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A dosing algorithm for individualized radioiodine treatment of cats with hyperthyroidism

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Abstract

Background: Radioiodine (^{131}I) is the treatment of choice for hyperthyroidism in cats, but current ^{131}I-dosing protocols can induce iatrogenic hypothyroidism and expose azotemia.

Objectives: To develop a cat-specific algorithm to calculate the lowest ^{131}I dose to resolve hyperthyroidism, while minimizing risk of iatrogenic hypothyroidism and subsequent azotemia.

Animals: One thousand and four hundred hyperthyroid cats treated with ^{131}I.

Methods: Prospective case series (before-and-after study). All cats had serum concentrations of thyroxine (T_4), triiodothyronine (T_3), and thyroid-stimulating hormone (TSH) measured (off methimazole ≥1 week). Using thyroid scintigraphy, each cat's thyroid volume and percent uptake of ^{99m}Tc-pertechnatate (TcTU) were determined. An initial ^{131}I dose was calculated by averaging dose scores for T_4/T_3 concentrations, thyroid volume, and TcTU; 80% of that composite dose was administered. Twenty-four hours later, percent ^{131}I uptake was measured, and additional ^{131}I administered, as needed, to deliver an adequate radiation dose to the thyroid tumor(s). Serum concentrations of T_4, TSH, and creatinine were determined 6 to 12 months later.

Results: The median calculated ^{131}I dose was 1.9 mCi (range, 1.0-10.6 mCi); 1380 cats required additional ^{131}I administration on day 2. Of the cats, 1047 (74.8%) became euthyroid, 57 (4.1%) became overtly hypothyroid, 240 (17.1%) became subclinically hypothyroid, and 56 (4%) remained hyperthyroid. More overtly (71.9%) and subclinically (39.6%) hypothyroid cats developed azotemia than euthyroid cats (14.2%; $P < .0001$).

Conclusions and Clinical Importance: Our algorithm for calculating individual ^{131}I doses resulted in cure rates similar to historical treatment rates, despite much lower ^{131}I doses. This algorithm appears to lower prevalence of both ^{131}I-induced overt hypothyroidism and azotemia.

KEYWORDS

^{131}I, feline, hypothyroidism, radioactive iodine, scintigraphy, thyroid gland, thyroid-stimulating hormone, thyroxine, triiodothyronine

Abbreviations: ^{131}I, radioiodine; IQR, interquartile range; mCi, millicurie; T_3, triiodothyronine; T_4, thyroxine; TcTU, percent thyroidal uptake of sodium ^{99m}Tc-pertechnetate; μCi, microcurie; fT_4, free thyroxine; TSH, thyroid-stimulating hormone; ds, dose standard.

1 | INTRODUCTION

Radioiodine (^{131}I) is considered the treatment of choice for hyperthyroidism in cats, but the optimal method of ^{131}I dose determination remains controversial. The goal of ^{131}I therapy is to restore euthyroidism without producing hypothyroidism. Most treatment protocols concentrate on "cure" of hyperthyroidism without regard for development of iatrogenic hypothyroidism. With current fixed-dose (eg, 3-5 mCi)[1-5] or variable-dose protocols (3-5 mCi),[3,6-8] iatrogenic hypothyroidism develops in 30% to 80% of cats within 6 months of ^{131}I treatment.[1-4,6-9] Increasing evidence suggests that clinicians should attempt to minimize iatrogenic hypothyroidism, which can worsen existing azotemia, enhance progression of kidney disease, and shorten survival time in cats with CKD.[10-14] A individual cat-specific approach that administers the "lowest ^{131}I dose possible" to achieve euthyroidism could reduce the odds of iatrogenic hypothyroidism and associated kidney disease. Importantly, administering a lower ^{131}I dose also limits the radiation exposure to veterinary staff and owners, consistent with the principle of reducing radiation exposure to levels that are as low as reasonably achievable (ALARA).[15]

In this study, we sought to develop an objective method of determining an ^{131}I dose that achieves euthyroidism with the lowest possible radiation dose, thereby reducing the risk of iatrogenic hypothyroidism. Specifically, we used the results of serum thyroid hormone concentrations, quantitative thyroid scintigraphy, and the percent thyroid ^{131}I uptake to calculate individual ^{131}I doses.

2 | MATERIALS AND METHODS

2.1 | Study population

All hyperthyroid cats referred to the Animal Endocrine Clinic for treatment with ^{131}I over the 7.5-year period from January 2013 to June 2020 were evaluated for inclusion in this prospective, consecutive controlled case series (before-and-after study).[16] To be eligible for inclusion, untreated hyperthyroid cats underwent an evaluation that included review of the past medical record, complete physical examination, routine laboratory testing (complete blood count, serum biochemical profile, complete urinalysis), determination of serum thyroid hormones (total T_4, T_3, and TSH),[2,17,18] and qualitative and quantitative thyroid scintigraphy.[19,20] In cats treated with methimazole, owners discontinued administration of the drug at least 1 week before evaluation.[19,20] Owners feeding a low-iodine diet (Hill's Prescription Diet y/d Feline, Topeka, KS) were instructed to feed an iodine-replete diet for at least 4 weeks before treatment.

We excluded hyperthyroid cats with preexistent azotemia (defined as serum creatinine >2.0 mg/dL) and cats with multifocal disease (≥3 separate tumor nodules or areas of increased radionuclide uptake on thyroid scintigraphy), in which thyroid carcinoma could not be excluded.[19-22]

The study was approved by our Institutional Animal Care and Use Committee, and all owners provided informed consent.

