienced operator. Secondary aims were to compare measurements between two operators, and to compare tumor size when applying volume measurements (VMs) using World Health Organization (WHO) criteria (Arnold et al., 2011) and uni-dimensional measurements using Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Eisenhauer et al., 2009).

In an exploratory subset, the effects of varying levels of urinary bladder distension and varying imaging modalities (2-D US versus computer tomography, CT) were determined. Our hypothesis was that a standardized 2-D US protocol would provide a reliable method for determining dimensions of urinary bladder tumors using WHO and RECIST guidelines when performed by a single experienced operator.

The study was approved by the Purdue University Animal Care and Use Committee (approval number 1111000124; date of approval 3 February 2014). Dogs with histologically diagnosed intraluminal bladder TCC, and with informed owner consent, were enrolled sequentially over an 8 month period at the Purdue University Veterinary Teaching Hospital, West Lafayette, Indiana, USA. Assessments were made to determine the agreement within (intra-operator) and between (inter-operator) two different ultrasound operators using a 2-D US protocol while following WHO and RECIST guidelines. One operator was experienced, while the other operator was less experienced.

Dogs were placed in right lateral recumbency to minimize urinary bladder movement. Ultrasonography (Biosound Esaote Megas ES) was used to determine the dimensions of the entire urinary bladder and the sizes of masses within the urinary bladder (apex, mid-body, trigone) in dorsal and transverse planes. VM were obtained by multiplying the area of the mass in the dorsal plane by the dorsal-ventral dimension of the mass in the transverse plane using ultrasound tracing by the operator (see Appendix:

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Table 1
Definitions of tumor response following World Health Organization (WHO) versus Response-Evaluation-Criteria-In-Solid-Tumors (RECIST) guidelines.

Response	WHO	RECIST
Complete remission (CR)	No detectable cancer remaining	Disappearance of all tumor lesions
Partial remission (PR)	≥50% decrease in tumor volume with no new lesions detected	At least 30% decrease in sum of longest diameters of tumor lesions and no new lesions
Stable disease (SD)	<50% change in tumor volume and no new lesions detected	Neither >30% shrinkage nor <20% growth to qualify for PR or PD and no new lesions
Progressive disease (PD)	≥50% increase in tumor volume or development of new lesions	At least 20% increase in sum of longest diameters of tumor lesions or appearance of one or more new lesions

Supplementary Fig. 1) (Chun et al., 1997; Naughton et al., 2012). If multiple masses were present, then the two largest masses were measured. These VM were used when applying WHO criteria (Arnold et al., 2011).

To apply RECIST criteria, the longest diameter (LD) of the mass or the two largest masses in the urinary bladder were recorded; when the two largest masses were measured, the sum of their LD was used for RECIST measurements (Eisenhauer et al., 2009). Each dog was evaluated by the same two operators on the first day of enrolment and again after 4–8 weeks of treatment with the urinary bladder distended to a similar level. The same imaging protocol was followed and tumor responses were determined (Table 1).

To determine if altering the degree of urinary bladder distension or employing a more advanced imaging modality (CT), would affect tumor measurements, additional imaging was performed on a subset of five previously enrolled dogs. Under anesthesia, a Foley catheter (Mila International) was placed to evacuate the urinary bladder and to instill sterile saline (Hospira) mixed with contrast medium (300 mg I_2/mL; iopromide, Ultravist, Bayer Healthcare Pharmaceuticals) (5 mL contrast medium per 500 mL saline). Three levels of distension were studied (1 mL/kg, 2.5 mL/kg and 5 mL/kg body weight) with 2-D US and CT (GE light speed QX/I multi-slice helical CT scanner, GE General Electric Company). After filling the urinary bladder to each level of distension, measurements were made using 2-D US followed by the acquisition of CT images (Fig. 1).

