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Roberts, Emma (2017) *Weight changes and gamma radiation emissions during the three-week isolation period following administration of radioactive iodine (I131) in cats with hyperthyroidism.* MVM(R) thesis.

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WEIGHT CHANGES AND GAMMA RADIATION EMISSIONS DURING THE THREE-WEEK ISOLATION PERIOD FOLLOWING ADMINISTRATION OF RADIOACTIVE IODINE (I^{131}) IN CATS WITH HYPERTHYROIDISM

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September 2016

ABSTRACT

Hyperthyroidism is the most common endocrine disorder seen in cats and is frequently associated with weight loss. Following treatment weight gain should be seen and therefore weight assessment should form part of the monitoring protocol for cats with this condition. Although several treatment options are available for hyperthyroidism in cats, radioactive iodine (I^{131}) is the gold standard treatment for this condition. I^{131} is offered by several institutions within the United Kingdom (UK); however, this treatment is associated with variable hospitalization periods due to the radiation hazards that these cats pose to their owners following treatment. Hospitalization length and costs associated with this treatment have both been found to have a negative impact on the frequency that I^{131} is offered and utilized by general practitioners and owners respectively.

The aims of the studies presented in this thesis were to assess the weight changes of hyperthyroid cats seen during the three-week isolation period following I^{131} administration and assess if an electronic personal dosimeter (EPD) could be used to document the levels of gamma (γ) radiation emitted from treated cats during the same time period. For the study assessing the weight changes in treated cats, weight changes were shown to be useful as an indicator of the reversal of biochemical hyperthyroidism; however, factors including the gender and age of the cat were not found to affect the weight changes that occurred. For the γ radiation emission study, it was also assessed whether the current 21-day hospitalization period at the Small Animal Hospital (SAH) could be shortened. It was shown that an EPD can be used to measure the γ radiation emitted from treated cats and that a reduction of the current isolation period to 14 days is possible in cats treated with $\leq$ 200 megabecquerels (MBq) of I^{131}.

Both of these studies have added to our knowledge and understanding of I^{131} treatment in cats and have demonstrated the merits of using weight changes in the assessment of treatment of hyperthyroidism and the utility of EPDs for measuring γ radiation emissions in treated cats.

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ACKNOWLEDGEMENTS

Firstly I would like to thank my supervisors Professor Ian Ramsey BVSc PhD DSAM DipECVIM-CA FHEA MRCVS and Alix McBrearty BVMS (Hons) MVM CertSAM DipECVIM-CA FHEA MRCVS for their support and advice throughout this project. I would also like to thank James Gray BA RPA RWA CRadP for his advice and technical support for the monitoring of gamma (γ) radiation emissions part of this study, as well as Tim Parkin BSc BVSc PhD DipECVPH FHEA MRCVS and Lisa Boden AB BVSc MANZCVS LLM PhD DipECVPH MRCVS for their assistance in statistical analysis. I am grateful to Eilidh Gunn BVMS DipECVIM-CA MRCVS for her help in the setting up of the electronic personal dosimeters (EPDs). Finally, I would also like to thank the veterinary nurses of the Small Animal Hospital (SAH) for their care of the cats included in this study.

AUTHOR'S DECLARATION

The work presented in this thesis was performed solely by the author except where the assistance of others has been acknowledged.

Emma Roberts, September 2016

DEFINITIONS

ALKP	Alkaline phosphatase
BCS	Body condition score
CT	Computed tomography
cTSH	Canine thyrotropin
DEXA	Dual-energy x-ray absorptiometry
ELISA	Enzyme-linked immunosorbent assay
EPD	Electronic personal dosimeter
FeLV	Feline leukaemia virus
fT3	Free triiodothyronine
fT4	Free thyroxine
FIV	Feline immunodeficiency virus
GFR	Glomerular filtration rate
Gy	Gray
keV	Kiloelectronvolt
IAEA	International Atomic Energy Agency
ICRP	International Commission on Radiological Protection
IRIS	International Renal Interest Society
I^{131}	Radioactive iodine
MBq	Megabecquerel
mCi	Millicurie
MeV	Megaelectronvolt
mR	Milliröntgen
mSv	Millisievert
PBDE	Polybrominated diphenyl ethers
PTU	Propylthiouracil
rhTSH	Recombinant human thyrotropin
SAH	Small Animal Hospital
Sv	Sievert
T3	Triiodothyronine
T4	Thyroxine
ΔT4	Change in serum T4 concentration
TB	Thyroid to background
TcTU	Percent thyroidal uptake of $^{99m}TcO^{-}_{4}$

TRH	Thyrotropin releasing hormone
TS	Thyroid to salivary
TSH	Thyrotropin
TSHR	Thyrotropin receptor
TT	Thyroid to thyroid
UK	United Kingdom
USG	Urine specific gravity
$^{99m}TcO^{-}_{4}$	Pertechnetate
α	Alpha
ß	Beta
γ	Gamma
µGy	Microgray
µSv	Microsievert

PUBLICATIONS AND PRESENTATIONS

Some of the work contained in this thesis has been the subject of the following publication or presentations:

Publication:

Roberts, E., Gray, J.M., Gunn, E. & Ramsey, I.K., 2015. A novel method of continuous cage-side monitoring of hyperthyroid cats treated with radio-iodine. *Veterinary Record* 177, 1

Conference proceedings:

Roberts, E., Boden, L.A. & Ramsey, I.K., 2014. Can weight change during the 3 week isolation period after treatment with radioactive I-131 be used as a measure of success of treatment of feline hyperthyroidism? Research Abstract Presentation. Proceedings of the British Small Animal Veterinary Association 57th Annual Congress, Birmingham, UK.

Roberts, E., Gray, J.M., Gunn, E. & Ramsey, I.K., 2014. A novel method of continuous cage-side monitoring of hyperthyroid cats treated with radio-iodine. Research Abstract Presentation. Proceedings of the British Small Animal Veterinary Association 57th Annual Congress, Birmingham, UK.

CHAPTER 1

1 REVIEW OF HYPERTHYROIDISM INCLUDING THE USE OF RADIOACTIVE IODINE (I^{131}) AND THE WEIGHT CHANGES SEEN FOLLOWING TREATMENT

1.1 The thyroid gland and thyroid hormone production

The thyroid gland is located on the lateral aspect of the proximal trachea. It develops from the fourth branchial pouch as an invagination in the pharyngeal floor and then migrates caudally along the midline of the trachea. The gland is bilobed in cats and each lobe is closely associated with two parathyroid glands, which secrete parathyroid hormone and are responsible for the control of calcium metabolism. The thyroid gland is enclosed by a capsule of connective tissue and the major blood supply is provided by the cranial thyroid arteries (Ohri *et al.*, 1994, Dyce *et al.*, 2010; Greco & Stabenfeldt, 2013).

The follicular cells of the thyroid gland are responsible for the production of two active thyroid hormones, triiodothyronine (T3) and thyroxine (T4). In order to make T3 and T4, iodide, which is converted from iodine in the gastro-intestinal tract, is taken up by iodide transporters and becomes trapped within the thyroid gland. Iodide is then oxidized to iodine and iodination of tyrosine residues in the glycoprotein thyroglobulin occurs, forming T3 and T4 (Peterson, 2006). Although T4 is the hormone predominantly secreted by the thyroid gland, T3 is more metabolically active. The synthesis and secretion of T3 and T4 is predominantly stimulated by an increase in thyrotropin (TSH) production from the pars distalis of the pituitary gland. In turn, the synthesis and secretion of TSH is stimulated by thyrotropin releasing hormone (TRH), which is produced by the hypothalamus. Thyroid hormones are transported in the circulation via plasma proteins e.g. thyroxine binding globulin and also to a lesser degree by lipoproteins. However, only the unbound and metabolically active fraction of T4, free T4 (fT4) is able to be taken up by tissues and exert its effects. Although T3 is synthesized by the thyroid gland, the majority of it is produced by deiodination of T4 in the cells of the peripheral tissues, including the kidneys, skeletal muscle, liver and skin (Visser, 1996; Mooney & Peterson, 2012).

Thyroid hormones bind to thyroid hormone receptors, which are located in the cell nucleus, and result in gene transcription (Bianco & Kim, 2006). Thyroid hormones increase the metabolic rate of cells and are responsible for the regulation of the metabolism of carbohydrates, lipids and proteins. They increase the rate of both glycolysis and lipolysis within cells and the cells uptake

of amino acids (Mooney & Peterson, 2012; Greco & Stabenfeldt, 2013). They are essential for normal growth and development and thyroid function is associated with both body weight and body mass index (Knudsen *et al.,* 2005; Fox *et al.,* 2008; Mullur *et al.,* 2014).

The circulating concentrations of thyroid hormones are controlled through a negative feedback loop of the hypothalamic-pituitary-thyroid axis, in which increases in T4 and T3 result in the suppression of TRH and/or TSH (Connors & Hedge, 1981; Yamada *et al.,* 1989).

Thyroid hormones are predominantly metabolised via deiodination by iodothyronine deiodinases; however, alternative pathways include conjugation of their phenolic hydroxyl group with sulfate or glucuronic acid, oxidative deamination and decarboxylation of the alanine side chain and cleavage of the ether link (Visser, 1996; Wu *et al.,* 2005; Bianco & Kim, 2006).

1.2 Hyperthyroidism in humans

Hyperthyroidism is a pathological disorder in which thyroid hormones are synthesized excessively. The prevalence of hyperthyroidism in humans increases with age, with the mean age of patients reported to be between 50 and 59 years old (Leese *et al.,* 2008; Abraham-Nordling *et al.,* 2011; De Leo et al., 2016). It is a condition more frequently seen in women (De Leo *et al.,* 2016).

The most common cause of hyperthyroidism is Graves's disease. This is an autoimmune condition in which the natural immunotolerance is lost and the development of antibodies, which bind to the TSH receptor and stimulate the follicular cells of the thyroid, occur (De Leo *et al.,* 2016).

Toxic nodular goiter is also a common cause of hyperthyroidism. In this condition, nodules that have developed in the thyroid autonomously produce thyroid hormones independent of the influence of TSH. There have been mutations documented both in the thyrotropin receptor (TSHR) gene and the adenylate cyclase stimulation protein $G_s\alpha$, which result in constitutive activation

of the gene and protein respectively, in many of these patients (De Leo *et al., 2016)*.

Treatment options for hyperthyroidism include surgery (thyroidectomy), anti-thyroidal medication and radioactive iodine (I^{131}). In Graves's disease, all three treatment modalities are utilized; however, in patients with toxic nodular goiter, anti-thyroidal medication only tends to be used to restore the euthyroid state prior to definitive treatment i.e. thyroidectomy or I^{131} treatment (De Leo *et al.,* 2016*)*.

In humans a syndrome of subclinical hyperthyroidism also exists, which is classified by a repeatedly low or undetectable serum TSH concentration in the face of normal serum fT4 and free T3 (fT3) concentrations. This condition is usually picked up on routine screening tests and patients may have either only mild signs of hyperthyroidism such as nervousness, heat intolerance and anxiety or no clinical signs at all (Biondi & Cooper, 2008). As there have been no controlled studies that have shown a benefit of treatment in these cases, treatment of this condition is currently controversial. However, if treatment is pursued, then I^{131} is thought to be the most appropriate (Bahn *et al.,* 2011).

1.3 Hyperthyroidism in cats

Feline hyperthyroidism, since being first reported in 1979, has become the most common endocrine disorder in cats (Peterson *et al.,* 1979; Peterson, 2012). It is clinically and pathologically similar to the condition toxic nodular goiter in humans and therefore comparisons between the two conditions can potentially be drawn (Kooistra, 2014; Peterson, 2014).

Hyperthyroidism in cats results from the excessive production of T3 and T4 from thyroid tissue, independent of TSH production from the pituitary gland. It is a disease that affects middle-aged and older cats and the average age of onset is 12-13 years old. An obvious gender predilection has not yet been found (Peterson, 2012; Mooney & Peterson, 2012).

In the majority of cases (> 95 %), hyperthyroidism is caused by adenomatous hyperplasia of the thyroid glands, with hyperplastic tissue identified on histopathological assessment (Hoenig *et al.,* 1982). Both thyroid glands are typically affected in cats; however, in some cases the disease can be unilateral in origin or even multifocal (≥ three tumour nodules) (Peterson & Broome, 2015). Similar to humans with toxic nodular goiter, mutations in the TSHR and the $G_s\alpha$ genes have been found in some hyperthyroid cats (Peeters *et al.,* 2002; Watson *et al.,* 2005; De Leo *et al.,* 2016). In rare cases, hyperthyroidism can result from a thyroid carcinoma; however, not all cases of thyroid carcinoma are hypersecretory (Hoenig *et al.,* 1982; Turrel *et al.,* 1988; Naan *et al.,* 2006; Hibbert *et al.,* 2009; Peterson & Broome, 2015; Peterson *et al.,* 2016a). Thyroid carcinomas can be further classified as follicular, papillary or compact and in some cases a mixture of adenomatous and carcinoma tissue can be detected on histopathological assessment (Turrel *et al.,* 1988; Hibbert *et al.,* 2009).

Hyperthyroidism is a progressive disease, ranging from a subclinical disease to a clinical and symptomatic disease. A low serum TSH concentration combined with histological evidence of nodular thyroid disease but a normal serum T4 concentration demonstrates subclinical disease. This is compared to the clinical phase of the disease when T4 is then produced excessively resulting in an increased serum T4 concentration (Wakeling *et al.,* 2007). As the duration of clinical disease lengthens, there is also further progression of the disease as shown by the findings of Peterson *et al.,* (2016a). In the Peterson *et al.,* (2016a) study it was shown that the prevalence of multifocal disease, large (4–8 cm^3) and huge (> 8 cm^3) thyroid tumours, thyroid carcinoma and intrathoracic tumours all increased with length of disease duration, as well as the median tumour volume and median serum T4 concentration when comparing cats with disease duration ≤ one year to cats with a disease duration > 4 - 6.1 years.

Hyperthyroidism is associated with an array of clinical signs in cats; however, none of these are pathognomonic for the condition. Clinical signs include polyphagia, weight loss, polyuria/polydipsia, gastro-intestinal signs (vomiting and diarrhoea), hyperactivity, irritability and tachypnoea, as well as skin changes and coat changes such as alopecia or an unkempt coat. Less common

clinical signs can include a decreased appetite, ventroflexion of the neck and decreased energy levels (Mooney & Peterson, 2012).

1.4 Prevalence of feline hyperthyroidism

The prevalence of hyperthyroidism in cats has increased over the last few decades (Edinboro *et al.,* 2004a). Edinboro *et al.,* (2004a) documented that the hospital prevalence of hyperthyroidism increased from 0.1 % during the time period 1978 to 1982, to 2 % during the time period 1993 to 1997.

The prevalence of hyperthyroidism may also be affected by geographical location. A prevalence of 3.93 % has been documented in cats ≥ 10 years old in Hong Kong, compared to a prevalence of 8.7 % in England, in cats of the same age group (De Wet *et al.,* 2009; Stephens *et al.,* 2014). An even higher prevalence of 12.3 % has been documented in Southern Germany (Kohler *et al.,* 2016). The Kohler *et al.,* (2016) study did use a different age cut-off of eight years old, rather than the age cut-off used in the two former studies and this may have affected their prevalence. However, as the age of onset of hyperthyroidism is 12-13 years old, this variance in age cut-off is unlikely to have significantly affected their findings (Mooney & Peterson, 2012). As the prevalence of hyperthyroidism has been found to have increased over time, it is also possible that differences in prevalence's between all these studies could have been affected by this, as well as geographical variation due to the studies being performed at different times.

1.5 Predictors and risk factors for the development of hyperthyroidism in cats

Predictors for the development of hyperthyroidism have included the presence of a goiter, serum alkaline phosphatase (ALKP) and TSH concentrations and breed. These predictors were identified in a study that evaluated which cats, aged nine years and over, did and did not develop hyperthyroidism over a 14-month follow up period. It was found that those cats that developed hyperthyroidism were significantly more likely to have a palpable goiter, a higher serum ALKP concentration and non-pure breed status at baseline, as well

as having an undetectable serum TSH concentration, when compared to cats that did not become hyperthyroid (Wakeling *et al.,* 2011).

Potential risk factors for cats developing hyperthyroidism have been proposed. These have included breed, the consumption of canned wet food, the use of cat litter, exposure to polybrominated diphenyl ethers (PBDEs) and the use of topical ectoparasite preparations (Kass *et al.,* 1999; Dye *et al.,* 2007). A more recent study by Wakeling *et al.,* (2009) also found similar risk factors to Kass *et al.,* (1999), as well as additional factors that included increasing age and a diet that included fish.

1.5.1 Breed

Pure bred cats, including Siamese, Persian, Himalayan and Burmese breeds have been documented to have a lower risk of developing hyperthyroidism compared to domestic shorthaired cats; however, this has not always been demonstrated (Kass *et al.,* 1999; Olczak *et al.,* 2005; De Wet *et al.,* 2009; Wakeling *et al.,* 2011; Stephens *et al.,* 2014). One study assessed this finding further and evaluated whether the metabolism of tyrosine, iodine or selenium was associated with coat colour/hyperthyroidism in cats that had light or pointed coats, but no associations were noted (Sabatino *et al.,* 2013).

1.5.2 Diet

Cats fed a canned wet food have been documented to be at higher risk for developing hyperthyroidism; however, the studies that identified this have been associated with limitations such as age differences between the case and control groups, which may have affected their findings (Kass *et al.,* 1999; Wakeling *et al.,* 2009).

Potential constituents of canned food that may be associated with the link with hyperthyroidism include the monomer bisphenol A, which is found in plastics and is used to line metal cans, as well as selenium and iodine levels in the diet and flavonoids (Kooistra, 2014; van Hoek *et al.,* 2015).

1.5.2.1 Bisphenol A

Bisphenol A can act as a thyroid hormone receptor antagonist as it is structurally similar to thyroid hormones. It has been shown to alter the transcriptional expression of genes involved in thyroid hormone synthesis and the genes involved with thyroid transcription factors in rats, as well as inhibiting iodide uptake (Wu *et al.*, 2016).

Although exposure to bisphenol A has been proposed as a potential risk factor in cats, a direct link with the development of hyperthyroidism has not been currently found (van Hoek *et al.*, 2015).

