

Survival times for cats with hyperthyroidism treated with iodine 131, methimazole, or both: 167 cases (1996–2003)

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Objective—To compare survival times for cats with hyperthyroidism treated with iodine 131, methimazole, or both and identify factors associated with survival time.

Design—Retrospective case series.

Animals—167 cats.

Procedure—Medical records of cats in which hyperthyroidism had been confirmed on the basis of high serum thyroxine concentration, results of thyroid scintigraphy, or both were reviewed.

Results—55 (33%) cats were treated with ¹³¹I alone, 65 (39%) were treated with methimazole followed by ¹³¹I, and 47 (28%) were treated with methimazole alone. Twenty-four of 166 (14%) cats had preexisting renal disease, and 115 (69%) had preexisting hepatic disease. Age was positively correlated ($r = 0.4$) with survival time, with older cats more likely to live longer. Cats with preexisting renal disease had significantly shorter survival times than did cats without preexisting renal disease. When cats with preexisting renal disease were excluded, median survival time for cats treated with methimazole alone (2.0 years; interquartile range [IQR], 1 to 3.9 years) was significantly shorter than median survival time for cats treated with ¹³¹I alone (4.0 years; IQR, 3.0 to 4.8 years) or methimazole followed by ¹³¹I (5.3 years; IQR, 2.2 to 6.5 years).

Conclusions and Clinical Relevance—Results suggest that age, preexisting renal disease, and treatment type were associated with survival time in cats undergoing medical treatment of hyperthyroidism. (*J Am Vet Med Assoc* 2006;228:559–563)

Various methods for treating cats with hyperthyroidism have been described,^{1,2} with the most common medical treatments involving administration of methimazole or radioactive iodine. Although several reports on the effects of treatment of hyperthyroid cats with methimazole³⁻⁷ or iodine 131⁸⁻¹⁶ have been published, to our knowledge, no studies directly comparing survival times for cats treated with methimazole versus ¹³¹I are available. In addition, we are not aware of any reports of outcome for hyperthyroid cats treated with methimazole followed by ¹³¹I. Thus, the purposes of the study reported here were to compare survival times for cats with hyperthyroidism treated with ¹³¹I,

methimazole, or methimazole followed by ¹³¹I and to identify factors associated with survival time.

Criteria for Selection of Cases

Medical records of all cats examined at the University of Florida Veterinary Medical Center between 1996 and 2003 in which a diagnosis of hyperthyroidism had been confirmed on the basis of high serum T₄ concentration, results of thyroid scintigraphy, or both were reviewed. Cases were eligible for inclusion in the study if the cat had been treated with methimazole, ¹³¹I, or methimazole followed by ¹³¹I and if adequate follow-up information was available. Cases for which the medical record was incomplete were excluded.

Procedures

Data obtained from the medical records included age, breed, reproductive status, physical examination findings, results of serum biochemical testing (including measurement of serum T₄ concentration) and urinalyses performed before and after treatment, radiographic findings, echocardiographic findings, date of diagnosis, date of treatment, and survival time. Information on body score and whether a thyroid nodule could be palpated was not collected because these data were not consistently recorded in the medical records.

For cases included in the study, cats were classified as having no evidence of cardiac disease or mild, moderate, or severe cardiac disease prior to treatment on the basis of the International Small Animal Cardiac Health Council scoring system.¹⁷ Before and after treatment for hyperthyroidism, cats were considered to have renal disease if serum creatinine concentration, urea nitrogen concentration, or both were greater than the upper reference limit and urine specific gravity was inappropriately low, taking hydration status into account. For the purposes of this study, cats were considered to have hepatic disease if alanine transaminase and alkaline phosphatase activity was greater than the upper reference limit. Follow-up information for cats that were not reexamined at the University of Florida was obtained by means of telephone conversations with or questionnaires mailed to referring veterinarians and owners.

Statistical analysis—Descriptive statistics were calculated, and data were tested for normal distribution and equal variance by means of the Kolmogorov-Smirnov test. Data that were normally distributed are

T₄ Thyroxine
IQR Interquartile (25th to 75th percentile) range

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reported as mean \pm SD. Data that were not normally distributed are reported as median and IQR.