2.2 | Protocol for calculating individualized ^{131}I doses

On the day of admission, each cat had blood drawn for determination of serum concentrations of thyroxine (T_4), triiodothyronine (T_3), and thyroid-stimulating hormone (TSH) (Figure 1), using previously described assays validated for use in cats.[2,17,18] Thyroid scintigraphy was then performed by injecting 3-5 mCi (111-185 MBq) of sodium ^{99m}Tc-pertechnetate ($^{99m}TcO^-_4$) into the saphenous vein and imaging 60 minutes later.[19,20] Qualitative analysis allowed us to classify cats into 1 of 3 patterns of thyroid disease—unilateral, bilateral, and multifocal disease (≥3 areas or nodules of increased radionuclide uptake)—and helped exclude thyroid carcinoma.[19,22] Quantitative thyroid scintigraphy allowed calculation of the percent thyroidal uptake of the injected sodium ^{99m}Tc-pertechnetate (TcTU) and determination of the volume of each cat's thyroid tumor (Figure 1), as previously described (see Supplemental Files 1 and 2 for more details).[19,20]

We next determined the ^{131}I dose (severity) scores for serum thyroid hormone (T_4 and T_3) concentrations, TcTU, and thyroid volume (Table 1, Figure 1). A composite ^{131}I dose score was then calculated by averaging the dose scores for thyroid hormone, thyroid volume, and TcTU dose; to avoid ^{131}I overdosage in cats with higher thyroid ^{131}I uptake values, we administered only 80% of this composite ^{131}I dose on day 1 (Table 1, Figure 1).

At the time of each cat's initial ^{131}I treatment, we prepared an ^{131}I dose standard using a 5-mL sterile glass vial, 20-mm outer diameter (ALK Life Science Solutions, Port Washington, NY) for the ^{131}I uptake studies (see Supplemental File 3 for more details). To this vial, 350-500 μCi (≈15 MBq) of ^{131}I was added, with the final volume contained in this dose standard ≈2 mL. Both the administered ^{131}I dose and the ^{131}I dose standard were measured by a dose calibrator (CRC-127R Dose Calibrator, Capintec, Inc, Florham Park, NJ).

Twenty-four hours after administration of this initial ^{131}I dose, we determined the percent thyroidal ^{131}I uptake (Figure 1; Supplemental File 4), as follows.[23] Neck radioactive counts were measured using a survey meter (Model 14C Survey Meter with Model 44-9 Pancake G-M Detector, Ludlum Measurements Inc, Sweetwater, TX) by placing its detector directly on the skin surface over the cats' hottest thyroid nodule. A background count was also measured over the cat's thigh using the same survey meter (see Supplemental File 4). Finally, the activity of the ^{131}I dose standard (ds) was also measured by placing it directly on the survey meter's pancake G-M detector, and these measured counts were used to calculate the counts of ^{131}I that had been administered to each cat, as follows:

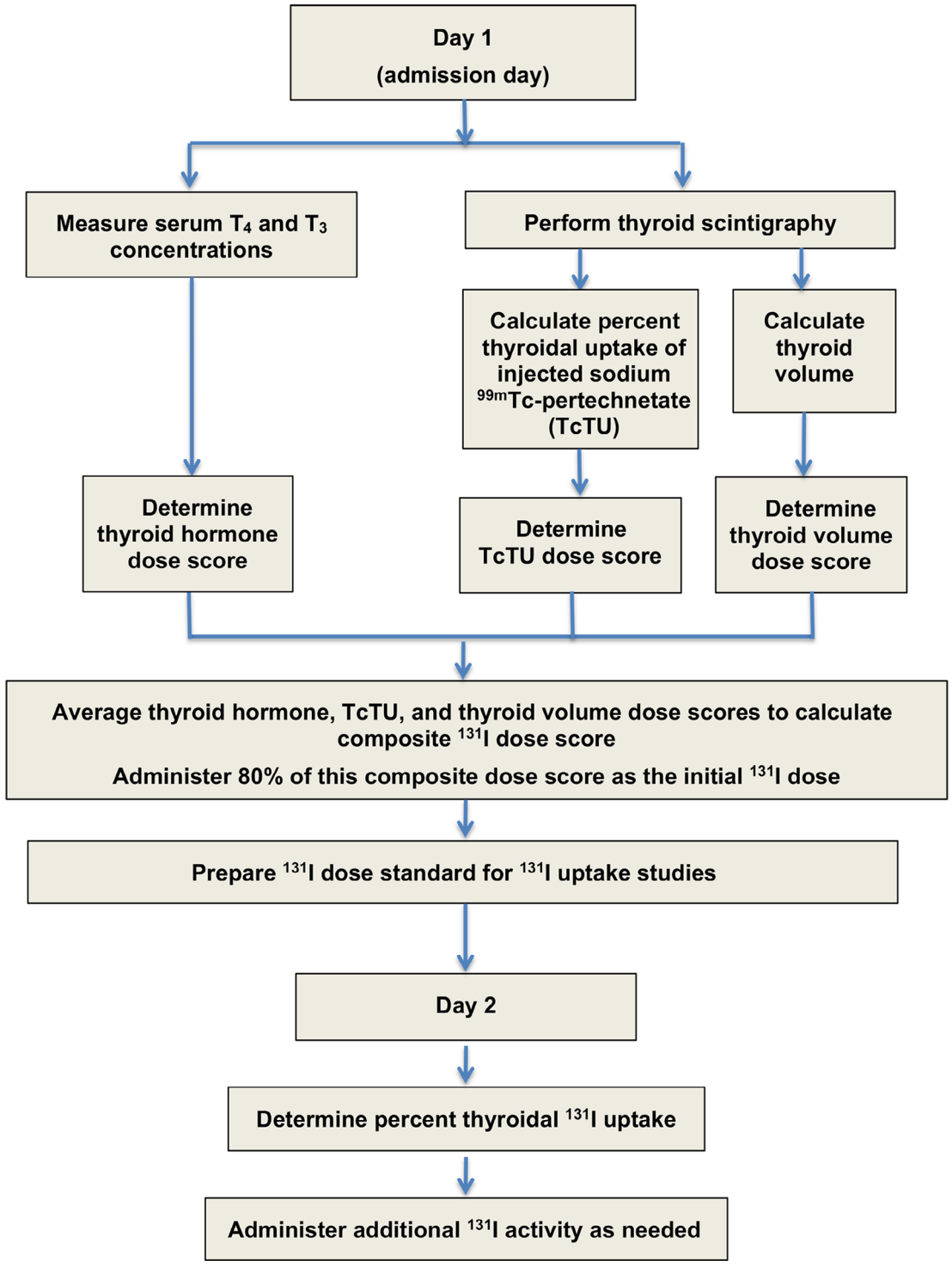


FIGURE 1 Flowchart showing protocol for calculating initial (day 1), composite ^{131}I dose based on 3 measures of disease severity (serum T_4 and T_3 concentrations, TcTU, and thyroid tumor volume). On day 2, thyroid ^{131}I uptake was measured and additional ^{131}I activity administered as needed

$$^{131}\text{I administered (cpm)} = \frac{\text{Inital } ^{131}\text{I (}\mu\text{Ci)}}{^{131}\text{I ds (}\mu\text{Ci)}} \times {}^{131}\text{I ds (cpm)}.$$

$$^{131}\text{I uptake (\%)} = \frac{\text{Thyroid counts (cpm)} - \text{Thigh counts (cpm)}}{^{131}\text{I administered (cpm)}} \times 100.$$

From this information, the percent ^{131}I thyroidal uptake was calculated (Table 1; Supplemental File 4):

Based on the ^{131}I uptake value, additional ^{131}I was administered on day 2, as needed to deliver an adequate radiation dose (200 μCi per cm^3) to the thyroid tumors (Figure 1; Table 1).

