Hyperthyroidism in cats
Part II: scintigraphic diagnosis and radioiodine treatment

Hyperthyreoïdie bij katten
Deel II: scintigrafische diagnose en radiojoodbehandeling

V. Volckaert, E. Vandermeulen, S. Daminet, J.H. Saunders, K. Peremans

Department of Small Animal Orthopedics and Medical Imaging, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium

veerlevolckaert@gmail.com

ABSTRACT

In the second part of this review article , the diagnostic aspects of thyroid scintigraphy are discussed, with major emphasis on hyperthyroidism, followed by an overview of radioiodine treatment.

SAMENVATTING

In het tweede deel van dit overzichtsartikel worden de diagnostische aspecten van schildklierscintigrafie besproken, met de nadruk op hyperthyreoïdie, gevolgd door een overzicht van de behandeling met radioactief jodium.

SCINTIGRAPHY

Scintigraphy stands out as an imaging modality by providing not only anatomical but also functional information. One of the most common applications of scintigraphy is the evaluation of thyroid function, i.e. to assess the degree of thyroid gland radionuclide uptake, to confirm hyperthyroidism in doubtful cases or for use in patients with non-thyroidal illness.

The radionuclide mostly used in thyroid scintigraphy is ^{99m}technetium (^{99m}Tc) or its chemical form pertechnetate ($^{99m}TcO_4^-$). ^{99m}Tc is obtained from a 99molybdenium (^{99}Mo) generator and has a physical half-life of six hours. It decays by emitting electromagnetic γ-radiation of 140 keV, which will be detected by the NaI crystal within the gamma camera (Kintzer and Peterson, 1994; Kowalsky, 2006).

Another radionuclide that can be used in thyroid imaging is ^{123}iodine (^{123}I), which decays by the emission of electromagnetic γ-rays (159 keV). In contrary to pertechnetate, ^{123}I will be organified in the thyroid gland and incorporated in the normal iodine metabolic pathway. It has a longer physical half-life of approximately 13 hours. The ideal imaging time for ^{123}I is strongly delayed at eight hours after injection compared to technetium that allows scanning from twenty minutes on. Another major drawback of ^{123}I is the high cost in comparison to pertechnetate (Kintzer and Peterson, 1994; Broome, 2006; Daniel and Brawner, 2006; Kowalsky, 2006). Although theoretically possible, another radioisotope of iodine, ^{131}I, is generally not used for imaging given its longer half-life, high cost and inferior image quality, which results from the high energy γ-photons (364 keV). Further, ^{131}I also emits β-particles that, given their destructive nature, are usable for therapeutic purposes but do not contribute to diagnostic scans (Kintzer and Peterson, 1994; Shiel and Mooney, 2007). This will be further addressed in the chapter about radioiodine therapy. Diagnostic scintigraphy in this article will always refer to the use of pertechnetate.

Protocol

Thyroid scintigraphy is based on the ability of the thyroid follicular cell's iodide pump to trap iodide as well as pertechnetate ($^{99m}TcO_4^-$). The pertechnetate ion has a similar size and charge as iodide and will be trapped, but is not used in thyroglobulin organification and hormone production, nor will it be stored in the colloid fluid like iodide is stored. It will be excreted into the bloodstream and removed from the body, mainly via the kidneys (Kintzer and Peterson, 1994; Broome, 2006; Daniel and Brawner, 2006).

It is important to remember that the iodide pumps are also present at the level of the salivary glands, the gastric mucosa, the choroid plexus, the ciliary body of the eye, the placenta and lactating mammary glands

Figure 1. Hyperthyroid cat positioned for a thyroid scan. The cat is placed on the scan bed in ventral recumbency. The head of the gamma camera underneath the table records the activity at the level of the thyroid glands. The head of the gamma camera on top is not active in this case.

(Daniel and Brawner, 2006; Capen, 2007). More specifically, uptake at the level of the head is seen in the nasal cavity, the region of the nasopharynx and soft palate, and at the level of the zygomatic, molar, parotid and mandibular salivary glands. The major hot focus seen on a typical feline pertechnetate scan represents the combination of the zygomatic and molar salivary glands. Radionuclide uptake in the area of the mediastinum may represent the esophagus containing saliva, or blood pool activity in one of the large vessels. Therefore, uptake in these areas should not be mistaken for an abnormality (Daniel and Brawner, 2006).

The radionuclide is injected intravenously prior to the scan to allow the substance to be trapped by the thyroid gland and cleared from the soft tissues. Cats will receive an activity of 18.5 to 148 MBq of pertechnetate, with an average of 74 MBq. Scans can be acquired from twenty minutes after injection onwards, with a peak uptake in feline thyroid glands seen at 45 - 60 minutes (Kintzer and Peterson, 1994; Daniel and Brawner, 2006; Daniel and Neelis, 2014). The cat is then positioned in ventral recumbency above the camera (Figure 1). The scan is performed using a low energy - high resolution (LEHR) collimator. Thyroid scans are count based, with a minimum of 100.000 counts advised. This means that the duration of the scan is determined by a preset number of counts and so the time of the scan varies from patient to patient (Kintzer and Peterson, 1994; Broome, 2006; Daniel and Brawner, 2006). The higher the uptake of pertechnetate in the thyroid gland (i.e. the more increased the thyroid function), the sooner the preset amount of counts is reached, thus resulting in a shorter scan. On average, a diagnostic feline thyroid scan takes approximately 1 to 1.5 minutes. The use of different sedatives or anesthetics protocols has been described: ketamine, a combination of ketamine and diazepam, propofol, and the use of inhalant anesthetics. Cats may also be scanned awake (Beck et al., 1985; Mooney et al., 1992; Daniel et al., 2002; Henrikson et al., 2005; Volckaert et al., 2012; Peterson and Broome, 2015; Volckaert et al., 2016). The preferred drug or ideal protocol may vary however from patient to patient.

