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Comparison of survival times of cats with hyperthyroidism treated with thyroidectomy or methimazole at a primary care hospital in Japan

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OBJECTIVE
We identified the associated factors and compared the survival times of feline hyperthyroidism (FHT) between thyroidectomy and methimazole alone.

METHODS
The medical records of 41 cats diagnosed with new-onset hyperthyroidism were retrospectively reviewed. The cats were categorized into the thyroidectomy (n = 15) and methimazole (26) treatment groups. Survival analyses using the Kaplan-Meier method, log-rank test, and Cox proportional hazards models were conducted to compare the time to the selected outcomes.

RESULTS
Univariate analysis revealed that survival time was significantly longer with thyroidectomy than with methimazole (P < .001). Multivariate analyses revealed thyroidectomy as an independent prognostic factor for good outcomes (hazard ratio, 0.209; 95% CI, 0.073 to 0.601; P = .004). The recurrence rate was significantly lower in cats that underwent thyroidectomy than in those that received methimazole alone (P = .011).

CLINICAL RELEVANCE
Compared with methimazole alone, thyroidectomy was associated with a longer survival time in FHT and can be considered an irreversible treatment modality in settings where radioisotopes are not available.

Keywords: cats, hyperthyroidism, methimazole, recurrence, thyroidectomy

Feline hyperthyroidism (FHT) is the most common endocrine disease in elderly cats, with a reported prevalence of up to 10% in cats aged > 10 years.[1] If left untreated, cats with hyperthyroidism can develop life-threatening thyrotoxicosis.[2] Among the various treatment modalities for FHT, methimazole administration,[2–4] radioactive iodine,[2–4] iodine-restricted diets,[5] and thyroidectomy[6–9] have been commonly applied. In general, radioactive iodine is selected as part of curative therapy because it has a high cure rate, does not require general anesthesia, and has minimal side effects.[2] However, legal restrictions on radioactive iodine use in certain areas or unavailability at primary care hospitals precludes the use of radioactive iodine therapy in cats. Furthermore, at primary hospitals in Japan, medical treatment is the most common form of treatment for thyroid diseases, whereas surgical treatment is less common and has uncertain effectiveness.

The common recommendation for newly diagnosed FHT is a reversible treatment to assure stable renal function before considering an irreversible treatment.[10] Medical management using oral methimazole is a commonly used reversible treatment modality. The median survival time (MST) of cats treated with methimazole alone was approximately 2 years, whereas those treated with methimazole followed by radioactive iodine had an MST of 5.3 years.[3] Another study[11] of 300 cats with hyperthyroidism treated with oral methimazole or carbimazole alone or in combination with thyroidectomy found an overall MST of 1.1 years. However, to the best of our knowledge, no studies have compared the survival time between methimazole alone and thyroidectomy in cats that died of natural causes without euthanasia.

This study identified the associated factors and compared the survival time between using thyroidectomy and using methimazole alone to treat cats newly

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diagnosed with FHT at a Japanese primary care hospital, where radiation therapy is not legally available. We hypothesized that compared with noncurative therapy with methimazole alone, surgical thyroidectomy with curative intent would result in a longer survival time by possibly preventing thyrotoxicosis.

Methods

Selection of cats from the medical records

In this retrospective study, we analyzed cats with newly diagnosed hyperthyroidism at Yuki Animal Hospital from December 2008 to December 2020. Review of medical records began in January 2021 and continued through March 2022. By means of paper medical records, data on cases with elevated serum total thyroxine (TT4) concentrations were extracted from a list of blood laboratory data. All cat owners provided written informed consent.

