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Inter- and intraobserver variability of (semi-)quantitative parameters commonly used in feline thyroid scintigraphy

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ABSTRACT

The aim of this study was to assess inter- and intraobserver variability of commonly used semi-quantitative and quantitative parameters in feline thyroid scintigraphy: thyroid to salivary gland ratio (T/S), thyroid to background ratio (T/B) and the percentage technetium pertechnetate uptake for the thyroid glands (%TcU_T). These parameters are being used to diagnose thyroid disease and to assess its severity, but may be influenced by operator related factors when processing the images. Additionally, inter- and intraobserver variability of the percentage technetium pertechnetate uptake for the salivary glands was determined (%TcU_{SG}). The study included technetium pertechnetate scans of 100 hyperthyroid cats. Variability within and between three observers was determined using a random effects model and variance components were estimated by the restricted maximum likelihood procedure. The %TcU for the thyroid and salivary glands, as well as the T/S ratio, showed little to no difference in inter- and intraobserver variability, whereas this was clearly present for the T/B ratio. Overall, the T/S ratio and %TcU_{SG} showed a good repeatability and reproducibility with low inter- and intraobserver variabilities. Inter- and intraobserver variability was higher for the %TcU_T, however variations were still considered to be acceptable. On the contrary, inter- and intraobserver variability was clearly larger for the T/B ratio. These findings suggest the preferential use of the T/S ratio or %TcU, especially in facilities with a less experienced staff.

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1. Introduction

Thyroid scintigraphy is the most common imaging modality used in the diagnosis or confirmation of hyperthyroidism in cats because of its ability to assess thyroid function and the anatomical distribution of hyperfunctional thyroid tissue, including possible ectopic tissue. Further, it can be used to evaluate the severity of the hyperfunctional state. Although visual inspection already allows interpretation of the anatomical distribution and a subjective evaluation of the amount of radionuclide uptake, a more objective evaluation can be performed by using parameters such as the thyroid to salivary gland ratio (T/S), the thyroid to background ratio (T/B) or the percentage uptake of injected radionuclide, either with radioactive iodine (RAIU, using ^{131}I or ^{123}I) or technetium pertechnetate (%TcU). The normal T/S ratio in literature varies substantially with a range of 0.48 to 1.9 (Beck et al., 1985; Lambrechts et al., 1997; Daniel et al., 2002; Henrikson et al., 2005; Page et al., 2006; Lee et al., 2010). The range is even larger for the T/B ratio, going from 1.6 up to 6.4 (Beck et al., 1985; Daniel and Brawner, 2006; Daniel and Neelis, 2014; Peterson and Broome, 2015). The %TcU in the thyroid glands was reported ranging from 0.21 up to 3.9% in normal cats, and from 0.7 to 61% in hyperthyroid cats (Mooney et al., 1992; Nap et al., 1994; Nieckarz and Daniel, 2001; Daniel et al., 2002; Fischetti et al., 2005; Daniel and Brawner, 2006; Lee et al., 2010).

Scintigraphy is an imaging modality with an inherent low resolution compared to other imaging techniques, and gamma camera sensitivity and resolution may differ between institutions. Additionally, manually drawing regions of interest (ROI) and possible patient dependent factors may result in variations between measurements of different clinicians and facilities. Despite the fact that these parameters have been reported extensively in literature for evaluation of thyroid function and therapeutic radioiodine (^{131}I) dose estimation, no studies are available assessing their variability between observers. The purpose of this study was therefore to assess inter- and intraobserver variability of these commonly used (semi-)quantitative parameters.

2. Materials and methods

Technetium pertechnetate ($^{99m}TcO_4^-$) thyroid scintigrams of 100 hyperthyroid cats, presented at our clinic for radioiodine treatment between 2010 and 2013, were selected. The cats were diagnosed with hyperthyroidism based on clinical symptoms and serum total thyroxine (TT4) concentration. The median age of the population was 12 years (range: 6–18 years), 46/100 were male, 54/100 were female. Seventy cats were selected with two hyperfunctional foci on the thyroid scans

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and 30 cats were selected with a single hyperfunctional focus. These numbers were chosen to approximate the normally described prevalence of bilateral and unilateral thyroid disease in cats (Mooney, 2010).

A median activity of 92.87 MBq (range: 48.1–148 MBq) was injected into the cephalic vein via an intravenous catheter (Daniel and Brawner, 2006). Thyroid scans were acquired 30 min after injection of technetium pertechnetate. For the scans the cats were anesthetized with propofol (4–8 mg/kg to effect, IV, Propovet; Ecuphar, 10 mg/ml) and scanned in ventral recumbency with the gamma camera, equipped with a low energy high resolution (LEHR) collimator, located underneath the table (GCA 7200 A, Toshiba). Zoomed 25.6 × 25.6 cm field-of-view planar images were acquired on counts (200 kcounts) in a 256 × 256 matrix, with a 0.1 cm pixel size. A syringe containing a known, small amount of technetium pertechnetate was placed on the scan bed next to the cat and was scanned simultaneously as a standard to calculate the percentage pertechnetate uptake.

Following parameters were obtained: percentage technetium uptake (%TcU) of thyroid glands and salivary glands ($\%TcU_T$ and $\%TcU_{SG}$), thyroid to salivary gland ratio (T/S) and thyroid to background ratio (T/B). To calculate these parameters regions of interest (ROI) were drawn manually using multimodality software (Hermes V5.0; Nuclear Diagnostics AB).