A pinhole collimator can be used in cats, even for quantitative measurements. It gives a more detailed image of the thyroid gland and can often distinguish two lobes when only one is seen on the two-dimensional or planar scan, potentially missing a diagnosis of bilateral hyperthyroidism. An important disadvan-

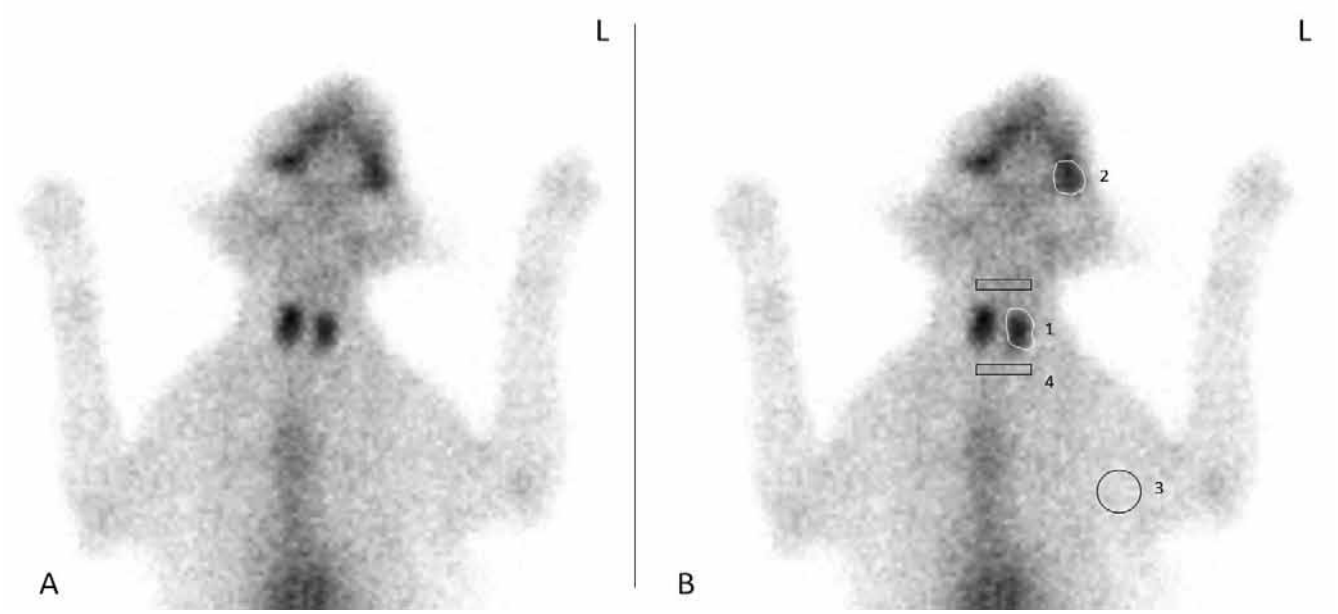

Figure 2. Thyroid scan of a normal cat. The same image is presented in A and B. B. shows the different regions of interest (ROI) typically drawn on a thyroid scan: thyroid lobe (1), salivary gland (2), background ROI in the axillary region (3), background ROIs in the cervical area (4). (L: left).

tage to the use of a pinhole collimator is the increased scan time due to a lower sensitivity, decreasing the tolerance to motion and requiring anesthesia (Mooney et al., 1992; Broome, 2006).

Thyroid scintigram

Thyroid scintigraphy is the number one imaging modality in the diagnosis of hyperthyroidism in cats. It is sporadically used in cases of suspected post-treatment hypothyroidism or rarely, in case of congenital hypothyroidism. A normal thyroid scintigram in cats shows the two thyroid lobes as elongated, oval structures in the cervical region, smoothly delineated, symmetrical in size and position and with a homogeneous distribution of the radionuclide (Figure 2). A certain level of thyroid lobe asymmetry can be present in euthyroid cats (Scrivani et al., 2007). Ectopic thyroid tissue is less commonly seen. It has been reported to be present in about 3.9% of hyperthyroid cats and is typically found on the midline and intrathoracic, usually in the cranial mediastinum (Beck et al., 1985; Kintzer and Peterson, 1994; Daniel and Brawner, 2006; Harvey et al., 2009; Daniel and Neelis, 2014; Peterson and Broome, 2015).

In case of hyperthyroidism, several uptake patterns can be observed. The remaining normal thyroidal tissue will be suppressed to a degree, depending on the serum T4 concentration and subsequent TSH suppression. In truly unilateral disease, the normal thyroid lobe should be entirely suppressed and is not visible on the scintigram. In hyperthyroid cats that are not under any form of treatment for hyperthyroidism, a normal looking thyroid lobe, aside a hyperactive lobe with marked increased radionuclide uptake is considered to be abnormal and indicates this lobe is also functioning autonomously. Multifocal nodular hyperplasia or adenomatous hyperplasia may have different features on the scintigram: an increased radionuclide uptake, homogeneous uptake, smooth margins, and usually bilateral in about 70% of the cases. With the help of a pinhole collimator, an enlarged, more detailed image of the thyroid gland can be obtained and the (multi) focal appearance may be observed. In case of cystic adenomas, the area of the cyst may be seen as a photopenic region, i.e. no accumulation of pertechnetate. When hyperactive nodules form a linear alignment rather than affecting the entire thyroid lobe, a "string of pearls" pattern can be seen.

Carcinomas are described as large areas of multifocal increased uptake, with a heterogeneous uptake pattern, irregular margins, and extending beyond the normal contours of the thyroid lobes (Figure 3). A linear multifocal pattern may indicate metastatic extension along the fascial planes, or uptake in ectopic tissue. The thorax can be included in the scanned area to search for pulmonary metastases (Kintzer and Peterson, 1994; Hofmeister et al., 2001; Daniel and Brawner, 2006; Daniel and Neelis, 2014; Peterson and Broome, 2015).