TABLE 1 Protocol for ^{131}I dose calculation, based on measured thyroid tumor volume, serum T_4 and T_3 concentrations, TcTU, and 24-hour thyroid ^{131}I uptake measurements

1. Measure serum T_4 and T_3 concentration
- Determine thyroid hormone ^{131}I dose score
- Average the individual scores for serum T_4 and T_3 concentrations, if different, to calculate the thyroid hormone dose score (see table below)

2. Measure percent TcTU
- Determine TcTU dose score (see table below)

3. Calculate thyroid tumor volume
- Determine thyroid volume dose score = 1 mCi (37 MBq) per cm^3 of tumor tissue

Serum T_4 µg/dL (nmol/L)	Serum T_3 ng/dL (nmol/L)	TcTU (%)	Dose score mCi (MBq)
<5.0 (65)	<75 (<1.15)	<1	1.3 (50)
5.0-7.5 (65-100)	75-150 (1.16-2.3)	1-3	1.7 (60)
7.6-10.0 (101-125)	151-200 (2.4-3.0)	3-5	1.9 (70)
10.1-12.5 (126-160)	201-250 (3.1-3.8)	5-7	2.2 (80)
12.6-15.0 (161-195)	251-300 (3.9-4.6)	7-10	2.7 (100)
15.1-17.5 (196-225)	301-350 (4.7-5.4)	10-13	3.3 (125)
17.6-20.0 (226-255)	351-400 (5.5-6.1)	13-17	4.0 (150)
20.1-27.5 (256-350)	401-500 (6.2-7.7)	17-23	5.0 (185)
27.6-35.0 (350-450)	501-600 (7.8-9.2)	23-30	6.5 (240)
>35.0 (>450)	>600 (>9.2)	>30%	8.5 (315)

4. Calculate the composite ^{131}I dose score (mCi) by averaging the 3 individual scores (thyroid hormone score, TcTU score, and thyroid volume score). To avoid ^{131}I overdosage in cats with high ^{131}I uptake, administer only 80% of this composite dose score as the initial ^{131}I dose

Initial ^{131}I dose (mCi) $= \left(\frac{\text{Thyroid hormone score} + \text{TcTU score} + \text{Thyroid volume score}}{3}\right) \times 0.8$

5. Measure 24-hour thyroid ^{131}I uptake and adjust final dose (administer additional ^{131}I activity, as needed), based on table below

Percent 24-hour ^{131}I uptake (%)	Multiply composite ^{131}I dose score by factor below
<6	1.7
>6-9	1.5
>9-12	1.3
>12-14	1.2
>14-16	1.1
>16–18	1.05
>18-22	1.0
>22-28	0.95
>28-34	0.90
>34-40	0.85
>40	0.80

Notes: To convert serum T4 concentration from µg/dL to nmol/L, multiply by 12.87. To convert serum T3 concentration from ng/dL to nmol/L, multiply by 0.154. To convert mCi to mBq, multiply by 37.
Abbreviations: ^{131}I, radioiodine; MBq, megabecquerel; TcTU, percent thyroidal uptake of sodium ^{99m}Tc-pertechnetate; µCi, microcurie.

For example, a cat with a serum T_4 concentration of 13.3 µg/dL, a serum T_3 concentration of 242 ng/dL, a thyroid volume of 2.5 cm^3, and a TcTU of 6% would score $[(2.7 + 2.2)/2] + 2.5 + 2.2)/3 =$ 2.38 mCi; 80% of this composite dose (1.9 mCi) would be administered on day 1. On day 2, the ^{131}I uptake would be calculated. If this cat had an ^{131}I uptake of 32%, the total dose to be administered would be 2.38 mCi*0.9 = 2.14 mCi. Therefore, an additional 0.24 mCi would be administered on day 2 to reach the final target ^{131}I dose. To facilitate dose calculations, we developed an Excel spreadsheet to calculate the initial (day 1) and final ^{131}I dose (Supplemental File 5).

2.3 | Follow-up monitoring and testing after ^{131}I treatment

After ^{131}I treatment, all cats were scheduled for evaluation at 1, 3, 6, and 12 months, with follow-up serum concentrations of T_4, TSH, and creatinine determined at each visit. To maintain enrollment compliance, the owners of ^{131}I-treated cats could either return to our clinic or have the follow-ups performed by the referring veterinarian, with samples submitted directly to 1 of 2 designated reference veterinary diagnostic laboratories (Antech Diagnostics, Lake Success, NY, or IDEXX Reference Laboratories, Westbrook, ME). We have shown that when serum samples were divided into 2 aliquots and submitted to both laboratories for analysis, there was good agreement for both T_4 and TSH concentrations, especially within the ranges for clinical decision surrounding their reference intervals (1.0-3.8 µg/dL and 0.03-0.3 ng/mL, respectively).[2,24]

2.4 | Classifying thyroid subgroups and azotemia after ^{131}I treatment

Based on the serum concentrations of T_4 and TSH at 6 to 12 months (median, 6 months) after treatment with ^{131}I, we classified the cats' thyroid status into 1 of 4 thyroid categories: euthyroid (T_4, 1.0-3.8 µg/dL; TSH ≤0.30 ng/mL), overtly hypothyroid (T_4 < 1.0 µg/dL; TSH >0.30 ng/mL), subclinically hypothyroid (T_4, 1.0-3.8 µg/dL; TSH >0.30 ng/mL), and persistently hyperthyroid (T_4 ≥ 3.9 µg/dL; TSH <0.03 ng/mL), as previously defined.[2,10,25,26] We also classified cats as azotemic or nonazotemic based on the serum creatinine concentration, with azotemia defined as a serum creatinine concentration above our institution's reference interval (>2.0 mg/dL).[10] We excluded cats lost to follow-up or only tested sooner than 6 months after ^{131}I treatment to prevent misclassification of cats that might still be recovering from TSH suppression secondary to the previous hyperthyroid state, as well as for cats with high serum T_4 concentrations that were still normalizing (some cats will require ≥6 months to become euthyroid).[27]

