Association of the risk of development of hypothyroidism after iodine 131 treatment with the pretreatment pattern of sodium pertechnetate Tc 99m uptake in the thyroid gland in cats with hyperthyroidism: 165 cases (1990–2002)

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Objective—To assess whether the risk of development of hypothyroidism after treatment with iodine 131 (131I) was associated with the pattern of sodium pertechnetate Tc 99m activity in the thyroid gland detected via scintigraphy before treatment in cats with hyperthyroidism.

Design—Retrospective study.

Animals—165 cats.

Procedure—Medical records of cats with hyperthyroidism that had been treated with 131I (from 1990 to 2002) and had undergone scintigraphy of the thyroid gland before treatment were reviewed; data regarding signalment, scintigraphic findings (classified as unilateral, bilateral-asymmetric, bilateral-symmetric, or multifocal patterns), serum total thyroxine (T4) concentrations before treatment and prior to hospital discharge, and 131I treatment were collected. A questionnaire was sent to each referring veterinarian to obtain additional data including whether the cats subsequently developed hypothyroidism (defined as serum total T4 concentration less than the lower reference limit) and 3 months after treatment.

Results—50 of 165 (30.3%) 131I-treated cats developed hypothyroidism. Hypothyroidism developed in 39 of 109 cats with bilateral, 10 of 50 cats with unilateral, and 1 of 6 cats with multifocal scintigraphic patterns of their thyroid glands. Cats with a bilateral scintigraphic pattern were approximately 2 times as likely to develop hypothyroidism (defined as serum total T4 concentration less than the lower reference limit) that cats with unilateral disease. The comparative risk of developing hypothyroidism after 131I treatment because of more thyroid tissue would be ablated. We hypothesized that cats with bilaterally symmetric lesions should have the greatest risk of developing hypothyroidism after 131I treatment and that cats with unilateral thyroid gland disease should have an increased risk of developing hypothyroidism after 131I treatment because the complications associated with 131I treatment is the development of hypothyroidism; this reportedly occurs in approximately 5% to 18% of treated cats. The therapeutic mechanism of this radioactive isotope is selective uptake by functional, hyperplastic thyroid gland tissue and consequent brachytherapy via β-particle emission, resulting in ablation of the abnormal tissue. The function of the remaining normal thyroid gland tissue is suppressed by negative feedback on the hypothalamic-pituitary-thyroid axis because of high concentrations of circulating thyroid hormone T3 released from the hyperplastic thyroid gland tissue. Theoretically, the normal thyroid gland tissue does not take up 131I. Therefore, this tissue should return to function following the ablation of the hyperplastic tissue, thereby preventing the development of hypothyroidism after 131I treatment. In our hospital, scintigraphy of the thyroid gland involving sodium pertechnetate Tc 99m (99mTc pertechnetate) is routinely performed prior to starting 131I treatment to confirm the diagnosis of hyperthyroidism and occasionally to provide data for calculation of the radioactive isotope dose. Abnormal scintigraphic findings indicative of thyroid gland disease are classified as 1 of 4 patterns: unilateral, bilateral-asymmetric, bilateral-symmetric, and multifocal. Given the mechanism of action of 131I, cats with bilateral thyroid gland disease should have an increased risk of developing hypothyroidism after 131I treatment because more thyroid tissue would be ablated. We hypothesized that cats with bilaterally symmetric lesions should have the greatest risk of developing hypothyroidism after 131I treatment and that cats with unilateral thyroid gland disease should have the lowest risk. The comparative risk of the development of hypothyroidism after 131I treatment in cats with multifocal disease was unclear. The purpose of the study of this report was to assess whether the risk of development of hypothyroidism in cats with hyperthyroidism after 131I treatment with 131I was associated with the pattern of 99mTc pertechnetate activity in the thyroid gland detected via scintigraphy before treatment.

Criteria for Selection of Cases
From January 1990 to August 2002, 483 cats with hyperthyroidism received 131I treatment at the Cornell University Hospital for Animals; the medical records of these patients were reviewed. A questionnaire was mailed to the veterinarians who referred these cats to the hospital to obtain additional information about these patients after treatment; telephone contact was made to these patients after treatment to confirm the diagnosis of hypothyroidism.
used to follow up with veterinarians who did not respond initially to facilitate further data collection.