The χ^2 test was used to compare sex and breed distributions for the study population with distributions for all cats examined at the University of Florida Veterinary Medical Center during the study period. Cats in the study population were grouped according to age (4 to 9 years old, 10 to 13 years old, 14 to 15 years old, and > 16 years old) as described,¹⁸ and 2-way ANOVA (parametric data) or ANOVA on ranks (nonparametric data) was used to determine whether age group was significantly associated with breed, sex, percentages of cats with renal disease before and after treatment, percentages of cats with hepatic disease before and after treatment, cardiac disease score before treatment, or treatment group (methimazole alone, ¹³¹I alone, and methimazole followed by ¹³¹I). The Holm-Sidak or Dunn method was used for post hoc pairwise comparisons. The Spearman rank order correlation method was used to identify correlations between serum biochemical values, urinalysis results, and serum T₄ concentration.

Survival time was calculated from the first day of treatment for hyperthyroidism. Median survival time was determined by means of the Kaplan-Meier product-limit method, and the Gehan-Breslow test was used to determine whether survival times differed significantly among treatment groups. Multiple logistic regression was used to identify factors associated with survival time. For analyses of survival time, cats were censored if they were alive at the time of the study or if they had died of any disease not typically associated with hyperthyroidism (eg, trauma). However, because most cats in the study population were older, cats that were reportedly euthanized because of "old age" and cats that died of renal failure were not censored.

All analyses were performed with standard statistical software.^{a-c} For all analyses, a value of $P < 0.05$ was considered significant.

Results

Study population—During the study period (1996 to 2003), 12,638 cats were examined at the University of Florida Veterinary Medical Center, of which 263 (2.1%) were recorded as having hyperthyroidism. Medical records for 96 of the 263 cases of hyperthyroidism were incomplete, and these cases were excluded from the study. The remaining 167 cases were included in the study. Of these, 55 (33%) involved treatment with ¹³¹I alone, 65 (39%) involved treatment with methimazole followed by ¹³¹I, and 47 (28%) involved treatment with methimazole alone.

Median age of the study population was 15.1 years (IQR, 13.4 to 16.9 years; range, 4 to 22 years), and study population cats were significantly ($P < 0.001$) older than the general population of cats examined at the teaching hospital during the study period (median, 6.9 years; IQR, 1.9 to 12.0 years). Age group (4 to 9 years old, 10 to 13 years old, 14 to 15 years old, and > 16 years old) was not significantly associated with breed, sex, percentages of cats with renal disease before and after treatment, percentages of cats with hepatic disease before and after treatment, cardiac disease score before treatment, or treatment group.

Of the 167 cats included in the study, 74 (44%) were male (73 castrated) and 93 (56%) were female (86 spayed). Ninety-eight cats (59%) were domestic short-hairs, 27 (16%) were domestic longhairs, 18 (11%) were domestic medium-haired cats, and 15 (9%) were Siamese. The remaining 9 (5%) cats represented various other breeds. Sex and breed distributions of the study population were not significantly different from distributions for the general population of cats examined at the Veterinary Medical Center during the study period.

Results of serum biochemical testing—Serum biochemical testing was performed prior to treatment for hyperthyroidism in all but 1 cat. Of the 166 cats that did undergo serum biochemical testing, 24 (14%) were classified as having renal disease and 115 (69%) were classified as having hepatic disease. Percentages of cats with renal or hepatic disease prior to treatment for hyperthyroidism did not vary significantly among treatment groups.

Follow-up serum biochemical testing was performed after treatment in only 67 of the 167 (40%) cats. Twenty-five of the 67 (37%) were classified as having renal disease; with 7 of the 25 treated with ¹³¹I, 13 treated with methimazole followed by ¹³¹I, and 5 treated with methimazole alone. Of these, 3 had been classified as having renal disease prior to treatment but the remaining 22 had not had evidence of renal disease prior to treatment. Unfortunately, owing to the small sample size, differences between groups could not be determined.