2.5 | Data and statistical analyses

Data were assessed for normality by the D'Agostino-Pearson test and by visual inspection of graphical plots.[28] Data were not normally

distributed; therefore, all analyses used were performed using nonparametric tests. Results for continuous data (eg, serum T_4, T_3, TSH, and creatinine concentrations) are expressed as median (interquartile range [IQR], 25th-75th percentile) and represented graphically as box-and-whisker plots (Tukey method).[29] Continuous variables were compared between groups by the Man-Whitney *U*-test or the Kruskal-Wallis test. Outcomes in previous studies were compared to the results of the current study with likelihood ratio chi-square tests, followed by pairwise comparisons using a Holm-Sidak adjustment for comparison-wise error.[30]

Untreated hyperthyroid cats were categorized into mild-to-moderate disease (dose scores <2.5 mCi) and severe disease (dose scores ≥2.5 mCi) groups based on their composite ^{131}I dose (severity) scores.

For all analyses, statistical significance was defined as $P \leq .05$. Statistical analyses were performed using proprietary statistical software (GraphPad Prism, version 9.0; GraphPad Software, La Jolla, CA) and a freeware software program (WINPepi version 11.65, http://www.brixtonhealth.com/pepi4windows.html).

3 | RESULTS

3.1 | Cat characteristics

Over the 7.5-year study period, we treated 1688 hyperthyroid cats that were eligible for inclusion and enrolled in the study; 288 cats were lost to follow-up after <6 months of ^{131}I treatment and were excluded from study (Figure 2). The remaining 1400 cats were reexamined and retested at a median of 6 months (IQR, 6-7 months; range, 6-12 months) after ^{131}I treatment.

The 1400 hyperthyroid cats ranged in age from 3 to 20 years (median, 12.0 years; IQR, 10-14 years). Breeds included domestic longhair and shorthair (1255 cats; 89.6%), Maine Coon (37 cats), Siamese (33 cats), Russian Blue (10 cats), Bengal (9 cats), Norwegian Forest Cat (9 cats), Burmese (7 cats), Ragdoll (6 cats), Bombay (5 cats), Persian (5 cats), Manx (3 cats), Scottish Fold (3 cats), Siberian (3 cats), American Curl (2 cats), Oriental (2 cats), Tonkinese (2 cats) and Abyssinian, American shorthair, Birman, Chartreux, Devon Rex, Havana Brown, Himalayan, Korat, and Ocicat (1 cat each). Of these, 650 (46.4%) were male and 750 (53.6%) were female; all had been neutered.

Body weight ranged from 1.6 to 9.2 kg (median, 4.4 kg; IQR, 3.7-5.3 kg); 376 (26.9%) cats were considered underweight, 826 (59%) had an ideal body condition score, and 198 (14.1%) were considered overweight. The time from diagnosis of hyperthyroidism to ^{131}I treatment ranged from 4 days to 6 years (median, 65 days; IQR, 31-97 days). Six hundred and seventy cats (48%) had never received methimazole treatment, and 728 (52%) cats had been treated with methimazole for a median time of 60 days. In all methimazole-treated cats, the drug was discontinued ≥1 week (median, 7 days; IQR, 7-15 days; range, 7-150 days) before treatment with ^{131}I. Nineteen (1.4%) cats had been fed a low-iodine diet (Hill's y/d), which was discontinued and changed to an iodine-replete diet for at least 4 weeks before treatment.

3.2 | Pretreatment serum T_4, T_3, TSH, and creatinine concentrations

Almost all untreated hyperthyroid cats (1374/1400; 98.4%) had high serum T_4 concentrations (Figure 3A). All 26 cats with normal serum T_4 concentrations had high serum free T_4 concentrations, as well as increased radionuclide uptake on thyroid scintigraphy (ie, 1 or more hot thyroid tumor nodules).

Before treatment, 1116 cats (79.7%) had high serum T_3 concentrations (Figure 3B). All 266 cats with the most severe hyperthyroidism (composite ^{131}I dose/severity score ≥ 2.5) had high serum T_3 concentrations; these severely affected cats also had serum T_3:T_4 molar ratios (0.022; IQR, 0.019-0.026) that were higher than those in the 1134 cats with mild-to-moderate hyperthyroidism (0.017; IQR, 0.014-0.021; $P < .001$).

Serum TSH concentration was below the limit of detection (<0.03 ng/mL) in 1366 cats (97.6%; Figure 3C).

3.3 | Thyroid scintigraphy findings

On qualitative scintigraphy, 753 (53.8%) hyperthyroid cats had bilateral disease, whereas 647 had unilateral thyroid nodules. These thyroid nodules had increased intensity of uptake, as evidenced by high thyroid-to-salivary gland ratio (median, 5.2; IQR, 3.1-8.8; RI <1.5).

Almost all cats (1357/1400; 96.9%) had a high thyroid uptake of pertechnetate (TcTU; Figure 4A). Similarly, almost all cats (1369/1400; 97.8%) had an increased thyroid tumor volume (Figure 4B).

3.4 | Individualized ^{131}I dose calculations

The composite ^{131}I dose score for the 1400 cats ranged from 0.9 to 10.4 mCi (median, 1.87 mCi; IQR, 1.67-2.27 mCi). On day 1, ≈80% of this composite dose score (median, 1.49 mCi; IQR, 1.33-1.8 mCi) was administered.

After adjusting the composite ^{131}I dose for the ^{131}I uptake value (Table 1, Figure 4C), the 1380 cats with ^{131}I uptake values <40% were treated with a second ^{131}I dose on day 2; the 20 cats with values >40% received no additional ^{131}I. The 261 cats with very low (<16%) ^{131}I uptakes received a higher second ^{131}I dose (median, 0.73 mCi; IQR, 0.63-0.91 mCi) than did the 818 cats with midrange ^{131}I uptakes (median, 0.36 mCi; IQR, 0.3-0.43 mCi) or did the 321 cats with high (>28%) ^{131}I uptakes (median, 0.19 mCi; IQR, 0.14-0.23 mCi; $P < .0001$).