In a study with 2096 hyperthyroid cats, the scintigraphic patterns of uptake were categorized and their percentage of occurrence was recorded as follows: 31.7% had unilateral disease, 50.6% had bilateral-asymmetric disease (two thyroid lobes of unequal size), 12.3% had bilateral-symmetric disease and 3.9%

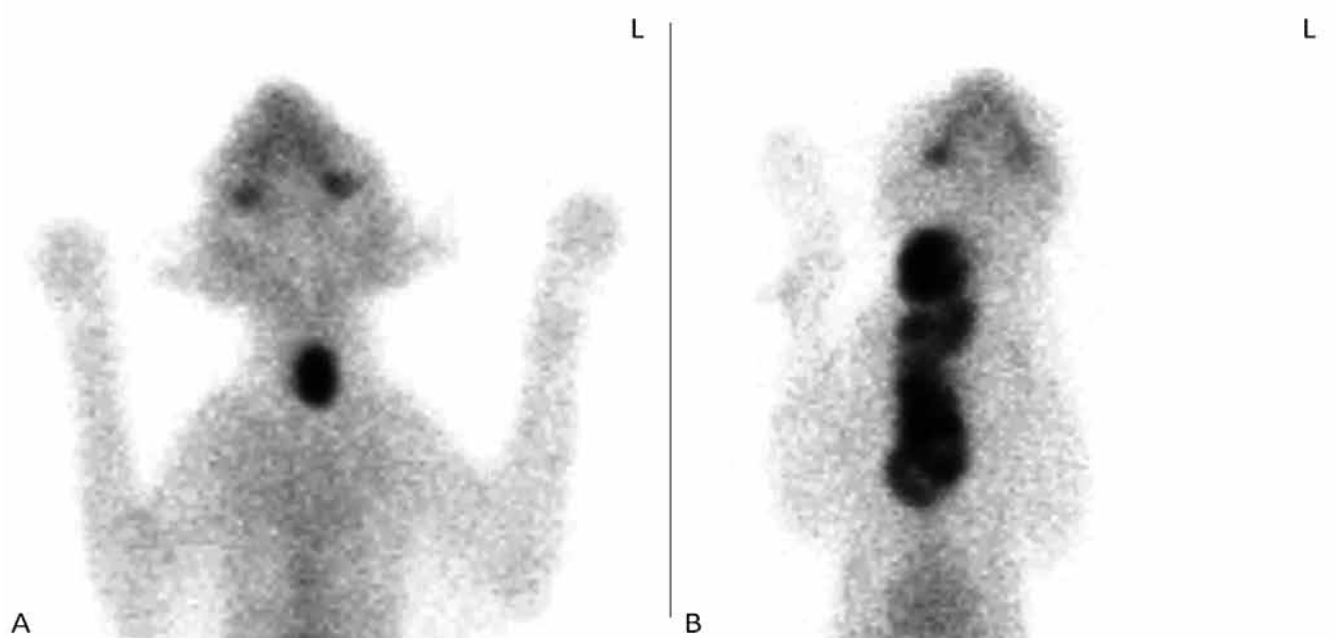

Figure 3. Thyroid scans of two cats with hyperthyroidism. A. typical image of a unilaterally affected hyperthyroid cat. The scan shows no features suggestive of malignancy. B. Image of excessive uptake of radionuclide over an area that is far more extensive than the normal contours of thyroid lobes. The uptake pattern is multifocal and heterogeneous. This patient also showed severe clinical signs of hyperthyroidism and thoracic X-rays demonstrated the presence of multiple pulmonary nodules, compatible with metastatic disease (L: left).

had multifocal disease, defined as three or more areas of increased uptake. Finally, 1.6% of the cats had a pattern not fitting into one of the categories. The most common location for foci of increased uptake was the cervical area (98.1%) followed by the thoracic inlet (13.5%) and the thoracic cavity (5.5%). A pattern consistent with thyroid carcinoma was seen in 1.7% of the hyperthyroid patients (Peterson and Broome, 2015). It is important to note that carcinomas may show benign scintigraphic characteristics and vice versa. A reliable differentiation between benign and malignant thyroid tissue can therefore not be made based on the scintigram (Daniel and Brawner, 2006; Harvey et al., 2009; Hibbert et al., 2009).

Quantitative thyroid scintigraphy

The uptake of radionuclide in the thyroid gland is proportional to its metabolic activity. Therefore, quantification of this uptake has been found to be a good assessor of thyroid activity. However, when evaluating quantitative parameters, it has to be borne in mind that several substances can interfere with the uptake by the thyroid sodium iodide symporters (NIS) and therefore with the uptake of pertechnetate or iodine.

Examples are competitive anion inhibitors (perchlorate, thiocyanate), sedatives and anesthetic medication, certain plants, thyroid hormone supplementation, the amount of dietary iodine, the administration of medicine, such as sulfonamide, phenylbutazone and anti-thyroid drugs (methimazole, carbimazole) or iodinated contrast media, e.g. iohexol (Nieckarz and Daniel, 2001; Fischetti et al., 2005; Daniel and Brawner, 2006; Capen, 2007; Shiel and Mooney, 2007; Lee et al., 2010; Klein, 2012).

The radionuclide uptake can be easily and reliably assessed visually, but to assess the uptake in a more objective quantitative manner, semi-quantitative ratios have been introduced. Commonly used is the thyroid to salivary gland ratio (T/S), a reproducible and reliable parameter (Page et al., 2006). Regions of interest (ROIs) will be drawn around the thyroid lobes and the ipsilateral salivary glands. The ratio of the mean counts of these ROIs is then calculated. The normal T/S ratio in cats varies in the literature, with a range from 0.48 up to 1.9 (Beck et al., 1985; Kintzer and Peterson, 1994; Lambrechts et al., 1997; Nieckarz and Daniel, 2001; Daniel et al., 2002; Henrikson et al., 2005; Daniel and Brawner, 2006; Page et al., 2006; Lee et al., 2010; Daniel and Neelis, 2014; Peterson and Broome, 2015). The T/S ratio increases up to twenty minutes after injection (Daniel et al., 2002). It has further been demonstrated that the T/S ratio will not significantly change within a time range of twenty minutes to two hours after the injection of pertechnetate. This is therefore a reliable time range to perform the thyroid scans (Nieckarz and Daniel, 2001; Fischetti et al., 2005; Daniel and Brawner, 2006). The T/S ratio of the most active thyroid lobe or an average ratio of both lobes has been reported to be a simple method and good representation of the metabolic thyroidal status, correlating with serum T4 concentration both in normal and hyperthyroid cats at twenty minutes after tracer injection (Chun et al., 2002; Daniel et al., 2002; Fischetti et al., 2005; Peterson and Broome, 2015). Cats with only mildly elevated T4 concentrations may show T/S ratios overlapping with the normal range and with a large range of normal values reported, a cut-off T/S ratio of 2 has been suggested as being both sensitive and specific for feline hyperthyroidism (Fischetti et al., 2005; Page et al., 2006). In a more recent study with 2096 cats, a lower cut-off ratio of 1.5 was proposed (Peterson and Broome, 2015).