Twelve of the 67 (18%) cats in which follow-up serum biochemical testing was performed had evidence of hepatic disease after treatment. Of these, 10 had been classified as having hepatic disease prior to treatment, and 2 had not had evidence of hepatic disease prior to treatment. Thirty-six of 46 cats classified as having hepatic disease prior to treatment no longer had evidence of hepatic disease at the time of follow-up testing. No other possible causes were identified in the medical records that could have explained the high hepatic enzyme activities prior to treatment other than the hyperthyroidism. Nineteen of 21 cats classified as not having hepatic disease prior to treatment still did not have evidence of hepatic disease at the time of follow-up testing.

Forty-six of the 166 (28%) cats in which serum biochemical testing was performed prior to treatment had hyperphosphatemia, and 33 (20%) had hypokalemia; none of the cats had hyperkalemia. Only 5 of the 33 cats that had hypokalemia were classified as having renal disease. There were significant negative correlations between pretreatment serum T₄ concentration and pretreatment serum creatinine concentration, between pretreatment serum T₄ concentration and pretreatment serum potassium concentration, between pretreatment urine specific gravity and pretreatment SUN concentration, and between pretreatment urine specific gravity and pretreatment serum creatinine concentration. Pretreatment serum phosphorus concentration was positively correlated with pretreatment serum alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase activities, and pretreatment

urine specific gravity was positively correlated with urine pH.

Cardiac abnormalities—Cats were only scored for severity of cardiac disease prior to treatment because so few cats underwent follow-up cardiac examinations after treatment. The most common cardiac abnormalities in the 167 cats prior to treatment were cardiac murmurs ($n = 58$ [35%]), tachycardia (28 [17%]), and tachypnea (23 [14%]). Forty-three of the 167 (26%) cats had radiographic or echocardiographic evidence of mild or moderate cardiomegaly, and 5 cats had evidence of hypertrophic cardiomyopathy. Overall, 77 (46%) cats were classified as having no evidence of cardiac disease, 50 (30%) were classified as having mild cardiac disease, 12 (7%) were classified as having moderate cardiac disease, and 28 (17%) were classified as having severe cardiac disease. Systolic blood pressure was measured in only 25 (15%) cats; median systolic blood pressure was 168 mm Hg.

Scintigraphic abnormalities—Thyroid scintigraphy was performed with sodium pertechnetate Tc 99m in 118 of the 167 (71%) cats. Of these, 91 (77%) had increased radiopharmaceutical uptake, compared with salivary gland uptake, in both thyroid glands and 27 (23%) had increased radiopharmaceutical uptake in a single gland.

Serum T_4 concentration—Only data for serum T_4 concentration measured prior to treatment and at the time of the first follow-up examination after treatment were recorded because of wide variations in additional times that serum T_4 concentration was measured. Mean serum T_4 concentration prior to treatment did not differ significantly among treatment groups. Overall mean \pm SD serum T_4 concentration was 9.2 ± 5.8 $\mu\text{g/dL}$ (range, 4 to 36.8 $\mu\text{g/dL}$; reference range, 0.8 to 4 $\mu\text{g/dL}$).

Serum T_4 concentration was measured after treatment in only 22 of the 55 (40%) cats treated with ^{131}I alone, 47 of the 65 (72%) cats treated with methimazole followed by ^{131}I , and 30 of the 47 (64%) cats treated with methimazole alone. The time from treatment to retesting varied substantially (median, 42 days; IQR, 18.3 to 171.3 days) but did not differ significantly among treatment groups. Overall mean \pm SD serum T_4 concentration after treatment was 2.3 ± 2.9 $\mu\text{g/dL}$. Posttreatment serum T_4 concentration for cats treated with ^{131}I alone (median, 4.5 $\mu\text{g/dL}$; IQR, 3.0 to 8.7 $\mu\text{g/dL}$) was significantly higher than posttreatment serum T_4 concentration for cats treated with methimazole alone (median, 1.3 $\mu\text{g/dL}$; IQR, 0.6 to 3.6 $\mu\text{g/dL}$).

In 8 of the 167 (5%) cats, pretreatment serum T_4 concentration was within reference limits. In 6 of these cats, the diagnosis of hyperthyroidism was confirmed by means of thyroid scintigraphy. In the other 2, serum T_4 concentration had previously been found to be high.

Twenty-two cats had posttreatment serum T_4 concentrations less than the lower reference limit. Of these, 10 had been treated with methimazole alone, 10 had been treated with methimazole followed by ^{131}I , and 2 had been treated with ^{131}I alone.