Each cat underwent physical examination; measurements of CBC (MEK-6550 Celltac α; Nihon Kohden Corp), serum biochemistry profile (Fuji DRI-CHEM 7000V; Fujifilm Corp), and TT4 concentrations; urinalysis; radiography; and ultrasound. The serum TT4 concentration was measured by chemiluminescent enzyme immunoassay with IMMULYZE 1000 (LSI Medience Corp), which had a normal reference range of 0.7 to 2.9 µg/dL, from December 2008 to March 2014, or IMMUNO AU10V (Fujifilm Corp), which had a normal reference range of 0.9 to 3.7 µg/dL, from March 2014 to March 2022. Feline hyperthyroidism was diagnosed based on clinical manifestations consistent with hyperthyroidism and increased serum TT4 concentration above reference range.[2,4]

At first presentation, all FHT cases were initially administered oral methimazole, starting at 1.25 mg twice daily for cats < 2.5 kg or 2.5 mg twice daily for cats ≥ 2.5 kg.[2,4] Thyroid function, physical examination, CBC, and serum biochemical profile were reevaluated every 2 to 6 weeks until the success of the initial treatment.[4] If methimazole treatment did not improve the clinical manifestations or decrease the TT4 concentrations to normal, its dose was increased to a maximum of 10 mg twice daily. Initial treatment was considered successful if the clinical signs of FHT improved and TT4 decreased to normal within 6 months after initiation of methimazole treatment.[12] Cases in which TT4 did not decrease to normal within 6 months were classified as treatment failure. The present study included cats with FHT that were successfully treated with methimazole as initial treatment before thyroidectomy or as maintenance methimazole and those that underwent thyroidectomy after failure of the maintenance methimazole. The cat owners were able to select the treatment modality between thyroidectomy and methimazole. During thyroidectomy, the thyroid gland was observed grossly to determine the presence of bilateral or unilateral enlargement. The resected thyroid tissue was assessed by veterinary pathologists.

After a successful initial treatment or thyroidectomy, TT4 levels were measured at least every year. Chronic kidney disease (CKD) was diagnosed based on plasma creatinine concentrations > 1.8 mg/dL, which is above the FUJI DRI-CHEM 7000V reference range, and urine specific gravity < 1.025 after FHT treatment. We excluded cats that had an incomplete diagnosis, that had initial treatment failure and did not undergo thyroidectomy, that were on iodine-restricted diets, that had no treatment for FHT, and that were diagnosed with neoplastic disorders, chronic heart failure, chronic liver failure, and CKD before the FHT diagnosis or at the time of successful initial treatment or thyroidectomy for FHT.

Data collection

Information on the clinical characteristics, such as breed, sex, neuter status, age at diagnosis, body weight, temperature, heart rate, myocardial hypertrophy, blood pressure, and blood tests, of the study population after thyroidectomy (thyroidectomy group) or initial methimazole treatment (methimazole group) was collected. Moreover, information on the cost and number of visits from the first medication to the end point of this study was collected. Recurrence of FHT was defined based on clinical manifestations and increased TT4 concentration; the recurrence-free time was recorded from the start of FHT treatment to recurrence. Survival times were calculated from the date of initial treatment with methimazole until the date of death or final visit. Survival outcomes were investigated based on interviews with the cat owners and review of the medical records.

Statistical analysis

The associations of TT4 concentration at the initial FHT diagnosis with methimazole dose, number of visits, and interval between the first administration and the success of initial treatment were evaluated via Spearman rank correlation coefficient (r_s). Age, TT4 concentration, and 1-year cost were compared between the methimazole and thyroidectomy groups via the Mann-Whitney *U* test. The effect of age, body weight, physical examination results, and blood test results on the survival time was assessed by the log-rank test for univariate analysis for the 2 groups that were categorized based on the respective median values. We generated survival curves using the Kaplan-Meier method and compared them using the log-rank test. Age and the factors that were statistically significant in the univariate analysis were subsequently included in the multivariate analysis, which used the Cox proportional hazards model. Age was included in the multivariate analysis to demonstrate that it was not a determinant of survival time. Hazard ratios (HRs) and 95% CIs were calculated. The Gray test was used to determine differences in the cumulative incidence among various factors.[13] Comparison of the cumulative incidence functions implied the probability of occurrence of the event of interest and, therefore, can be translated to the actual number of factors with the outcome of interest. In all analyses, a *P* value of < .05 was considered statistically significant. Statistical analyses were performed with Easy R (Yoshinobu Kanda).[14]