Another ratio that has been introduced is the thyroid to background ratio (T/B). This ratio is independent of potential salivary gland disease and variation in uptake. The T/B ratio is calculated in a similar way to the T/S ratio, using the average counts of two ROIs, one around the thyroid and the second one at the level of the shoulder or axillary region, with a size similar to the thyroid ROI or using a fixed size ROI. The normal T/B ratio has a larger range, from 1.6 to 6.4 (Beck et al., 1985; Daniel and Brawner, 2006; Daniel and Neelis, 2014; Peterson and Broome, 2015). A correlation with serum T4 has also been observed for the T/B ratio and a cut-off ratio of 6.1 has been proposed to be very sensitive to diagnose hyperthyroidism. However, the sensitivity of the T/S ratio has been found to be still slightly higher (Peterson and Broome, 2015). Persistent post-therapy hyperthyroidism has been correlated to the T/B ratio, and cut-off ratios of ≥ 5.8 (> 148 MBq) and ≥ 11 (259 MBq) have been suggested by the authors to increase the dose of radioiodine (Wallack et al., 2010).

Whether the thyroid gland image and the T/S and T/B ratio change with age is not certain. In a study by Beck et al., these features were found to be similar between two age groups. However, the age range of the young adult group was not mentioned in the study, the ages of the group of older cats ranged from nine to eleven years. Another limitation of that study was the low number of patients included (n=10) (Beck et al., 1985).

Finally, the percentage of the injected radionuclide that is accumulated by the thyroid gland can be measured. When using a form of radioactive iodine for this purpose, this is called a radioactive iodine uptake (RAIU) study. This study can be performed using 123I or 131I. The uptake of 131I in normal cats has shown to be variable in time, with 33% of the injected activity in the thyroid gland at 1 hour after injection, 21% between 4 and 24 hours after injection and 18% remaining at 48 hours after injection (Lambrechts et al., 1997). In the past, these tracer studies were used for dose determination for therapeutic purposes (Broome et al., 1988). The percentage of radionuclide uptake by the thyroid gland can also be calculated using the safer technetium pertechnetate, as % technetium uptake or % thyroid uptake (%TcU). In the literature, the normal %TcU value ranges from 0.25 to 3.9% (Mooney et al.,

1992; Nap et al., 1994; Daniel et al., 2002; Daniel and Brawner, 2006; Lee et al., 2010). In hyperthyroid cats, a correlation between the serum T4 and T3 with the %TcU at twenty minutes after injection of technetium has been demonstrated (Mooney et al., 1992; Fischetti et al., 2005). The mean %TcU at twenty minutes after injection has been determined in hyperthyroid cats as 7% with a large range of 0.7 up to 61% (Mooney et al., 1992; Daniel et al., 2002; Fischetti et al., 2005). In contrast to the T/S ratio, the %TcU still increases in normal and hyperthyroid cats up to four hours after injection, and a significant difference has been reported in hyperthyroid cats between quantification at twenty and sixty minutes after injection (Nieckarz and Daniel, 2001; Fischetti et al., 2005). This has been contrasted in an earlier study, in which the maximum uptake was seen at one hour after injection, and therefore considered the ideal imaging time, followed by a decrease in %TcU, in both normal and hyperthyroid cats (Nap et al., 1994). However, different measurement techniques were used in the evaluation of the percentage of technetium uptake, which could explain the different findings.

In the literature, the potential role of the thyroid:thyroid (T:T) ratio in the diagnosis of hyperthyroidism has been reported only once (Scrivani et al., 2007). The T:T ratio refers to a lobe-to-lobe ratio, where the value of the most active thyroid lobe is divided by the value of the less active lobe. The T:T ratio in normal, euthyroid cats have been found to range from 1 to 2.1 (median 1.2), whereas in hyperthyroid cats, the T:T ratio ranges from 1.1 up to 12.6 (median 2.5). A cut-off value of 1.5 has been suggested to be a good differentiator between normal and hyperthyroid cats, but the interpretation has to be made with care, since the T:T ratio has shown that asymmetry, although less commonly, may occur in normal cats as well (Scrivani et al., 2007). The use of these (semi-) quantitative parameters lies in a more complete evaluation of the disease status of the patient and more patient-based dosimetric calculations for treatment with radioiodine as opposed to a fixed dose strategy.

Diagnostic pertechnetate scans have also been used to estimate thyroid lobe volume in hyperthyroid cats, and different formulas have been proposed to approach the true volume. In the literature, total thyroid volume estimated on scintigraphy in hyperthyroid cats ranges from a mean minimum total thyroid volume of 1089 mm^3 (standard deviation: 575) to a maximum of 28400 mm^3, whereas thyroid single lobe volume has been described to range from 113 to 29157 mm3, depending on the formula used (Forrest et al., 1996; Volckaert et al., 2012; Volckaert et al., 2016).

Neither method is perfect to diagnose and evaluate hyperthyroidism. The serum T4 concentration, as well as the T/S or T/B ratio on scintigraphy can fall within the normal reference range in cats with hyperthyroidism. However, the sensitivity of both semi-quantitative ratios measured on the scintigrams has been reported to be superior to basal serum T4 concentrations and allow an earlier detection of the disease (Peterson, 2014; Peterson and Broome, 2015). It is therefore important to combine tests when there is a strong clinical suspicion of occult or mild hyperthyroidism.