Treatment—In all but 1 of the 47 cats treated with methimazole alone, treatment was initiated immediate-

ly after the diagnosis of hyperthyroidism was made. The dosage of methimazole ranged from 2.5 to 10 mg/d. For cats treated with ^{131}I alone, the median time from diagnosis to treatment was 20 days (IQR, 11.3 to 65.8 days). Dosage of ^{131}I was 5 mCi (185 MBq), SC. For cats treated with methimazole followed by ^{131}I , the median duration of methimazole treatment was 88 days (IQR, 40.3 to 212.5 days).

Survival time—Univariate analysis revealed that age, age group, pretreatment renal disease, and treatment group were significantly associated with survival time. Age was positively correlated ($r = 0.4$; $P < 0.01$) with survival time, with older cats more likely to live longer. When survival curves for age groups were compared (Figure 1), the survival curve for the youngest age group (1 to 9 years old) was significantly ($P = 0.02$) different from curves for the other 3 groups, whereas survival curves for the other 3 age groups did not differ significantly from each other. Cats classified as having renal disease prior to treatment had significantly ($P = 0.023$) shorter survival times than did cats without evidence of renal disease prior to treatment (Figure 2). Survival times for cats treated with ^{131}I alone or with methimazole followed by ^{131}I were significantly longer than survival time for cats treated with methimazole alone (Figure 3); however, survival time for cats treated with ^{131}I alone was not significantly different from survival time for cats treated with methimazole followed by ^{131}I . Similar results were found when the 24 cats classified as having renal disease prior to treatment were excluded from analysis of the association between treatment group and survival time, with median survival time for cats treated with methimazole alone (2.0 years; IQR, 1 to 3.9 years) significantly shorter than median survival time for cats treated with ^{131}I alone (4.0 years; IQR, 3.0 to 4.8 years) or methimazole followed by ^{131}I (5.3 years; IQR, 2.2 to 6.5 years).

When survival time for cats treated with methimazole followed by ^{131}I was calculated from the date of ^{131}I

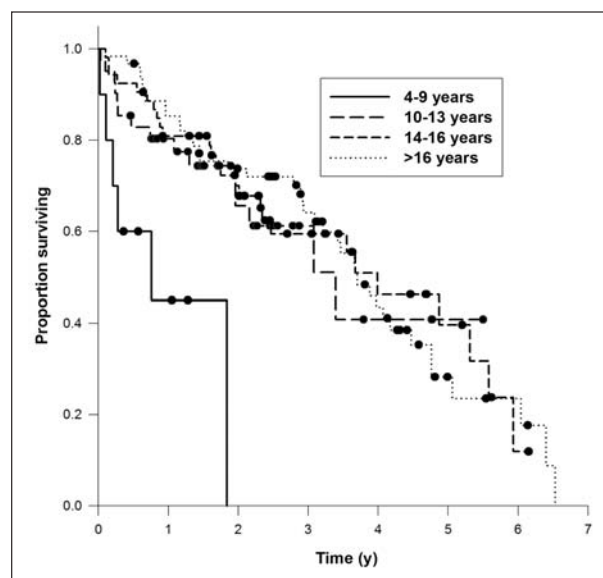


Figure 1—Kaplan-Meier curves of survival times for 167 hyperthyroid cats treated with methimazole, iodine 131, or methimazole followed by ^{131}I and grouped according to age at the time of initial treatment. Circles represent censored individuals.