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Results

Clinical characteristics

The case selection flowchart is presented in **Figure 1**. Of the 88 newly diagnosed FHT cases, 41 were included in this study. At the end of this study, 31 cats had died, 4 were alive, and 6 had been lost to follow-up. Cat breeds were crossbred (n = 31), American Shorthair (4), Russian Blue (3), Scottish Fold (2), and Chinchilla (1). There were 19 females (13 spayed) and 22 males (18 castrated). The clinical signs of FHT were weight loss (n = 24), polyphagia (9), diarrhea (8), vomiting (6), lethargy (5), increased activity (4), and increased vocalization (2). At the time of FHT diagnosis, the median (IQR) values were 14.5 years (range, 11.9 to 16.0 years) for age, 3.50 kg (range, 3.00 to 4.20 kg) for weight, 38.3 °C (range, 37.8 to 38.5 °C) for temperature, and 210 beats/min (150 to 240 beats/min) for heart rate. Of the 11 cats with available blood pressure measurements, 8 had hypertension. Myocardial hypertrophy was observed in 8 cats.

The blood test results (reference range and unit of measure) and their respective median (IQR) values were as follows: RBC count (5.00 X 10^6 to 10.00 X 10^6 cells/µL) of 9.91 X 10^6 cells/µL (8.83 X 10^6 to 10.64 X 10^6 cells/µL), WBC count (5.50 X 10^6 to 19.50 X 10^3 cells/µL) of 8.80 X 10^6 cells/µL (5.78 X 10^6 to 12.03 X 10^6 cells/µL), ALT level (22 to 84 IU/L) of 191 IU/L (100 to 308 IU/L), BUN level (17.6 to 32.8 mg/dL) of 27.5 mg/dL (22.5 to 34.5 mg/dL), creatinine level (0.90 to 1.80 mg/dL) of 1.10 mg/dL (0.80 to 1.30 mg/dL), and TT4 concentration of 7.90 µg/dL (6.35 to 9.23 µg/dL). There were no abnormal findings on radiographs and ultrasound examinations in the 33 cats, except that the cat was diagnosed with cardiomyopathy on the first visit.

In this study, 9 cats had adverse reactions after initial treatment with methimazole; the owners of 2 cats that developed facial pruritus opted for thyroidectomy, which treated the symptoms. Before the success of the initial treatment, remaining cats had gastrointestinal upset (n = 3), elevated liver enzyme levels (2), mild thrombocytopenia (1), and facial pruritus (1) 14 days after the dose of methimazole was increased. The clinical signs of 4 cats improved with dose reduction, and 3 cats with gastrointestinal upset improved with symptomatic treatment. After 28 days (IQR, 21 to 64 days) of the initial administration of methimazole and 3 visits (IQR, 3 to 5 visits), the final dose at the time of successful treatment was 5 mg/kg/d (IQR, 5 to 5 mg/kg/d). The initial TT4 concentration did not correlate with the final methimazole dose (r_s = 0.096; P = .536); number of visits (r_s = −0.254; P = .108); and interval between the first administration and success of initial treatment (r_s = −0.010; P = .956).

After the success of the initial treatment, 26 cats were maintained on methimazole. In the methimazole group, the median time from the initiation to the completion of treatment was 28 days (IQR, 21 to 66 days). Modified extracapsular thyroidectomy[15] was performed on 15 cats. In the thyroidectomy group, initial treatment was successful in 12 cats and unsuccessful in 3 cats. In 12 cats that underwent unilateral thyroidectomy, the diagnoses were benign adenoma in 11 and thyroid hyperplasia in 1. Of the 3 cats that underwent bilateral thyroidectomy, 2 cats were diagnosed with benign adenoma, and 1 cat was diagnosed with thyroid hyperplasia.