1.5.2.2 Selenium

Selenium has been found to increase the expression and activity of the sodium iodide symporter in rats, which then mediates the iodine uptake by the thyroid follicular cells (Leoni *et al.*, 2015). Although a selenium deficient diet has been found to result in a significant increase in both serum fT4 and T4 concentrations in chickens, the effect of selenium has yet to be found as a possible cause of hyperthyroidism in cats in studies performed to this date (Foster *et al.*, 2001; Sabatino *et al.*, 2013; Huang *et al.*, 2016).

1.5.2.3 Iodine

Cats that are fed a non-iodine supplemented commercial diet have been found to be more than four times more likely to develop hyperthyroidism, when compared to a population of cats fed an iodine-supplemented diet (Edinboro *et al.*, 2004b). A marked variation in the iodine content of canned food has also been found and this may contribute to the development of nodular hyperplasia and subsequently hyperthyroidism, if diets go from being deficient in iodine to excessive (Edinboro *et al.*, 2013).

Iodine deficiency has also been shown to be a risk factor for developing hyperthyroidism in humans, as the prevalence of toxic nodular goiter is higher in areas that are iodine deficient (De Leo *et al.*, 2016).

1.5.2.4 Flavonoids

The feeding of a soy-based diet, which contain isoflavone a type of flavonoid, has been found to result in significantly higher serum T4 and fT4 concentrations in cats, when compared to cats fed a soy-free diet; however, serum T3 concentrations were unaffected. It is thought that these changes in thyroid hormone concentrations are due to either inhibition of 5'-iodothyronine deiodinase or due to enhanced clearance of T3 (White *et al.,* 2004). The highest median isoflavone content in cat food has been found to be in the wet commercially-prepared foods (Bell *et al.,* 2006).

1.5.3 Cat litter

Cats that use cat litter have been found to have a three-fold increased risk of hyperthyroidism (Kass *et al.,* 1999; Wakeling *et al.,* 2009). However, it has been suggested that this association between cat litter and hyperthyroidism may actually be due to the improved level of care seen in these cats, rather than the use of cat litter being a direct cause of hyperthyroidism (Kooistra, 2014).

1.5.4 Polybrominated diphenyl ethers (PBDEs)

Cats have been shown to be highly exposed to PBDEs and it has also been shown that hyperthyroid cats have higher levels of PBDEs in their serum compared to euthyroid cats (Dye *et al.,* 2007; Norrgran *et al.,* 2015).

Research has suggested that PBDEs result in enhanced excretion of T4 or that they competitively bind to T4, preventing it from binding with its receptor, therefore interfering with the thyroid hormone transport system (Birnbaum & Staskal, 2004).

Suggested exposure routes of cats to PBDEs have included the diet or ingestion of house dust, with most studies suggesting the dominant exposure to be from house dust (Dye *et al.,* 2007; Guo *et al.,* 2012; Mensching *et al.,* 2012). A recent study has also found that cats fed food containing fish flavours are exposed to the methoxylated derivatives of PBDEs and that this may explain the previously

noted association between cats fed fish flavoured food and a higher incidence of hyperthyroidism (Wakeling *et al.,* 2009; Mizukawa *et al.,* 2016).

Although PBDE exposure could be a potential risk factor for hyperthyroidism in cats, not all studies have found an association between the two (Guo *et al.,* 2012; Chow *et al.,* 2015). In humans a link between PBDE exposure and thyroid dysfunction has also not been identified, with no effect on thyroid hormone levels in children or the development of thyroid cancer demonstrated by PBDE exposure (Gascon *et al.,* 2011; Aschebrook-Kilfoy *et al.,* 2015).

1.6 Diagnosis of hyperthyroidism in cats

1.6.1 Physical examination

Physical examination in the vast majority of hyperthyroid cats identifies either a unilateral or bilateral palpable goiter; however, goiters are not detected in all cases due to the presence of ectopic thyroid tissue e.g. in the thorax, as well as the palpation technique. Goiters can also be detected in euthyroid cats and therefore goiter detection is not a pathognomonic finding (Norsworthy *et al.,* 2002; Paepe *et al.,* 2008; Wakeling *et al.,* 2011; Peterson, 2013). Other physical examination findings can include poor body condition, muscle wastage, pyrexia, tachycardia, a gallop rhythm or arrhythmia and auscultation of a cardiac murmur, as well as signs consistent with congestive heart failure such as dyspnoea, crackles and muffled thoracic auscultation (Mooney & Peterson, 2012).

1.6.2 Blood tests

1.6.2.1 Thyroxine (T4)

In hyperthyroidism the production of T4 increases. Therefore, the measurement of serum T4 concentration is usually the first diagnostic test pursued when hyperthyroidism in a cat is suspected; however, false negative and positive results can occur with this test (Peterson *et al.,* 1983; Lurye *et al.,* 2002). In mild cases of hyperthyroidism up to 35 % of cases have been reported to have a

normal serum T4 concentration (Peterson *et al.*, 1987; Peterson *et al.*, 2001; Peterson, 2013). Serum T4 concentration can be measured using multiple different assays including radioimmunoassays, chemiluminescent enzyme immunoassays, point-of-care enzyme-linked immunosorbent assays (ELISA) and enzyme immunoassays (Peterson, 2013). However, results from in-house ELISAs should be interpreted with caution as false positive results may be seen (Lurye *et al.*, 2002).

The serum T4 concentration has also been shown to alter with disease duration in hyperthyroidism with significant increases seen as the duration of disease lengthens. This observation was documented in a recent study that assessed 2096 cats with hyperthyroidism and identified that the median serum T4 concentration in cats with a disease duration ≤ one year was 100 nmol/l, compared to 315 nmol/l in cats with a disease duration of > 4-6.1 years (Peterson *et al.*, 2016a). Therefore, in cats with chronic hyperthyroidism, testing of the serum T4 concentration is more likely to result in a definitive answer compared to the use of this test in hyperthyroid cats with early disease (Peterson *et al.*, 1987).

1.6.2.2 Triiodothyronine (T3)

The production of T3 also increases in hyperthyroidism; however, the measurement of serum T3 concentration as a screening test for hyperthyroidism has been shown to have a poor sensitivity with 42 % of hyperthyroid cats having a normal serum T3 concentration in one study (Peterson, 2013). As with serum T4 concentrations, serum T3 concentrations have been shown to fluctuate in and out of the reference interval in cases of mild hyperthyroidism (Peterson *et al.*, 1987). This makes measurement of serum T3 concentrations in cases of mild/early hyperthyroidism of minimal diagnostic utility, as these cats tend to have a serum T3 concentration within the reference interval (Peterson, 2013). It is therefore of no additional use over measurement of serum T4 concentration.

1.6.2.3 Free T4 (fT4)

The production of fT4 increases in hyperthyroidism and it can be used to help diagnose this condition. It is reported to have a high sensitivity, with only 2/100 hyperthyroid cats documented to have a serum fT4 concentration within the reference interval (Peterson, 2013). Despite the high sensitivity of this test, the specificity can be poor with a 20 % false positive rate documented in cats with chronic kidney disease; however, lower false positive rates (6.3 %) have also been reported in non-thyroidal illness (Peterson *et al.,* 2001; Wakeling *et al.,* 2008). Despite the concerns regarding its specificity, the main utility of fT4 is in cases where hyperthyroidism is suspected but the serum T4 or T3 concentrations are within the reference interval (Peterson *et al.,* 2001).

1.6.2.4 Canine thyrotropin (cTSH)

In hyperthyroidism due to the excessive production of thyroid hormones, TSH production is suppressed (Peterson *et al.,* 2015). Although TSH is measured in humans with suspected hyperthyroidism, a commercially available feline TSH for the same use is not currently available in cats. However, the measurement of cTSH has been shown to have a high sensitivity (98 %) in diagnosing feline hyperthyroidism but a poor specificity (69.9 %). One of the main concerns with the use of cTSH is that it cannot accurately differentiate between a low-normal TSH concentration, which can be found in some euthyroid cats, from a low/suppressed concentration present in the vast majority of hyperthyroid cats. It is therefore advised to combine cTSH with measurement of either serum fT4 or T4 concentrations, increasing its specificity to 98.8% (Peterson *et al.,* 2015).

1.6.2.5 T3 suppression test

This test assesses the suppression of serum T4 production following administration of T3 and the degree of suppression should be reduced in cats with hyperthyroidism compared to non-hyperthyroid cats. This test has been evaluated in a study population including cats with hyperthyroidism, cats with non-thyroidal illness and healthy cats. It was shown that the mean serum T4 concentration following the suppression test was significantly higher and the

percentage decrease in serum T4 concentration was significantly lower in cats with hyperthyroidism, compared to the other two groups. Although suppression of serum T4 concentration by > 50 % was only documented in non-hyperthyroid cats, there was a small amount of overlap between all three groups if a decrease in serum T4 concentration > 35 % was used as a cut-off for excluding hyperthyroidism (Peterson *et al.*, 1990). Therefore, this test is predominantly now used to exclude the presence of hyperthyroidism, rather than to diagnose it (Mooney & Peterson, 2012).

1.6.2.6 Thyrotropin releasing hormone (TRH) stimulation test

This test assesses the response of serum T4 concentrations to the administration of TRH and has been evaluated in cats with hyperthyroidism, cats with non-thyroidal illness and healthy cats. Although the absolute difference between the mean basal and TRH stimulated concentrations of serum T4 was significantly less in cats with hyperthyroidism than the other two groups, there was a large amount of overlap, limiting the usefulness of this test (Peterson *et al.*, 1994). A later study also showed that the ability of this test to differentiate between cats with hyperthyroidism and cats with severe non-thyroidal illness was poor (Tomsa *et al.*, 2001). Due to these findings, this test is now rarely used in the diagnosis of hyperthyroidism.

1.6.2.7 Thyrotropin (TSH) stimulation test

This test assesses the response of serum T4 concentrations to administration of TSH. This test is not commonly used in cases of suspected feline hyperthyroidism as it cannot differentiate cats with mild hyperthyroidism i.e. equivocal baseline serum T4 concentrations, from healthy cats (Mooney *et al.*, 1996).

1.6.3 Imaging

1.6.3.1 Thyroid scintigraphy

In cases of clinically suspected hyperthyroidism in which the serum T4 concentration is within the reference interval, thyroid scintigraphy, if available,

may be the next test that is utilized (Peterson, 2013). This imaging modality produces a visual display of functional thyroid tissue based on the selective uptake of various radionuclides by the thyroid tissue itself, enabling ectopic thyroid tissue to also be identified (Broome, 2006; Peterson *et al.*, 2016a).

Pertechnetate ($^{99m}Tc0_4^-$) is the most commonly used radioisotope in thyroid scintigraphy. The pertechnetate ions are trapped by the thyroidal iodide concentrating mechanism, as they mimic iodide ions; however, they are not retained within the thyroid gland. The percentage uptake of $^{99m}Tc0_4^-$ by the thyroid gland has been shown to be increased in cases of feline hyperthyroidism when compared to euthyroid cats (Mooney *et al.*, 1992; Nap *et al.*, 1994).

Pertechnetate is used in thyroid scintigraphy instead of radioiodine nucleotides due to the compared relative in-expense of it, the short physical half-life (six hours), the lower associated radiation dose, the shorter scanning time required and the shorter time interval required between its administration and the start of imaging, which is about 20 minutes (Peterson & Becker, 1984). It can be given as an intravenous or a subcutaneous injection (Page *et al.*, 2006; Peterson *et al.*, 2016b).

Measurements that can be obtained from thyroid scintigraphy include the thyroid to salivary (TS) ratio, the thyroid to background (TB) ratio, the percent thyroidal uptake of $^{99m}TcO^-_4$ (TcTU) and the thyroid to thyroid (TT) ratio (Page *et al.*, 2006; Peterson *et al.*, 2016b).

Although thyroid lobe asymmetry is found to occur frequently in hyperthyroid cats, the TT ratio is not relied on in the diagnosis of hyperthyroidism due to the presence of thyroid lobe asymmetry in some euthyroid cats as well (Scrivani *et al.*, 2007). Of the other quantitative scintigraphic parameters, a high TB ratio (> 6.1) was detected in 96.1 % of hyperthyroid cats by Peterson and Broome (2015) and the TS and TB ratios and TcTU were all found to be significantly higher in cats with hyperthyroidism than in euthyroid or healthy cats by Peterson *et al.*, (2016b). All three of these parameters have been found to be both sensitive and specific for the diagnosis of hyperthyroidism (Peterson *et al.*, 2016b). Of the quantitative scintigraphic parameters, the TS ratio is the most commonly used

for differentiating euthyroid from hyperthyroid cats and it has been found to have the highest test accuracy (Henrikson *et al.*, 2005; Peterson *et al.*, 2016b). The TS ratio is high (> 1.5) in 98.7 % of hyperthyroid cats (Peterson & Broome, 2015).

In the study by Peterson *et al.*, (2016b), the TcTU was found to have a higher correlation with serum T3 and T4 concentrations and estimated thyroid volume than the TS ratio. This would suggest that TcTU would be the best parameter to use to predict the functional volume of the thyroid gland (Peterson *et al.*, 2016b).

1.6.3.2 Computed Tomography (CT)

CT has been compared to the use of thyroid scintigraphy in its ability to characterise the thyroid lobes in hyperthyroidism. Although CT has been found to be a potential alternative modality for determining the more active thyroid lobe in hyperthyroid cats, it is not able to differentiate unilateral from bilateral disease (Lautenschlaeger *et al.*, 2013). Due to this CT is a less useful imaging modality if surgery is being considered as the treatment for hyperthyroidism.

1.6.3.3 Ultrasonography

Ultrasonography has also been directly compared to the use of thyroid scintigraphy to assess the size and appearance of thyroid glands. Although an 85.7 % agreement between scintigraphy and ultrasonography was found in their ability to differentiate normal from abnormal thyroid lobes, ultrasonography cannot assess for the presence of either ectopic thyroid tissue or metastatic lesions which can limit its usefulness (Wisner *et al.*, 1994).

1.6.3.4 Medical infrared thermal imaging

Recently, the use of medical infrared thermal imaging, which records cutaneous thermal patterns in the form of a colour map, has also been assessed as a screening method for feline hyperthyroidism (Waddell *et al.*, 2015). This identified an 87.5 % accuracy of differentiating hyperthyroid cats from euthyroid

cats, as long as the hair was clipped over the ventral aspect of the neck prior to using this modality. However, as this method has only recently been used and the study population did not include cats with non-thyroidal illness, further studies will need to be performed to further evaluate the use of it in feline hyperthyroidism.

1.7 Treatment

The main treatment options for feline hyperthyroidism include antithyroid thionamides [methimazole (thiamazole)(Felimazole; Dechra), carbimazole (Vidalta; MSD Animal Health)], surgical thyroidectomy, I^{131} and an iodine-restricted diet (Mooney, 1994; Naan *et al.,* 2006; Daminet *et al.,* 2014; Hui *et al.,* 2015).

Other treatment options including the use of percutaneous radiofrequency heat ablation and percutaneous ethanol injections have also been evaluated (Wells *et al.,* 2001; Mallery *et al.,* 2003). Percutaneous radiofrequency heat ablation was found to result in a reduction in serum T4 concentration in the nine cats included in the study; however, a euthyroid state was only achieved for a mean time period of four months and hyperthyroidism recurred in all cats (Mallery *et al.,* 2003). The longest period of euthyroidism following the use of percutaneous ethanol injections was slightly longer at 27 weeks; however, this modality was associated with complications including Horner's syndrome, laryngeal paralysis and dysphonia (Wells *et al.,* 2001). Due to the complications seen in the Wells *et al.,* (2001) study and the short period of euthyroidism obtained in both the Wells *et al.,* (2001) and Mallery *et al.,* (2003) studies, these treatment modalities are not currently widely utilized.

Propylthiouracil (PTU) was also previously used for feline hyperthyroidism. However, as methimazole has been found to have better bioavailability than PTU and be more potent, and PTU is associated with a high incidence of adverse effects, PTU is no longer used (Peterson *et al.,* 1984; Trepanier *et al.,* 1991; Trepanier, 2006).

1.7.1 Radioactive iodine (I^{131})

Radioactive iodine was first used to treat hyperthyroidism in humans in 1941 and it is now also one of the treatment modalities available for feline hyperthyroidism (Sawin & Becker, 1997; Peterson, 2006). Radioactive iodine is deemed by many to be the gold standard treatment for this condition in cats with ≥ 94 % success rate reported (Mooney, 1994; Peterson & Becker, 1995; Peterson, 2006).

Institutions need to have fulfilled specific requirements from their regional radiation protection services to be allowed to use I^{131} as a treatment modality for feline hyperthyroidism. This requirement has resulted in this treatment modality only being offered at a few institutions in the UK, limiting the availability of it.

1.7.1.1 Physical properties of I^{131} and radiobiology

As the cells of the thyroid gland cannot differentiate between stable iodine and radioactive iodine, ~ 30 % of administered I^{131} is taken up by the thyroid follicular cells via iodide transporters and becomes trapped in the thyroid glands (Peterson, 2006; Mumtaz *et al.*, 2009; Wyszomirska, 2012).

Radioactive iodine emits ionising radiation in the form of beta (β) and gamma (γ) radiation and it has a physical half-life of 8.1 days (Reiners *et al.*, 2008). Beta radiation, which takes the form of either an electron or a positron particle, has a mean energy of 191 kiloelectronvolts (keV) and is emitted from I^{131} atoms first, followed by the emission of γ radiation, which consists of photons of energy and has major radiations at 364 and 637 keV (Wyszomirska, 2012). The radiation emissions from the β particles and γ rays are responsible for 90 % of the radiation emitted by I^{131} (Robbins & Schlumberger, 2005). Due to the higher energy of γ radiation it can penetrate tissues easily, compared to β radiation which only penetrates two mm into tissue once injected (Kurland & Freedberg, 1951).

Once taken up by the thyroid follicular cells, there are three phases of the interaction of ionising radiation emitted by I^{131} with living tissue (Wyszomirska, 2012):

- Phase 1: the physical phase. Radiation results in ionisation of cells, which results in damage to proteins and DNA within the cells as well as disruption of chemical bonds, creating free radicals.
- Phase 2: the chemical phase. In this phase the created free radicals react with components of the cell.
- Phase 3: the biological phase. During this phase enzymatic reactions occur within the cell, aiming to repair the damage done during the chemical phase. Cell death occurs in those cells that are impossibly damaged or are repaired improperly.