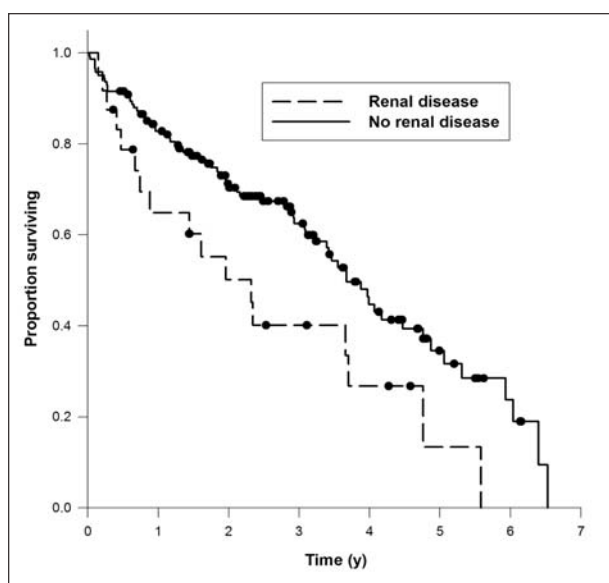


Figure 2—Kaplan-Meier curves of survival times for 167 hyperthyroid cats treated with methimazole, ^{131}I , or methimazole followed by ^{131}I and grouped according to whether they did or did not have serum biochemical evidence of renal disease prior to initiation of treatment. Circles represent censored individuals.

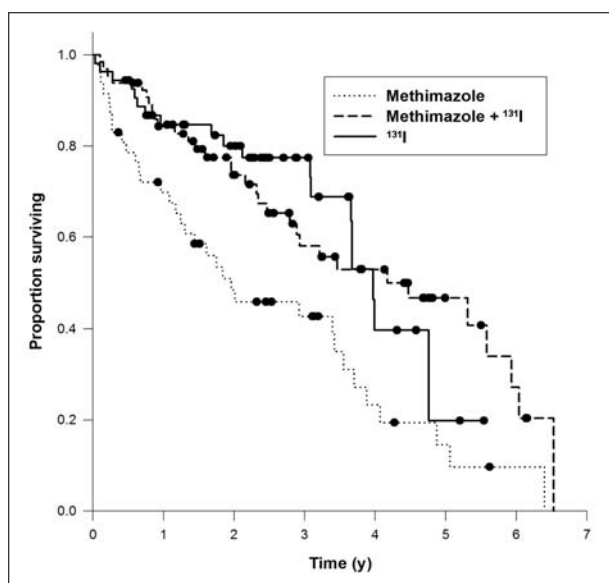


Figure 3—Kaplan-Meier curves of survival times for 167 hyperthyroid cats treated with methimazole, ^{131}I , or methimazole followed by ^{131}I and grouped according to treatment. Circles represent censored individuals.

administration rather than from the date of initial treatment, survival time for cats treated with methimazole alone was no longer significantly different from survival time for cats treated with methimazole followed by ^{131}I . However, survival time for cats treated with ^{131}I alone was still significantly longer than survival time for cats treated with methimazole alone.

The following variables were included in multivariate analyses: sex, age, pretreatment cardiac score, pretreatment renal disease, pretreatment hepatic disease, pretreatment serum T_4 concentration, and treatment group. Posttreatment renal disease and posttreat-

ment hepatic disease were excluded because of incomplete data; age group was excluded because of the small size of the lowest age group.

Age, pretreatment renal disease, and treatment group were found in multivariate analyses to be significantly ($P = 0.007$) associated with survival time. Pretreatment renal disease was negatively associated with survival time, and treatment with ^{131}I alone and age were positively associated with survival time. When cats classified as having renal disease prior to treatment were excluded from the analysis, only treatment group was found to be significantly associated with survival time.

Median age of cats censored in survival analyses (14.6 years; IQR, 13.1 to 16.3 years) was significantly ($P = 0.02$) shorter than median age of cats that were not censored (15.4 years; IQR, 14.1 to 17.5 years). To explain the possible bias, the effect of censoring within age groups was examined. Only cats in the age group 4 to 9 years were significantly ($P < 0.001$) different, with younger cats (mean \pm SEM, 6.1 ± 0.52 years; $n = 4$) more likely to be censored than older cats (mean \pm SEM, 8.9 ± 0.4 years; 6).

Discussion

Results of the present study suggest that age, the presence of renal disease prior to treatment, and treatment type were associated with survival time in cats undergoing medical treatment of hyperthyroidism. Cats that were younger, had evidence of renal disease prior to treatment, and were treated with methimazole alone had shorter survival times than did cats that were older, did not have evidence of renal disease prior to treatment, and were treated with ^{131}I or methimazole followed by ^{131}I .

