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STANDARD ARTICLE

Investigation of a novel variable dosing protocol for radioiodine treatment of feline hyperthyroidism

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Background: Radioiodine is the treatment of choice for hyperthyroidism in cats. The ideal method of dose determination of radioiodine remains controversial.

Objective: To compare a method of radioiodine dose determination that utilized thyroid scintigraphy with a standard fixed dose for treatment of hyperthyroidism.

Animals: Fifty-seven and 23 client-owned hyperthyroid cats in the variable and fixed dose groups, respectively.

Methods: Cats with a percent dose uptake using ^{99m}Tc-pertechnetate uptake on thyroid scintigraphy <5%, 5%-10%, and >10% were to receive 3, 3.5, or 4.5 millicuries (mCi) of radioiodine, respectively, administered SC. Radioiodine dose was adjusted according to thyroid gland size as determined by the thyroid:salivary size ratio and categorized as <5:1, 5-10:1, and >10:1. If the thyroid size fell into a higher dosing category than the percent dose uptake, the dose was increased accordingly. Cats in the fixed dose group received 4.5 mCi. Six months after treatment, cats were determined to be euthyroid, hypothyroid, or hyperthyroid based on serum thyroxine and thyroid stimulating hormone concentrations.

Results: No difference in outcome was found between the variable and fixed dose treatment groups. Euthyroidism, hypothyroidism, and persistent hyperthyroidism developed in 61, 30, and 9% of cats in the fixed dose group compared to 58, 26, and 16%, respectively, in the variable dose group.

Conclusions: A variable dosing method of radioiodine based on percent dose uptake primarily and thyroid gland size secondarily did not improve outcome compared to a standard fixed dose method.

KEYWORDS

feline, hyperthyroid, radioiodine, scintigraphy

1 | INTRODUCTION

Radioactive iodine (^{131}I) is the treatment of choice for hyperthyroidism in cats. However, the optimal method for calculation of the appropriate dose of ^{131}I has not been determined. None of the 3 methods of radioiodine dose determination: tracer technique, fixed dose method, or variable dose method has consistently resulted in euthyroidism. The efficacy of various modified fixed dose methods is difficult to assess because of substantial variation in, and often incomplete description of, how the dose was determined. The technique uses one or more variables, including severity of clinical signs, patient weight, thyroid tumor size or volume, and serum thyroxine (T4) concentration to determine a tiered dose of

Abbreviations: ^{131}I, radioactive iodine; $^{99m}TcO_4$, pertechnetate; CPM, counts per minute; mCi, millicuries; ROI, region of interest; T4, thyroxine; T:S, thyroid to salivary ratio; TSH, thyroid stimulating hormone

radioiodine. A study using a variable dose technique, based on thyroid volume alone, was ineffective for cats with severe hyperthyroidism.[1] Another study using a variable dose technique based on the number of thyroid nodules present and body weight resulted in 4% remaining hyperthyroid and 9% becoming hypothyroid.[2] Studies determining radioiodine dose based on severity of clinical signs, thyroid gland size, and serum T4 concentration resulted in 1.5%-9.5% being persistently hyperthyroid and 2.1%-30% becoming hypothyroid. Cats with bilateral disease and larger thyroid volumes were at increased risk for developing hypothyroidism.[3–6] These studies had different criteria for classifying hypothyroidism, different means of measuring thyroid volume, various tiered dosing schemes, and inconsistent follow-up periods that make comparisons problematic. The development of hypothyroidism is of particular concern because of its association with the advent or worsening of azotemia, potentially shortening survival.[7] A more objective method of radioiodine dose determination is warranted.

In an attempt to improve outcome of radioiodine treatment, the treatment protocol in our hospital was changed from a fixed dose of 4.5 millicuries (mCi) ^{131}I to a novel variable dosing treatment with cats tiered to receive 3, 3.5, or 4.5 mCi based on evaluation of scintigraphic findings. This change presented a unique opportunity to compare the 2 methods of radioiodine dose determination. Our goal was to evaluate an objective, repeatable, and transferable method of radioiodine dose determination for treating cats with hyperthyroidism. This novel method of radioiodine dose determination was based on thyroid gland size and percent ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$) uptake by the thyroid gland using scintigraphy. The rate of persistent hyperthyroidism development of hypothyroidism was determined after using this dosing method. Secondarily, treatment outcomes were compared to those obtained of a standard fixed dose protocol using 4.5 mCi of radioiodine that had been used by our facility previously. We hypothesized that our novel variable method of radioiodine dose determination would be superior to a fixed dose technique in achieving euthyroidism in cats treated with radioactive iodine. Specifically, we expected to see a decreased proportion of cats remaining hyperthyroid and a lower occurrence of hypothyroidism than in the fixed dose group.