The median time from the start of initial treatment to thyroidectomy was 35 days (IQR, 33 to 68 days). In the thyroidectomy group, the cat, which underwent bilateral thyroidectomy, diagnosed with thyroid hyperplasia had an ectopic hyperplastic thyroid tissue and was confirmed to have FHT 12 days after surgery. This cat was treated postoperatively with 5.0 mg of

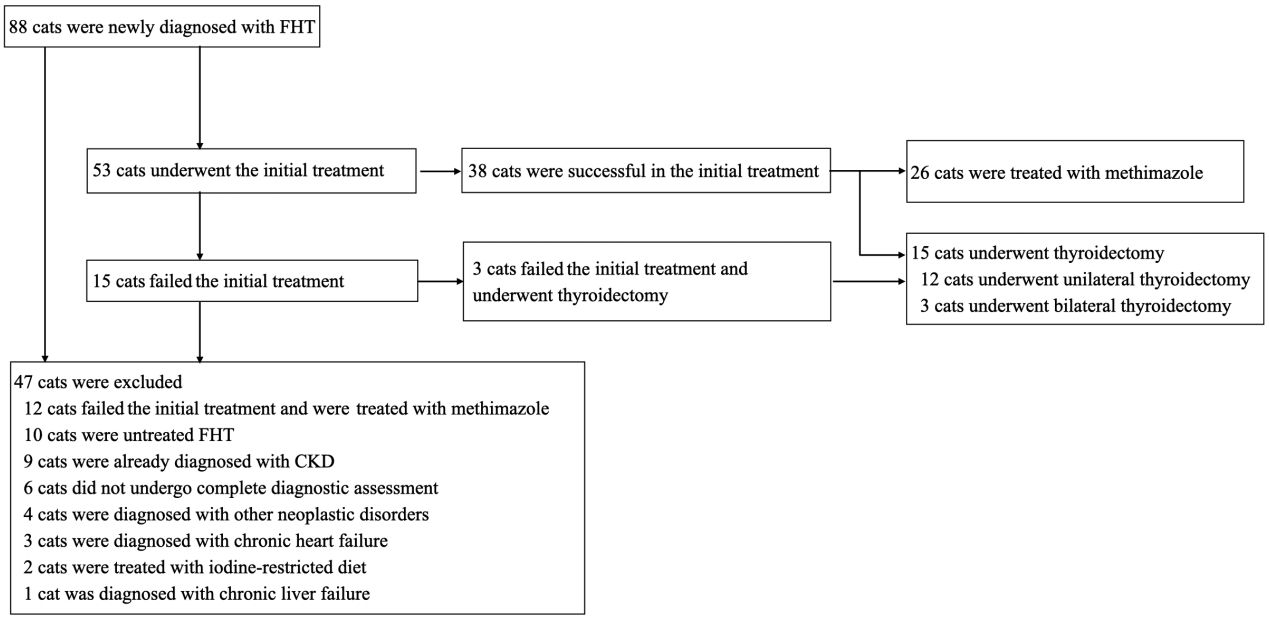

Figure 1—Flowchart of the case selection process. FHT = Feline hyperthyroidism. CKD = Chronic kidney disease.

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methimazole twice daily. One cat had postoperative hoarseness; however, it was in good general condition and was followed up on. None of the cats died at the time of surgery or during the perioperative period. There was no significant difference in age of the cats in the thyroidectomy and methimazole groups (P = .218). Additionally, there was no significant difference in the TT4 concentration at the first diagnosis of FHT between methimazole and thyroidectomy (8.00 µg/dL [IQR, 7.42 to 9.83 µg/dL] vs 8.00 µg/dL [IQR, 6.30 to 9.20 µg/dL], respectively; P = .349). Moreover, there was no significant difference in the 1-year cost between methimazole and thyroidectomy ($754 [IQR, $594 to $1,196] vs $1,000 [IQR, $802 to $1,147], respectively; P = .283). The mean and MSTs of 31 cats that died at the end point in this study were 1,164 and 961 days (range, 67 to 3,471 days; IQR, 461 to 1,813 days), respectively.