The total ^{131}I dose administered to the 1400 cats ranged from 0.95 to 10.6 mCi (median, 1.90 mCi; IQR, 1.70-2.20 mCi). Of the cats, only 235 (16.8%), 133 (9.5%), and 52 (3.7%) received a ^{131}I dose ≥2.5 mCi, ≥3 mCi, and ≥4 mCi, respectively.

3.5 | Thyroid and renal outcome status 6 to 12 month after ^{131}I treatment

After ^{131}I treatment, 1047 (74.8%) cats became euthyroid, 57 (4.1%) cats developed overt hypothyroidism, 240 (17.1%) cats had subclinical

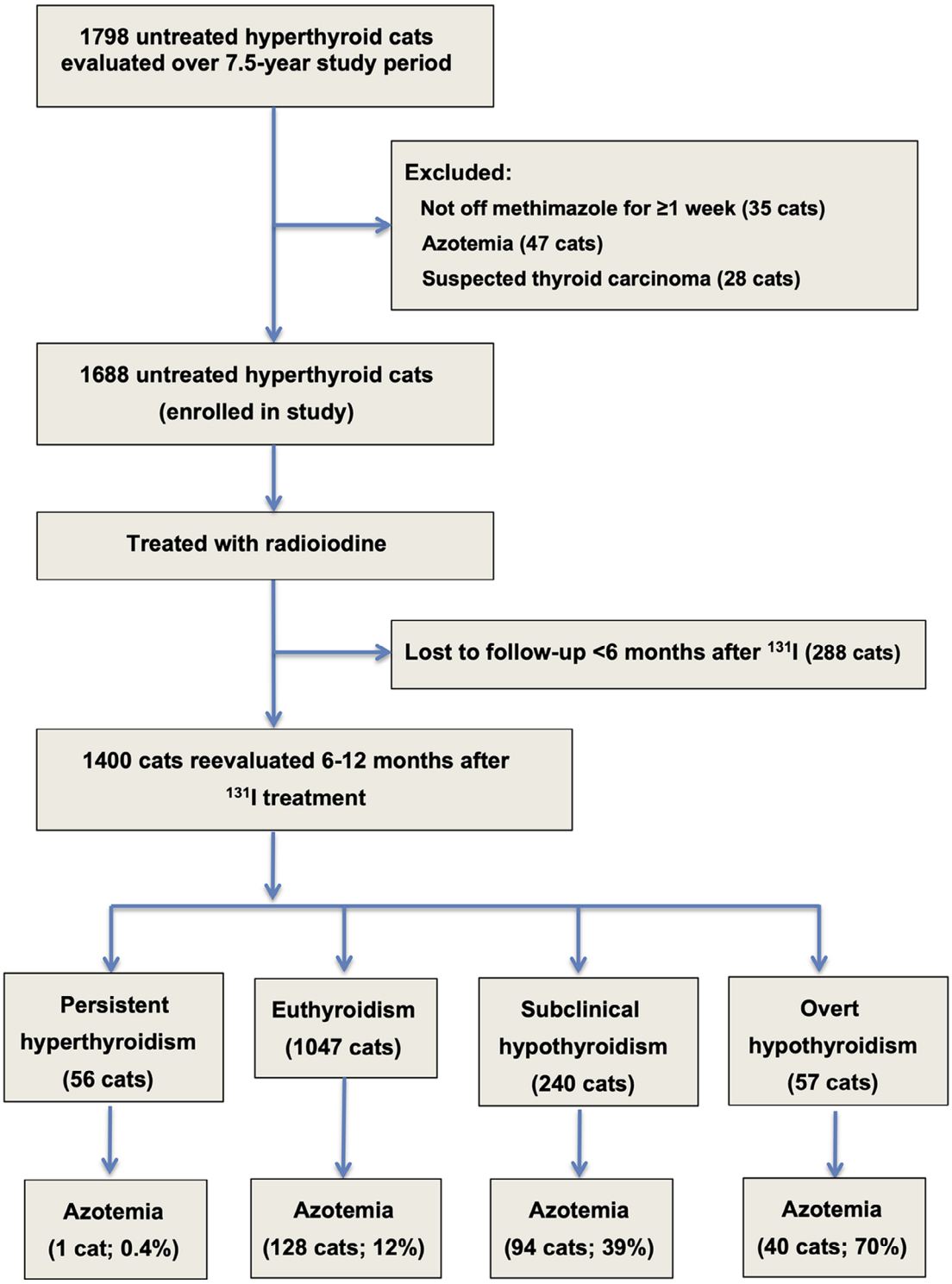
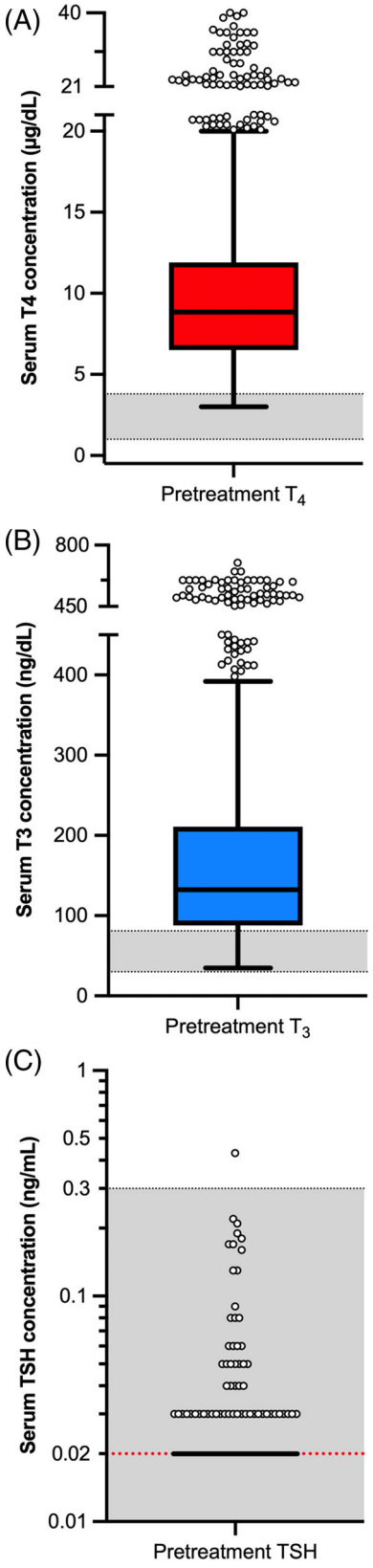