To be included in the study, cats must have undergone scintigraphic examination of the thyroid gland before \(^{131}\)I treatment and have had at least 1 assessment of serum total \(T_4\) concentration 3 months or more after \(^{131}\)I treatment. This criterion was based on preliminary assessment of the data, which indicated that all cats that were hypothyroid immediately following treatment and subsequently became euthyroid did so within 3 months of treatment. Cats with concurrent disease (ie, disease unrelated to the thyroid gland such as cardiac disease or renal failure) that might have resulted in low serum total \(T_4\) values were excluded. Cats were considered euthyroid if the most recent serum total \(T_4\) measurement was within the reference range and no treatment with thyroid hormone supplements was given. Hypothyroidism was diagnosed if the serum total \(T_4\) value was below the lower limit of the reference range ≥ 3 months after treatment, and onset of hypothyroidism was designated as the date on which low serum total \(T_4\) concentration was first detected.

For cats receiving thyroid hormone supplements, the onset of hypothyroidism was designated as the date on which the serum total \(T_4\) concentration that prompted administration of the supplements was determined. The serum total \(T_4\) concentration reference ranges used in these assessments were those provided by the laboratory performing the analysis.

**Procedures**

Data regarding the age and sex of each cat, serum total \(T_4\) concentration and the pattern of \(^{99m}\)Tc pertechnetate uptake before treatment, dose of \(^{131}\)I administered, and serum total \(T_4\) concentration after treatment (ie, prior to hospital discharge [typically 10 to 14 days after \(^{131}\)I injection]) were obtained from the medical records. Abnormal scintigraphic findings indicative of thyroid gland disease are classified as 1 of 4 patterns: unilateral, bilateral-asymmetric, bilateral-symmetric, and multifocal. Cats with hyperthyroidism were treated with various doses of \(^{131}\)I that were based on a subjective assessment of the severity of the clinical signs, estimated size of the thyroid gland nodule, and the serum \(T_4\) concentration before treatment. As part of the standard protocol for \(^{131}\)I treatment, medication for hyperthyroidism was discontinued a minimum of 2 weeks prior to radioactive iodine treatment.

The questionnaire mailed to the referring veterinarians requested additional information about these patients after treatment; the data collected included serum total \(T_4\) concentration (including laboratory reference ranges and dates of examinations [1 or more]), detection of any clinical signs attributed to hyperthyroidism, detection of any clinical signs attributed to other non–thyroid gland diseases that may result in decreased serum total \(T_4\) concentration, concurrent medications, and whether treatment for hyperthyroidism was prescribed and the response to that treatment.

For cats with and without hypothyroidism, the duration of follow-up was calculated by subtracting the date of \(^{131}\)I treatment from the date of diagnosis of hypothyroidism or from the date of the last serum total \(T_4\) measurement, respectively. The probability or risk of developing hypothyroidism over time after \(^{131}\)I treatment was estimated for cats with each of the scintigraphic thyroid gland patterns by use of the Kaplan-Meier product-limit method in a software package. This software calculates not only the probability of remaining disease-free (ie, survival curves) but also the complementary failure curves (1 minus survival estimates). The failure curves display the probability of developing disease (hypothyroidism) with time after \(^{131}\)I treatment. Kaplan-Meier curves were compared by use of the log-rank test. The Cox proportional hazards model was used to evaluate the effects of the scintigraphic pattern classification of the thyroid gland on the risk of developing hypothyroidism (controlling for dose, age, and sex).

Significance was set at a value of \(P \leq 0.05\).