Univariate and multivariate analyses

Univariate analyses **(Table 1 and Figure 2)** revealed that longer survival was significantly associated with thyroidectomy (P = .001) and high body weight (≥ 3.50 kg) at the first diagnosis of FHT (P = .016). Multivariate analyses **(Table 2)** revealed that thyroidectomy (HR, 0.209; 95% CI, 0.073 to 0.601; P = .004) is an independent predictor of good outcome; body weight (HR, 1.179; 95% CI, 0.735 to 1.892; P = .495) and age of the cat (HR, 1.111; 95% CI, 0.970 to 1.273; P = .126) at the first diagnosis of FHT were not independent predictors of good outcome.

Table 1—Univariate analysis of survival time using the log-rank test.

	Patients (n)	Range	MST (d)	95% CI (d)	*P* value
Age (y)					.533
< 14.5	21	3.0–14.4	1,345	730–1,860	
≥ 14.5	20	14.5–19.6	961	334–2,270	
Sex					.273
Female	18		961	453–1,260	
Male	23		1,766	570–1,919	
Breed					.785
Crossbreed	31		1,174	651–1,766	
Purebred	10		761	269–NA	
Neutering					.986
Non-neutered	10		476	125–NA	
Neutered	31		1,174	730–1,860	
Body weight (kg)					.016
< 3.50	20	2.10–3.45	952	469–1,061	
≥ 3.50	21	3.50–6.00	1,766	651–2,270	
Temperature (°C)					.309
< 38.3	20	36.1–38.2	1,061	437–1,766	
≥ 38.3	21	38.3–40.0	965	570–2,270	
Heart rate (beats/min)					.089
< 210	20	120–200	1,766	534–1,919	
≥ 210	21	210–270	961	469–1,174	
RBCs (X 10^6 cells/µL)					.107
< 9.91	20	7.26–9.90	1,260	570–2,281	
≥ 9.91	21	9.91–12.79	961	437–1,860	
WBCs (X 10^3 cells/µL)					.812
< 8.80	20	2.80–8.20	1,766	469–1,893	
≥ 8.80	21	8.80–31.53	1,061	476–1,345	
ALT (U/L)					.123
< 191	19	49–190	1,345	476–2,448	
≥ 191	22	191–2,104	965	469–1,766	
BUN (mg/dL)					.218
< 27.5	20	14.5–26.4	1,766	952–1,893	
≥ 27.5	21	27.5–70.7	730	437–1,260	
Creatinine (mg/dL)					.727
< 1.1	21	0.4–1.0	1,174	651–1,893	
≥ 1.1	20	1.1–2.1	961	453–1,860	
Total thyroxine (µg/dL)					.078
< 7.9	19	5.2–7.8	961	453–1,260	
≥ 7.9	22	7.9–24.0	1,893	651–2,270	
Myocardial hypertrophy					.827
No	9		1,061	67–NA	
Yes	8		651	275–NA	
Systemic blood pressure					.070
Normal	3		469	275–NA	
Hypertension	8		651	534–NA	
Treatment					.001
Thyroidectomy	15		1,893	961–2,448	
Methimazole	26		730	453–1,174	

MST = Median survival time.