FIGURE 2 Flowchart for enrollment of hyperthyroid cats, separated into 4 thyroid outcome groups, as well as the development of azotemia after treatment with radioiodine

hypothyroidism, and 56 (4%) cats remained hyperthyroid (Figures 2 and 5A,B). A higher proportion of cats with severe hyperthyroidism failed treatment and remained persistently hyperthyroid (29/266; 10.9%) than did cats with mild-to-moderate disease (27/1134; 2.3%; $P < .0001$). In contrast, a higher proportion of cats with mild-to-moderate disease developed ^{131}I-induced hypothyroidism (253/1134; 22.3%) than did the cats with severe disease (44/266; 16.5%; $P = .04$). When compared to previously published studies, the individualized algorithm protocol resulted in more euthyroid cats and fewer overtly hypothyroid cats, without an increase in persistently hyperthyroid cats (Table 2).

Azotemia (serum creatinine >2.0 mg/dL) developed in 263 (18.8%) of the 1400 cats. The prevalence of posttreatment azotemia was higher in the cats with overt (40/57; 70.2%) and subclinical (94/240; 39.2%) hypothyroidism than in the cats that remained euthyroid (128/1047; 12.2%) or had persistent hyperthyroid (1/56; 1.8%) after ^{131}I treatment (Figure 5C; $P < .0001$). When compared to previously published studies, the individualized algorithm protocol resulted in similar to lowered prevalence of azotemia (Table 2).



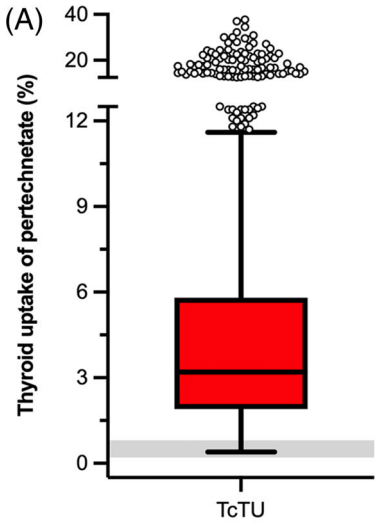
4 | DISCUSSION

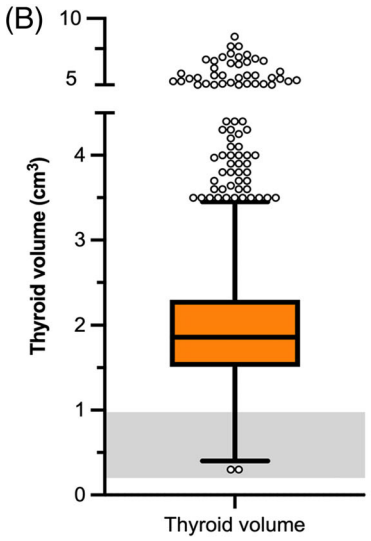
This study indicates that our protocol for calculating individual ^{131}I doses produces cure rates similar to or better than previously published studies, despite administration of much lower ^{131}I doses (Table 2). Because of the lowered ^{131}I dose, the protocol decreased the risk of ^{131}I-induced hypothyroidism but did not increase the risk of treatment failure (persistent hyperthyroidism; Table 2). Almost all cats with mild to moderate hyperthyroidism responded to very low doses of radioiodine (<2 mCi [<75 MBq]). These ^{131}I doses are lower than the lowest dose given with most variable scoring protocols (2-3 mCi [75-110 MBq])[3,6,8,27,31] and much lower than doses administered with traditional fixed-dose methods (4-5 mCi [148-185 MBq]).[1,2,9] In contrast, cats with severe hyperthyroidism and large thyroid tumor volumes (but without scintigraphic evidence of malignancy) sometimes required up to 10 mCi (370 MBq) of ^{131}I to restore euthyroidism. These calculated radioiodine doses are much higher than the highest dose given with most variable scoring or fixed-dose methods.[1-4,6-9,27,31]

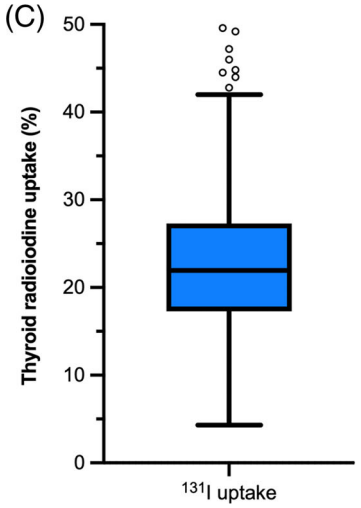
Our protocol uses 4 objective measures—serum thyroid hormone (T_4 and T_3) concentrations, thyroid volume, TcTU, and 24-hour percent ^{131}I uptake—to determine an individualized, calculated ^{131}I dose score for each cat. The first 3 indices all represent different ways at looking at the severity of a cat's hyperthyroid disease (ie, higher serum T_4 and T_3 concentrations, higher percent TcTU, and larger thyroid tumor volume all indicate more severe hyperthyroid disease).[20,32] The 24-hour percent ^{131}I uptake, on the other hand, evaluates the ability of the thyroid tumor to take up and concentrate ^{131}I, which is required to deliver an adequate radiation dose to the cat's thyroid tumor nodule(s).[33] If the 24-hour ^{131}I uptake is too low, the delivered radiation dose may be inadequate to irradiate and ablate the thyroid nodule, resulting in treatment failure.[23,33,34] On the other hand, if the ^{131}I uptake is higher than expected, a cat could receive an excessive dose, resulting in iatrogenic hypothyroidism.[23,33,35]