2 | MATERIALS AND METHODS

2.1 | Animals

Cats referred to the Virginia-Maryland College of Veterinary Medicine (VMCVM) for radioiodine treatment of hyperthyroidism were eligible for the study. Cats were determined to be hyperthyroid based on increased serum concentrations of T4 with concurrent thyroid stimulating hormone (TSH) concentrations below the detection limit of the assay, appropriate clinical signs of hyperthyroidism including ≥1 of the following (palpable thyroid enlargement, tachycardia, history of weight loss, history of hyperactivity, polyphagia, polyuria, polydipsia, heart murmur, and hypertension), and having characteristic diagnostic features of hyperthyroidism (increased thyroid size and increased radionuclide uptake) on nuclear scintigraphy. Exclusion criteria included a documented major illness other than hyperthyroidism or a history of consumption of a restricted iodine diet. Cats that had previously been treated with methimazole were included, although treatment had to have been discontinued for a minimum of 2 weeks before presentation. The study was approved by the Virginia Tech Institutional Animal Care and Use Committee, VMCVM Veterinary Teaching Hospital Board, and informed consent was obtained from all clients.

2.2 | Experimental protocol

Cats initially were evaluated by history, physical examination, noninvasive blood pressure testing, fundoscopic examination, CBC, serum biochemical profile, urinalysis, serum T4 and TSH concentrations, and urine culture. All laboratory testing were performed in the VMCVM clinical pathology laboratory. Serum T4 and TSH concentrations were measured using chemiluminescent enzyme immunoassays (Immulite Canine Total T4 and Immulite Canine TSH, Immulite 1000; Siemens Healthcare Diagnostics, Tarrytown, New York) as previously described.[8] Cats confirmed to have hyperthyroidism without any of the aforementioned exclusion criteria had thyroid scintigraphy performed. If needed for restraint, cats were sedated with a drug deemed appropriate by the attending veterinarian. The majority of cats in each group were sedated with butorphanol alone, butorphanol and alfaxalone with or without midazolam, and then given propofol as necessary. An IV catheter was placed and cats were given 3 mCi $^{99m}TcO_4^-$ IV. Each dose was verified by measuring the activity of the $^{99m}TcO_4^-$ in the syringe before and after administration using a dose calibrator (Atomlab 500, Biodex Medical Systems, Shirley, New York). Twenty minutes after $^{99m}TcO_4^-$ administration, cats underwent a thyroid scan using a large field-of-view scintillation gamma camera fitted with a Low Energy All-Purpose (LEAP) collimator (Omega 500, Technicare Inc., Solon, Ohio). The animals were positioned first in ventral recumbency, then in right and left lateral recumbency.

Scintigraphic findings were evaluated for functional status, presence of ectopic thyroid tissue, and pattern of uptake (unilateral, bilateral, asymmetrical bilateral, or atypical that included cysts or patterns suggestive of malignancy[9]). For each cat, percent uptake of $^{99m}TcO_4^-$ in the thyroid gland, thyroid gland size, and thyroid intensities were calculated using Nuclear MAC software (Scientific Imaging, PO Box 3691, Crested Butte, Colorado). Region of interests (ROIs) were drawn around each thyroid lobe, both zygomatic salivary glands, and an area adjacent to the thyroid for determining background activity as previously described, by a single individual to avoid interobserver variability.[10,11] A specially designed inverted gray-scale lookup table with a red color threshold set at 10% of maximum thyroid counts was used to assist in the drawing of the ROIs around the thyroid gland. This lower threshold was used to capture as much thyroid tissue as possible, especially in cases of asymmetrical bilateral disease. The imaging software determined the amount of radioactivity within each ROI. The radioactivity within the thyroid gland was corrected by removing background activity (BKD) (radioactivity measured within the thyroid ROI but originating deep and superficial to the gland), radioactive decay, and soft tissue attenuation (absorption of radioactivity by the

tissues between the thyroid gland and gamma camera), using the following formulas, respectively:

$$\text{Net thyroid counts} = \text{Gross thyroid count} \times \left\{ \frac{\text{BKD counts per minute(cpm)}}{\text{BKD\#pixels}} \times \text{\#thyroid pixels} \right\}$$

$$\text{Decay corrected thyroid counts} = \text{Thyroid count} \times e^{\left(\ln(2)/6.02\ \text{h} \times \text{time difference}\right)}$$

$$\text{Depth corrected thyroid counts} = \text{Gross thyroid count} \times e^{-0.152\ \times\ \text{depth in cm}}$$