The β radiation emitted from I^{131} is the clinically useful component in thyroid disease as it accounts for 80 % of the radiation dose delivered to the thyroid tissue (Wyszomirska, 2012). The β radiation destroys the abnormally functioning follicular cells in the adenomatous hyperplastic thyroid tissue, resulting in resolution of the autonomous production of thyroid hormones and a gradual reduction in the thyroid volume (Mumtaz *et al.,* 2009). As β radiation does not penetrate far into tissue the damaging effects are restricted to the thyroid cells, with sparing of the adjacent cells (Wyszomirska, 2012).

The γ radiation only accounts for 10 % of the radiation dose of I^{131}. The majority of γ radiation leaves the body via the skin surface and can be detected with a radiation detector (Robbins & Schlumberger, 2005).

1.7.1.2 Methods of I^{131} administration

In cats, I^{131} can be administered either as an intravenous injection, subcutaneously or orally (Meric *et al.,* 1986; Malik *et al.,* 1993; Theon *et al.,* 1994). The injectable route of administration (intravenous versus subcutaneous), has not been found to affect the uptake of I^{131} by the thyroid gland and therefore the efficacy of treatment appears to be unaffected by this. However, subcutaneous administration has been associated with lower levels of radiation exposure to staff (Theon *et al.,* 1994). When I^{131} is administered orally, higher

doses tend to be needed and handling of the tablets can also pose additional risks to the handler (Malik *et al.,* 1993). Orally administered I^{131} has also been found to result in a higher chance of treatment failure compared to the use of I^{131} intravenously (Forrest *et al.,* 1996). Therefore, due to the lower levels of radiation that personnel are exposed to and the lower dose of I^{131} required, the subcutaneous route of administration of I^{131} is advised (Malik *et al.,* 1993; Theon *et al.,* 1994).

In the human field, laser treatment combined with I^{131} has been assessed recently (Chianelli *et al.,* 2014). This combination treatment was found to result in a faster and greater improvement in local and systemic symptoms when compared to the use of I^{131} alone. This treatment combination has yet to be assessed in cats.

1.7.1.3 Dose of I^{131} administered in humans

In the human field the dose of I^{131}, in megabecquerels (MBq), which is administered to patients with hyperthyroidism can be either a variable calculated dose or a fixed dose (Szumowski *et al.,* 2012; Rokni *et al.,* 2014).

When using a variable dose approach, the administered dose can be calculated using Marinelli's formula (Szumowski *et al.,* 2012). Marinelli's formula, as shown below, takes into account the volume of the thyroid gland and the percentage of I^{131} uptake in the nodules:

$$A = \frac{25 \times m \times D}{T_{24} \times T_{eff}}$$

A = I^{131} therapeutic activity (MBq)
25 = unit conversion coefficient
m = volume of thyroid gland calculated from ultrasound of the thyroid in grams
D = absorbed dose in grays (Gy). D = P x 400 Gy, where P = percentage of I^{131} uptake in nodules expressed as a common fraction. 400 Gy is the maximum absorbed dose for autonomous toxic nodule(s) as agreed in the literature.
T_{24} = 24 hours I^{131} uptake (%)

T_{eff} = effective I^{131} half-life in thyroid gland (days) = $T_{biolog} \times T_{phys}/T_{biolog} + T_{phys}$ where T_{biolog} is the rate of iodine excretion from the thyroid and T_{phys} is the physical half-life of I^{131}.

The use of Marinelli's formula for the calculated dose approach to toxic nodular goiter in humans has been found to result in euthyroidism being obtained in ≥ 90 % of patients and ≤ 4 % of patients becoming hypothyroid in a study that included 2190 patients (Szumowski *et al.*, 2012).

There are also simpler calculations for calculating the dose of I^{131}, as documented in the study by Alexander & Larsen (2002). In that study the dose of I^{131} was calculated by the equation below with the percentage uptake of I^{123} being determined by scintigraphy 24 hours after its administration:
Dose of I^{131} = (8 millicurie (mCi) x 100)/(% uptake of I^{123} at 24 hours).

The efficacy of a fixed dose of I^{131} in humans has been directly compared to a calculated dose (Huysmans *et al.*, 1993). In the study by Huysmans *et al.*, (1993) the incidence of resolution of hyperthyroidism was 73 % and the incidence of hypothyroidism was 7 % in cases administered a low fixed dose. This was compared to an 88 % incidence of resolution of hyperthyroidism and a 7 % incidence of hypothyroidism in cases administered a calculated dose. It was also demonstrated that humans administered a low dose of I^{131} needed a significantly higher number of I^{131} administrations than humans dosed using a calculated method.

A recent meta-analysis of the human literature that assessed the efficacy of different I^{131} protocols in 669 patients with toxic nodular goiter, found that a calculated dose resulted in a 9.6 % higher cure rate then use of a fixed dose and only a 0.3 % higher rate of permanent hypothyroidism. The meta-analysis also identified that if using a fixed dose of I^{131}, a fixed high dose (which ranged in studies from 600 to 1200 MBq) resulted in an 18.1 % higher cure rate but a 23.9 % higher rate of developing permanent hypothyroidism compared to the use of a low dose (which ranged in studies from 148 MBq to 555 MBq) (Rokni *et al.*, 2014).

The conclusions from the meta-analysis were that a calculated dose of I^{131} may be preferred over a fixed method due to the higher cure rate. However, use of a calculated method can result in a slightly higher occurrence rate of permanent hypothyroidism (Rokni *et al.*, 2014).

1.7.1.4 Dose of I^{131} administered in cats

The dose of I^{131} that can be administered to cats with hyperthyroidism can depend on local radiation legislation, with some institutions being restricted to a fixed dose protocol (Boland *et al.*, 2014). As in humans there has been research performed assessing the optimal dose of I^{131} to administer in cases of feline hyperthyroidism (Mooney, 1994; Peterson & Becker, 1995; Forrest *et al.*, 1996).

Forrest *et al.*, (1996) assessed the use of the volume of hyperfunctioning thyroid tissue, calculated from thyroid scintigraphy scans using $^{99m}Tc0_4^-$, as the basis on which the dose of I^{131} was based. Although 71/80 cats were cured using this treatment method, it was found that those cats with a larger volume of abnormal hyperfunctioning thyroid tissue were more likely to fail treatment. This study concluded that basing the dose of I^{131} on the volume of abnormal thyroid tissue alone is inadequate for cases of hyperthyroidism that have large volumes of abnormal thyroid tissue (Forrest *et al.*, 1996).

Although Marinelli's formula or the formula used by Alexander & Larsen (2002) are not used in feline hyperthyroidism, there have been studies looking at algorithms for calculating a dose of I^{131} to be administered (Mooney, 1994; Peterson & Becker, 1995). Both Mooney (1994) and Peterson & Becker (1995) based the dose of I^{131} that was administered on the results of a scoring system. The scoring system in each study was based on the combination of three factors: severity of clinical signs, size of the thyroid gland and magnitude of the serum T4 concentration. In Mooney (1994) each factor was scored between one and five, where as in Peterson & Becker (1995) a score between one and three was given. In Peterson & Becker (1995) 524 cats were treated using this system and only a 1.5 % rate of continuation of hyperthyroidism and a 2.1 % prevalence of clinical hypothyroidism was reported. In Mooney (1994), a slightly lower success rate of 94 % was reported but a 0 % prevalence of clinical hypothyroidism.

However, only 50 cases were included in the Mooney (1994) study, which may have resulted in the differences in the reported success rate and rate of clinical hypothyroidism between the two studies. One weakness of the scoring systems is the subjective nature of scoring the severity of clinical signs and size of the thyroid gland. However, research has shown that despite there being varying methods to palpate the size of goiter in a cat, the estimation of the goiter size is not affected by palpation technique (Paepe *et al.,* 2008).

The uptake of I^{131} by the thyroid gland in hyperthyroid cats has been shown to be increased by the use of an iodine-restricted diet, the use of recombinant human thyrotropin (rhTSH) and recent discontinuation of methimazole (Nieckarz & Daniel, 2001; van Hoek *et al.,* 2008a; Scott-Moncrieff *et al.,* 2015). Therefore, this may result in a higher thyroidal uptake of I^{131} than calculated, which could potentially lead to a higher occurrence rate of hypothyroidism post-treatment (Rokni *et al.,* 2014). However, the advantage of an increased uptake of I^{131} is the possibility that diet, rhTSH and methimazole could be used as methods to lower the dose of I^{131} administered.

1.7.1.5 Radiation hazards

As I^{131} is a source of ionising radiation, radiation safety monitoring needs to be used in both the feline and human fields, as patients treated with I^{131} can act as a source of radiation exposure to their families, staff members and members of the general public (Feeney *et al.,* 2003; Pant *et al.,* 2006; Lamb *et al.,* 2013; Ostinelli *et al.,* 2015; Vogiatzi *et al.,* 2015). This is especially prudent for staff working in close proximity to patients treated with I^{131}, as they are at a higher risk of radiation exposure (Happel *et al.,* 2013).

I^{131} can act as both an internal and external potential hazard. External radiation hazards are hazards that arise from a source of radiation outside of the body and internal radiation hazards are due to radioactive material entering the body, either through injection, inhalation, ingestion or absorption across the skin (Lamb *et al.,* 2013). The main external radiation hazard to personnel from cats treated with I^{131} is from the γ radiation emitted from the internalized I^{131} trapped in the thyroid gland and this γ radiation can be measured by radiation

detectors (Feeney *et al.*, 2003). Up to 75 % of the injected dose of I^{131} is reported to be excreted in the urine and faeces of treated cats and it has also been detected in the saliva of treated cats as well (Chalmers *et al.*, 2006; Lamb *et al.*, 2013). Therefore, urine, faeces and saliva can act as internal radiation hazards, should they be ingested.

Due to concerns regarding ionising radiation, there are dose limits on the effective dose and dose constraints put in place to reduce the radiation risks to personnel (Environment Agency, 2012). As there are several terms currently utilized when discussing radiation safety these are defined below for further information (Environment Agency, 2012):

- Equivalent dose. This is defined as 'the absorbed dose in a tissue or organ, weighted for the type and quality of the radiation by a radiation weighting factor'. This is measured in Sieverts (Sv).
- Effective dose. This is defined as 'the sum of the equivalent doses from radiation in all tissue and organs of the body, having been weighted by their tissue weighting factors'. This is measured in Sv.
- Absorbed dose. This is defined as 'the ionising radiation energy absorbed in a material per unit mass' and is measured in Gy.
- Dose constraint. This is defined as the 'restriction on annual dose to an individual from a single source or site, such that when aggregated with doses from all sources excluding natural background and medical procedures, the dose limit is not likely to be exceeded.' The maximum dose constraint in the UK is currently 0.3 millisieverts (mSv)/year.
- Dose limit. This is defined as the 'maximum permissible dose resulting from ionising radiation' and they apply to the 'sum of relevant doses from external exposures' during a specified period. The limit in the UK is currently one mSv/year.

1.7.1.6 Post-treatment hospitalization of cats

Due to the external and internal radiation hazards posed by cats to hospital staff and the public following treatment with I^{131}, they are isolated following treatment. However, the isolation time is variable amongst institutions nationally, as well as internationally (Boland *et al.*, 2014; Roberts *et al.*, 2015;

Kopecny *et al.,* 2016). This is mainly due to local radiation regulations, which vary dependent on the location of the institution and the dose of I^{131} that is administered (Lamb *et al.,* 2013; Boland *et al.,* 2014).

The isolation duration will also depend on the effective half-life of I^{131}. This has been previously calculated using γ camera dosimetry to be 2.5 ± 0.7 days (Puille *et al.,* 2002). The effective half-life of I^{131} is a combination of the fixed physical half-life and the biological half-life, which is variable. The biological half-life can be affected by the rate of I^{131} uptake by the thyroid gland and the excretion rates of it into the urine, faeces and also the saliva. It has been shown that the level of radiation emitted from urine soaked litter and faeces, from cats treated with ≤ 200 MBq of I^{131} administered subcutaneously does decrease over time. However, the radioactivity levels of the urine and faeces are still too high to allow them to be disposed of in the general refuse for the first two weeks following treatment, as the radioactivity levels are > 0.4 MBq/0.1 m^3 (Lamb *et al.,* 2013). As saliva can also emit radiation, Chalmers *et al.,* (2006) assessed the level of removable radioactivity from cats treated with I^{131} with daily wipe tests using varying sites (the flanks and paws). These wipe tests showed that the level of removable radioactivity of these cats exceeded the local state limit of New York i.e. > 200 disintegrations per minute/100 cm^2, within the first week following treatment. This study demonstrated that significant surface contamination can occur but this may be a combination of saliva and soiled litter. The findings from both Chalmers *et al.,* (2006) and Lamb *et al.,* (2013) demonstrate that the radioactivity levels from surface contamination on the cats' coats and from their urine and faeces need to be considered when deciding on the length of post-treatment isolation.

Cats that are treated with higher doses of I^{131} are routinely hospitalized for longer durations due to the higher radiation risk they pose to the staff and public (Lamb *et al.,* 2013). In the Lamb *et al.,* (2013) study there was one cat included that was administered an I^{131} dose of 1000 MBq and was hospitalized for six weeks, which was 50 % longer than cats treated with lower doses i.e. ≤ 200 MBq. Weichselbaum *et al.,* (2003) showed the effect of I^{131} dose on the length of isolation, by demonstrating that the dose of I^{131} could be used to calculate the number of days that the cat should remain in isolation for using the calculation:

days in isolation = 3.2 + [2.66 x mCi of the I^{131} dose]. In that study the γ radiation emission rate at discharge had to be < 2.0 milliröntgen (mR)/hour at skin surface at the level of the thyroid gland. The findings in that study clearly identified that the dose of I^{131} administered will have an effect on the length of isolation (Weichselbaum *et al.,* 2003).

Although several factors can affect the length of isolation following I^{131} treatment, many centres use a γ radiation emission rate cut-off to determine the length of time that cats remain in isolation for, which can enable a variable isolation period to be used (Feeney *et al.,* 2003; Weichselbaum *et al.,* 2003). This is performed by detecting the γ radiation emission at the skin surface at the level of the thyroid gland using a Geiger- Müller instrument and has been shown to be a valid method to assess isolation lengths (Feeney *et al.,* 2003). However, due to differences in local and national radiation legislation, release criteria will vary between different states and countries (Weichselbaum *et al.,* 2003; Martin *et al.,* 2015).

1.7.1.7 Measuring radiation emission post-treatment in humans

Guidelines in humans by the International Atomic Energy Agency (IAEA), recommend that in patients treated with I^{131} residual activity should be determined at hospital discharge (IAEA, 2009). This can be performed by means of evaluating the dose rate or determining the amount of residual activity combined with other considerations, which are patient based; a single measurement of ambient dose equivalent rate at one metre < 0.030 mSv/hour is suggested (De Crescenzo *et al.,* 2014). However, the criteria to determine a patients release from hospital may vary as in the study by Grigbsy *et al.,* (2000), which was based in the United States, patients treated with I^{131} were deemed safe to be discharged home as long as the calculated radiation dose to the maximally exposed person was < five mSv. This was determined by measuring the total body count recorded by a sodium iodide monitor 3.1 metres from the xiphoid process.

A recent study that developed a new procedure to estimate residual I^{131} activity, which was based on a mathematical model and external radiometric assays, has

been found to be comparable to performing the measurement of ambient dose equivalent rate. Therefore, this could be used as an alternative method and it is also simple and reliable (Ostinelli *et al.,* 2015).

Although radioactivity levels need to be assessed in patients at the time of discharge, work has also been performed in the patients' home environment to ensure that the radiation exposure to household members and even household pets from treated patients is within radiation legislation guidelines (Grigsby *et al.,* 2000). In the study by Grigsby *et al.,* (2000), the radiation exposure was measured using continuous optically stimulated luminescence dosimeters and it was found that both household members and household pets received relatively equal radiation exposure during the 10 day period following I^{131} treatment. However, the levels of radiation were below the regulation limit of the United States Nuclear Regulatory Commission.

Radiation exposure to humans following I^{131} has also been assessed with electronic personal dosimeters (EPDs) (Barrington *et al.,* 1999; Marriott *et al.,* 2007). Electronic personal dosimeters continuously monitor for ionising radiation, which can include ß radiation, γ radiation, neutron radiation and x-ray radiation and will alert a user if the preset dose and dose rate thresholds are exceeded. They have been used to measure the radiation exposure to caregivers from patients treated with I^{131} on an hourly basis (Marriott *et al.,* 2007). The data from the EPDs identified that a third of the radiation exposure occurred during the journey home from the hospital; therefore, showing that a large proportion of radiation exposure occurs shortly after administration of I^{131} (Marriott *et al.,* 2007).

Electronic personal dosimeters have also been provisionally assessed for their use in monitoring cage-side radiation exposure from cats treated with I^{131} in a pilot study at the Small Animal Hospital (SAH) of the University of Glasgow (Roberts *et al.,* 2015).

1.7.1.8 Treatment success and predictors of I^{131} treatment outcome

Radioactive iodine is associated with a high treatment success rate for hyperthyroidism in cats (Mooney, 1994; Peterson & Becker, 1995). However, the definition of success in papers differs, with some defining success as the induction of euthyroidism and others defining success as the induction of a euthyroid or biochemical hypothyroid state i.e. resolution of hyperthyroidism (Malik *et al.,* 1993; Mooney, 1994; Theon *et al.,* 1994; Peterson & Becker, 1995; Puille *et al.,* 2002). Success is usually dictated by measurement of the serum T4 concentration following treatment, which is then compared to the reference interval to allow classification of treatment as successful (depending on the definition of success in the individual study), unsuccessful i.e. treatment failure or the induction of a biochemical/clinical hypothyroid state.