RADIOIODINE (^{131}I) THERAPY IN HYPERTHYROID CATS

Four treatment options are available for cats with hyperthyroidism: the use of radioactive iodine, medicinal treatment, dietary adjustments and surgery (thyroidectomy). Medicinal treatment means daily pilling and potential adverse side effects on other organs systems. Dietary adjustments in the form of low iodine diets, have been proposed for the management of hyperthyroidism. A specifically commercially developed food for this purpose is Hill's® Y/D Prescription Diet, Hill's, USA. To this day, no long-term follow-up studies are available assessing these diets. A very strict diet is required, as other foods and treats might contain high iodine content, and similar to antithyroid medication, the underlying pathology is not cured. This may result in an increased risk for malignant transformation secondary to continuing and therefore prolonged disease duration (Peterson, 2013a; Peterson et al., 2015; Scott-Moncrieff, 2015; Scott-Moncrieff et al., 2015). Surgery is an invasive procedure, holds an anesthetic risk in patients that often suffer from concurrent cardiac or renal disease and recurrence of disease occurs when not all thyroid tissue has been removed, especially when irresectable ectopic tissue is present. Another potential complication is the inadvertent removal of parathyroid tissue, with hypoparathyroidism as a consequence. Radioiodine treatment has evidently also some drawbacks, such as the need for appropriate equipment, infrastructure and licenses, and a hospitalization period that varies between institutions depending on national radioprotection regulation, ranging from five days to several weeks after treatment. Moreover, if successful, radioiodine therapy is a permanent treatment. This is an important factor as hyperthyroid cats can suffer from concomitant disease, i.e. commonly underlying chronic kidney disease, which might be easier to monitor and control with medicinal treatment. On the other hand, in cats of which the current health status allows so, radioiodine therapy is a safe, easy and permanent solution in most cases and does not require anesthesia (Kintzer, 1994; van Hoek et al., 2007; Mooney, 2010; Peterson, 2014). Radioiodine therapy has also been reported to be associated with a significantly longer survival time than in case of the use of medicinal treatment only. Cats treated with radioiodine show an increased median survival time of two years compared to cats treated with methimazole. Cats that were treated with a combination of methimazole followed by radioiodine show an extra median survival time of 3.3 years compared to those treated with methimazole only (Milner et al., 2006). Today, if the patient's condition allows so, radioiodine is the therapy of choice in the majority of cases.

Radioiodine therapy

The radionuclide used for therapy is ^{131}I. It differs from ^{123}I by emitting not only γ-rays (364 keV), but also the therapeutic β- particles. It has a physical half-life of 8.06 days and is excreted mainly by the kidneys, saliva and feces. Radioactive iodine is treated by the body in the same way as non-radioactive iodine, and will be trapped by the follicular cells of the thyroid gland and organified. The uptake of iodine may be influenced by the same factors that influence technetium uptake, i.e. antithyroid drugs, alimentary iodine, contrast media and iodine-based surgical solutions (Kintzer and Peterson, 1994; Adams, 2006; Peremans et al., 2008). When the 131I decays, it will emit its high energy, mostly in the form of β- particles, for 90% in a radius of ± 1 mm with a maximum travel distance of 2 mm and an average path length of 400 µm. This will create destruction of tissues in the immediate vicinity, sparing surrounding structures like the external parathyroid glands. Due to the low TSH concentration in hyperthyroidism, the functionality of normal thyroid tissue will be suppressed and this tissue will therefore not concentrate the radioactive iodine. The remaining 10% of the local radiation is γ-radiation, which can be used for imaging purposes (Gerber et al., 1994; Mooney, 1994, Kintzer and Peterson, 1994; Adams, 2006; Peterson, 2014). As expected, a significantly increased uptake and higher turnover of radioiodine are seen in hyperthyroid cats versus euthyroid cats. The peak of uptake in normal cats is at 48 hours after injection (20.6%), whereas in hyperthyroid cats, the maximum uptake is faster and occurs around 24 hours (56%). In this population, the uptake may range up to 87.7% (Sjollema et al, 1989). In a study by Lambrechts et al.,(1997), a different uptake pattern after oral administration of radioiodine in euthyroid cats was described, with a mean uptake of 33% at one hour followed by a decline to 18% at 48 hours. As with pertechnetate, the use of anti-thyroid medication, such as methimazole, may influence the uptake of radioiodine. It is generally advised to discontinue any possible anti-thyroid medication before therapy. The time of discontinuation however varies from institution to institution, and depends on whether the patient's clinical condition allows a prolonged time off medication. A time range of 4 to 14 days has been reported in the literature (Slater et al., 1994; Théon et al., 1994; Peterson and Becker, 1995; Forrest et al., 1996; Nykamp et al., 2005; Peterson and Broome, 2015). A so called "rebound effect" has been reported, where an increased uptake of radioiodine is observed after stopping anti-thyroid medication. The uptake is most significantly increased four to nine days after the withdrawal (Nieckarz and Daniel, 2001; Shiel and Mooney, 2007). At the department of Small Animal Orthopedics and Medical Imaging of the Faculty of Veterinary Medicine (UGent), a withdrawal of 14 days is generally recommended to avoid any possible rebound effect. If the patient's condition does not allow this, a withdrawal of three days is considered acceptable, again allowing enough time to avoid a possible rebound effect.

Regarding radioiodine dose estimation, different protocols may be found in the literature. A scoring system has been proposed, based on the severity of clinical signs, pretherapy serum T4, size and number of thyroid nodules, and the patient's body weight. Radioiodine dose can also be estimated based on the total thyroid volume or weight, on the T/B ratio or on RAIU tracer studies. Another method is a fixed empirical dose system (Turrell et al., 1984; Broome et al., 1988; Meric and Rubin, 1991; Mooney, 1994; Kintzer and Peterson, 1994; Slater et al., 1994; Théon et al., 1994; Peterson and Becker, 1995; Forrest et al., 1996; Chun et al., 2002; Nykamp et al., 2005; Adams, 2006; Wallack et al., 2010). The empirical dose advised, is 148 to 185 MBq for adenomas or adenomatous hyperplasia, administered by intravenous or subcutaneous injection. Both routes of administration have been found effective, without side effects and with the same final outcome (Meric and Rubin, 1990; Mooney, 1994; Théon et al., 1994; Peterson and Becker, 1995; Adams, 2006). The ideal method of dose estimation has not yet been determined, although most methods seem to be effective for a positive treatment outcome. Oral administration of radioiodine has also been reported, using slightly higher doses in the form of capsules. The major disadvantage is the high risk of spilling, increasing the exposure of personnel and potential contamination of the premises, as cats may not always be cooperative. Additionally, the hospitalization period for these patients is longer (Malik et al., 1993).