The percent dose uptake was determined by the following formula:

$$\text{Percent dose uptake} = \frac{\text{Corrected cpm in thyroid}}{\text{Radionuclide dose in cpm}} \times 100$$

Thyroid gland size was expressed as a ratio comparing thyroid size to the zygomatic salivary gland using the following formula:

$$\text{T : S size ratio} : \frac{\text{Number of pixels in thyroid ROI}}{\text{Number of pixels in salivary ROI}}$$

Thyroid intensity was expressed as a ratio comparing thyroid counts to the ipsilateral zygomatic salivary gland using the following formula:

$$\text{T : S intensity ratio} : \frac{\text{Mean counts per pixels in thyroid ROI}}{\text{Mean counts per pixels in salivary ROI}}$$

Average T:S intensity ratio was calculated using the average thyroid density from both thyroid lobes. In cases of unilateral disease, 1 thyroid was used in the intensity ratio. The maximum T:S intensity ratio was calculated from the most intense thyroid lobe.

Normal percent dose uptake was considered to be 0.2%-0.4%.[10] Cats were grouped as follows for radioiodine dose determination: percent uptake of <5% (mild), 5%-10% (moderate), and >10% (severe). Once percent uptake was calculated, thyroid size was stratified by calculating the T:S size ratio with a T:S size ratio of <5:1 being considered mild, 5-10:1 moderate, and >10:1 severe. The dose of ^{131}I that was given first was determined by measuring percent uptake. If the thyroid size fell into a higher dosing category than percent uptake, the dose was increased to coincide with the category for size. Dosages were as follows: low dose (mild) 3.0 mCi, medium dose (moderate) 3.5 mCi, and high dose (severe) 4.5 mCi. All cats in the fixed dose group were given 4.5 mCi. The ^{131}I was administered SC. The dose administered was verified using the activity of ^{131}I in the syringe before and after administration using a dose calibrator (Atomlab 500, Biodex Medical Systems).

2.3 | Post-treatment testing

Reevaluation was performed by the referring veterinarian at 1, 3, and 6 months after treatment when blood and urine were collected for measurement of serum concentrations of T4, TSH, and creatinine, as well as urine specific gravity. All samples were analyzed in the VMCVM laboratory. Treatment outcome was determined by serum T4 and TSH concentrations 6 months after treatment using reference intervals of 16-37.7 nmol/L and 0.03-0.3 ng/mL, respectively. Cats were categorized as euthyroid (T4, 16-37.7 nmol/L; TSH, <0.3 ng/mL), hypothyroid (T4, <16-37.7 nmol/L; TSH, >0.3 ng/mL), or persistently hyperthyroid (T4, >37.7 nmol/L; TSH, <0.03 ng/mL). Subclinical and overt hypothyroid cats were analyzed as a single hypothyroid group. Azotemia was defined as a serum creatinine concentration above the reference range (0.8-1.8 mg/dL) and a urine specific gravity <1.035. During the follow-up period, any cat with a low serum T4 concentration at the 1- or 3-month evaluation and development or worsening of azotemia was treated with levothyroxine and classified hypothyroid at the 6-month follow-up if still receiving supplementation. Cats were excluded if they did not have a 6-month follow-up evaluation.

2.4 | Statistical analysis

Statistical analysis was performed using a commercial statistical software program (SAS Version 9.4, Cary, North Carolina). Normal probability plots showed that age and body weight followed a normal distribution, whereas T4 concentrations, percent dose uptake, T:S size ratio, and average and maximal T:S intensity ratios were skewed. Chi-square analysis was used to determine the association between dose determination method and outcome and for categorical data within and between groups. Normally distributed data were analyzed using a *t* test or one-way analysis of variance, whereas nonparametric data were analyzed using a Wilcoxon rank sum test or the Kruskal-Wallis test. Associations with outcome for both groups were determined using Chi-square analysis for categorical data, one-way analysis of variance for normally distributed data, and the Kruskal-Wallis test for nonparametric data. Logistic regression analysis tested the association of initial serum T4 concentration, percent dose uptake, T:S size ratio, average and maximal T:S intensity ratio, scintigraphic pattern of uptake, age, weight, and sex with outcome in both groups. Significance of all tests was set at $P < .05$.