Other methods to evaluate treatment success in hyperthyroid cats have also been assessed, including ultrasonography of the thyroid glands and the use of medical infrared thermal imaging. Ultrasonography can assess the size and vascularity of the thyroid glands and at evaluation six months after treatment with I^{131}, there was a reduction in median thyroid volume and heterogeneity of the thyroid glands, as well as decreased vascularity seen in cats successfully treated (Barberet *et al.,* 2010). The use of medical infrared thermal imaging has been shown to demonstrate treatment success in 92.86 % of treated cats one month after treatment and at three months post-treatment, a 100 % accuracy was recorded using this method (Waddell *et al.,* 2015). Although these methods can be used as part of the evaluation of treatment success, they have not been assessed at the time of hospital discharge, unlike the measurement of serum T4 concentration and therefore, measurement of serum T4 concentration should still be performed (Peterson & Becker, 1995).

In humans with either toxic nodular goiter or Graves' disease, which are treated with a fixed dose of I^{131}, it has been found that gender, age, severity of hyperthyroidism and goiter size act as independent prognostic factors for achievement of a euthyroid or hypothyroid state following a single treatment of I^{131}. Negative prognostic factors for obtaining resolution of hyperthyroidism following treatment have included male gender, younger patients (< 40 years

old), patients with severe hyperthyroidism and patients with medium and large sized goiters (Allahabadia *et al.,* 2001).

Palpation of the goiter to evaluate its size can form part of the calculation to determine what dose of I^{131} should be administered in cats (Mooney, 1994; Peterson & Becker, 1995). However, due to the presence of ectopic thyroid tissue in some cases of hyperthyroidism, palpation is not always capable of accurately defining the thyroid volume and therefore, this could result in a suboptimal dose of I^{131} being administered and a higher rate of treatment failure (Peterson & Broome, 2015).

Due to the concern that goiter palpation cannot allow an accurate estimation of thyroid volume, other ways to calculate thyroid volume have been assessed, including the use of scintigraphy. In a study by Forrest *et al.,* (1996) thyroid volume, as calculated by scintigraphy, was reported to influence the outcome of hyperthyroid cats treated with a modified fixed dose of I^{131}, with cats with larger thyroid volumes being more likely to fail treatment. However, more recently thyroid size, again calculated by scintigraphic results, has not been found to affect the outcome of treatment; however, a much more variable dosing regimen for I^{131} was used in that study (Volckaert *et al.,* 2016). One disadvantage of using thyroid scintigraphy to determine thyroid volume is that many of the calculations used result in different thyroid volumes to those calculated from ultrasound findings; therefore, raising into question their validity (Volckaert *et al.,* 2012). Due to the recent findings that TcTU has the best thyroid scintigraphic value accuracy for predicting thyroid volume, further work may be warranted to assess if this can be used, not only as a predictor for treatment success but also to assess if it can be used to help calculate the dose of I^{131} administered to cats (Peterson *et al.,* 2016b).

Although thyroid volume calculated via scintigraphy cannot be definitively associated with treatment outcome, the TB ratio can be. It has been shown that the TB ratio is significantly higher in cats that remain hyperthyroid following treatment when a fixed dose of I^{131} (148 MBq) is used, when compared to cats that were successfully treated, which in this study was defined as the achievement of euthyroidism or hypothyroidism (Wallack *et al.,* 2010).

Therefore, if scintigraphy is used pre-treatment, this ratio could potentially be used as a predictor for treatment failure and in these cases there should be additional consideration as to whether a higher dose of I^{131} should be used to maximize the possibility of achieving treatment success.

In humans, the use of anti-thyroidal medication in the two week period either before or after administration of I^{131} has been shown to result in a significantly lower cure rate when using a low fixed dose of 185 MBq; however, the same effect was not seen when higher doses were used i.e. 375 MBq (Allahabadia *et al.,* 2001).

However, recent use of anti-thyroidal medication in cats has not been shown to have an effect on the response to a fixed dose of I^{131} (148 MBq), as there was no significant difference in treatment response when methimazole was discontinued either < five days or ≥ five days prior to intravenous I^{131} administration (Chun *et al.,* 2002). Despite these findings anti-thyroidal medication is still usually discontinued prior to administration of I^{131} in cats to facilitate evaluation of the serum T4 concentration, as this forms part of the algorithm when deciding the dose of I^{131} to administer (Mooney, 1994; Peterson & Becker, 1995).

There has also been some concern raised regarding the recent use of iohexol, which is used to assess the glomerular filtration rate (GFR) and the success of I^{131} treatment in cats. Iohexol has been found to result in a significant decrease in the absorbed dose of I^{131} if used within 24 hours of I^{131} administration and a higher prevalence of residual hyperthyroidism (Peremans *et al.,* 2008). Although only 46 hyperthyroid cats were included in the study, the results would suggest that the use of iohexol prior to I^{131} treatment should be avoided.

1.7.1.9 Delayed successes following I^{131} treatment

The success of I^{131} can be delayed in some cases as the induction of euthyroidism following treatment may take up to six months in cats (Peterson & Becker, 1995; Boag *et al.,* 2007). In the study by Peterson and Becker (1995), 15.3 % of treated cats were still hyperthyroid post-treatment but this had reduced to only 1.5 % by

six months post-treatment. Due to these findings it would be advised to continue to monitor the serum T4 concentration in those cats that are biochemically hyperthyroid following treatment to assess for further decreases in this parameter, as further treatment for hyperthyroidism may not be required in all cases.

1.7.1.10 Development of hypothyroidism following treatment with I^{131}

Treatment with I^{131} can result in the induction of hypothyroidism that may be transient, as the remaining normal thyroid cells return to full function, or it can be permanent and subsequently result in cats requiring lifelong treatment with levothyroxine supplementation (Peterson & Becker, 1995). Biochemical hypothyroidism occurs quite frequently following treatment with I^{131}, with a prevalence as high as 56 % reported (Mooney, 1994). However, clinical hypothyroidism requiring levothyroxine supplementation is reported to be uncommon with Peterson & Becker (1995) only reporting this in 11/524 (2.1 %) treated cats. The incidence of biochemical hypothyroidism post-treatment may be influenced by the number of thyroid lobes affected as Nykamp *et al.,* (2005) identified that cats with bilateral disease, based on thyroid scintigraphic findings, were twice as likely to become hypothyroid following treatment with I^{131} compared to cats with unilateral disease.

There is also a concern that the development of a hypothyroid state following treatment with I^{131} could lead to an increased risk of azotaemia due to a decline in the GFR. This concern was proposed by the study by van Hoek *et al.,* (2009) following their findings that 80 % of cats with a post-treatment azotaemia and low GFR (≤ 1.1 ml/minute/kg) also had serum T4 concentrations below the reference interval. Due to this concern it would suggest that it is important to try to minimize the risks of hypothyroidism occurring in cats post-treatment by trying to use the lowest dose of I^{131} possible, whilst also trying to ensure that cases do not receive a dose that is too low to achieve a clinical cure.

1.7.1.11 Renal function pre- and post-treatment

Cats with pre-existing renal disease have been found to have significantly shorter survival times when treated with I^{131} than cats that do not have pre-existing renal disease. However, this finding is not specific to the use of I^{131} as the same finding is also seen in cats treated with methimazole (Milner *et al.*, 2006).

Following treatment with I^{131} the GFR in hyperthyroid cats has been found to decrease, with the majority of this decrease noted by four weeks post-treatment (Rogers *et al.*, 2000; Boag *et al.*, 2007; van Hoek *et al.*, 2008b; van Hoek *et al.*, 2009). A substantial number of cats can develop azotaemia following treatment with 63 % of cats in one study showing biochemical evidence of renal disease at the one month point post-treatment (Rogers *et al.*, 2000). However, the incidence of post-treatment renal azotaemia does appear to vary between studies, with a prevalence of only 28 % also reported (Milner *et al.*, 2006). Differences in follow up periods may account for the variation in prevalence reported as Milner *et al.*, (2006) did not specify when the post-treatment azotaemia was documented. The azotaemia that can develop during the 90 days following I^{131} treatment has been shown to be of a similar magnitude to that seen with the treatment modalities of surgery and methimazole (DiBartola *et al.*, 1996).

Cats with lower GFRs pre-treatment have been shown to be at higher risk for developing post-treatment azotaemia (Adams *et al.*, 1997; Rogers *et al.*, 2000). In the Rogers *et al.*, (2000) study, cats that developed renal azotaemia tended to have lower GFRs pre- and post-treatment than cats that did not develop renal azotaemia; however, specific values of GFR were not discussed. In that study, due to a large variance in the pre-treatment GFR, it could not be used to predict the occurrence of renal azotaemia occurring post-treatment. In Adams *et al.*, (1997), all cats that developed post-treatment renal azotaemia had a pre-treatment GFR < 2.25 ml/kg/min; however, these results may have been affected by the inclusion of nine cats with renal azotaemia pre-treatment. Taking the findings of both these studies together, measurement of GFR prior to treatment could potentially help but not definitively predict the occurrence of

renal azotaemia post-treatment. However, it should also be remembered that the use of iohexol to measure GFR within 24 hours of I^{131} administration could result in a higher chance of treatment failure and should therefore be avoided (Peremans *et al.*, 2008).

Although the assessment of GFR has been shown to be of potential use in the prediction of azotaemia occurring post-treatment, this has not been the case for pre-treatment haematological or biochemical parameters (including serum creatinine and serum urea nitrogen) or urine specific gravity (USG) (Riensche *et al.*, 2008). This was shown by Riensche *et al.*, (2008) that showed that these parameters could not predict the development of renal insufficiency (defined as azotaemia and inadequate urine concentration) occurring following treatment with either I^{131} or methimazole. This study in particular advised that the finding of a USG > 1.035 prior to treatment could not be used as a predictor for a reduced risk of renal azotaemia developing. Boag *et al.*, (2007) also showed that pre-treatment serum biochemistry parameters and USG could not predict the percentage change in GFR post-treatment either.

1.7.1.12 Long-term follow up

Recurrence of hyperthyroidism following treatment with I^{131} is uncommon. In Peterson & Becker (1995), a recurrence of hyperthyroidism was only reported in 2.5 % of the cases and this occurred between 1.1 and 6.5 years later. An even lower prevalence of 0 % was reported in Mooney (1994); however, the follow up time in that study was shorter at 32 months.

Median survival times post-treatment have been reported to be between two and five years (Peterson & Becker 1995; Slater *et al.*, 2001; Milner *et al.*, 2006). In the study by Slater *et al.*, (2001), 231 cats that were treated with I^{131} were followed up and their post-treatment survival was found to range from as little as three days to as long as eight years. In that study only age at diagnosis and the gender of the cat were predictors of survival, with both increasing age and male gender associated with shorter survival times. An even larger study that looked at 524 cats treated with I^{131} found that the percentage of cats alive one, two and three years following treatment were 89 %, 72 % and 52 % respectively

(Peterson & Becker, 1995). The most recent study assessing long-term outcome has shown that median survival times can be as long as four years post-treatment (Milner *et al.,* 2006).

Many cats treated with I^{131} will develop further health problems later on including renal disease and neoplasia, which is not unexpected in an older population of cats (Slater *et al.,* 1994; Slater *et al.,* 2001). In the study by Slater *et al.,* (1994), 15-27 % of cats that were euthyroid or hypothyroid post-treatment were found to develop renal disease on follow up and 9-10 % of them were found to develop neoplasia.

1.7.1.13 Concerns of using I^{131}

Although I^{131} treatment is a highly successful treatment option for hyperthyroidism in cats, previous work has highlighted that costs involved with it can deter both referring vets in general practice and owners (Boland *et al.,* 2014; Higgs *et al.,* 2014). However, if costs were not a factor when considering treatment options, the number of general practitioners selecting I^{131} as their preferred treatment modality would significantly increase (Higgs *et al.,* 2014; Kopecny *et al.,* 2016).

Another concern voiced by owners is the length of hospitalization associated with I^{131} treatment (Boland *et al.,* 2014). Therefore, the length of time that a cat is hospitalized for could have a significant effect on whether I^{131} is pursued by the owners of hyperthyroid cats.

Knowledge of this treatment modality may also influence the pursuit of it by both clients and veterinarians. In the study by Caney (2013), nearly 30 % of clients of hyperthyroid cats had only been offered anti-thyroidal medication as a treatment option. This finding has been corroborated by Boland *et al.,* (2014) that found that 53.3 % of owners of hyperthyroid cats were not aware of the possibility of I^{131} as a treatment option. These study findings would suggest that lack of knowledge about I^{131} could have a significant effect on the frequency that this treatment modality is utilised in hyperthyroidism.

Comorbidities can be seen in hyperthyroid cats, including chronic kidney disease (27 %), osteoarthritis (5.4 %), diabetes mellitus (4.5 %), alimentary lymphoma and chronic enteropathies, which is not surprising given the average age of cats affected by hyperthyroidism (Caney, 2013; Puig *et al.,* 2015). In some cases these comorbidities can have an effect on whether I^{131} is pursued due to concerns regarding progression of comorbid disease during or after hospitalization, or a change in the owners decision following detection of them (Puig *et al.,* 2015).

1.7.2 Anti-thyroidal medication

The use of anti-thyroidal medication is an alternative option for treatment of hyperthyroidism in cats; however, unlike I^{131} treatment it does not result in a cure of hyperthyroidism and clinical signs will recur when this medication is stopped. This medication also does not affect the size of the thyroid tumour (Behrend, 2006).

Anti-thyroidal medication has been documented to be the preferred treatment modality by general practitioners in the UK and Australia and was reported in one study to have been offered to 92 % of owners of hyperthyroid cats (Caney, 2013; Higgs *et al.,* 2014; Kopecny *et al.,* 2016).

The main anti-thyroidal drugs used in hyperthyroidism include methimazole and carbimazole (Bucknell, 2000). Methimazole inhibits the enzyme thyroid peroxidase, which is involved in the oxidation of iodide to iodine, the incorporation of iodine into thyroglobulin and the formation of T3 and T4 by coupling tyrosine residues; carbimazole is the prodrug of methimazole (Peterson & Aucoin, 1993; Trepanier, 2006). There appears to be some worldwide variation in regards to which of these two drugs is predominantly used, with methimazole used more commonly in the UK and carbimazole used more commonly in Australia (Caney, 2013; Kopecny *et al.,* 2016).

Methimazole and carbimazole are routinely used as an oral medication; however, transdermal forms of methimazole are also available (Hoffmann *et al.,* 2003; Lécuyer *et al.,* 2006; Boretti *et al.,* 2014).

1.7.2.1 Efficacy/safety

The efficacy and safety of methimazole have been assessed in a large study, which included 262 cats that received it either as sole therapy or pre-operatively prior to thyroidectomy at a dose of 10-15 mg/day. In that study it was found that the serum T4 concentration decreased significantly after two to three weeks of methimazole treatment, from a mean of 156 nmol/l pre-treatment to a mean of 27 nmol/l afterwards. Those cats that remained on treatment long-term were found to require a mean dose of 11.9 mg/day (Peterson *et al.*, 1988). The high efficacy of methimazole has been corroborated by a later study that found the use of oral methimazole to result in 87.5 % of hyperthyroid cats becoming euthyroid within two weeks of starting treatment, at a lower dose of 2.5 mg per os twice daily (Sartor *et al.*, 2004).

Twice daily administration of methimazole is preferred over once daily use. This is due to the findings by Trepanier *et al.*, (2003) that found that serum T4 concentrations were significantly higher following two and four weeks of treatment in cats treated orally once daily versus twice daily and that the proportion of cats becoming euthyroid after two weeks of treatment was lower in cats treated once daily versus twice daily at 54 % and 87 % respectively. For owners of cats treated with anti-thyroidal medication, the use of once daily dosing of medication is not ranked as the most important treatment priority and so this should not influence the dose frequency chosen (Caney, 2013).

A study comparing oral versus transdermal methimazole found the oral version to be more efficacious at the two week mark but this was no longer apparent four weeks following the start of treatment (Sartor *et al.*, 2004). However, the location of transdermal application can have an effect on the efficacy of the product and it is advised to apply it to the internal pinna. This is due to more complete absorption from this area when compared to other sites on the body such as the groin, neck and thorax; however, variation in absorption can still occur between ears (Hill *et al.*, 2015a; Hill *et al.*, 2015b).

Clinical side effects of methimazole including anorexia, vomiting, lethargy, icterus caused by a hepatopathy, bleeding diathesis caused by thrombocytopenia

and self-induced excoriation of the face and neck can occur, with a documented prevalence of 18.3 % (Peterson *et al.,* 1988). Haematological side effects including eosinophilia, lymphocytosis and mild leukopenia can also occur in 16.4 % of treated cats (Peterson *et al.,* 1988). Less common side effects, including the development of generalised lymphadenopathy, pyogranulomatous mural folliculitis and myasthenia gravis have also been reported (Niessen *et al.,* 2007; Bell *et al.,* 2012; Castro López *et al.,* 2014).

Transdermal application of methimazole can result in fewer gastro-intestinal side effects when compared to the oral version, whilst also still being able to significantly decrease serum T4 concentration; however, it does not decrease the risk of neutropenia, hepatotoxicity or facial excoriation occurring (Sartor *et al.,* 2004). Dosing frequency of oral methimazole has not been shown to have an effect on the prevalence of gastro-intestinal adverse effects (Trepanier *et al.,* 2003).

Carbimazole given once daily has been shown to result in significant reductions in serum T4 concentrations as well, from a mean of 118 nmol/l prior to treatment to a mean of 33 nmol/l after 10 days of treatment in a study that included 44 cats. Clinical signs of hyperthyroidism were also found to improve/resolve in nearly all treated cats. Suspected adverse reactions, which were mainly gastro-intestinal in origin, were noted in 44 % of cases (Frénais *et al.,* 2009). Generalised lymphadenopathy has also been reported in association with the use of this drug (Atkinson, 2008).

The clinical/biochemical response of hyperthyroid cats seen in clinical studies when using anti-thyroidal medication is also mirrored by the views of their owners, as they also find this treatment modality to be efficacious. In Caney (2013), owners reported that the use of methimazole resulted in a cure or substantial improvement in 75 % of cats and in 72.2 % of cats treated with carbimazole.

1.7.2.2 Monitoring

It has recently been advised by a consensus panel that dosages of anti-thyroidal drugs be titrated to obtain a serum T4 concentration in the bottom half of the reference range; however, this is not evidence-based (Daminet *et al.*, 2014). A recent survey in the UK has confirmed that this practice is followed by the majority of general practitioners (Higgs *et al.*, 2014).

The timing of blood sampling to assess the serum T4 concentration of treated cats has not been shown to be a significant factor when assessing treatment response in cats receiving methimazole (Rutland *et al.*, 2009). Therefore, a blood sample can be obtained at any time during the day, making this a convenient way to monitor treatment efficacy for both owners and practitioners.