In order to calculate the percentage technetium uptake, the background activity had to be corrected for. To correct the standard activity a mirrored version of the ROI drawn over the standard was used and placed in the FOV as far away from the patient and the standard as possible. Similarly, ROIs to correct for background activity originating from within the patient were placed. For the salivary glands, ROIs were drawn over the glands, and then copies of these ROIs were placed within the contours of the head. For the thyroid gland(s), ROIs were drawn manually over the gland(s) and background correction was done using three different methods; 1: two rectangular, fixed-size ROIs were placed cranial and caudal to the thyroid lobe(s) and the obtained values from these ROIs were averaged (background "neck"); 2: a fixed-size circular ROI was placed in the ipsilateral axillary region of the patient (background "circle"); 3: a copy of the thyroid ROI was placed in the ipsilateral axillary region (background "copy ROI"). The T/B ratio was calculated as the ratio of the mean counts per pixels of the thyroid ROI and the mean counts per pixels of the three different body background ROIs, which were also used for %TcU calculations. The T/S ratio was calculated as the ratio of the mean counts per pixels of the thyroid ROI to the mean counts per pixels of the ipsilateral salivary gland ROI.

In contrast to the calculation of %TcU, background correction is not performed for the T/S ratio and the T/B ratio. The standard activity was often masked from the image in a second step, as the relatively high activity in this region made it otherwise difficult to visualize the image of the patient, even after adjusting window settings ("count stealing" phenomenon). Placement of the different regions of interest on the scintigram is demonstrated in Fig 1. Three different observers with variable experience in scintigraphy (VV, an ECVDI resident; EV, a nuclear medicine clinician and KP, Dipl. ECVDI), performed all measurements twice. Time in between the two sessions was 3 weeks.

A random effects model was fitted with thyroid gland, observer nested in the thyroid gland, and measurements nested in the observer as random effects. The restricted maximum likelihood procedure was used to estimate the variance components. These variance components were then used to derive the 95% ranges for the differences between two measurements of the same observer and of two different observers on the same thyroid gland.

3. Results

The variance components due to repeated measurements (σ^2), observers (σ_o^2) and thyroid glands (σ_t^2) are given in Table 1. Remark that the variance components denote the extra variation due to the particular source. For instance, σ_o^2 refers to the extra variation when two measurements are performed by two different observers; a value of 0 for σ_o^2 signifies that the variation between two measurements is the same regardless whether the measurement comes from the same or a different observer. The variance components can be used to depict the 95% reference ranges that contain 95% of the differences between two measurements from the same or from a different observer (Fig. 2). The 95% reference ranges for between observer differences were small for the

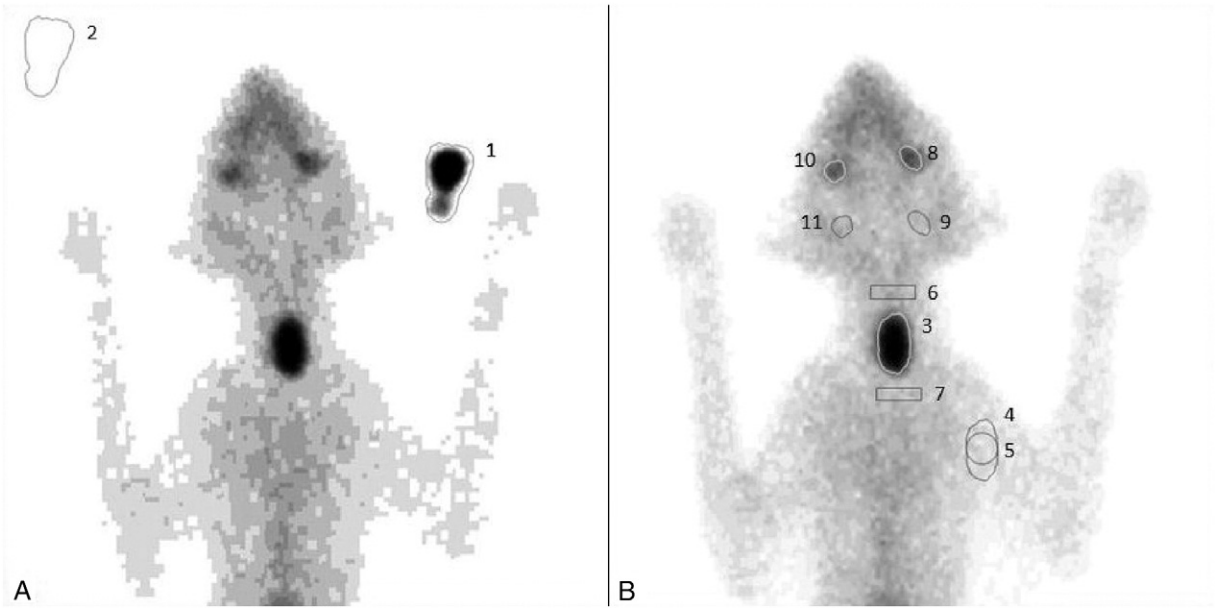

Fig 1. Different regions of interest in a cat with unilateral hyperthyroidism used for the calculation of the investigated parameters. Before (A) and after (B) masking the standard, mildly improving image quality in this case. Following ROIs are manually placed on the ventral planar scan: 1) ROI standard, 2) background standard, 3) left thyroid lobe, 4) left thyroid lobe copied ROI as a background ROI in the axillary region, 5) fixed-size circular ROI in the axillary region (superimposed onto 4), 6 + 7) fixed-size rectangular ROIs in the cervical region, 8) left salivary gland ROI, 9) left salivary copied ROI as a background ROI in the caudal aspect of the head, 10) right salivary gland ROI, 11) right salivary copied ROI as a background ROI in the caudal aspect of the head. Note that in this patient the axillary region and the head are still well visible in A, and masking would not have been absolutely necessary in this case.

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