3 | RESULTS

3.1 | Study groups

Ninety-four cats were treated with radioiodine at the VMCVM from November 2013 through July 2016, the study period for the novel variable radioiodine dose group. Seventy-seven cats were enrolled in the study, with 17 being excluded because of prior treatment with radioiodine,[3] lymphoma,[1] consumption of restricted iodine diet,[3] or treatment using a different dose determination than used in the study.[10] Of the 77 cats enrolled in the study, 20 were excluded because of incomplete data collection,[13] receiving radioiodine dose outside of the target desired dose range,[2] or death during the 6-month follow-up period.[5] Cause of death was neoplasia in 1 cat and unknown in 4 cats. Of the 57 cats in the novel variable radioiodine dose group that completed the study, 32 were neutered males and 25 were spayed females. Breeds included domestic shorthair (46), domestic longhair,[5] Siamese,[2] Himalayan,[2] Maine Coon,[1] and Russian Blue.[1] Mean age was 12.0 years (standard deviation [SD] ± 2.0) and mean weight was 4.4 kg (SD ± 1.3). All cats had a serum T4 concentration above the reference range (16-37.7 nmol/L) and a TSH

concentration below the detectable limit of the assay (0.03 ng/mL). The median initial serum T4 concentration was 157 nmol/L with a range of 39.4-411 nmol/L.

Twenty-three cats treated with radioiodine at VMCVM between June 2011 and March 2013 meeting the same criteria as the novel variable dose group comprised the control group that received a fixed target dose of 4.5 mCi ^{131}I. These cats have been described in part in another study.[8] Fifty-six cats initially were included in the study, with 33 cats being excluded because of incomplete data collection (30), consumption of y/d (Hill's Pet Nutrition Inc, Topeka KS 66601) diet (2), or euthanasia during the 6-month follow-up period (1). There were 12 neutered males and 11 spayed females. Breeds included domestic shorthair (15) and domestic longhair (8). Mean age was 12.2 years (SD ± 2.8) and mean weight was 4.1 kg (SD ± 0.9). All cats had a serum T4 concentration above the reference range and a TSH concentration below the detectable limit of the assay. The median initial serum T4 concentration was 131 nmol/L, with a range of 48-263 nmol/L. No significant differences were found between the groups with respect to initial T4 concentration, age, weight, or sex.

3.2 | Scintigraphic characteristics

All cats had increased thyroid uptake of pertechnetate noted on scintigraphy. No significant differences were found in scintigraphic pattern of disease, presence of ectopic tissue, percent dose uptake, or maximal T:S intensity ratio between the novel variable dose and fixed dose groups (Tables 1 and 2). The T:S size ratio ($P < .0001$) and the average T:S intensity ratio ($P = .02$) in the fixed dose group were higher than in the novel variable dose group (Table 2).

3.3 | Response to treatment

At 6 months after treatment, 31/57 (54%) and 11/23 (48%) were euthyroid, 17/57 (30%) and 10/23 (43%) were hypothyroid, and 9/57 (16%) and 2/23 (9%) were persistently hyperthyroid in the novel variable and fixed dose groups, respectively. Of the hypothyroid cats, 7/17 (41%) and 4/10 (40%) were subclinical and 10/17 (59%) and 6/10 (60%) were overtly hypothyroid in the novel variable and fixed dose groups, respectively. Five cats in the novel variable dose group were treated with levothyroxine because of overt hypothyroidism and azotemia and were classified as hypothyroid. One cat in the novel dose group was treated with methimazole because of persistent hyperthyroidism.

TABLE 1 Proportion of cats in novel and fixed radioiodine dosage groups with unilateral, bilateral, asymmetrical bilateral, atypical, and ectopic thyroid tissue scintigraphic pattern of disease (*Using Fisher's exact test)

Pattern of disease	Novel dose (number/%)	Fixed dose (number/%)	*P* value*
Unilateral	21 (37%)	9 (39%)	1.00
Bilateral	5 (9%)	5 (22%)	.71
Asymmetrical bilateral	27 (47%)	9 (39%)	.62
Atypical	4 (7%)	0 (0%)	.62
Ectopic thyroid tissue	8 (14%)	1 (4%)	.43

TABLE 2 Percent dose uptake, T:S size ratio, average intensity, and maximal intensity as determined by thyroid scintigraphy in novel and fixed dose groups of cats. Data are expressed as median and range (*Using Wilcoxon two-sample test)

Characteristic	Novel dose	Fixed dose	*P* value*
% dose uptake	3.8 (0.3-34.5)	4.4 (0.5-14.2)	.99
T:S size ratio	3.9:1 (1.4-17.2)	6.5:1 (2.9-38.7)	<.0001
Average T:S intensity ratio	2.9:1 (0.8-23.3)	4.4:1 (0.9-16.8)	.02
Maximal T:S intensity ratio	4.3:1 (0.8-23.3)	5.6:1 (1.2-20.2)	.18

Data from these 6 cats were excluded from the analysis of serum T4 concentration. Azotemia developed in 15/57 and 2/23 in the novel and fixed dose groups, respectively. No difference in outcome ($P = .44$) or development of azotemia ($P = .08$) was found between the groups.