When cats were grouped according to age, a significant effect of censoring was found in the 4- to 9-year-old group. These cats were also more likely to be censored if they were younger. Cats in this age group also had shorter survival times. A possible explanation for these findings is that 4 of the 10 (40%) cats in this age group were censored because they were still alive at the end of the study. In addition, 3 cats in this age group were classified as having severe cardiac disease prior to treatment. Thus, the finding that cats in the youngest age group had the shortest survival time should be interpreted with caution. Nevertheless, age, as a continuous variable, was found to be significantly associated with survival time in the multivariate analysis. This is in contrast to the intuitive sense that older cats would have shorter survival times and findings in a previous study¹² in which age was negatively associated with survival time among cats treated with ^{131}I .

Twenty-four of 166 (14%) cats in the present study had serum biochemical evidence of renal disease prior to treatment for hyperthyroidism. Unfortunately, follow-up serum biochemical testing was performed in only 67 cats, so no conclusions could be drawn as to whether treatment had an effect on development of renal disease. Nevertheless, even when accounting for the effects of treatment group, pretreatment renal disease was found to be negatively associated with survival time.

Importantly, treatment type was independently associated with survival time in the present study. Cats

treated with methimazole alone had a shorter median survival time than did cats treated with ^{131}I alone or cats treated with methimazole followed by ^{131}I , and even when cats with preexisting renal disease were excluded, the results were the same. Possible reasons for shorter survival times in cats treated with methimazole include problems with owner compliance with regular administration of the drug and possible drug toxicoses. Two previous studies^{12,13} reported median survival times of 2.1 and 2 years for hyperthyroid cats treated with ^{131}I , whereas median survival time for cats in the present study treated with ^{131}I alone was closer to 4 years.

Weaknesses of the present study include potential biases in case selection, the relatively low number of cases in certain groups, and potential concerns with the accuracy of information recorded in the medical records. Furthermore, given that most cats in the study were older, it was often difficult to determine what role, if any, hyperthyroidism may have played in the death of individual cats.

The population of cats referred to the University of Florida Veterinary Medical Center for treatment of hyperthyroidism may likely not reflect the general population of hyperthyroid cats. Nevertheless, we believe that our results have relevance for hyperthyroid cats in general because any biases that did occur were small. In particular, breed and sex distributions for hyperthyroid cats in the present study were not significantly different from distributions for the general population of cats examined at the teaching hospital during the study period, and clinical signs in the cats included in the present study were similar to those reported previously.^{1,19} For instance, the incidence of cardiac disease in the study population was consistent with incidences in previous reports,^{19,20} and pretreatment serum biochemical values, particularly those related to hepatic enzyme activities and serum phosphorus concentration, were consistent with values given in previous reports.^{19,21,22} On the other hand, the 20% incidence of hypokalemia in the present study was higher than that reported previously.¹⁹ In addition, the median age of hyperthyroid cats in the present study (15.1 years) was somewhat higher than that reported previously, but the range (4 to 22 years) was comparable.

Overall, 159 of the 167 (95%) cats in the present study had high serum T_4 concentrations prior to treatment. A previous report¹⁹ has suggested that a percentage of cats with hyperthyroidism will have serum T_4 concentrations within reference limits, and this has been attributed to early disease, differences in reference ranges for different laboratories, and concurrent nonthyroidal disease. Not unexpectedly, serum T_4 concentration was retested more frequently in cats treated with methimazole than in cats treated with ^{131}I . Median posttreatment serum T_4 concentration was significantly lower in cats treated with methimazole than in cats treated with ^{131}I , and 20 of the 22 cats with posttreatment serum T_4 concentrations less than the lower reference limit had been treated with methimazole or methimazole followed by ^{131}I . Low serum T_4 concentrations have been reported previously in conjunction with methimazole treatment²³ and are not considered a clinical problem as long as serum triiodothyronine concentration is within reference limits. The higher median posttreatment serum T_4 con-

centration in cats treated with ^{131}I suggests that more precise dosing of ^{131}I may be required.²¹

- a. SigmaStat for Windows, version 3.00, SPSS Inc, Chicago, Ill.
- b. SigmaPlot for Windows, version 8.02, SPSS Inc, Chicago, Ill.
- c. Statistica, version 6, StatSoft Inc, Tulsa, Okla.

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