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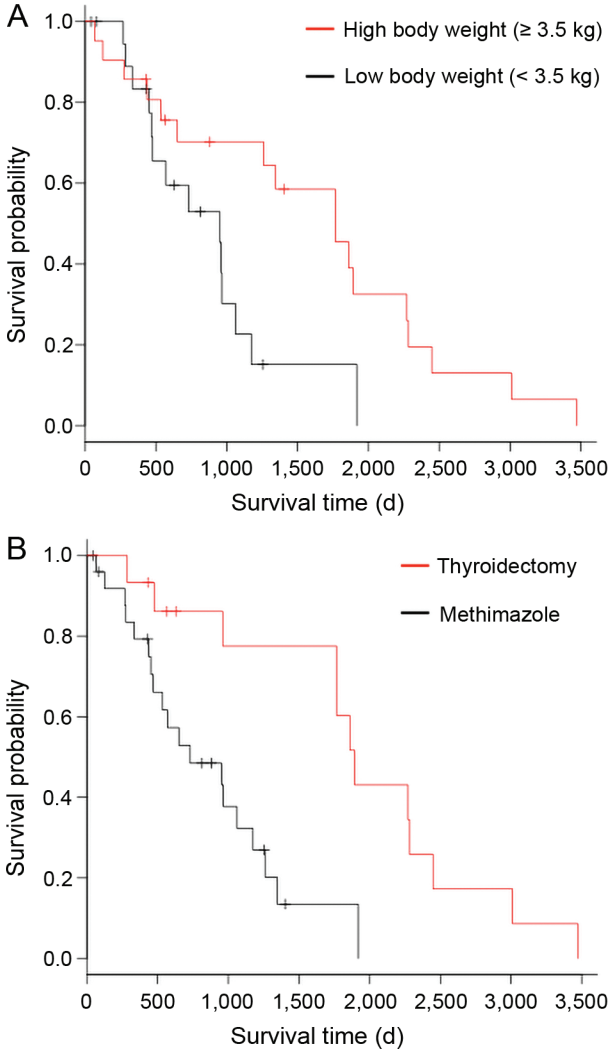

Figure 2—Kaplan-Meier curves of survival time. The survival times of the cats showed significant differences according to body weight (A; low vs high; *P* = .016) and treatment modality (B; thyroidectomy vs methimazole; *P* = .001).

Table 2—Multivariate analysis of the factors that affect survival time using a Cox proportional hazards model.

	Hazard ratio	95% CI	*P* value
Age (y)			
< 14.5	1.111	0.970–1.273	.126
≥ 14.5	Referent		
Body weight (kg)			
< 3.50	1.179	0.735–1.892	.495
≥ 3.50	Referent		
Treatment			
Thyroidectomy	0.209	0.073–0.601	.004
Methimazole	Referent		

Hazard ratio results were shown in the upper row against the lower row (Referent).

Recurrence rate comparisons between thyroidectomy and methimazole

Feline hyperthyroidism recurred in 9 cats, 2 of which had undergone unilateral thyroidectomy. The median TT4 concentration at the time of FHT recurrence was 8.00 µg/dL (IQR, 7.20 to 17.20 µg/dL). In the methimazole group, the median time to recurrence was 641 days (IQR, 445 to 1,047 days) in 7 cats. In all 7 cases, the methimazole dose was increased; however, the dose increments were stopped in 3 cats because of increased liver enzyme levels, facial pruritus, and difficulty taking the drug internally. In the thyroidectomy group, 2 cats had recurrence on days 955 and 1,160, respectively; their owners refused repeat surgery and opted for methimazole instead. The recurrence rate was significantly lower in the thyroidectomy group than in the methimazole group (*P* = .011; **Figure 3**). The calculated 1-, 2-, and 3-year recurrence-free fractions were 96%, 85%, and 77%, respectively, in the methimazole group and 100%, 100%, and 93%, respectively, in the thyroidectomy group.