In the novel variable dose group, 3/4 (75%) cats with atypical scans were persistently hyperthyroid, with 1 each in the low, medium, and high dose categories. The 1 cat with an atypical scan that became euthyroid was treated with a high dose. No cat in the fixed dose group had an atypical scan. Two of the 8 (25%) cats in the novel variable dose group with ectopic thyroid tissue remained hyperthyroid, and 1 (13%) became hypothyroid. The only cat in the fixed dose group with ectopic thyroid tissue remained hyperthyroid.

3.4 | Novel variable dosage group characteristics and response to treatment

The low, medium, and high doses of ^{131}I were administered to 28 (49%), 20 (35%), and 9 (16%) of the 57 cats in the novel variable dose group, respectively (Table 3). The mean dose of radioiodine administered to cats in the low, medium, and high dose groups was 3.07 mCi (SD ± 0.14), 3.51 mCi (SD ± 0.07), and 4.46 mCi (SD ± 0.17), respectively.

No difference was found between the dosage groups with regard to age, sex, weight, pattern of disease, 6-month serum T4 concentration, and final outcome (Table 3). The low dose group had the lowest frequency of hyperthyroidism (7%), the medium dose group the lowest frequency of hypothyroidism (15%), and the medium and high dose groups each had the highest frequency of hyperthyroidism (25%) and (22%), respectively, but these differences were not statistically significant. As percent dose uptake and T:S size ratio increased, the dosage administered increased ($P < .0001$). Based on study design, as average T:S intensity ratio and maximal T:S intensity ratio increased, dosage increased ($P < .0001$), because percent dose uptake is directly related to T:S intensity ratio. The initial serum T4 concentration was directly correlated with dosage ($P < .0001$).

There was no association of outcome in the novel dosage groups with age, sex, weight, pattern of disease, ectopic disease, T:S size ratio, average and maximal T:S intensity ratios, initial serum T4 concentration or percent dose uptake (Table 4). There was no association of dose with development of azotemia.

3.5 | Fixed dose group characteristics and response to treatment

The mean dose of radioiodine in the fixed dose group was 4.45 mCi (SD ± 0.09). There was no association with outcome in the fixed dose

TABLE 3 Sex, age, percent dose uptake, T:S size ratio, average intensity, maximal intensity, pattern of disease, initial T4, 6-month T4, and 6-month outcome in novel dose group of cats in low, medium, and high dosage groups. Data are expressed as mean ± SD for normally distributed data and as median and range for nonparametric data

	Low dose (3.0 mCi) 28 cats (49%)	Medium dose (3.5 mCi) 20 cats (35%)	High dose (4.5 mCi) 9 cats (16%)	*P* value
Sex	14 nm,14 sf	15 nm,5 sf	3 nm,6 sf	.10+
Age	12.1 ± 2.1	11.9 ± 2.4	12.1 ± 1.8	.65++
Percent dose uptake	2.3 (0.3-4.6)	5.6 (1.7-9.6)	16.3 (11.5-34.5)	<.0001+++
T:S size ratio	2.9:1 (1.4-5.5)	4.2:1 (1.9-7.4)	6:1 (4.1-17.2)	<.0001+++
Average T:S intensity ratio	2.4:1 (0.8-5.4)	3.7:1 (1.6-7.7)	8.3:1 (4.5-23.3)	<.0001+++
Maximal T:S intensity ratio	3.3:1 (0.8-7.1)	5.2:1 (2.0-7.7)	13.3:1 (5.6-23.3)	<.0001+++
Pattern of disease	U: 11 (39%) B: 1 (3.5%) AB: 15 (54%) A: 1 (3.5%) E: 1 (3%)	U: 8 (40%) B: 2 (10%) AB: 9 (45%) A: 1 (5%) E: 4 (21%)	U: 2 (22%) B: 3 (33.5%) AB: 3 (33.5%) A: 1 (11%) E: 3 (33%)	.24++++
Initial T4 nmol/L	97 (39.4-193)	171 (64.7-308)	243 (178-411)	<.0001+++
6-month T4 nmol/L	22.7 (9.3-102)	22.1 (14.3-60.5)	26 (6.4-62.0)	.75+++
Outcome	Euth: 15 (54%) Hyper: 2 (7%) Hypo: 11 (39%)	Euth: 12 (60%) Hyper: 5 (25%) Hypo: 3 (15%)	Euth: 6 (67%) Hyper: 2 (22%) Hypo: 1 (11%)	.56++++

Abbreviations: U, unilateral; B, bilateral; AB, asymmetric bilateral; A, atypical; E, ectopic; +, Chi-square; ++, one-way ANOVA; +++, Kruskal-Wallis test; +++ +, Fisher's exact test.