Doses used for thyroid carcinomas are three to ten times higher than for benign disease, typically reported around 1110 to 1480 MBq and administered intravenously (Adams, 2006; Harvey et al., 2009; Hibbert et al., 2009). In case the patient remains hyperthyroid, the treatment can then be repeated. Radioiodine is well tolerated, even in higher doses. The only important complication reported in cats is the induction of iatrogenic hypothyroidism. In a study by Turrell et al., (1984), a transient voice change was reported in a cat and Peterson and Becker (1995) reported a transient period of difficulty in swallowing, presumably induced by radiation thyroiditis. After radioiodine therapy, control scans can be performed to confirm sufficient uptake. When a thyroid carcinoma is suspected or confirmed, follow-up scans are advised at four to six weeks after therapy and to be repeated at a three to six months' interval to ensure tumor regression or detect potential tumor recurrence.

The effect of radioiodine on the serum T4 concentration occurs rapidly. The most rapid decrease is seen the first three to six days after treatment. Fifty-five percent of patients were shown to have normal serum T4 4 days after treatment, 74% was reached after eight days and 83% had normal serum T4 by one month (Meric et al., 1986). Follow-up of the serum T4 concentration may first show a marked decreased value, below reference range, without any clinical consequence. This transient, post-therapy hypothyroidism

is presumed to be the time when normal tissue, previously suppressed, starts to regenerate and slowly starts functioning normally again. With a small delay, the T4 concentration then restores itself to normal values in most cases. Regular monitoring is therefore useful, and more importantly, a final control blood test should not be performed too early after treatment. Waiting six months is often advised. However, the ideal time for a recheck after treatment is unknown and may vary from patient to patient (Meric and Rubin, 1990; Mooney, 1994; Théon et al., 1994; Peterson and Becker, 1995). Given the negative effect of a decreased thyroid function on the renal function, it may be indicated to start thyroid supplementation before six months after therapy (Brooke et al., 2012; Dragović, 2012; Vikrant et al., 2013). In these cases, it is also important to exclude possible non-thyroidal illness and make a good but often difficult diagnosis of true hypothyroidism (Mooney et al., 1996; Shiel and Mooney, 2007; Mooney, 2010; Peterson, 2013b).

Radioiodine therapy outcome

In the literature, radioiodine therapy is generally considered a very effective treatment with a success rate ranging from 70 to 95% (Meric et al., 1986; Meric and Rubin, 1990; Malik et al., 1993; Kintzer and Peterson, 1994; Mooney, 1994; Slater et al., 1994; Théon et al., 1994; Peterson and Becker, 1995; Forrest et al., 1996; Nykamp et al., 2005; Wallack et al., 2010). The definition of a successful therapy is however not always clearly defined and could refer to the resolution of clinical signs, as well as a serum T4 within the normal reference range, or the combination of both. Some studies therefore include cats that are (sub) clinically hypothyroid in their successful group. The median time of follow-up also ranges strongly from 1 to 18 months (Meric et al., 1986; Meric and Rubin, 1990; Slater et al., 1994; Théon et al., 1994; Peterson and Becker, 1995; Forrest et al., 1996; Nykamp et al., 2005; Wallack et al., 2010).

Several factors influencing and/or predicting radioiodine therapy outcome have been suggested. In a study by Peremans et al. (2008), iohexol, a commonly used iodinated contrast medium in radiography and CT, was surprisingly not found to have any significant impact on the outcome when given 24 hours prior to treatment, despite clear decreased thyroid absorption of the radioiodine. However, the dose of iodine (iohexol) administered in this study for glomerular filtration rate (GFR) measurements in hyperthyroid cats, was lower than the dose normally used for most contrast studies. Moreover, only a relatively small group of cats was included precluding definite conclusions (Peremans et al., 2008). The pre-therapy serum T4 concentration was observed to correlate to post-therapy T4 measurements, but not to a degree where it could predict therapy outcome (Chun et al., 2002; Wallack et al., 2010). In earlier studies, higher pre-therapy serum T4 concentrations have been suggested to increase the risk of persistent hyperthyroidism (Peterson and Becker, 1995; Forrest et al., 1996). Significantly higher T/B ratios have been noted in cats that showed persistent hyperthyroidism after radioiodine therapy, suggesting this ratio could predict therapy failure or alarm clinicians to increase the administered dose of radioiodine (Wallack et al., 2010). The pre-therapy T/S ratio, the severity of clinical signs or the timing at which methimazole treatment was stopped prior to the radioiodine therapy have not been found factors, which may help to predict therapy outcome (Chun et al., 2002; Wallack et al., 2010). In addition, no significant relationship with a persistent hyperthyroid outcome has been found for the presence of ectopic tissue, bilateral versus unilateral disease or previous anti-thyroid medication (Forrest et al., 1996). On the contrary, Nykamp et al. (2005) observed a significant effect of bilateral disease towards a hypothyroid outcome, with an almost double increased chance of post-therapy hypothyroidism in patients with bilateral disease.

Thyroid volume estimated on diagnostic pertechnetate scans, has also been suggested as a factor influencing radioiodine therapy outcome. Larger total thyroid volumes have been reported to increase the risk of persistent hyperthyroidism after treatment. However, no cut-off values have been determined (Peterson and Becker, 1995; Forrest et al., 1996; Volckaert et al., 2016). Forrest et al. (1996) also suggested that oral administration of radioiodine is less successful than the intravenous route.

CONCLUSION

Thyroid scintigraphy is a commonly used and excellent modality in the diagnosis and management of feline hyperthyroidism and should ideally be performed in all hyperthyroid patients, especially when definitive treatment like radioiodine or surgery is considered. Radioiodine treatment shows a good outcome in most patients and is not associated with any significant side effects. It remains therefore the treatment of choice, if the patient's condition allows it.

REFERENCES

Adams W.H. (2006). Thyroid Radiotherapy: Iodine-131. In: Daniel G.B., Berry C.R. (editors). *Textbook of Veterinary Nuclear Medicine*. Second edition, American College of Veterinary Radiology, Koxville, Tennessee, USA, p. 393 – 400.

Beck K.A., Hornof W.J., Feldman E.C. (1985). The normal feline thyroid. *Veterinary Radiology 26*, 35 – 38.

Brooke V., Goswami S., Mohanty A., Kasi P.M. (2012). Aortic dissection and renal failure in a patient with severe hypothyroidism. *Case Reports in Medicine 2012*, 1–6.

Broome M.R., Turrel J.M., Hays M.T. (1988). Predictive value of tracer studies for 131I treatment in hyperthyroid cats. *American Journal of Veterinary Research 49*, 193 – 197.