1.7.2.3 Long-term follow up

Median survival times in cats treated with anti-thyroidal medication have been reported to be two years, which is significantly lower than the four years reported with I^{131} treatment (Milner *et al.*, 2006).

Treatment with anti-thyroidal medication can result in iatrogenic hypothyroidism, with a 35 % occurrence rate over the six months following the start of treatment documented by Williams *et al.*, (2010); however, this is usually resolved with a dose amendment and is therefore reversible (Boretti *et al.*, 2014). The induction of a hypothyroid state has not been found to significantly affect survival times, with median survival times of 794 days versus 625 days reported in euthyroid and hypothyroid cats respectively (Williams *et al.*, 2010).

Treatment with methimazole has also been found to result in a significant decrease in GFR (Becker *et al.*, 2000). However, earlier studies found contrasting evidence as to whether significant increases in serum urea nitrogen and creatinine concentrations occur in these patients (DiBartola *et al.*, 1996; Becker *et al.*, 2000). In Becker *et al.*, (2000) no significant increases in serum urea nitrogen or creatinine concentrations were seen four to six weeks post-

treatment, compared to DiBartola *et al.,* (1996) in which significant increases in both parameters were seen at the 30 and 90 day points post-treatment. These differences may have been due to the difference in sample size at 12 cats and 58 cats respectively, as well as the timing of the blood tests. A more recent study by Williams *et al.,* (2010) would tend to support the findings by DiBartola *et al.,* (1996), as they documented a 40 % occurrence of azotaemia in cats during the six month period following treatment; however, cats included in that study were treated with anti-thyroidal medication (methimazole or carbimazole) alone, as well as being combined with surgery.

Although azotaemia can occur with the use of anti-thyroidal medication, this does not appear to affect median survival times as long as euthyroidism is maintained (Williams *et al.,* 2010). In Williams *et al.,* (2010) the median survival time of euthyroid cats that developed azotaemia was 728 days, which was not significantly different from that of euthyroid cats that did not develop azotaemia at a median of 794 days. However, the combination of azotaemia and hypothyroidism does appear to have an effect on survival times as these cats have significantly shorter survival times than hypothyroid cats that remain non-azotaemic, with median survival times of 456 versus 905 days respectively (Williams *et al.,* 2010). In those cases with a combination of hypothyroidism and azotaemia, restoration of euthyroidism may result in an improvement in renal function as this has been shown to result in a decrease in the serum creatinine concentration and an increase in packed cell volume (Williams *et al.,* 2014).

Although development of azotaemia alone following treatment has not been found to affect survival times, pre-existing azotaemia has been (Milner *et al.,* 2006; Williams *et al.,* 2010). Milner *et al.,* (2006) documented that cats with pre-existing renal disease treated with methimazole had significantly shorter survival times when compared to cats without pre-existing renal disease; however, specific median survival times were not reported.

As anti-thyroidal medication is not a curative treatment and tumour volume and magnitude of serum T4 concentration has been shown to increase with the duration of the disease, further increases in the doses of anti-thyroidal medication may be required over time (Peterson *et al.,* 2016a). Cases of

hyperthyroidism may also become refractory to anti-thyroidal medication with time, due to the previously reported increased prevalence of thyroid carcinoma with increasing length of disease duration (Hibbert *et al.,* 2009; Peterson *et al.,* 2016a).

1.7.3 Surgical thyroidectomy

Hyperthyroidism can be treated by removal of the affected thyroid tissue and in most cases a bilateral thyroidectomy is required (Flanders, 1999). Surgical thyroidectomy has been documented to result in 94 % of hyperthyroid cats being free of recurrence of hyperthyroidism at the three year mark post-treatment (Naan *et al.,* 2006). Surgery is associated with a low complication rate; however, damage to the recurrent laryngeal nerve can occur (Naan *et al.,* 2006; Trepanier, 2007). There are also risks associated with anaesthetising hyperthyroid cats for surgery, as ventricular arrhythmias can occur which can be fatal and therefore, it is important to try to stabilize the patient prior to surgery with anti-thyroidal medication (Mooney & Peterson, 2012).

Due to the presence of co-existing ectopic hyperfunctional thyroid tissue in some cases, a recurrence or a continuation of a hyperthyroid state can occur following surgery (Naan *et al.,* 2006; Peterson *et al.,* 2016a). This was shown in the study by Harvey *et al.,* (2009) in which 61 % of cats that were referred for recurrent hyperthyroidism, having previously undergone either a unilateral or bilateral surgical thyroidectomy, were identified to have ectopic hyperfunctional thyroid tissue on scintigraphy. Due to the concern that cats with ectopic hyperplastic thyroid tissue are more likely to have a recurrence of hyperthyroidism following thyroidectomy, the use of thyroid scintigraphy prior to surgery could be considered. Thyroid scintigraphy also provides additional benefit in cases that will be treated surgically, as it enables the surgeon to assess if the disease is unilateral or bilateral in origin, which can influence the surgical procedure (Naan *et al.,* 2006).

Post-operative hypocalcaemia can occur following surgery and this can be transient or permanent (Flanders *et al.,* 1987; Welches *et al.,* 1989). When performing a bilateral thyroidectomy, the surgical technique used has been

shown to influence the frequency of post-operative hypocalcaemia occurring, with the lowest rate (11 %) seen when a bilateral thyroidectomy is staged three to four weeks apart. The highest rate of hypocalcaemia (82 %) was found to occur in cats that had a bilateral extracapsular dissection performed (Flanders *et al.,* 1987). To aid the normalization of serum calcium levels following a bilateral thyroidectomy, it is advised that parathyroid gland autotransplantation be performed when parathyroidectomy has occurred; autotransplantation of parathyroid glands has also been found to reduce morbidity (Padgett *et al.,* 1998).

As with other treatment modalities, changes in serum renal parameters can occur post-treatment; however, the specific occurrence of post-renal azotaemia has not been reported (DiBartola *et al.,* 1996). In the study by DiBartola *et al.,* (1996) the mean serum creatinine concentration of hyperthyroid cats treated with a bilateral thyroidectomy was found to be significantly higher 30 days post-treatment at 195 µmol/l, compared to the mean pre-treatment value of 150 µmol/l. However, this study did not comment on how many cats had a serum creatinine concentration above the reference interval post-treatment and 27 % of the cats included had a serum creatinine concentration above the reference interval pre-treatment.

1.7.4 Iodine-restricted diet

As iodine is required for the synthesis of thyroid hormones, restriction of dietary iodine can reduce the synthesis of serum T4 production (Melendez *et al.,* 2011). Due to this an iodine-restricted diet has been recently assessed in hyperthyroid cats (van der Kooij *et al.,* 2014; Hui *et al.,* 2015; Scott-Moncrieff *et al.,* 2015). In the study by van der Kooij *et al.,* (2014), hyperthyroid cats (n = 225) were treated with an iodine-restricted diet and serum T4 concentrations significantly decreased four weeks into the diet trial. There were also significant improvements in the clinical signs of the cats, which had included vomiting, polyuria, polydipsia, polyphagia, hyperactivity, weight loss and quality of life. However, there were no further significant changes in serum T4 concentrations after eight weeks of the diet and only 51/68 cats had a serum T4 concentration within the reference interval at this stage.

The efficacy of the diet may be affected by the pre-treatment serum T4 concentration. In the study by Hui *et al.,* (2015), it was found that those cats with higher pre-treatment serum T4 concentrations were significantly less likely to normalize their serum T4 concentration using the diet alone, compared to cats with lower pre-treatment serum T4 concentrations, with 17 % of cats continuing to be hyperthyroid 61-180 days following the start of the diet. Although these results contradict those of Scott-Moncrieff *et al.,* (2015), in which the use of an iodine-restricted diet resulted in resolution of hyperthyroidism in 100 % of the cases, this difference may have been due to the smaller study size at eight cats and the fact that their study cats had lower pre-treatment serum T4 concentrations than the 49 cats in the Hui *et al.,* (2015) study.

The occurrence rates of azotaemia developing in hyperthyroid cats treated with an iodine-restricted diet have not been specifically documented (van der Kooij *et al.,* 2014; Hui *et al.,* 2015; Scott-Moncrieff *et al.,* 2015). However, in the van der Kooij *et al.,* (2014) and Hui *et al.,* (2015) studies it was found that the serum creatinine concentration significantly decreased in cats on the diet, but this finding may have been affected by the lack of weight gain documented in cats in both studies.

As serum T4 concentrations have been found to increase with the duration of the disease and the iodine-restricted diet appears to be less effective in cases where severe hyperthyroidism is present, there is a theoretical concern as to whether this diet will remain an efficacious treatment in cats treated long-term (Hui *et al.,* 2015; Peterson *et al.,* 2016a). The diet may also not be suitable for all hyperthyroid cats due to the need to ensure that treated cats do not gain access to food sources with non-restricted iodine content, therefore theoretically limiting this diet to indoor cats.

1.8 Weight changes in patients following treatment for hyperthyroidism

1.8.1 Weight gain in humans

A main concern in humans following treatment for hyperthyroidism is weight gain as this can be excessive; this weight gain is commonly reported and occurs in children as well as adults (Pears *et al.,* 1990; De La Rosa *et al.,* 1997; Abid *et al.,* 1999; Dale *et al.,* 2001; Crocker & Kaplowitz, 2010).

The weight gain experienced by these patients has been found to continue for at least six months following achievement of a euthyroid state and in some studies it can continue for as long as five years after treatment, with sustained increases in body mass index during this time period (De La Rosa *et al.,* 1997; Dale *et al.,* 2001; Rathi *et al.,* 2008). A study specifically performed to determine the prevalence of obesity following therapy for hyperthyroidism, found the prevalence to be as high as 32 %. In that study the main weight gain occurred during the first two years following treatment and the main factors that contributed to the excess weight gain were poor control of thyroid function and the need for replacement thyroxine treatment (Brunova *et al.,* 2003).

Although this weight gain can continue for months to years after treatment for hyperthyroidism, the majority (54-67 %) appears to occur in the first three months following treatment (Pears *et al.,* 1990). The predominant early cause of this weight gain is due to increases in the lean mass of patients (De La Rosa *et al.,* 1997; Lönn *et al.,* 1998). This was documented by the finding that significant increases in the fat-free mass of patients occur at the three and 12 month points post-treatment with I^{131} (Lönn *et al.,* 1998). Fat and bone mineral content have also been found to increase over the first year following treatment but these occur to varying levels of significance (De La Rosa *et al.,* 1997; Lönn *et al.,* 1998).

The early weight gain seen in patients following treatment can be predictive of longer term weight gain, with one study showing that body weight changes at 40-60 days post-surgery were highly predictive of the outcome at nine months (Rotondi *et al.,* 2014).

Although weight gain is mainly reported following treatment of clinical cases of hyperthyroidism, it has also been noted when treating subclinical hyperthyroidism as well. Treatment with I^{131} of subclinical hyperthyroidism caused by toxic nodular goiter, has been found to impact the body composition of humans > 65 years old. The weight gained by these patients was found to reflect increases in both lean and fat mass (Boj-Carceller *et al.*, 2015).

All of the weight gain that occurs following treatment for hyperthyroidism may not be directly due to its treatment. A study that followed patients treated with I^{131} and compared them to a control group of euthyroid patients, found that both groups gained weight over time. Although the treated patients gained more weight than the controls over the first year, there was no significant difference in weight gain between the two groups by the three year mark (Scheidhauer *et al.*, 2002). These study results therefore raise the question as to whether all weight gain following treatment of hyperthyroidism can be solely attributed to resolution of their hyperthyroid state.

1.8.1.1 Effect of weight loss prior to treatment

Weight loss prior to definitive treatment of hyperthyroidism in humans may have an effect on the weight gain seen in these patients following treatment. This was shown in a study that demonstrated the largest weight gain in patients during the 12 month period post-treatment, to be experienced by those patients that had actually gained the least amount of weight over the preceding 12 months (Lang *et al.*, 2016). Similar findings were also documented in an earlier study that showed weight loss at presentation could predict weight gain following treatment (Dale *et al.*, 2001). In Dale *et al.*, (2001) those patients that had lost weight prior to presentation gained significantly more weight than those patients that had either gained weight or their weight had remained stable.

1.8.1.2 Effect of baseline thyroid test results

Serum fT4 concentrations have been shown to predict weight gain in humans. Those patients with higher serum fT4 concentrations prior to treatment have been shown to gain substantially more weight than those patients with lower

serum fT4 concentrations, with a median weight difference of 4.3 kg at the one year point post-treatment reported (Gibb *et al.,* 2013).

Alterations in serum TSH concentrations have also been found to be associated with changes in body weight in both male and female patients with hyperthyroidism (Lang *et al.,* 2016). However, this finding does not appear to be specific to hyperthyroidism as alterations in serum TSH concentrations can also affect weight gain in patients without thyroid disease (Bjergved *et al.,* 2014). In patients with hyperthyroidism, higher baseline serum TSH concentrations have recently been shown to be significant factors of weight gain at the 12 month point post-treatment (Lang *et al.,* 2016). However, this finding has not been previously reported, with Rotondi *et al.,* (2014) finding no association between baseline serum TSH concentrations and weight changes at the nine-month point post-treatment. The production of TSH should decrease from excessive thyroid hormone production due to negative feedback at the level of the pituitary gland (Connors & Hedge, 1981; Yamada *et al.,* 1989). Therefore, it would be expected that patients with higher serum fT4 concentrations, who have already been found to gain more weight post-treatment than patients with lower serum fT4 concentrations, would also have lower baseline serum TSH concentrations (Gibb *et al.,* 2013). As the results from Lang *et al.,* (2016) contradict this, further studies are warranted to further investigate the effect of baseline serum TSH concentrations in hyperthyroid patients and subsequent weight changes.

1.8.1.3 Effect of treatment modality used

Weight gain following treatment appears to occur regardless of which treatment modality for hyperthyroidism is used. However, there are contradicting results as to whether the magnitude of weight change may be affected by treatment choice (Pears *et al.,* 1990; Dale *et al.,* 2001). Pears *et al.,* (1990) originally documented that there were no significant differences in the amount of weight gained by patients between treatment modalities, which included carbimazole, surgical thyroidectomy and I^{131}; however, the group size in that study only included 65 cases. These preliminary results have now been contradicted by a bigger study by Dale *et al.,* (2001) that included 162 patients and found that

patients treated surgically gained more weight than patients treated with I^{131} or anti-thyroidal medication.

Treatment combination has also been found to affect weight gain as patients that underwent a surgical thyroidectomy were found to be less likely to gain weight when compared to those patients that had first received I^{131} and then had a surgical thyroidectomy performed (Schneider *et al.*, 2014). However, there has been no noted effect of the extent of surgery performed on weight gain, as no significant difference was detected between those patients that underwent a hemithyroidectomy and those patients that underwent a total thyroidectomy (Lang *et al.*, 2016).

1.8.1.4 Effect of gender and race/ethnicity

Weight gain in humans could also be linked to gender and racial/ethnic differences; however, there are contradictory findings in regards to gender in the literature. Male gender, black race and Hispanic ethnicity were found to be independent predictors of weight gain following treatment with I^{131} in one study (Ariza *et al.*, 2010). However, other studies have either found that female patients gain more weight or they have found that gender is not actually always a predicting factor of weight gain (Dale *et al.*, 2001; Scheidhauer *et al.*, 2002; Rathi *et al.*, 2008).

1.8.1.5 Effect of age

It is not clear whether patient age has an effect on the post-treatment weight gain in patients treated for hyperthyroidism. Both Dale *et al.*, (2001) and Lang *et al.*, (2016) found that weight gain was greater in younger patients, where as Ozdemir *et al.*, (2010) found the opposite. The latter paper had a smaller sample size and used a different cut-off for old versus young (45 years), compared to 30 years in the Dale *et al.*, (2001) paper; a cut-off for age was not used by Lang *et al.*, (2016). These variances may account for the difference in findings between the papers.

1.8.1.6 Effect of post-treatment thyroid hormone concentrations

It has been shown that human patients that become biochemically hypothyroid during treatment of hyperthyroidism, gain significantly more weight than those patients who remain euthyroid during the treatment period (Dale *et al.,* 2001). Dale *et al.,* (2001) also showed that the weight gain seen in these patients was significantly more in those that became hypothyroid permanently and required T4 supplementation, compared to those patients that either became transiently hypothyroid or were never hypothyroid.

Hypothyroid patients have a reduced capacity to excrete water through the kidneys, which is demonstrated by both a lower plasma osmolality and lower free water clearance in affected patients, which both normalise with treatment (Sahun *et al.,* 2001). Other causes of water retention in human hypothyroidism have included an increased extravascular mass of albumin as well as inadequate lymphatic drainage. These variables have also been found to return to normal with treatment of the hypothyroid state (Parving *et al.,* 1979). This increased water retention may therefore contribute to the weight gain seen in patients with hypothyroidism.

Weight changes associated with hypothyroidism have also been shown to be due to alterations in lean mass, which may again be linked to altered water excretion, as identified by Karmisholt *et al.,* (2011). In that study, dual-energy x-ray absorptiometry (DEXA) scans in hypothyroid patients following levothyroxine supplementation, identified that a significant decrease in the lean mass sub compartment was seen, with only a minimal decrease in the fat sub compartment and no change in the bone mass sub compartment. Lean mass identified on DEXA scans is known to include water, proteins, glycogen and minerals that are not tied into the bone (Pietrobelli *et al.,* 1996). It was therefore concluded that the weight loss observed in these patients following treatment, was due to the loss of excess body water, resulting in a decreased lean mass sub compartment (Karmisholt *et al.,* 2011).

The findings of the Karmisholt *et al.,* (2011) study combined with findings from Lönn *et al.,* (1998), which assessed weight changes in hyperthyroid patients

following treatment, both demonstrate that weight changes in thyroid dysregulation are associated with changes in the lean mass of the patients. It could therefore be speculated that as patients who become hypothyroid following treatment for hyperthyroidism gain more weight than those patients that become euthyroid, the lean mass increases in the former group would be higher (Dale *et al.,* 2001).

The effect of post-treatment serum TSH concentrations on weight gain has also been investigated. However, serum TSH concentrations following thyroidectomy were not found to be related to weight gain (Rotondi *et al.,* 2014).