TABLE 4 Sex, age, percent dose uptake, T:S size ratio, average intensity, maximal intensity, pattern of disease, ectopic thyroid tissue, and initial serum T4 concentration in relation to outcomes in fixed dose and novel dose groups. Data are expressed as mean ± SD for normally distributed data and as median and range ( ) for non-parametric data

	Fixed dose group				Novel dose group			
	Euthyroid 11 cats (48%)	Hyperthyroid 2 cats (9%)	Hypothyroid 10cats (43%)	*P* value	Euthyroid 31cats 54%)	Hyperthyroid 9 cats (16%)	Hypothyroid 17 cats (30%)	*P* value
Sex	5 nm 6 sf	2 nm 0 sf	5 nm 5sf	.36+	18 nm 13 sf	6 nm 3 sf	9 nm 8 sf	.60+
Age	12.5 ± 2.8	14 ± 0	11.6 ± 3.2	.54++	11.8 ± 2.0	11.9 ± 3.1	12.5 ± 1.8	.56++
Weight (kg)	4.5 ± 1.1	4.2 ± 0.1	3.5 ± 0.4	**.03**++	4.6 ± 1.1	4.5 ± 1.4	4.0 ± 1.5	.41++
% Dose Uptake	4.5 (0.53-14.2)	7.5 (4.1-11)	4.2 (1.2-8.00)	.68+++	4.3 (0.3-24.2)	5.5 (0.6-34.5)	2.6 (0.98-16.3)	.52+++
T:S size ratio	7.7:1 (3.07-12.6)	27.9:1 (17.2-38.7)	5.3.1 (2.9-10.0)	**.01**+++	4:1 (1.4-8.5)	5.3:1 (1.9-17.2)	3.2:1 (1.9-6.3)	.42+++
Initial T4	131 (48-192)	177.5 (172-183)	114.5 (51-263)	.49+++	148 (39-332)	170 (100-411)	105 (58-243)	.10+++
T:S intensity ratio	3.9:1 (0.92-14.3)	4.5:1 (3.0-5.9)	4.81 (1.7-16.77)	.92+++	3.5:1 (1.2-23)	4.9:1 (0.8-12.1)	2.4:1 (1.5-13.7)	.16+++
Ectopic	0	1	0	.09+++	5	2	1	.46+++
Pattern	AB:6, B:1, U:4	B:2	AB:3, B:2, U:5	.14+++	AB:15, AT:1, B:2, U:13	AB:3, AT:3, B:1, U:2	AB:9, B:2, U:6	.14+++

Abbreviations: U, unilateral; B, bilateral; AB, asymmetric bilateral; A, atypical; +, Fisher's exact test; ++, one-way ANOVA; +++, Kruskal-Wallis test.

group with respect to sex, age, initial mean serum T4 concentration, mean percent dose uptake, mean average T:S intensity ratio or mean maximal T:S intensity ratio, pattern of disease, or presence of ectopic tissue (Table 4). There was an association of outcome with T:S size ratio in that cats with larger thyroid size had an increased rate of persistent hyperthyroidism (P = .01) in the fixed dose group (Figure 1). There also was an association with weight and cats with the lowest weight were more likely to become hypothyroid (P = .03).

3.6 | Characteristics and response to treatment in all hyperthyroid cats

When the novel variable and fixed dose groups were combined, cats that remained persistently hyperthyroid had the highest initial serum T4 concentrations (median, 172 nmol/L; range, 100-411 nmol/L) and those that became hypothyroid had the lowest initial serum T4 concentrations (median, 109 nmol/L; range, 51-263 nmol/L), but this difference was not statistically significant (P = .05). Pattern of disease affected outcome (P = .02) in that 3/4 of cats with an atypical pattern of disease were persistently hyperthyroid.

4 | DISCUSSION

We failed to detect differences in outcome between our novel method of dosing based on thyroid scintigraphy and a fixed dose of radioiodine in hyperthyroid cats. Our hypothesis that radioiodine dosing utilizing percent dose uptake and thyroid size as determined by scintigraphy would increase euthyroidism while decreasing development of hypothyroidism post-radioiodine treatment was not supported.