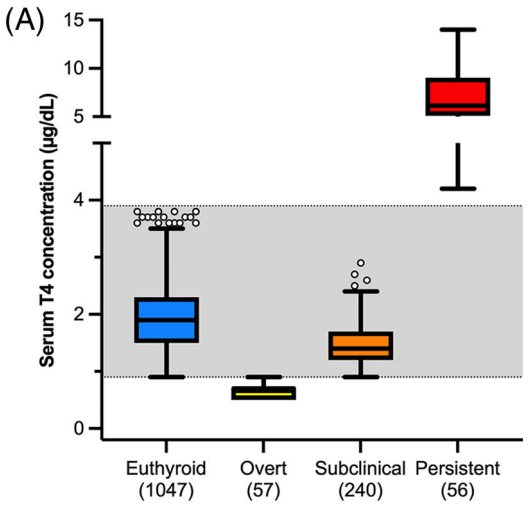
Although use of serum T_4 concentration is routinely used as a primary measure of disease severity for ^{131}I dosing protocols in hyperthyroid cats, we could find no published ^{131}I dosing protocol for

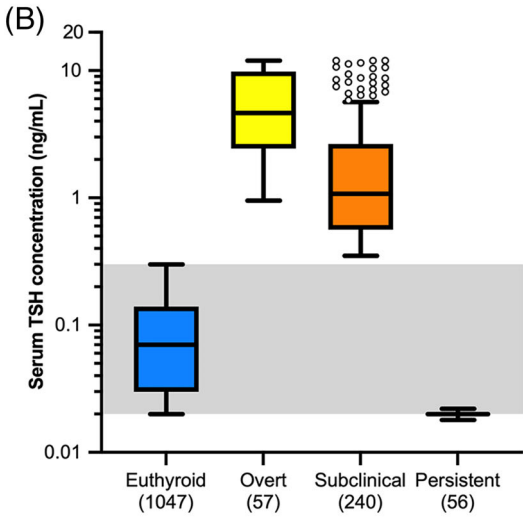
FIGURE 3 Boxplots of serum thyroid hormone and TSH concentrations in 1400 hyperthyroid cats before treatment with radioiodine (^{131}I). A, thyroxine (T_4); B, triiodothyronine (T_3); C, thyroid-stimulating hormone (TSH). Boxes represent the interquartile range from the 25th to 75th percentile. The horizontal bar in each box represents the median value. The whiskers indicate the range of data values unless outliers are present, in which case the whiskers extend to a maximum of 1.5 times the interquartile range.[29] Such outlying data points are represented by open circles. The shaded area indicates the reference interval











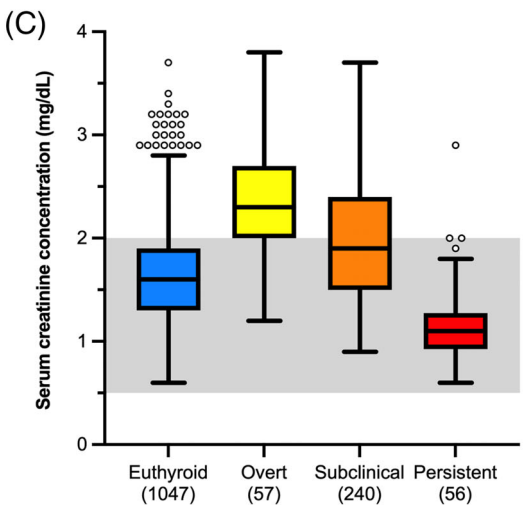


FIGURE 4 Boxplots of quantitative scintigraphic results and 24-hour thyroidal ^{131}I uptake used in our algorithm for calculating individual ^{131}I doses in 1400 hyperthyroid cats. A, percent thyroidal uptake of ^{99m}Tc-pertechnetate (TcTU); B, thyroid volume; C, percent ^{131}I uptake. See Figure 1 for key

FIGURE 5 Boxplots of serum thyroid hormone and creatinine concentrations in 1400 hyperthyroid cats, treated with individual ^{131}I doses calculated with our algorithm, divided into 4 thyroid outcome groups. A, thyroxine (T_4); B, thyroid-stimulating hormone (TSH); C, creatinine. See Figure 1 for key

TABLE 2 Comparison of ^{131}I treatment outcomes in hyperthyroid cats in recent studies that used various fixed and variable dosing protocols

Study	Dosing type	Median T_4 (μg/dL)	Median ^{131}I dose (mCi)	Sample size	Euthyroid (%)	Persistent (%)	Hypothyroid (%)	Azotemia (%)
Nykamp et al[1]	Fixed	8.1	4.5	165	115 (70%)	0^{A} (0%)	50^{Aa} (30.3%)	NA
Morre et al[3]	Fixed	10.2	4.5	23	11^{A} (48%)	2 (9%)	10^{A} (43%)	2 (9%)
Finch et al[4]	Fixed	9.3	3.0	24	15 (63%)	2 (8%)	7 (29%)	7 (29%)
Yu et al[5]	Fixed	NA	4.0	161	133 (82.6%)	4 (2.5%)	24^{a} (15%)	31 (32%)
Boag et al[6]	Variable	10.2	4.0	84	57 (68%)	1 (4.2%)	19^{a} (32%)	10 (41%)
Morre et al[3]	Variable	12.2	3.5	57	31^{A} (54%)	9^{A} (16%)	17 (30%)	15 (26%)
Fernandez et al[8]	Variable	12.7	3.5	55	22^{A} (40%)	4 (7%)	29^{A} (52.7%)	14 (28%)
Current study	Variable	8.9	1.9	1400	1047 (75%)	56 (4%)	297 (21%)	272 (19%)

Notes: Cells in each column with the superscript "A" have a different proportion of the outcome of interest than the current study.
[a]Serum TSH not measured, so this reflects only the cats with overt hypothyroidism (ie, prevalence of subclinical hypothyroidism not determined).

human patients that include circulating T_4 (or T_3) concentrations as a parameter. Rather, individual dose calculations are based primarily on the patient's thyroid volume and ^{131}I uptake measurements.[33,36,37] Our dose algorithm retains serum T_4 concentrations as an index of disease severity but includes thyroid tumor volume and percent 24-hour ^{131}I uptake, as described in most human dosing protocols.[36,38-40] We also included serum T_3 concentrations as an index of disease severity, because T_3 concentrations appear to reflect the severity of hyperthyroidism better than serum T_4 concentrations.[41,42] In accord with that, serum T_3:T_4 molar ratios were significantly higher ($P < .0001$) in our cats with severe hyperthyroidism (0.022) compared with cats with mild-to-moderate hyperthyroidism (0.017). This also agrees with findings in human patients, in which more T_3 than T_4 is progressively secreted as the thyrotoxicosis worsens.[43]

We used thyroid scintigraphy to objectively determine individual thyroid tumor volumes, as previously described (see Supplemental file 2).[24,32] Use of quantitative thyroid imaging avoids the subjective nature of thyroid palpation and expected variability among clinicians when estimating thyroid size. Furthermore, compared to quantitative thyroid imaging, cervical palpation underestimates the total thyroid volume in cats with thyroid nodules that cannot be palpated (eg, intrathoracic or ectopic thyroid masses) or are missed on examination.