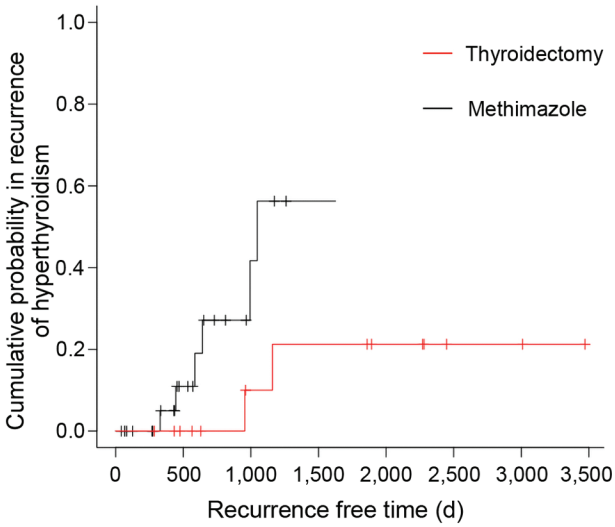

Figure 3—Cumulative probability of recurrence of hyperthyroidism according to treatment modality. The recurrence-free time was significantly different between thyroidectomy and methimazole (*P* = .011).

Causes of death in cats with FHT

At the end of the study period, 19 cats in the methimazole group died. The most common cause of death was heart failure (n = 7; 37%); 3 of these cats had hypertrophic cardiomyopathy (HCM) and TT4 concentrations of 7.80, 8.00, and 17.80 µg/dL at the time of heart failure diagnosis. The second-most-common cause of death was CKD (n = 5; 26%), followed by suspected pulmonary tumor (2; 11%), diabetes mellitus (1; 5%), biliary hepatitis (1; 5%), and unknown etiologies (3; 16%). The MSTs of cats with heart failure, CKD, pulmonary tumor, diabetes mellitus, biliary hepatitis, and unknown etiologies were 534 days (range, 275 to 1,061 days), 1,260 days (range, 453 to 1,919 days), 952 days (730 and 1,174 days), 125 days, 469 days, and 269 days (range, 67 to 437 days), respectively.

In the thyroidectomy group, 12 cats died by the end of the study period. The most common cause of death in this group was CKD (n = 7; 58%), followed by alimentary canal lymphoma (2; 17%) and unknown etiologies (3; 25%). The MSTs of cats with CKD, alimentary canal lymphoma, and unknown etiologies

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were 1,860 days (range, 961 to 3,471 days), 1,367 days (285 and 2,448 days), and 1,893 days (range, 476 to 2,281 days), respectively.

Discussion

In FHT, curative therapy is generally selected; however, fewer reports are available on thyroidectomy than on reversible therapy. Our study revealed that compared with methimazole, thyroidectomy was associated with longer survival and lower FHT recurrence rate. A previous study[12] reported no significant difference in the survival time between cats treated with methimazole and those that underwent thyroidectomy. The study included cats with hyperthyroidism, most of which were euthanized when their quality of life reached an unacceptable level because of various conditions. However, all cats in the present study died from natural causes. A previous study[9] reported low recurrence-free rates of 100%, 96%, and 94% after 1, 2, and 3 years, respectively, after thyroidectomy. These results were similar to those of the present study. Thyroidectomy may decrease the complications related to thyrotoxicosis and prolong the survival by preventing recurrence. In addition, this study showed that the 1-year cost was not significantly different between the thyroidectomy and methimazole groups. Notably, a previous study[10] indicated that medical treatment for > 1 year may be more costly than surgical treatment, which may encourage owners to choose thyroidectomy.