**Results**

Of the 483 questionnaires mailed to veterinarians requesting follow-up information, 287 (59.4%) were returned. Of the 287 cats to which these data related, 165 met the inclusion criteria. Some cats were euthyroid after \(^{131}\)I treatment but became hypothyroid during the follow-up interval in association with development of renal disease, hepatic disease, lymphoma, cardiomyopathy, transitional cell carcinoma, or other undiagnosed disease prior to euthanasia. We did not consider that \(^{131}\)I treatment was the cause of hypothyroidism in those cats, which is why those cats were excluded from the final analysis. Cats were also excluded if thyroid hormone supplements were prescribed within the 3-month period after treatment because some of those cats might have been hypothyroid transiently. Among the 162 cats for which data regarding sex were available, 91 (56.2%) were spayed females, 69 (42.6%) were castrated males, and 2 (1.2%) were sexually intact males. The mean ± SD age of the 165 cats was 14.1 ± 2.4 years. The median follow-up time for the 165 cats was 10.3 months (range, 3 months to 5 years). Thirty-six percent (60/165) of the cats in the cohort had developed hypothyroidism or were lost to follow-up by 6 months after treatment, 65% (107/165) by 1 year after treatment, and 76% (125/165) by 1.5 years after treatment.

Among the 165 cats meeting all inclusion criteria, the scintigraphic pattern of the thyroid gland was bilateral-asymmetric in 100 (60.6%), bilateral-symmetric in 9 (5.5%), unilateral in 50 (30.3%), and multifocal in 6 (3.6%). The median dose of \(^{131}\)I was 4.3 mCi (range, 3.5 to 23.0 mCi) in the cats with bilateral-asymmetric scintigraphic patterns, 4.5 mCi (range, 3.5 to 5.8 mCi) in the cats with bilateral-symmetric scintigraphic patterns, 4.5 mCi (range, 3.5 to 20.0 mCi) in the cats with unilateral scintigraphic patterns, and 6.9 mCi (range, 4.6 to 24.0) in the cats with multifocal scintigraphic patterns. The dose of \(^{131}\)I differed significantly (\(P = 0.02\)) by scintigraphic pattern classification. The median dose for cats with multifocal scintigraphic patterns was significantly greater than the doses administered to cats with bilateral-symmetric, bilateral-asymmetric, or unilateral scintigraphic patterns of the thyroid gland. The median doses for cats with bilateral-asymmetric, bilateral-symmetric, and unilateral scintigraphic patterns were not significantly different.
Hypothyroidism developed after treatment in 50 of 165 (30.3%) cats. Of these 50 cats, information regarding clinical signs of hypothyroidism was reported for 34. Nineteen of these 34 (56%) cats had clinical signs of hypothyroidism. Information regarding thyroid hormone supplements was reported for 44 of the 50 cats; 23 (52%) cats were being treated with a thyroxine supplement. No cats had recurrence of hyperthyroidism during the study period. Before 131I treatment, the cats that subsequently developed hypothyroidism had a median serum T4 concentration of 7.32 ng/dL and those that did not develop hypothyroidism had a median serum T4 concentration of 8.1 ng/dL. This difference in median concentration values was not significant (P = 0.47).

Thirty-six of 100 cats with bilateral-asymmetric scintigraphic patterns, 3 of 9 cats with bilateral-symmetric scintigraphic patterns, 10 of 50 cats with unilateral scintigraphic patterns, and 1 of 6 cats with multifocal scintigraphic patterns developed hypothyroidism after 131I treatment. Initially, the failure curves (probability of developing hypothyroidism) for cats with bilateral-symmetric (n = 9) and bilateral-asymmetric (100) scintigraphic patterns were derived, but because they were very similar and not significantly different, the data for these groups were combined for the final analysis. Similarly, because the number of cats with a multifocal scintigraphic pattern was small (6 cats of which 1 developed hypothyroidism), there was little precision with which to estimate the failure curve and low statistical power to detect differences from the other scintigraphic patterns. Therefore, this group was excluded from further consideration.

The failure curve (ie, the probability of developing hypothyroidism with time after treatment) was significantly (P = 0.03) higher in cats with a bilateral scintigraphic pattern, compared with the curve derived for cats with a unilateral scintigraphic pattern (Figure 1).

Controlling for sex, age, or dose of 131I did not affect the significance of the comparison of risks among the unilateral and bilateral (symmetric or asymmetric) scintigraphic patterns of the thyroid gland. Cats with either bilateral scintigraphic pattern were approximately 2 times as likely to develop hypothyroidism than cats with a unilateral scintigraphic pattern (hazard ratio, 2.1; 95% confidence interval, 1.04 to 4.20).