In human patients with toxic nodular goiter (most similar to the feline disease[44]), some investigators have added TcTU measurements to the ^{131}I dosing protocol to increase efficacy of treatment.[45-48] Because TcTU provides useful quantitative information concerning the overall functional and metabolic activity of the toxic nodular goiter tissue in both hyperthyroid humans and cats,[20,45-48] we included TcTU as a marker of disease severity for our individual ^{131}I dose calculations in this study.

Thyroid ^{131}I uptake is routinely included as part of the variable ^{131}I dosing protocols used in human hyperthyroid patients,[33,36-40] but these measurements are routinely done a few days prior to ^{131}I therapy by administration of a much smaller "tracer" dose of ^{131}I (50-250 μCi [2-10 mBq]).[49-51] Similar pretherapeutic tracer studies have been reported in hyperthyroid cats.[52-54] However, when pretherapeutic ^{131}I uptakes are compared to those measured after administration of therapeutic doses of ^{131}I, the ^{131}I uptake values do not always agree.[49,54-57] One possible reason for this discrepancy is that ^{131}I therapy might induce early radiobiological effects, which changes the ^{131}I uptake and limits the usefulness of pretherapeutic dosimetry.[49,55-57] To avoid these discrepancies, some investigators have proposed doing a 2-step ^{131}I treatment in human patients, as needed based on ^{131}I uptakes measured after administration of an initial ^{131}I therapy dose.[58] We decided to forgo pretherapeutic tracer ^{131}I uptake measurements and instead to measure only posttherapeutic ^{131}I uptake. This approach had the advantage of knowing the true, albeit conservative, therapeutic ^{131}I uptake value, as well as avoiding the extra day or 2 of workup needed for pretherapeutic ^{131}I uptake testing with a small tracer dose of ^{131}I.

Our ^{131}I dosing protocol has some distinct disadvantages. First of all, it requires that the radioiodine facility have a gamma (scintillation) camera to perform thyroid scintigraphy (and therefore determine thyroid volume and TcTU); a dose calibrator to accurately measure the ^{131}I doses administered to the cats, as well as the dose standard for ^{131}I uptake studies; and a survey meter/probe (Geiger counter) to count the cat's neck and thigh 24 hours after initial ^{131}I treatment, as well as the dose standard to calculate the percent ^{131}I uptake.[59] In virtually all instances, the survey meter used to measure the cats' thyroid ^{131}I uptake can be the same meter used for radiation safety monitoring purposes, as well as to determine when the radiation emitted from the cat has reached a level that poses no radiation safety threat to the general public (allowing the cat to be discharged).[15,60,61] Second, our protocol is more time-consuming that most other ^{131}I dosing methods. Finally, performing posttherapeutic ^{131}I uptake studies exposes the veterinary staff to radiation, but this can be kept to a minimum with a short duration of exposure (ie, time needed to count most cats for thyroid uptake is generally <3 minutes, thereby limiting one's exposure). The primary author of this study (MEP) personally counted each of the 1400 cats for the ^{131}I uptake studies in this study and his exposure rates were always well below the dose limits for radiation workers set by the Nuclear Regulatory Commission.[62]

One limitation of this study was the sole use of serum creatinine concentrations to define the presence or absence of azotemia in our

^{131}I-treated cats. Hyperthyroidism can complicate or mask the diagnosis of chronic kidney disease (CKD) because it increases glomerular filtration rate (GRF) and decreases body muscle mass, both of which can lower serum creatinine concentrations.[63] Although GRF falls to normal (or low) levels within a few weeks of treatment, many cats remain slightly muscle wasted, which could contribute to falsely low creatinine concentration.[64] Therefore, it is certainly possible that some our ^{131}I-treated cats had undetected CKD, underestimating the prevalence of posttreatment azotemia. In addition, it is also possible that we misclassified a cat with azotemia (based on the finding of slightly high serum creatinine concentration) that would have had a normal GFR on direct measurement.

Our study lacked any control or comparison groups of hyperthyroid cats treated with other ^{131}I protocols; therefore, we lack unequivocal evidence of the benefit of our protocol. We did compare our results to all other ^{131}I studies over the last 2 decades that reported treatment outcomes (Table 2). However, the populations of cats in those studies could differ from those in our study in severity and duration of disease, route of ^{131}I administration, length of follow-up, and diagnostic criteria for iatrogenic hypothyroidism (serum T_4 concentration alone or together with serum TSH measurements). Consequently, any comparisons should be made cautiously.

Whether the split-dose ^{131}I protocol we used in this study improved outcome would require comparison against a randomized, simultaneously treated cohort that received the full initial dose (rather than 80%), without further adjustment of the ^{131}I dose according to the 24-hour ^{131}I uptake. Obviously, the split-dose ^{131}I protocol is more time-consuming and requires additional dose calculations. However, if this protocol results in fewer hypothyroid cats, such inconveniences might be worthwhile.

In conclusion, use of this novel algorithm for calculating individual ^{131}I doses based on serum thyroid hormone concentrations, thyroid scintigraphy (tumor volume and TcTU), and ^{131}I uptake by the thyroid tumor works well to cure a large proportion of hyperthyroid cats, while reducing the risk of overt hypothyroidism and not increasing the risk of treatment failure. This algorithm reduces ^{131}I doses for most cats, as compared to other dosing protocols, thereby reducing radiation exposure to veterinary staff and owners. By lowering the prevalence of iatrogenic hypothyroidism, this low-dose algorithm also lowers the rate of azotemia that develops after ^{131}I treatment.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict 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

Approval from the Animal Endocrine Clinic IACUC.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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