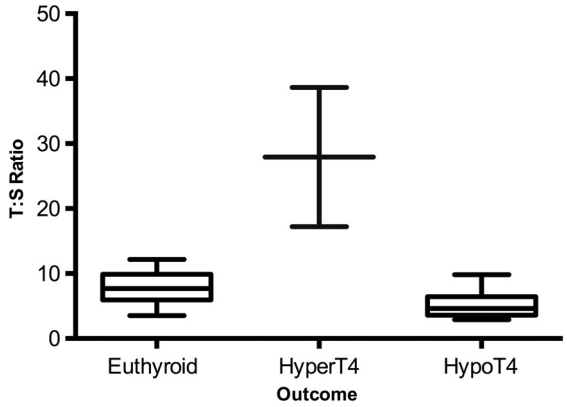

FIGURE 1 Fixed dose thyroid size in relation to euthyroid, persistently hyperthyroid, and hypothyroid outcomes. The boxes indicate the 25th to 75th percentile and the whiskers 10 and 90 percentiles. Those cats with a larger thyroid size were more likely to become persistently hyperthyroid, $P = .01$

The high prevalence of hypothyroidism in the novel variable dose group was in large part the result of the low dose of 3 mCi being excessive, considering that 11/17 (64%) cats that became hypothyroid were in the low dose group. Recently, it was shown that a ^{131}I dose of 2 mCi was highly efficacious in treating cats with mild hyperthyroidism, defined as serum T4 concentration <167 nmol/L (4.43 times the upper limit of reference range).[12] In our study, 25/28 cats in the novel variable dose group receiving a low dose of radioiodine had a pretreatment serum T4 concentration that was <4.43 times the upper limit of the reference range. Eleven of these 25 cats became hypothyroid, indicating that 3 mCi was excessive for many of the mildly affected cats.

The increased prevalence of higher serum T4 concentrations being associated with persistent hyperthyroidism is consistent with other studies. However, it is likely not the sole factor because some cats with markedly increased serum T4 concentrations in other studies have become hypothyroid.[3,13,14] Although serum T4 concentrations often are directly correlated with thyroid gland size, this finding is not consistent and hypothyroidism can occur in cats with markedly increased serum T4 concentrations and smaller thyroid gland size.[13]

In the fixed dose group, the largest thyroid gland sizes were associated with persistent hyperthyroidism, suggesting that 4.5 mCi of ^{131}I is inadequate for cats with more severe disease. This observation is consistent with a previous study in which 7 cats with greatly enlarged thyroid glands treated with 4.0-6.0 mCi of ^{131}I remained persistently hyperthyroid.[3]

The majority of cats in our study with euthyroid outcome in both groups had asymmetrical bilateral or unilateral disease. This presumably is because suppressed thyroid tissue was spared damage and regained normal function.

Although numerous studies have evaluated the fixed dose and variable dose methods of radioiodine dose determination, we are not aware of studies directly comparing these techniques. In addition, the novel variable dose method used in our study is unique in its use of percent dose uptake and thyroid size based on scintigraphy as the sole parameters to determine radioiodine dose. Other studies investigating modified fixed dose methods have based dosing on criteria including serum T4 concentration, clinical signs, and thyroid gland size, but have not used well-described and repeatable methods of dose calculation.[2–4,6] Unfortunately, the dosing scheme used in our study failed to provide more favorable results.

The proportion of cats developing hypothyroidism with both dosing methods was higher than in many other studies that had prevalence of post-treatment hypothyroidism ranging from 5 to 30%.[14–16] Possible reasons for the differences include variations in the definition of hypothyroidism, the presence of concurrent illness, variable time of follow-up, variable dosages, and differences in the severity and pattern of disease.

Hyperthyroidism persisted after treatment in 16% of cats in the novel variable dose group, which is higher than the 1.5%-12% noted in studies using different variable dosing methods.[1–3,6] Cats with more severe disease as indicated by significantly higher serum T4 concentrations and higher volumes of hyper-functioning thyroid tissue have a high rate of persistent hyperthyroidism.[1] Additionally, carcinomas have been shown to respond poorly to standard doses of radioiodine.[17] Consistent with this, 3/4 cats in our novel group that had an atypical scintigraphic pattern of disease remained hyperthyroid. Because no atypical pattern of disease was present in the fixed dose group, this may at least partially explain the lower incidence of persistent hyperthyroidism in this group. The presence of ectopic tissue has been shown to affect outcome in a previous study.[6] In our study, no association was found between the presence of ectopic tissue in either dosage group and outcome, but ectopic tissue was not quantified as in a previous study.[6]

Because the lowest dosage group had the lowest occurrence of persistent hyperthyroidism and the medium dosage group had the lowest occurrence of hypothyroidism, the variables used to set the division between the low and medium dose appear to be valid. This may not be the case for the parameters determining the division between the medium and high dosage groups, because 25% of the cats in the medium dosage group remained hyperthyroid after treatment, suggesting that a higher dose should have been used in some cats. These cats had variable serum T4 concentrations and patterns of disease that lacked definitive variables that might have suggested a higher dose. Perhaps other variables, such as clinical signs and duration of disease, should be used to determine an ideal dose.