1.8.1.7 Causes of weight gain

There have been several other suggested causes of the weight gain seen in humans following treatment of hyperthyroidism, apart from changes in lean mass/body water described above. They have included:

1) A reduction in metabolic rate secondary to decreased thyroid hormone concentrations (Abid *et al.,* 1999).
2) An initial increase in food energy intake by patients following treatment, in order to maintain their premorbid weight (Abid *et al.,* 1999).
3) Subnormal levels of 24 hour energy expenditure and spontaneous physical activity resulting from thyroid hormone suppression (Jacobsen *et al.,* 2006).

Increased dietary intake as a cause of weight gain following treatment for hyperthyroidism is also supported by the study by Alton & O'Malley (1985). They identified weight gain to be lower in patients provided with formal dietary advice, who therefore had a lower level of energy intake, compared to patients not provided with dietary advice.

1.8.2 Weight gain in cats

Weight gain is also commonly associated with successful treatment of hyperthyroidism in cats and monitoring their body weight after treatment should form part of the routine monitoring in these cases (Jaillardon *et al.,* 2012;

Daminet *et al.,* 2014). However, the amount of weight gained by hyperthyroid cats that are treated is not as well documented within the literature as it is in humans (Boag *et al.,* 2007; Finch *et al.,* 2012; Jaillardon *et al.,* 2012; Hui *et al.,* 2015; Scott-Moncrieff *et al.,* 2015).

Weight gain has been documented to occur over a variable time period in cats post-treatment, with significant weight gain reported as early as three weeks following treatment (Boag et al., 2007; van Hoek et al., 2009; Finch et al., 2012). The study by van Hoek *et al.,* (2009) tried to assess this post-treatment weight gain in more detail by assessing the body weight of cats at one, four, 12 and 24 weeks post-treatment with I^{131} and found that weight gain increased significantly between week one post-treatment and week 24 post-treatment.

The main cause of the early weight gain seen in hyperthyroid cats treated with I^{131} is thought to be due to increases in fat-free mass (Finch *et al.,* 2012). In the Finch *et al.,* (2012) study there was a median increase of fat-free mass by 5 % within the first three weeks post-treatment. The fat-free mass was calculated using a previously validated feline specific prediction formula: -0.164 + (0.41 x body weight in kg) + (0.054 x forelimb height in cm) x (0.098 x right forelimb circumference in cm) – (0.028 x hindlimb height in cm). These increases in fat-free mass resulted in a median weight gain of 0.28 kg and a median percentage increase in body weight of 9.66 % (range 5.97-32.8) during the three weeks. These findings agree with the similar findings in humans that changes in fat-free mass occur early on following treatment of hyperthyroidism (Lönn *et al.,* 1998).

Increases in leptin, an adipocytokine secreted by adipose tissue, have been found to occur in the three month period following the start of treatment with methimazole (Jaillardon *et al.,* 2012; Cao, 2014). This increase in leptin was also found to correlate with body weight changes. As leptin reflects the amount of body fat mass this would suggest that increases in fat mass also occur in treated cats (Jaillardon *et al.,* 2012). However, this increase in fat mass may occur after the initial three-week period due to the findings by Finch *et al.,* (2012).

In the Boag *et al.,* (2007) study, cats treated with I^{131} were found to gain 0.94 kg on average during the six month follow up period. This is suggestive that weight

gain continues past the three-week point post I^{131} treatment documented by Finch *et al.,* (2012) and would also be supported by the findings of van Hoek *et al.,* (2009). However, as specific values for the weight changes were not reported in the van Hoek *et al.,* (2009) study and body weight in that study was only presented in diagrammatic form with a box-plot, a direct comparison between the Boag *et al.,* (2007) and van Hoek *et al.,* (2009) studies cannot be made.

A limitation of the studies that have been performed on weight changes following I^{131} treatment is that only small case numbers have been included with 27, 21 and 10 cases in the *Boag et al.,* (2007), van Hoek *et al.,* (2009) and Finch *et al.,* (2012) studies respectively and therefore this may have affected their findings.

1.8.2.1 Effect of treatment modality used

Although weight gain is reported with the use of I^{131} and anti-thyroidal medication in hyperthyroid cats, there have been no studies performed that have directly compared the degree of weight changes seen amongst the different treatment modalities, as it has been done in humans (Pears *et al.,* 1990; Boag *et al.,* 2007; Jaillardon *et al.,* 2012).

Cats treated successfully with anti-thyroidal medication (methimazole) have been documented to have a median increase in their body weight of 0.7 kg over a three month period, compared to a median weight gain of 0 kg in cats unsuccessfully treated. Treatment success in that study was defined by a serum fT4 concentration ≤ 30 pmol/l (Jaillardon *et al.,* 2012). Although the cats treated with I^{131} in the Boag *et al.,* (2007) study were documented to gain more weight than the cats in the Jaillardon *et al.,* (2012) study, the weight changes were documented three months later at six months, therefore a direct comparison cannot be made between the two studies.

Route of administration and dose frequency of methimazole have been investigated as to whether they could have an effect on weight gain in the first month of treatment in cats (Trepanier *et al.,* 2003; Sartor *et al.,* 2004). In these

studies median weight changes were not significantly different between once daily and twice daily administration or between oral and transdermal administration of methimazole at either the two or four week points post-treatment. However, neither study separated the weight changes into groups dependent on treatment success, which may have affected their findings.

Despite the weight changes seen with I^{131} and anti-thyroidal medication, weight has not been found to significantly change with the use of an iodine-restricted diet (Hui *et al.,* 2015; Scott-Moncrieff *et al.,* 2015). In the studies by Hui *et al.,* (2015) and Scott-Moncrieff *et al.,* (2015), cats were followed up for six and two month periods respectively, but significant weight changes were not identified despite the majority of cats having a serum T4 concentration within the reference interval. In the Hui *et al.,* (2015) study, which included 49 cats, 83 % of cats had a serum T4 concentration within the reference interval but the mean body weight only increased by 0.1 kg, from 3.8 to 3.9 kg after 61-180 days on the diet. The same weight change of 0.1 kg was also seen in the Scott-Moncrieff *et al.,* (2015) study after eight weeks on the diet, when 87.5 % of cats had a serum T4 concentration within the reference interval; however, this study included a smaller number of cats with only eight cases. An additional study assessing the use of an iodine-restricted diet over a time period of two months but in much larger numbers (n = 225), showed that body condition score (BCS) did not alter during treatment. This was despite owners reporting their cat's weight loss to have improved in the questionnaire. Unfortunately, weights were not available for assessment/comparison in this study (van der Kooij *et al.,* 2014).

Although one study comparing weight changes in cats treated with the different treatment modalities has not been performed, the differences in weight gain noted between studies does raise the question as to whether variances may occur, especially considering the lack of weight gain seen in studies assessing iodine-restricted diets (Hui *et al.,* 2015; Scott-Moncrieff *et al.,* 2015).

The effect of other factors such as age and gender of the patient on weight gain post-treatment, which have already been assessed in the human field, have not

yet been investigated in feline hyperthyroidism and this remains an area to be explored (Dale *et al.*, 2001; Scheidhauer *et al.*, 2002).

1.8.2.2 Effect of post-treatment serum T4 concentration

It is not clear whether the post-treatment serum T4 concentration has an effect on the post-treatment weight changes in cats. Jaillardon *et al.*, (2012) documented weight gain to be significantly lower in cats with a three month post-treatment serum fT4 concentration > 30 pmol/l, compared to cats with a serum fT4 concentration lower than this; however, they did not assess if weight changes were different between euthyroid and hypothyroid cats. In Hui *et al.*, (2015) no effect of post-treatment serum T4 concentration on body weight was found; however, they only compared the weight changes of cats with a low-normal serum T4 concentration to cats with a high-normal serum T4 concentration, two to six months following treatment.

No studies to date have been specifically performed to assess the effect of post-treatment serum T4 concentration on weight gain in cats treated with I^{131}, nor has a study evaluated whether weight changes following treatment for hyperthyroidism are different between cats that become euthyroid, cats that become hypothyroid and cats that remain hyperthyroid.

1.9 Aims of the thesis

This literature review has shown that treatment of hyperthyroidism with I^{131} is viewed as either the preferential treatment option or one of the preferential treatment options for hyperthyroidism in cats and humans (when caused by toxic nodular goiter), respectively.

This thesis assesses two different aspects of monitoring cats during the initial three-week isolation period following administration of I^{131} for treatment of hyperthyroidism. The aims of the first part of the thesis will be to assess the weight changes that are seen in these cats during the isolation period in a larger number of cases than previously reported and to evaluate whether factors such

as the gender and post-treatment serum T4 concentrations of the patient have an effect on this.

The aim of the second part of the thesis will be to expand the original data set used for the study by Roberts *et al.,* (2015), to further assess the emission of γ radiation from treated cats during the isolation period using an EPD and evaluate if a fixed isolation period could be used at the SAH, University of Glasgow.

CHAPTER 2

2 WEIGHT CHANGES IN CATS DURING THE THREE-WEEK ISOLATION PERIOD FOLLOWING ADMINISTRATION OF I^{131} FOR TREATMENT OF HYPERTHYROIDISM

2.1 Introduction

Weight gain has been found to occur in humans and cats following treatment for hyperthyroidism, as discussed in depth in chapter one (Dale *et al.,* 2001; Boag *et al.,* 2007; Jaillardon *et al.,* 2012). Although the gold standard treatment for hyperthyroidism in cats is I^{131}, weight gain following its administration has not been well described in the literature (Boag *et al.,* 2007; van Hoek *et al.,* 2009; Finch *et al.,* 2012). Those studies on I^{131} treatment in cats that have included the monitoring of weight changes in their study findings have been associated with limitations such as the inclusion of only small case numbers or a lack of regular documentation of weight changes during the initial isolation period following treatment (Boag *et al.,* 2007; Finch *et al.,* 2012). The largest number of cats included in a study assessing weight changes post I^{131} treatment has been 27 cats in van Hoek *et al.,* (2009); however, in that study the body weight changes were only described diagrammatically with box and whisker plots and no specific values were documented in the body of the text.

Although weight gain in cats treated successfully with anti-thyroidal medication has been found to be significantly greater than cats unsuccessfully treated, this has not yet been investigated when using I^{131}, nor has weight gain been assessed to evaluate if it could be used as a predictor of the outcome of I^{131} treatment (Jaillardon *et al.,* 2012).

Successful treatment following administration of I^{131} has been defined differently in previous studies on cats, with some defining it as the achievement of a euthyroid state, whilst others defining it as the achievement of a euthyroid or hypothyroid state i.e. reversal of biochemical hyperthyroidism (Mooney, 1994; Theon *et al.,* 1994). Recently, a consensus statement on anti-thyroidal treatment for hyperthyroidism has suggested that for treatment success, a reduction of the serum T4 concentration into the lower half of the reference interval should be aimed for (Daminet *et al.,* 2014). However, this suggestion was not evidence based and the consensus statement did not include a discussion on treatment with I^{131}. Despite these differing opinions on the definition of treatment success, there have yet to be any studies performed that assess if the weight changes between these definitions is different.

In humans, it has also been shown that those patients that become biochemically hypothyroid following treatment gain significantly more weight than those that that remain euthyroid (Dale *et al.,* 2001). The effect of induction of a biochemical hypothyroid state on weight gain has yet to be evaluated in cats.

Following treatment for hyperthyroidism, azotaemia can occur quite commonly and the development of post-treatment hypothyroidism is thought to contribute to this (Williams *et al.,* 2010). Only one study has tried to evaluate whether the development of renal dysfunction could have an effect on weight gain; however, that study included only a small number of cases (van Hoek *et al.,* 2009).

In humans, factors including the gender and age of the patient have also been assessed to evaluate whether they can affect the amount of weight gained following treatment; however, there have yet to be any studies performed that assess these factors in cats (Dale *et al.,* 2001; Ariza *et al.,* 2010; Lang *et al.,* 2016).

2.2 Aims and hypotheses

The aims of this study were to document the weight changes during the initial three-week isolation period following administration of I^{131} in a larger number of cases than included in the Finch *et al.,* (2012) study and to also assess whether weight gain could be affected by factors that have been previously evaluated in humans such as age of the patient (Dale *et al.,* 2001). The aims are shown in more detail below:

1) To determine the amount of weight gained by cats treated with I^{131} in the three-week isolation period following treatment.
2) To determine if the weight gain of cats that become biochemically euthyroid or hypothyroid following treatment is different to those cats that remain biochemically hyperthyroid; to therefore assess whether weight gain could be used as a predictor of whether treatment has led to reversal of overt hyperthyroidism. It was hypothesised that those cats that remain biochemically hyperthyroid will gain less weight than those cats that become biochemically euthyroid or hypothyroid, and due to this,

weight gain could be used as a predictor of the reversal of overt hyperthyroidism.

3) To determine if the weight gain of cats that become biochemically hypothyroid following treatment is different to those cats that become biochemically euthyroid. It was hypothesised that weight gain would be greater in cats that become biochemically hypothyroid than in those cats that become biochemically euthyroid.
4) To determine if the amount of weight gained by cats treated with I^{131} is affected by variables such as age, gender, previous treatment of hyperthyroidism and/or the development of post-treatment azotaemia.

2.3 Materials and methods

This was a retrospective study that included cats that were presented to the SAH between January 2010 and September 2013 for I^{131} treatment of confirmed hyperthyroidism. These cats had been previously diagnosed with hyperthyroidism in general practice and subsequently referred. Any cat that had been referred for I^{131} treatment of their hyperthyroidism was eligible for inclusion into this study.

2.3.1 Exclusion criteria

All cases that were treated with I^{131} during the allotted time frame were then assessed in regards to the exclusion criteria. Any cases that matched one or more of the criteria shown below were excluded.

1) Cats that did not have either a pre- and/or post-treatment weight recorded. The pre-treatment weight could have been recorded at any time between the day of the primary consultation at the SAH and the day they were injected with I^{131}. This time period is typically three to four days in duration. The post-treatment weight had to have been recorded between the day the cat left the I^{131} isolation unit and the date of their discharge from the SAH. This time period is typically one to two days in duration.

2) Cats treated with I^{131} doses > 200 MBq. This was because these cats would have had to have remained in the isolation unit longer than the standard 21 days following treatment.
3) Cats with known concurrent illnesses pre-treatment e.g. azotaemia or congestive heart failure. Azotaemia in this study was defined as a serum creatinine concentration > 180 μmol/l (the high end of our laboratory reference interval). This exclusion criterion was included because concurrent illnesses may have affected the weight gain of treated cats. It should be noted that for this study vomiting and diarrhoea were not used as exclusion criteria as gastro-intestinal signs can be reported clinical signs in hyperthyroidism.

2.3.2 Additional data collected

For those cases that were not excluded additional data was then collected. This data included the cat's age, gender and breed. Data was also collected on whether there had been previous treatment of hyperthyroidism in each case and which treatment modality had been used i.e. surgical thyroidectomy, anti-thyroidal medication, an iodine-restricted diet or a combination of these treatment options.

Any cat that had a serum T4 concentration > 50 nmol/l (reference interval 15-50 nmol/l) after the three-week isolation period was classified as biochemically hyperthyroid and subsequently followed up. This was to assess if they were a true failure i.e. the serum T4 concentration did not return to normal within the six month period after treatment, or whether they became euthyroid during this time period, as has been documented previously when using I^{131} (Peterson & Becker, 1995). Those cases that had a serum T4 concentration < 15 nmol/l after the three-week isolation period and were classified as biochemically hypothyroid were also followed up. This was to assess if their serum T4 concentration increased back up into the normal reference interval or if they remained hypothyroid.

2.3.3 Protocol for I^{131} treatment at the SAH

As part of the protocol for I^{131} treatment, the use of either anti-thyroidal medication or an iodine-restricted diet were stopped two weeks prior to the cat's primary consultation at the SAH. This was due to two reasons:

1) The cats serum T4 concentration was used as part of the decision making process when deciding on the dose of I^{131} that each cat received (Mooney, 1994).
2) The use of an iodine-restricted diet or cessation of anti-thyroidal medication just prior to receiving I^{131} have both been shown to affect the uptake of it (Nieckarz & Daniel, 2001; Scott-Moncrieff *et al.*, 2015).

Following the initial consultation with the owner of each cat, when a full clinical history was taken and a physical examination of the cat performed, the hyperthyroid cat was then admitted into the hospital. As part of the physical examination, the cat was weighed using Soehnle 8310 baby weight scales (www.soehnle-professional.com) and their weight recorded. The same scales were used for all cases and the scales were calibrated monthly using calibration weights. Blood was then collected from each cat by jugular venepuncture and this was submitted for a complete blood count, serum biochemistry and serum T4 concentration assessment. The serum T4 concentration was measured using a chemiluminesence assay (Siemens Immulite 2000; reference interval 15 – 50 nmol/l with 3.2 nmol/l being the lowest limit of detection), the serum biochemistry was run using an Olympus AU640 chemistry analyzer and the complete blood count using a Siemens Advia 120. As part of the standardized protocol blood was also submitted for detection of feline leukaemia virus (FeLV) antigen using an ELISA and feline immunodeficiency virus (FIV) antibodies and feline coronavirus antibody titres using immunofluorescent assays. A urine sample obtained either by free catch or cystocentesis was submitted for full urine analysis.

Cats were then hospitalised within a cat ward for between three and four days following the initial consultation prior to I^{131} being administered. This hospitalisation period was to allow the cats to acclimatize to the hospital environment before going into the I^{131} isolation unit. This was to ensure they

would eat, drink, urinate and defaecate when placed into isolation. It also allowed time for the blood results to be interpreted to ensure there was no biochemical or haematological concerns that would preclude treatment with I^{131}, and to confirm that the cats were truly hyperthyroid. Following the acclimatization period cats were first sedated (with either medetomidine and butorphanol or midazolam and ketamine) and then injected subcutaneously with varying doses of I^{131}, of between 80 and 200 MBq. The dose administered to each cat was adapted from an original scoring system described by Mooney (1994). The scoring system used both in the Mooney (1994) study and this study, utilises the severity of the cats clinical signs, the size of the thyroid gland and the magnitude of the serum T4 concentration to dictate what dose of I^{131} is injected in each case (Table 1).