The failure curves can be used to estimate the proportion of cats that would be expected to develop hypothyroidism by various time points after treatment according to their scintigraphic pattern (Figure 1). For example, by 6 months after treatment, the probability that cats with a unilateral scintigraphic pattern will develop hypothyroidism is approximately 6%, whereas the probability for cats with a bilateral scintigraphic pattern is approximately 20%. By 1 year after 131I treatment, cats with a unilateral scintigraphic pattern have an approximately 15% risk of developing hypothyroidism, compared with a risk of approximately 37% among cats with a bilateral scintigraphic pattern. Among the cats that developed hypothyroidism, 6 of 10 with a unilateral scintigraphic pattern and 33 of 39 with a bilateral scintigraphic pattern had developed hypothyroidism within 1 year after 131I treatment. It should be noted that the probability estimates for development of hypothyroidism in cats after 131I treatment for hyperthyroidism become less precise (ie, have larger confidence intervals) as time after treatment increases because of decreases in the number of cats followed for longer periods of time after treatment.

**Discussion**

The hyperfunctional thyroid gland tissue selectively takes up radioactive iodine, whereas the normal, functionally suppressed gland tissue is not affected. It is proposed that the therapeutic action of 131I is achieved via β-particle emission (94% of the total emitted radiation). The path length of an emitted β particle is approximately 0.4 to 0.5 mm; therefore, the normal surrounding tissue is spared the biological effects of radiation. Iodine 131 also emits gamma radiation, which is thought to contribute very little to the biological effect. The biological effects of 131I include acute necrosis, impaired replication of follicular cells, fibrosis, and chronic inflammatory responses. Given the mechanism of localization and the limited range of the β particles, it seems reasonable to speculate that cats with bilateral thyroid gland disease, which is presumed to involve all or most of the gland, should have an increased risk of developing hypothyroidism after 131I treatment and that cats with unilateral thyroid gland disease should be less likely to develop hypothyroidism after 131I treatment.

In humans, the rate of development of hypothyroidism ranges from 2% to 64% during the first year following 131I treatment. An additional 3.2% to 4.6% of patients develop hypothyroidism each year after 131I treatment. This relatively high rate of development of hypothyroidism after 131I treatment and the wide range of incidence are partly due to the difference in treatment responses between patients with Graves’ disease and those with toxic nodular goiter.
(Plummer's disease). Graves' disease is an autoimmune disorder of the thyroid gland that is known to have spontaneous development of hypothyroidism at a rate of approximately 0.7%/y. Hyperthyroidism in cats more closely resembles toxic nodular goiter in humans in that a hyperplastic nodule is present that secretes excess thyroid hormone, resulting in suppression of the function of the remaining thyroid gland tissue. Humans with toxic nodular goiter are able to tolerate higher doses of \(^{131}I\) with less risk of development of hypothyroidism after treatment. In these people, the reported rate of hypothyroidism is approximately 2%/y.