Thyroid gland size and intensity of uptake were higher in the fixed dose compared to the novel variable dose group. Disease duration may be related to thyroid gland size as has recently been reported, and that more chronic disease requires a higher dose of radioiodine to achieve euthyroidism.[18] Another study suggested that increased thyroid volume (by number of foci) is associated with a hypothyroid outcome.[6] Fewer than 25% of cats in the fixed dose group had symmetric bilateral disease and only 1 had ectopic foci. If the number of foci was directly correlated with the development of hypothyroidism, hypothyroidism would have been expected to occur less frequently in the population of cats in the fixed dose group. Only 1 of the 8 cats (12.5%) in the novel dose group with ectopic tissue was hypothyroid after treatment. This is lower than the overall prevalence of hypothyroidism in this group, indicating that factors other than the presence of ectopic tissue lead to the development of hypothyroidism.

As average and maximal T:S intensity ratios increased, dosage increased as a result of our study design, because T:S intensity ratios are directly correlated with percent dose uptake. This suggests that T:S intensity ratio increased with disease severity. A direct correlation of initial serum T4 concentration with dose also was noted. This is consistent with previous studies that have shown that serum T4 concentration was positively correlated with percent dose uptake.[8,19] Despite these correlations, serum T4 concentration, percent dose uptake, and T:S intensity ratio were not associated with outcome.

One of the limitations of our study was small sample size. A larger sample size may have produced different results. Many cats were excluded because they were lost to follow-up for unknown reasons. In addition, the population studied may not adequately represent the general population of cats undergoing radioiodine treatment, because many cats were referred for radioiodine treatment because of difficulty in controlling their hyperthyroidism, thereby suggesting more severe disease. Another limitation is that the duration of hyperthyroidism was not recorded. Duration of disease has been suggested to increase disease severity, and possibly affect response to treatment.[18] This may explain why the lowest novel dosage group had the lowest rate of persistent hyperthyroidism. Because drugs used for sedation can affect scintigraphy, failure to use a standard sedation protocol for all cats during this procedure could have influence stratification of patients into dosage categories.[20]

Treatment outcome in our study was classified on the basis of serum T4 and TSH concentrations. Serum TSH concentration is useful in establishing thyroid status in cats when used in conjunction with serum T4 concentration. Serum T4 concentrations fluctuate in hyperthyroid cats and may be within the reference range at a given time point in cats with mild hyperthyroidism.[21] Cats with a serum T4 concentration in the reference range but undetectable TSH are at increased risk for developing hyperthyroidism.[22] In addition, evidence is accumulating that an increased serum TSH concentration is diagnostic for hypothyroidism.[12,23] Scintigraphic confirmation of hypothyroidism after radioiodine treatment has been noted in cats with serum TSH concentration above the reference interval despite serum T4 or free T4 concentrations within their respective reference intervals.[23] The specificity of an increased serum TSH concentration is very high, even in cats with nonthyroidal illness, including chronic kidney disease, and it is unlikely that cats classified as hypothyroid in our study were euthyroid.[23]

Several methods to determine thyroid gland volume or size have been described, and the method used in our study based on a T:S size ratio is unique.[4,11,24] Our goal was to use a simple method of determining thyroid size that had little interobserver error. This technique was chosen because of its simplicity and ease of use to compare thyroid size among cats. Salivary gland shape and location do not vary substantially among cats, which makes identification of the salivary gland margins easier to place an ROI around. This ratio also removed the impact of variable field of view size. A calculated method of volume assumes a symmetrical shape to the thyroid gland and determines the volume using length, width, and sometimes height measurement. One could argue that the assumptions of shape do not hold true in many abnormal thyroid gland lobes. Dimensions of the thyroid gland measured from the thyroid scan are also prone to errors. A 10% threshold was chosen for the calculation of the thyroid ROI to decrease the likelihood of missing thyroid tissue, especially in cats with asymmetrical bilateral disease. Without a gold standard, the threshold for ROI placement is arbitrary. It is possible that, by using this technique, the amount of thyroid tissue present was overestimated as compared to using a higher threshold. Calculating thyroid gland volume using another method may have produced different results.

In summary, our novel method of radioiodine dosing based on percent dose uptake and thyroid size did not result in improved overall outcomes compared to a standard fixed dose method. In fact, rates of post-treatment persistent hyperthyroidism and development of hypothyroidism exceeded those found in other studies of modified fixed dosing methods.[3–6]

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflicts of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

This study was approved by Virginia Tech IACUC as well as the VMCVM Veterinary Teaching Hospital Board.

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