Following the injection of I^{131}, treated cats were then placed into the I^{131} isolation unit for 21 days. The cats were fed a variable but large quantity of food once daily during the isolation period, with the aim of achieving *ad libitum* feeding. A mixture of dry and wet cat food was provided, depending on the cats' preference. This was based on a combination of the diet history obtained during the primary consultation with the owners and by assessment of their preferred food type during the acclimatization period in the SAH.

On exit from the isolation unit all cats had a repeat physical examination and repeat jugular venepuncture performed. Blood was submitted for repeat serum biochemistry and serum T4 concentration assessment. The cats were then weighed using the same scales as before treatment (Soehnle 8310 baby weight scales).

Score	Severity of clinical signs	Serum T4 concentration (nmol/l)	Size of goiter
One	Mild	< 80	< 1 cm
Two	Mild to moderate	80 to < 100	1 to < 1.5 cm
Three	Moderate	100 to < 150	1.5 to < 2 cm
Four	Moderate to severe	150 to < 400	≥ 2 cm
Five	Severe	≥ 400	Non-palpable

Table 1. The scoring system for classifying the severity of hyperthyroidism in each case. For each column, a score of one to five was assigned depending on the individual cats clinical signs, their serum T4 concentration and their goiter size. The three scores were then added together to give a total score, with a minimum possible value of three and a maximum possible value of 15. Using the algorithm, cats with low scores (3-9) were administered ≤ 120 MBq, cats with medium scores (10-12) were administered > 120 to ≤ 150 MBq and cats with high scores (> 12) were administered > 150 MBq (up to 200 MBq).

2.4 Statistical analysis

The pre- and post-treatment weight of each included cat was entered into a computer database (Microsoft Excel) and the weight gain or loss was then calculated. This was then converted into a percentage weight gain or loss of their pre-isolation weight.

The cases were then divided into groups for further statistical evaluation to assess if gender, age, dose of I^{131} administered, pre-referral treatment, post-treatment serum T4 concentration and development of azotaemia post-treatment had an effect on the amount of weight gained during the isolation period. For any cat that had a serum T4 concentration below the limit of detection i.e. < 3.2 nmol/l, its serum T4 concentration was recorded as 3.19 nmol/l.

1) For the effect of gender the cases were divided into two groups:
    - Male (entire or neutered).
    - Female (entire or neutered).
2) For the effect of age the cases were divided into three groups dependent on their age at the time of treatment:
    - Group one) < 10 years old.
    - Group two) ≥ 10 years old but ≤ 13 years old.
    - Group three) > 13 years old.
3) For the effect of I^{131} dose, the cases were divided into five groups dependent on the dose they had been administered:
    - 80 MBq
    - 120 MBq
    - 150 MBq
    - 180 MBq
    - 200 MBq
4) For the effect of previous treatment of hyperthyroidism on weight gain, the cases were divided into five groups:
    - Group a) No previous treatment for hyperthyroidism.
    - Group b) Treatment with anti-thyroidal medication.
    - Group c) Treatment with surgery.

- Group d) Treatment with an iodine-restricted diet.
- Group e) Combination treatment e.g. anti-thyroidal medication and surgery.

5) For the evaluation of the effect of post-treatment serum T4 concentration on weight gain, the cases were divided into four groups dependent on their post-treatment serum T4 concentration:
    - Group A) Biochemical hypothyroidism: serum T4 concentration < 15 nmol/l.
    - Group B) Biochemical euthyroidism, low normal: serum T4 concentration 15-35 nmol/l.
    - Group C) Biochemical euthyroidism, high normal: serum T4 concentration > 35 but ≤ 50 nmol/l.
    - Group D) Biochemical hyperthyroidism: serum T4 concentration > 50 nmol/l.
6) For the effect of the development of acute azotaemia following treatment on weight gain, the cases were divided into two groups dependent on the serum creatinine concentration three weeks post-treatment:
    - Azotaemic. Azotaemia was defined as a post-treatment serum creatinine concentration > 180 μmol/l, with the laboratory reference interval being 91-180 μmol/l.
    - Non-azotaemic. This was defined by a post-treatment serum creatinine concentration ≤ 180 μmol/l.

The percentage weight gain variable was tested for normality using the Shapiro Wilks test in STATA/SE 12.0 for Windows. The data were not found to be normally distributed (P-value = 0.03). Non-parametric tests (Kruskal-Wallis equality of populations rank test and two-sample Wilcoxon rank-sum test) were employed to investigate any differences in this parameter by gender, age, prior treatment of hyperthyroidism, dose of I^{131} administered, development of azotaemia and post-treatment serum T4 concentration.

The absolute change in serum T4 concentration between pre- and post-treatment bloods (ΔT4) and the relative change of serum T4 concentration (ΔT4/pre-treatment serum T4 concentration) were assessed for correlation with

percentage weight gain using Pearson's correlation coefficient. The receiver operator characteristics (ROC) procedure was used to assess the calculated percentage weight gain three weeks after being treated with I^{131} as a predictor for reversal of overt hyperthyroidism. It was also used for selecting cut-off points and calculating corresponding sensitivities and specificities for the prediction of reversal of overt hyperthyroidism. P values < 0.05 were considered statistically significant for all tests applied.

2.5 Results

2.5.1 Study population

During the time period January 2010 to September 2013, 136 cats were referred to the SAH for treatment of their hyperthyroidism with I^{131}. This study population was then reviewed in further detail to assess if they were eligible for inclusion in the study.

2.5.2 Exclusions

Upon further assessment 22/136 cases had to be excluded, resulting in a study population of 114 cats, which were then statistically evaluated. Reasons for exclusion from the study included:

1) Administration of an I^{131} dose > 200 MBq. One case was excluded due to this criterion as they were injected with 1000 MBq of I^{131} and kept in the isolation unit for six weeks.
2) Absence of a recorded weight post-treatment upon exit from the isolation unit (n = 21).

2.5.3 Study group demographics

The median age of the study population was 12 years with a range of 6-16 years. The majority of the study cats were domestic short-hairs (n = 103); however, other breeds included domestic long-hairs (n = 9) and one each of Siamese and Maine Coon cats. The median body weight of the whole study group before

treatment was 3.7 kg (interquartile range (IQR) 2.93-4.41) and the median serum T4 concentration prior to treatment was 188 nmol/l (IQR 114.5 to 260).

2.5.4 Overall weight gain

The median weight of the study cats following treatment was 4.05 kg (IQR 3.39-4.87) and the median weight gain of the whole study population was 0.36 kg (IQR 0.15-0.58). This translated to a median percentage weight gain of 11.35 % (IQR 3.81-17.38) for the whole study population.

2.5.5 Gender

Of the study group 48 cats were male neutered and 66 cats were female neutered; there were no entire cats in the study population. The male neutered cats were found to have a median percentage weight gain of 7.3 % (IQR 2.75-15.68) compared to the female neutered cats that had a median percentage weight gain of 12.3 % (IQR 5.43-17.75). The percentage weight gain following treatment with I^{131} was not found to be significantly different between male neutered and female neutered cats (P = 0.179).

2.5.6 Age

When the study population was divided into their respective age groups, there were 16 cats in group one, 74 cats in group two and 24 cats in group three.

The median age before treatment of those cats with post-treatment serum T4 concentrations ≤ 50 nmol/l was not significantly different from those cats with post-treatment serum T4 concentrations > 50 nmol/l, at 12 years versus 10 years respectively. Cats in age group one had a median percentage weight gain of 6.5 % (IQR 0.68-15.2), cats in age group two had a median percentage weight gain of 11.6 % (IQR 4.15-18.98) and cats in age group three had a median percentage weight gain of 11.1 % (IQR 3.75-14.88). There was no statistical difference between the percentage weight gain of cats in the three different age groups (P = 0.61) (Figure 1).

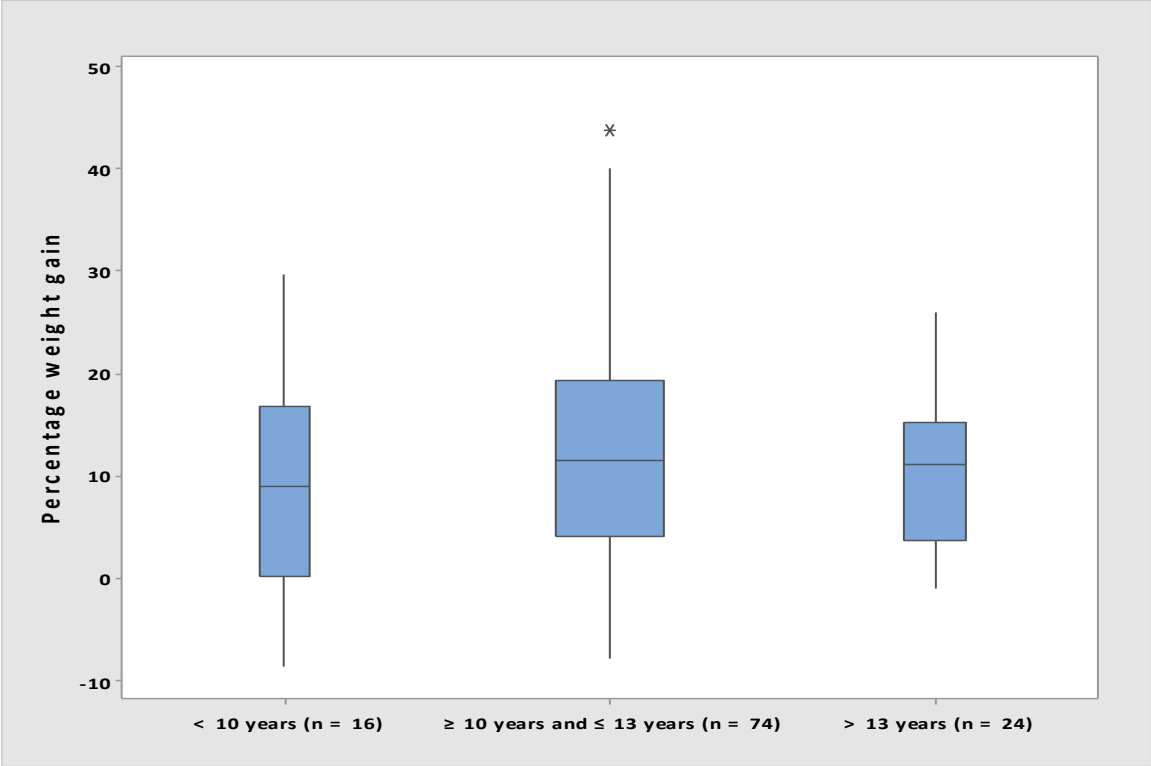

Figure 1. A box and whisker plot illustrating the distribution of the study population by age (x-axis) and percentage weight gain (y-axis). The horizontal line in the box reflects the median value. Outliers are depicted by asterisks. The width of the boxes is relative to the number of cases in each group.

2.5.7 Dose of I^{131} administered

Nineteen of the cats were injected with 80 MBq of I^{131}, 30 of the cats were injected with 120 MBq, 37 of the cats with 150 MBq, four cats with 180 MBq and 24 cats with 200 MBq.

The median and IQR of percentage weight gain of the study cats dependent on the dose of I^{131} administered were as follows: 80 MBq (8.1 %, 3.05-14.45), 120 MBq (12.5 %, 6.6-16.83), 150 MBq (11.9 %, 3.6-20.2), 180 MBq (15.05 %, 13.29-20.95) and 200 MBq (5.5 %, 0.47-20.95). The percentage weight gain of the study cats was not found to be significantly different between the doses of I^{131} that had been administered ($P = 0.15$) (Figure 2).

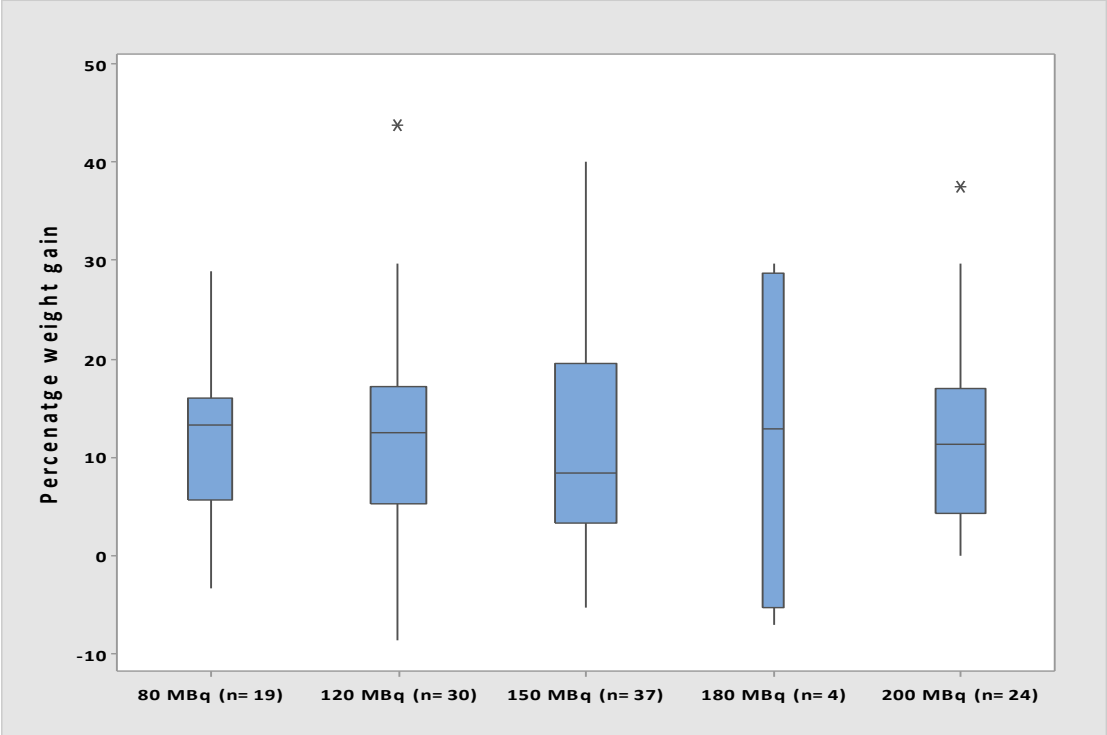

Figure 2. A box and whisker plot illustrating the distribution of the study population by dose of I^{131} administered (x-axis) and percentage weight gain (y-axis). The horizontal line in the box reflects the median value. Outliers are depicted by asterisks. The width of the boxes is relative to the number of cases in each group.

2.5.8 Previous treatment

Out of the 114 cats included in this study, 49 cats had not received any previous treatment for hyperthyroidism (group a) and had a median pre-treatment serum T4 concentration of 148 nmol/l.

Of the remaining 65 cats:

- There were 58 cats that had been previously treated with anti-thyroidal medication (either methimazole or carbimazole) and had a median pre-treatment serum T4 concentration of 245.5 nmol/l (group b).
- One cat had been treated surgically prior to referral and had a pre-treatment serum T4 concentration of 185 nmol/l (group c).
- No cats had been placed onto an iodine-restricted diet (group d).
- There were six cats that had been treated with a combination of surgery (thyroidectomy) and anti-thyroidal medication (methimazole or carbimazole) and had a median pre-treatment serum T4 concentration of 102 nmol/l (group e).

Those cats in group a had a median percentage weight gain of 12.3 % (IQR 5.1 to 16.1) and those cats in group b had a median percentage weight gain of 11.5 % (IQR 3.7-19.2). The one cat in group c gained 2.6 % of their pre-treatment body weight and the cats in group e had a median percentage weight gain of 0.9 % (IQR -5.5 to 4.83). Percentage weight gain was found to differ statistically between pre-referral treatment, with cats in groups c and e gaining significantly less weight than cats in group a and b ($P = 0.037$) (Figure 3).

To assess pre-referral treatment for hyperthyroidism further, the study population was then divided into those cats that had received treatment for hyperthyroidism prior to referral (n = 65) and those cats that had not received any treatment (n = 49). The median pre-treatment serum T4 concentration of those cats that had not received treatment was 148 nmol/l, compared to 234 nmol/l for those cats that had received prior treatment. With this division of cases there was no statistical difference found between the percentage weight gain of cats that received pre-referral treatment and the percentage weight gain of cats that had not ($P = 0.302$) (Figure 4).

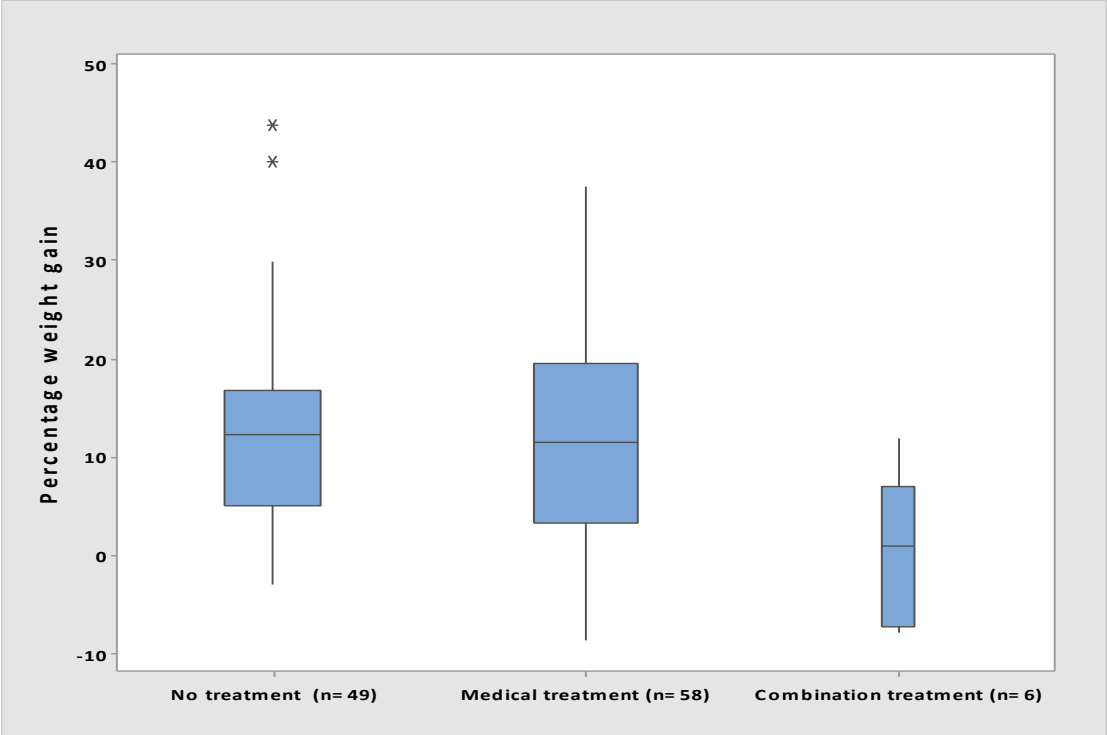

Figure 3. A box and whisker plot illustrating the distribution of the study population by pre-referral treatment (x-axis) and percentage weight gain (y-axis). The horizontal line in the box reflects the median value. Outliers are depicted by asterisks. The width of the boxes is relative to the number of cases in each group. As there was only one case that had surgery as its only pre-referral treatment, this was excluded from this box plot.