The inter-operator and intra-operator reliability in determining VM and LD were assessed using the concordance correlation coefficient (CCC). Cohen's κ statistics were used to determine the agreement in the classification of tumor response to treatment based on WHO and RECIST criteria. Statistical analyses were performed using MedCalc for Windows, version 16.2. Significance was set at $P < 0.05$.

Twenty-three dogs with 34 histopathologically confirmed TCCs of the urinary bladder were enrolled in the study (see Appendix: Supplementary Table 1). The results of the inter-operator and intra-operator reliability assessment are summarized in Fig. 2. Eighteen dogs were available for repeat 2-D US after 4–8 weeks of treatment. Tumor responses assigned by the two operators disagreed in 8/18 cases using WHO criteria and in 7/18 cases using RECIST criteria (see Appendix: Supplementary Table 2). When comparing tumor response as defined by WHO criteria versus RECIST, responses varied in 11/18 cases for the experienced operator ($\kappa = 0.471$, $P = 0.043$) and in 8/18 cases for the less experienced operator ($\kappa = -0.097$, $P = 0.582$). The measurements obtained with 2-D US varied from those obtained with CT, especially when the level of urinary bladder distension was altered (Fig. 1).

The findings demonstrate that 2-D US is a reliable technique for measurement of the size of TCCs of the canine urinary bladder when the procedure is standardized for an experienced operator, equipment, dog position, image acquisition and level of urinary bladder distension. The study also confirmed discrepancies in measurements if urinary bladder distension varies and if multiple imaging modalities are used. In some cases, measurements were larger with 2-D US VM than with CT. This was most likely because the 2-D US protocol, as defined, could overestimate the size of an irregularly shaped mass, while CT assessment would be expected to be more precise, since the area of each slice is calculated.

This study demonstrates the importance of having the same operator perform 2-D US on each visit where tumor size is

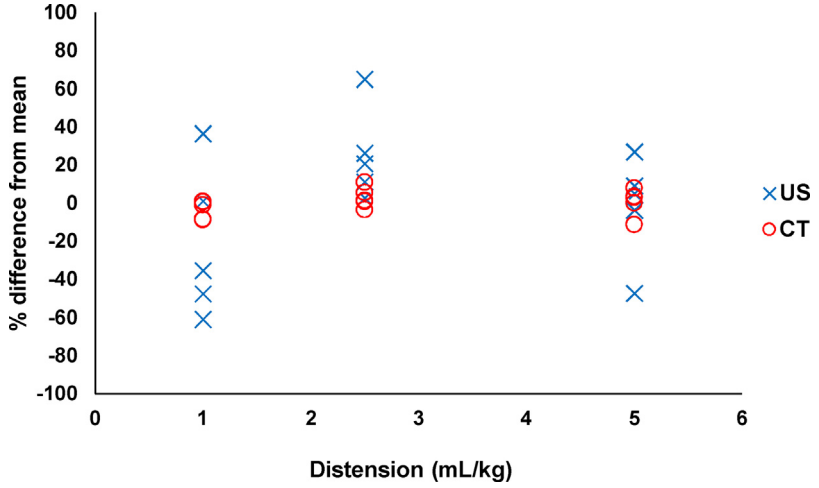

Fig. 1. Measurements of canine urinary bladder transitional cell carcinomas (TCC) in five dogs using computed tomography (CT; ○) and two-dimensional ultrasound (2-D US; ×) performed at three different urinary bladder distensions (instillation with 1 mL/kg, 2.5 mL/kg, 5 mL/kg sterile saline mixed with contrast solution) using WHO guidelines. CT data were analyzed using a region of interest drawn on each post-contrast slice to indicate the tumor perimeter. The software program (GE automated workstation, version 4.1_04), via proprietary algorithm, calculated the area of tumor on each slice and multiplied it by the slice thickness (1.25 mm) to determine the volume in each tumor slice. Slice volumes were then summed to determine the total tumor volume (Naughton et al., 2012).