In general, FHT is a progressive disease that may gradually become resistant to treatment, although it initially responds well to medical therapy.[15] However, increasing the dose of methimazole may increase the cat's burden and side effects. Given that cats with hyperthyroidism are often aggressive and difficult to medicate, thyroidectomy may effectively reduce the burden on the owner.[15] Furthermore, in 3 cats, the side effects after increasing the methimazole dose were increased liver enzyme levels, onset of face scratching, and difficulty taking the drug internally. The most common side effects of methimazole include hepatotoxicity; hematologic abnormalities such as severe leukopenia, anemia, and thrombocytopenia; gastrointestinal upset; lethargy; and facial pruritus. However, the frequency and severity of these side effects have not been proven to be dose related.[16,17] These results indicated that compared with oral methimazole, thyroidectomy can be less burdensome for owners and cats in the long term because it can prevent recurrence longer and prolong survival by avoiding thyrotoxicosis. However, not all cats in the methimazole group in this study were diagnosed on the basis of histopathological examination. In addition, in Japan, methimazole is available only in tablet form. Therefore, our study could not assess the effect of the route of methimazole administration. In the future, the association between histopathological findings and treatment modalities, such as thyroidectomy and oral or transdermal methimazole, should be confirmed.

In this study, the most common cause of death was heart failure in the methimazole group and CKD in the thyroidectomy group. The relatively high recurrence rate of FHT in the methimazole group may have resulted in gradual worsening of the cardiac disease secondary to FHT. Furthermore, all cats were not able to tolerate increasing doses of methimazole, which may lead to heart failure secondary to the progression of the cardiac disease that was reversible otherwise. However, the relatively low recurrence rate of FHT in the thyroidectomy group suggested that thyrotoxicosis was prevented and an FHT course that was similar to that reported in old cats (ie, CKD as the common cause of death).[18,19] Among the small number of cats with recurrent hyperthyroidism in our study, the timing of onset of cardiac abnormalities and TT4 at the time of recurrence were unknown.

The findings of this study showed shorter survival durations in cats with a body weight of < 3.5 kg than in those with a body weight ≥ 3.5 kg before the initial methimazole therapy. Similarly, a previous study revealed significantly shorter survival duration in cats with a body weight of ≤ 3.1 kg than in those with a body weight > 3.1 kg before radioactive iodine therapy.[20] Given the known physiological effects of thyroid hormone excesses on energy expenditure and muscle and fat loss, cats with severe hyperthyroidism are likely to have relatively low body weight and small size and relatively severe muscle wasting.[21–23] Although objective and accurate, body weight only partially reflects the body condition, which markedly changes in hyperthyroid cats.[24] Body and muscle condition scores could be better indicators than body weight; however, medical data records of the cats included in this study were unavailable. Hence, they could not be used as variables in the Cox model. Nevertheless, our study demonstrated no correlation between low body weight and comorbidities, although the possibility of latent FHT and residual confounding factors could not be excluded.

This study had several limitations that should be considered. One major limitation was the nonrandom preference for thyroidectomy. Given the retrospective design, the decision to perform thyroidectomy was determined by the clinician and owner, based on clinical signs, treatment adverse effects, monitoring intervals, and perioperative cost. Therefore, there was a possibility of bias in the relationship between treatment and outcomes. Another limitation was a small sample size. Moreover, some cats may have had other unidentified chronic disorders, such as CKD, cardiomyopathy, and chronic liver disease, which could have affected their hematological parameters. In this study, 2 cats underwent both bilateral and unilateral thyroidectomy; the latter was performed, along with methimazole administration, for treating recurrence of hyperthyroidism. In the future, the correlation between recurrence and prognosis after unilateral or bilateral thyroidectomy for FHT needs to be investigated. Of the 7 cats that died of heart failure in the methimazole group, 3 were diagnosed with HCM during the treatment period and had elevated TT4 levels with thyrotoxicosis, which could have been caused by the methimazole deficiency. In the remaining cats, TT4 was normal (n = 1) or was not tested (3), leaving the possibility of

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overestimation. Further studies on the relationship between HCM and TT4 concentrations are required in the future.

In conclusion, this study demonstrated that, compared with methimazole administration, thyroidectomy can potentially prolong survival and decrease the recurrence rate of FHT. Thyroidectomy is cost-effective because it can avoid long-term antithyroid medication and is a useful irreversible treatment in settings where radioisotopes are not available or allowed.

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