The proportion of cats developing hypothyroidism after \(^{131}I\) treatment ranges widely among studies. The variation is probably a result of differences in the doses of \(^{131}I\) administered, length of follow-up, and diagnostic criteria for hypothyroidism. The induction of hypothyroidism in humans after \(^{131}I\) treatment can be divided into 2 categories: early incidence (defined as within 2 years of treatment) and late incidence.15 The mechanism of the early-incidence hypothyroidism is unknown but appears to be dose related.15,16,18 Two mechanisms of cell death have been proposed to account for early-incidence hypothyroidism, which suggest that the \(^{131}I\) dose is adequate to result in primary cell death or that the decline in hormone output stimulates the cells to divide, at which point they undergo mitotic death.15 The induction of hypothyroidism after >2 years is considered independent of the dose of \(^{131}I\) administered, suggesting that the mechanism is dependent on biological factors such as a chronic inflammatory response or fibrosis.11,12,13 An autoimmune process is 1 mechanism of late incidence of hypothyroidism in humans with Graves' disease. Another possible explanation is that thyroid gland cells have a finite capacity to proliferate that is reached early in patients treated with \(^{131}I\) because of the decreased number of viable cells after radioisotope treatment. When this capacity to proliferate is exhausted, the result is hypothyroidism.15 In our study, most of the \(^{131}I\)-treated cats became hypothyroid within 18 months and a significant correlation between \(^{131}I\) dose and the development of hypothyroidism was not identified. The predominance of early-incidence hypothyroidism may reflect the fact that the disease in cats with \(^{131}I\)-induced hypothyroidism closely resembles toxic nodular goiter of humans than an autoimmune process. However, it may also be apparent because many of the cats were not followed for longer than 2 years as a result of death or loss to follow-up. These results are consistent with the hypothesis that when disease affects most of the thyroid gland, there will be an increased risk of developing hypothyroidism after \(^{131}I\) treatment because the entire gland will be ablated due to the effects of the radioactive iodine. However, if it is true that only hyperfunctional thyroid gland tissue takes up \(^{131}I\) and normal thyroid gland tissue does not, then development of hypothyroidism in \(^{131}I\)-treated cats that initially had a unilateral scintigraphic pattern of the thyroid gland needs more explanation. One hypothesis is that as serum T4 concentration decreases when the cat becomes euthyroid, thereby increasing the severity of renal dysfunction. Cats that become hypothyroid after \(^{131}I\) treatment are theoretically at greater risk of deterioration of renal function. Our data suggest that thyroid gland scintigraphy may be used to identify cats at increased risk for developing hypothyroidism, which may facilitate more effective management of these cases.

An important limitation to the present study is the lack of definitive criteria for diagnosis of hypothyroidism in cats other than assessment of serum total T4 measurements. Also, any retrospective study is typically hampered by missing data, nonstandard clinical descriptions, and loss of individuals to follow-up; in a study involving clinicopathologic data, different reference ranges from various laboratories also influence assessments. It is possible that detection of low serum T4 concentration on 1 occasion is not an adequate criterion for the diagnosis of hypothyroidism in cats. Further, perhaps measurement of serum total T4 concentration is not the best test for hypothyroidism; other assessments of thyroid gland function are available at some laboratories, but measurement of serum total T4 concentration was consistently performed in the cats of the present study. Also, although we suggest monitoring thyroid function in cats at specific intervals after \(^{131}I\) treatment (eg, 1, 2, 3, 6, and 12 months, then yearly thereafter), thyroid gland tests were performed at variable intervals in the cats of the present study, which was attributed to differences in owner and referring veterinarian compliance. Adherence to each laboratory's reference range for serum total T4 concentration was strict, and it is possible that classification of certain cats with serum total T4 values at or near the lower reference limit may have changed with further evaluation. Similarly, differences in reference ranges among laboratories may have led to misclassification of some cats as having hypothyroidism. Setting the criteria for diagnosis of hypothyroidism to include only cats with low serum total T4 concentration and clinical signs of hypothyroidism may have been a more conservative method of classification. We chose more liberal criteria to capture all cats at risk for inclusion in the analyses. Whether administration of thyroid hormone supplements is necessary for all cats with hypothyroidism is another decision.

Assessment of thyroid gland mass was not a routine procedure at this institution; therefore, \(^{131}I\) dose was selected subjectively on the basis of assessment of the serum total T4 value. Most of the cats with hyperthyroidism received 4 to 5 mCi of \(^{131}I\). In a few cats in which thyroid carcinoma was suspected, the dose was...
much larger (as much as 23 mCi). This is a potential limitation, as a high dose of 131I may have resulted in a rapid decrease in serum total T₄ concentration, subsequent increase in serum concentration of thyroid-stimulating hormone, and increased uptake of ¹³¹I by the thyroid gland. However, results of a study in which the use of fixed doses of ¹³¹I in cats was investigated indicated that the incidence of hypothyroidism after radioisotope treatment was not increased.

The results of the present study suggest that scintigraphic evaluation (involving the use of ⁹⁹mTc pertechnetate) of the thyroid gland of cats with hyperthyroidism can provide information with which to predict the risk of the development of hypothyroidism in those cats after ¹³¹I treatment. In cats with unilateral thyroid disease, the development of hypothyroidism after ¹³¹I treatment cannot be explained by the currently accepted mechanism of action of this radioisotope and further investigation into other explanations is required.

References