Broome M.R. (2006). Thyroid scintigraphy in hyperthyroidism. *Clinical Techniques in Small Animal Practice 21*, 10 – 16.

Capen C.C. (2007). Endocrine glands, thyroid gland. In: Jubb K.V.F., Kennedy P.C. Palmer N.C. (editors). *Pathology of Domestic Animals*. Fifth edition, Saunders Elsevier, St. Louis, Missouri, USA, p. 379 – 407.

Chun R., Garrett L.D., Sargeant J., Sherman A., Hoskinson J.J. (2002). Predictors of response to radioiodine therapy in hyperthyroid cats. *Veterinary Radiology and Ultrasound 43*, 587 – 591.

Daniel G.B., Sharp D.S., Nieckarz J.A., Adams W. (2002). Quantitative thyroid scintigraphy as a predictor of serum thyroxin concentration in normal and hyperthyroid cats. *Veterinary Radiology and Ultrasound 43*, 374 – 382.

Daniel G.B., Brawner W.R. (2006). Thyroid scintigraphy. In: Daniel G.B., Berry C.R. (editors). *Textbook of Veterinary Nuclear Medicine*. Second edition, American College of Veterinary Radiology, Knoxville, Tennessee, USA, p. 181 – 198.

Daniel G.B., Neelis D.A. (2014). Thyroid scintigraphy in veterinary medicine. *Seminars in Nuclear Medicine 44*, 24 – 34.

Dragović T. (2012). Reversal deterioration of renal function accompanied with primary hypothyroidism. *Vojnosanitetski Pregled 69*, 205–208.

Fischetti A.J., Drost W.T., DiBartola S.P., Chew D.J., Schenck P.A., Meadows C. (2005). Effects of methimazole on thyroid gland uptake of ^{99m}Tc-pertechnetate in 19 hyperthyroid cats. *Veterinary Radiology and Ultrasound 46*, 267 – 272.

Forrest L.J., Baty C.J., Metcalf M.R., Thrall D.E. (1996). Feline hyperthyroidism: efficacy of treatment using volumetric analysis for radioiodine dose calculation. *Veterinary Radiology & Ultrasound 37*, 141–145.

Gerber H., Peter H., Ferguson D.C., Peterson M.E. (1994). Etiopathology of feline toxic nodular goiter. *Veterinary Clinics of North America: Small Animal Practice 24*, 541 – 565.

Harvey A.M., Hibbert A., Barrett E.L., Day M.J., Quiggin A.V., Brannan R.M., Caney S.M. (2009). Scintigraphic findings in 120 hyperthyroid cats. *Journal of Feline Medicine and Surgery 11*, 96 – 106.

Henrikson T.D., Armbrust L.J., Hoskinson J.J., Milliken G.A., Wedekind K.J., Kirk C.A., Nachreiner R.F. (2005). Thyroid to salivary ratios determined by technetium-99^{m} pertechnetate imaging in thirty-two euthyroid cats. *Veterinary Radiology and Ultrasound 45*, 521 - 523.

Hibbert A., Gruffydd-Jones T., Barrett E.L., Day M.J., Harvey A.M. (2009). Feline thyroid carcinoma: diagnosis and response to high-dose radioactive iodine treatment. *Journal of Feline Medicine and Surgery 11*, 116 – 124.

Hofmeister E., Kippenes H., Mealey K.L., Cantor G.H., Löhr C.V. (2001). Functional cystic thyroid adenoma in a cat. *Journal of the American Veterinary Medical Association 219*, 190-3.

Kintzer P.P. (1994). Considerations in the treatment of feline hyperthyroidism. *Veterinary Clinics of North America: Small Animal Practice 24,* 577 – 585.

Kintzer P.P., Peterson M.E. (1994). Nuclear medicine of the thyroid gland. Scintigraphy and radioiodine therapy. *Veterinary Clinics of North America: Small Animal Practice 24*, 587 – 605.

Klein B.G. (2012). Endocrine glands and their function. In: Klein B.G. (editors). *Cunningham's Textbook of Veterinary Physiology*. Fifth edition, Saunders Elsevier, St. Louis, Missouri, USA, p. 428 – 464.

Kowalsky R.J. (2006). Radioactive decay, radioactivity, Tc-99m generator, and radiopharmaceuticals. In: Daniel G.B., Berry C.R. (editors). *Textbook of Veterinary Nuclear Medicine*. Second edition, American College of Veterinary Radiology, Knoxville, Tennessee, p. 1 – 24.

Lambrechts N., Jordaan M.M., Pilloy W.J.G., van Heerden J., Clauss R.P. (1997). Thyroidal radioisotope uptake in euthyroid cats: a comparison between ^{131}I and $^{99m}TcO_4^-$. *Journal of the South African Veterinary Association 68*, 35 – 39.

Lee W.R., Pease A.P., Berry C.R. (2010). The effects of iohexol administration on technetium thyroid scintigraphy in normal cats. *Veterinary Radiology and Ultrasound 51*, 182 – 185.

Malik R., Lamb W.A., Church D.B. (1993). Treatment of feline hyperthyroidism using orally administered radioiodine: a study of 40 consecutive cases. *Australian Veterinary Journal 70*, 218 – 219.

Meric S.M., Hawkins E.C., Washabau R.J., Turrel J.M., Feldman E.C. (1986). Serum thyroxine concentrations after radioactive iodine therapy in cats with hyperthyroidism. *Journal of the American Veterinary Medical Association 188*, 1038 – 1040.

Meric S.M., Rubin S.I. (1991). Serum thyroxine concentrations following fixed-dose radioactive iodine treatment in hyperthyroid cats: 62 cases (1986 – 1989). *Journal of the American Veterinary Medical Association 197*, 621 – 623.

Milner R.J., Channell C.D., Levy J.K., Schaer M. (2006). Survival times for cats with hyperthyroidism treated with iodine 131, methimazole, or both: 167 cases (1996 – 2003). *Journal of the American Veterinary Medical Association 228*, 559 – 563.

Mooney C.T., Thoday K.L., Nicoll J.J., Doxey D.L. (1992). Qualitative and quantitative thyroid imaging in feline hyperthyroidism using technetium-99m as pertechnetate. *Veterinary Radiology and Ultrasound 33*, 313 – 320.

Mooney C.T. (1994). Radioactive iodine therapy for feline hyperthyroidism: Efficacy and administration routes. *Journal of Small Animal Practice 35*, 289 – 294.

Mooney C.T., Little C.J.L., Macrae A.W. (1996). Effect of illness not associated with the thyroid gland on serum total and free thyroxine concentrations in cats. *Journal of the American Veterinary Medical Association 208*, 2004 – 2008.

Mooney C.T. (2010). Hyperthyroidism. In: Ettinger S.J., Feldman E.C. (editors). *Textbook of Veterinary Internal Medicine*. Seventh edition, Volume 2, Saunders Elsevier, St. Louis, Missouri, USA, p. 1761 – 1779.

Nap A.M.P., Pollak Y.W.E.A., van den Brom W.E., Rijnberk A. (1994). Quantitative Aspects of Thyroid Scintigraphy With Pertechnetate ($^{99m}TcO_4^-$) in Cats. *Journal of Veterinary Internal Medicine 8*, 302 – 303.

Nieckarz J.A., Daniel G.B. (2001). The effect of methimazole on thyroid uptake of pertechnetate and radioiodine in normal cats. *Veterinary Radiology and Ultrasound 42*, 448 – 457.

Nykamp S.G., Dykes N.L., Zarfoss M.K., Scarlett J.M. (2005). 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). *Journal of the American Veterinary Medical Association 226*, 1671 – 1675.

Page R.B., Scrivani P.V., Dykes N.L., Erb H.N., Hobbs J.M. (2006). Accuracy of increased thyroid activity during pertechnetate scintigraphy by subcutaneous injection for diagnosing hyperthyroidism in cats. *Veterinary Radiology and Ultrasound 47*, 206 – 211.

Peremans K., Vandermeulen E., van Hoek I., Daminet S., Vermeire S., Bacher K. (2008). Interference of iohexol with radioiodine thyroid uptake in the hyperthyroid cat. *Journal of Feline Medicine and Surgery 10*, 460 – 465.

Peterson M.E., Becker D.V. (1995). Radioiodine treatment of 524 cats with hyperthyroidism. *Journal of the American Veterinary Medical Association 207*, 1422 – 1428.

Peterson M.E. (2013a). Retrieved November 2nd, 2015, from http://www.animalendocrine.com/yd/.

Peterson M.E. (2013b). Diagnostic testing for feline thyroid disease: hypothyroidism. *Compendium on Continuing Education for the Practising Veterinarian 35*, E1–E6.

Peterson M.E. (2014). Feline hyperthyroidism: an animal model for toxic nodular goiter. *Journal of Endocrinology 223*, T97 – 114.

Peterson M.E., Broome M.R. (2015). Thyroid scintigraphy findings in 2096 cats with hyperthyroidism. *Veterinary Radiology and Ultrasound 56*, 84 – 95.

Peterson M.E., Broome M.R., Rishniw M. (2015). Prevalence and degree of thyroid pathology in hyperthyroid cats increases with disease duration: a cross-sectional analysis of 2096 cats referred for radioiodine therapy. *Journal of Feline Medicine and Surgery*; pii: 1098612X15572416

Scott-Moncrieff J.C. (2015). Feline Hyperthyroidism. In: Feldman E.C., Nelson R.W., Reusch C., Scott-Moncrieff J.C. , Behrend E. (editors). *Canine and Feline Endocrinology*. Fourth edition, Saunders Elsevier, St. Louis, Missouri, USA, p. 136 – 195.

Scott-Moncrieff J.C., Heng H.G., Weng H.Y., Dimeo D., Jones M.D. (2015). Effect of a limited iodine diet on iodine uptake by thyroid glands in hyperthyroid cats. *Journal of Veterinary Internal Medicine 29*, 1322 – 1326.

Scrivani P.V., Dykes N.L., Page R.B., Erb H.N. (2007). Investigation of two methods for assessing thyroidlobe asymmetry during pertechnetate scintigraphy in suspected hyperthyroid cats. *Veterinary Radiology and Ultrasound 48*, 383 – 387.

Shiel R.E., Mooney C.T. (2007). Testing for hyperthyroidism in cats. *Veterinary Clinics of North America: Small Animal Practice 37*, 671 – 691.

Sjollema B.E., Pollak Y.W.E.A., van den Brom W.E., Rijnberk A. (1989). Thyroidal

radioiodine uptake in hyperthyroid cats. *The Veterinary quarterly 11*, 165 – 170.

Slater M.R., Komkov A., Robinson L.E., Hightower D. (1994). Long-term follow-up of hyperthyroid cats treated with iodine-131. *Veterinary Radiology and Ultrasound 35*, 204 – 209.

Théon A.P., Van Vechten M.K., Feldman E. (1994). Prospective randomized comparison of intravenous versus subcutaneous administration of radioiodine for treatment of hyperthyroidism in cats. *American Journal of Veterinary Research 55*, 1734 – 1738.

Turrell J.M., Feldman E.W., Hays M., Hornof W.J. (1984). Radioactive iodine therapy in cats with hyperthyroidism. *Journal of the American Veterinary Medical Association 184*, 554 – 559.

Van Hoek I., Peremans K., Waelbers T., Vandermeulen E., Daminet S. (2007). Non-surgical treatment of feline hyperthyroidism: options and considerations. *Vlaams Diergeneeskundig Tijdschrift 76*, 69 – 80.

Vikrant S., Chander S., Kumar S., Gupta D. (2013). Hypothyroidism presenting as reversible renal impairment: an interesting case report. *Renal Failure 35*, 1292–1294.

Volckaert V., Vandermeulen E., Saunders J.H., Combes A., Duchateau L., Peremans K. (2012). Scintigraphic thyroid volume calculation in hyperthyroid cats. *Journal of Feline Medicine and Surgery 14*, 889 – 894.

Volckaert V., Vandermeulen E., Dobbeleir A., Duchateau L., Saunders J.H., Peremans K. (2016). Effect of thyroid volume on radioiodine therapy outcome in hyperthyroid cats. *Journal of Feline Medicine and Surgery 18*, 144 – 149.

Wallack S., Metcalf M., Skidmore A., Lamb C.R. (2010). Calculation and usage of the thyroid to background ratio on the pertechnetate thyroid scan. *Veterinary Radiology and Ultrasound 51*, 554 – 560.