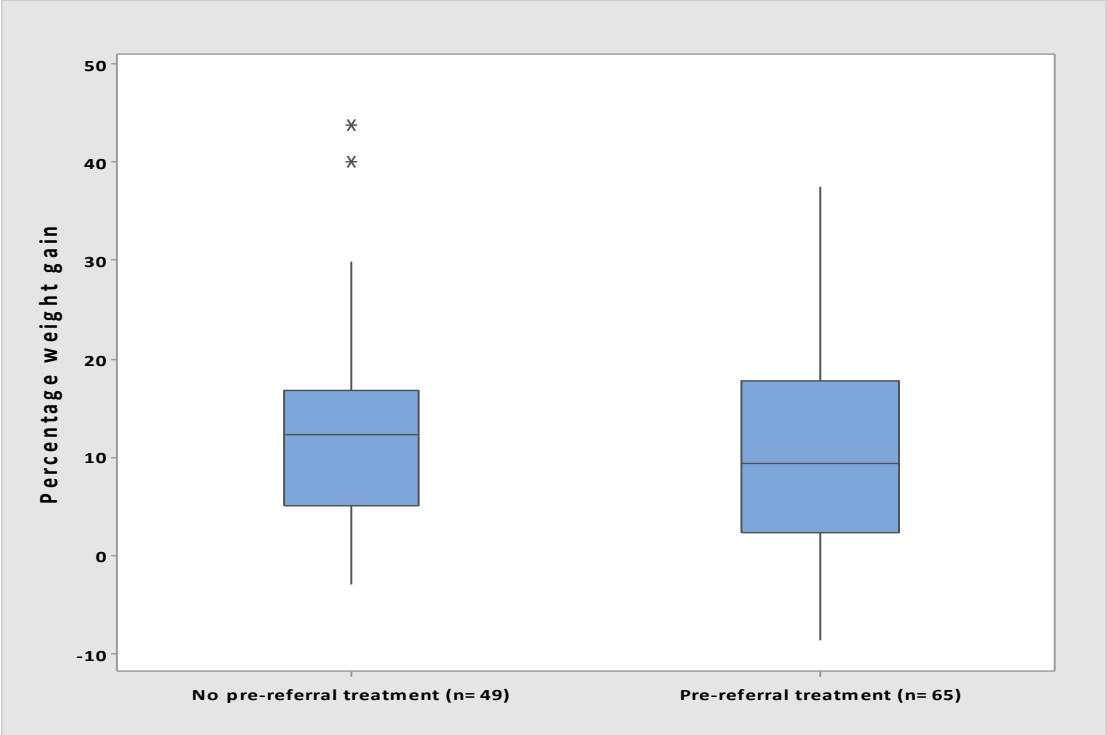

Figure 4. A box and whisker plot illustrating the distribution of the study population by pre-referral treatment (x-axis) and percentage weight gain (y-axis). The horizontal line in the box reflects the median value. Outliers are depicted by asterisks. The width of the boxes is relative to the number of cases in each group.

2.5.9 Serum T4 concentration post-treatment

The median post-treatment serum T4 concentration was 4.65 nmol/l, with a range of 3.19 nmol/l to 819 nmol/l. The mean post-treatment serum T4 concentration was 33.7 nmol/l. Following the three-week isolation period after treatment with I^{131}, only 13/114 cats had a serum T4 concentration above the reference interval with a range of 51.1 to 819 nmol/l, a mean value of 230.68 nmol/l and median value of 88 nmol/l and were classified as the biochemical hyperthyroidism group (group D) (Table 2). Five of these cats failed to gain weight during the three-week isolation period. These 13 cases were followed up to assess if their serum T4 concentration normalised over the following six months. Four of the 13 cases were found to become euthyroid during the following six months and therefore became delayed successes and 3/13 cases were lost to follow-up following treatment at the SAH. Therefore, there were only six cats that were known to be persistently hyperthyroid following treatment.

For those cats that had a post-treatment serum T4 concentration ≤ 50 nmol/l, their median body weight pre-treatment was 3.8 kg. For those cats that had a post-treatment serum T4 concentration > 50 nmol/l, their median body weight before treatment was 3.4 kg. This difference was not statistically significant ($P > 0.05$).

Once the serum T4 concentration post-treatment of the other study cats had been assessed, this resulted in 85 cats being in group A (biochemical hypothyroidism), 12 cats being in group B (biochemical euthyroidism, low normal) and four cats being in group C (biochemical euthyroidism, high normal). The mean and median post-treatment serum T4 concentrations of these three groups respectively were: group A (4.83 nmol/l and 3.19 nmol/l), group B (21.23 nmol/l and 22.2 nmol/l) and group C (230.68 nmol/l and 88 nmol/l).

Cats in group D (n = 13) (Table 2) gained a median of 3.9 % (range -8.6 % to 37.6 %) of their pre-treatment body weight. This was compared to a median percentage weight gain of 12.3 % (range -5.3 % to 43.8 %) in group A, 8.75 % (range -0.48 % to 25 %) in group B and 8.25 % (range 3.6 to 13.2 %) in group C.

The median percentage weight gain of groups A to C combined was 12.2 %. Cats in group D were found to gain significantly less weight than groups A to C combined ($P = 0.007$). However, the differences in percentage weight gain between groups A, B and C were not statistically significant ($P > 0.05$) (Figure 5).

Of the four cats in group D that became euthyroid over the six months following treatment, three were found to have gained weight (3.9 %, 6.5 % and 9.35 %) during the isolation period and only one cat lost weight (-3.3 %). Of the 101 cats in groups A to C, 91 of the cases gained weight during the three-week isolation period.

Case	Age	Gender	Dose	Weight pre-tx	Weight post-tx	% weight gain	Serum T4 conc. pre-tx	Serum T4 conc. post-tx	ΔT4	Follow-up treatment
1	10	FN	150	3.4	3.71	9.39	468	255	213	Thyroidectomy
2	13	MN	150	4.5	4.35	-3.33	292	81.6	210.4	Became euthyroid
3	13	FN	200	2.7	2.49	-7.78	585	265	320	I^{131} + medical management
4	11	FN	200	3.1	3.39	9.35	621	88	533	Became euthyroid
5	8	MN	200	2.43	2.22	-8.6	768	819	+ 51	Medical management
6	16	MN	200	2.8	2.91	3.9	213	74	139	Became euthyroid
7	6	MN	200	3.44	3.2	-7	660	432	228	I^{131} + medical management
8	9	MN	200	3.45	3.48	0.9	624	527	97	No further treatment
9	13	MN	200	4.36	4.31	-1.1	420	201	219	Medical management
10	9	MN	80	5.55	5.91	6.5	126	51.1	74.9	Became euthyroid
11	13	FN	150	2.43	2.63	7.6	350	70.9	279.1	Lost to follow up
12	10	MN	120	4.5	5.14	14.2	185	76.6	108.4	Lost to follow up
13	10	FN	180	1.89	2.6	37.6	524	57.7	466.3	Lost to follow up

Table 2. See legend on next page.

Table 2. A table showing the age (in years), gender (male neutered (MN) or female neutered (FN)), dose of I^{131} administered (in MBq), the pre-treatment (pre-tx) and post-treatment (post-tx) weights (in kg), the percentage weight gain, the pre-treatment (pre-tx) and post-treatment (post-tx) serum T4 concentration (in nmol/l), the ΔT4 (in nmol/l) and the follow-up treatment for the 13 cases that were still biochemically hyperthyroid post-treatment (group D).

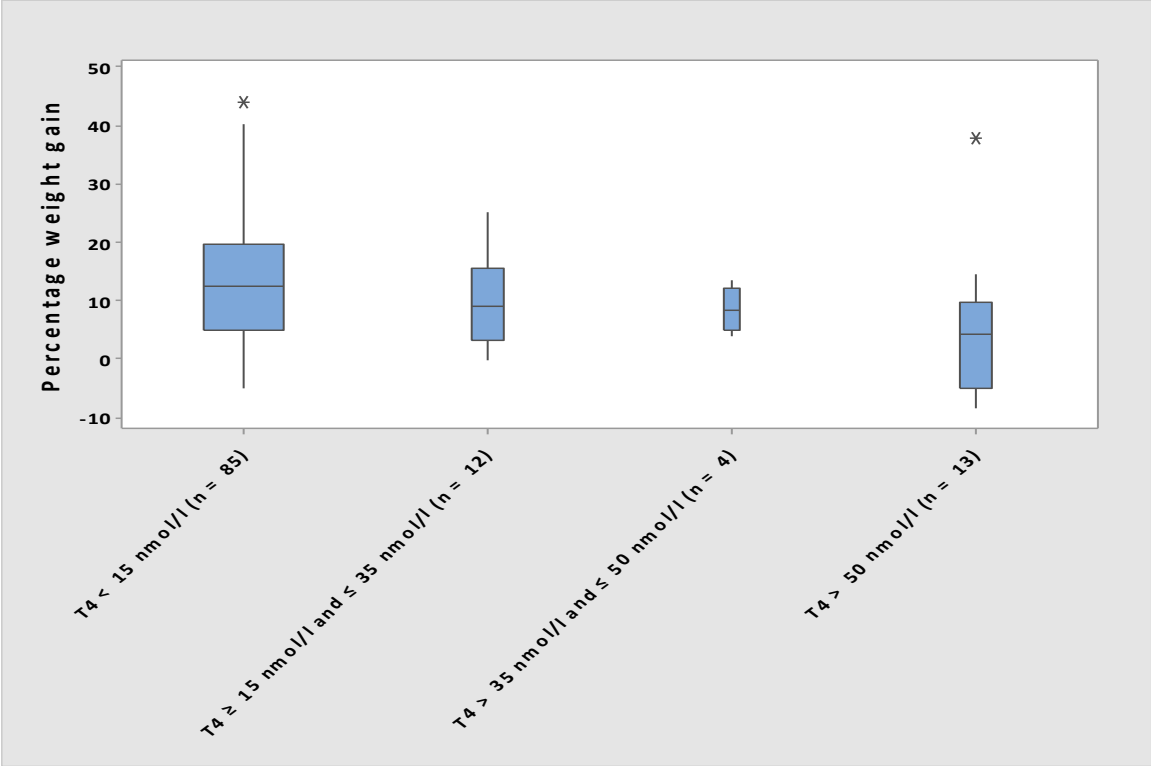

Figure 5. A box and whisker plot illustrating the distribution of the study population by post-treatment serum T4 concentration (x-axis) and percentage weight gain (y-axis). The horizontal line in the box reflects the median value. Outliers are depicted by asterisks. The width of the boxes is relative to the number of cases in each group.

2.5.10 Additional treatment for biochemically hyperthyroid cats post-treatment

Of the six cats that were found to be persistently hyperthyroid during the six months following treatment with I^{131}, five cats went on to have further treatment for their hyperthyroid state (Table 2). Two of the cats had a second treatment of I^{131} using a 200 MBq dose; however, they both continued to be hyperthyroid following this and were subsequently treated with methimazole. Both of these cats lost weight during the isolation period with 7.78 % and 7 % losses of their pre-treatment weight. Two of the other cats that failed treatment were placed onto medical management with anti-thyroidal medication. Both of these cats were also found to have lost weight during the isolation period, with 8.6 % and 1.1 % losses of their pre-treatment weight. One of the six cats underwent a thyroidectomy seven weeks following treatment with I^{131} at the referring practice and subsequently died. This cat gained 9.39 % of their pre-treatment weight during the isolation period. The last cat in this group did not receive any further treatment for hyperthyroidism due to the owners' wishes and this cat gained 0.9 % of their pre-treatment weight during the isolation period.

2.5.11 Biochemical hypothyroidism

Of the 85 cats that had a post-treatment serum T4 concentration <15 nmol/l (group A), 53 cases were lost to follow up. Of the 32 cases with follow up, only six were found to be persistently hypothyroid and required levothyroxine supplementation (Table 3). Unfortunately, assessment of cTSH was only available for two out of the six cases, but in both cases in which it was measured, it was increased (> 0.15 ng/ml) (Wakeling, 2010).

Case	Age	Gender	Dose	Weight pre-tx	Weight post-tx	% weight gain	Serum T4 conc. pre-tx	Serum T4 conc. post-tx	ΔT4	Serum creatinine conc. pre-tx	Serum creatinine conc. post-tx
1	9	FN	80	3.44	3.28	-4.7	118	3.19	114.81	112	146
2	8	MN	80	4.9	5.76	17.6	81.5	7.85	73.65	122	130
3	13	FN	150	4.04	4.26	5.4	221	3.19	217.81	79	133
4	13	FN	150	4.22	4.29	1.7	252	3.19	248.81	86	120
5	15	FN	80	3.6	4.05	12.5	92.9	3.19	89.71	124	240
6	13	FN	80	4.22	4.9	16.1	112	3.19	108.81	83	141

Table 3. A table showing the age (in years), gender (MN or FN), dose of I^{131} administered (in MBq), the pre-treatment (pre-tx) and post-treatment (post-tx) weights (in kg), the percentage weight gain, the pre-treatment (pre-tx) and post-treatment (post-tx) serum T4 concentrations (in nmol/l), the ΔT4 (in nmol/l) and the pre-treatment (pre-tx) and post-treatment (post-tx) serum creatinine concentrations (in μmol/l) for the six cats that were found to be persistently hypothyroid following treatment.

2.5.12 Change in serum T4 concentration (ΔT4)

The ΔT4 of the whole study group was normally distributed and had a mean value of 183.14 nmol/l, with a range of 28.6 to 466.3 nmol/l. Only one cat had an increase in their serum T4 concentration during the three-week isolation period (Case 5, Table 2). There was no correlation detected between the percentage weight change of the treated cats and ΔT4 ($r = 0.098$, $P = 0.305$). However, a weak correlation was detected between the percentage weight change of the treated cats and the relative change of T4 ($r = 0.288$, $P = 0.02$).

2.5.13 Azotaemia/other illnesses

On review of the clinical notes, physical examinations and pre-treatment blood work of the cats in the study, no cats were found to be azotaemic pre-treatment, nor were they known to have any concurrent illnesses e.g. congestive heart failure.

Only 8/114 cats were found to be azotaemic at the time of the three-week post-treatment venepuncture, with the range of serum creatinine concentration of those eight cases being 181 to 250 μmol/l. These eight cats had pre-treatment serum creatinine concentrations of 81-156 μmol/l and the largest noted increase in serum creatinine concentration between pre- and post-treatment concentrations was 134 μmol/l (Table 4). All eight of these cats had post-treatment serum T4 concentrations < 15 nmol/l. These eight cats had a weight gain range of 2.6 to 22.6 % with a median percentage weight gain of 11.5 % (Table 4) compared to a median percentage weight gain of 11.35 % in the non-azotaemic cats. The development of azotaemia was not found to have a statistically significant effect on weight gain ($P = 0.909$).

One of the eight cats with post-treatment azotaemia also required treatment for hypothyroidism and was started on levothyroxine supplementation one month following administration of I^{131} (Case 5, Tables 3 and 4). Despite levothyroxine supplementation resulting in an increase of the serum T4 concentration into the reference interval, there was no noted improvement in the level of azotaemia.

This cat gained 12.5 % of their pre-treatment body weight during the three-week isolation period.

Case	Age	Gender	Dose	Weight pre-tx	Weight post-tx	% weight gain	Serum T4 conc. pre-tx	Serum T4 conc. post-tx	Serum creatinine conc. pre-tx	Serum creatinine conc. post-tx
1	8	MN	120	5.28	5.54	4.92	74.9	14	115	184
2	12	FN	120	3.52	3.95	12.3	163	3.19	81	215
3	12	MN	120	6.05	6.6	9.1	111	3.19	121	211
4	14	FN	120	3.07	3.4	10.7	131	3.19	112	181
5	15	FN	80	3.6	4.05	12.5	92.9	3.19	124	240
6	12	FN	150	3.23	3.87	19.8	143	3.19	83	185
7	11	FN	120	2.48	3.04	22.6	136	3.19	113	223
8	15	MN	80	5.47	5.61	2.6	102	3.19	156	250

Table 4. See legend on next page.

Table 4: A table showing the age (in years), gender (MN or FN), dose of I^{131} administered (in MBq), the pre-treatment (pre-tx) and post-treatment (post-tx) weights (in kg), percentage weight change, the pre-treatment (pre-tx) and post-treatment (post-tx) serum T4 concentrations (in nmol/l) and the pre-treatment (pre-tx) and post-treatment (post-tx) serum creatinine concentrations (in μmol/l) for the eight cats that were found to be azotaemic following treatment. Case number five is also included in table 3, as they required levothyroxine supplementation.

2.5.13.1 Percentage weight gain as a predictor of post-treatment serum T4 concentration ≤ 50 nmol/l

The ROC analysis of percentage weight gain as a predictor of a serum T4 concentration ≤ 50 nmol/l had an area under the curve of 0.730 (P = 0.006, 95 % confidence interval (CI), 0.64-0.81) (Figure 6). The optimal cut-off point that provided a high specificity with reasonable sensitivity was found to be a percentage weight gain of 9.39 %, corresponding to a sensitivity and specificity of 59.41 % and 84.62 %, respectively. This would suggest that if a cat gained > 9.39 % of their pre-treatment body weight during the three-week isolation period, the probability that overt hyperthyroidism had been reversed was nearly 85 %. A specificity of 100 % was obtained when a cut-off of 37.6 % weight gain was used.

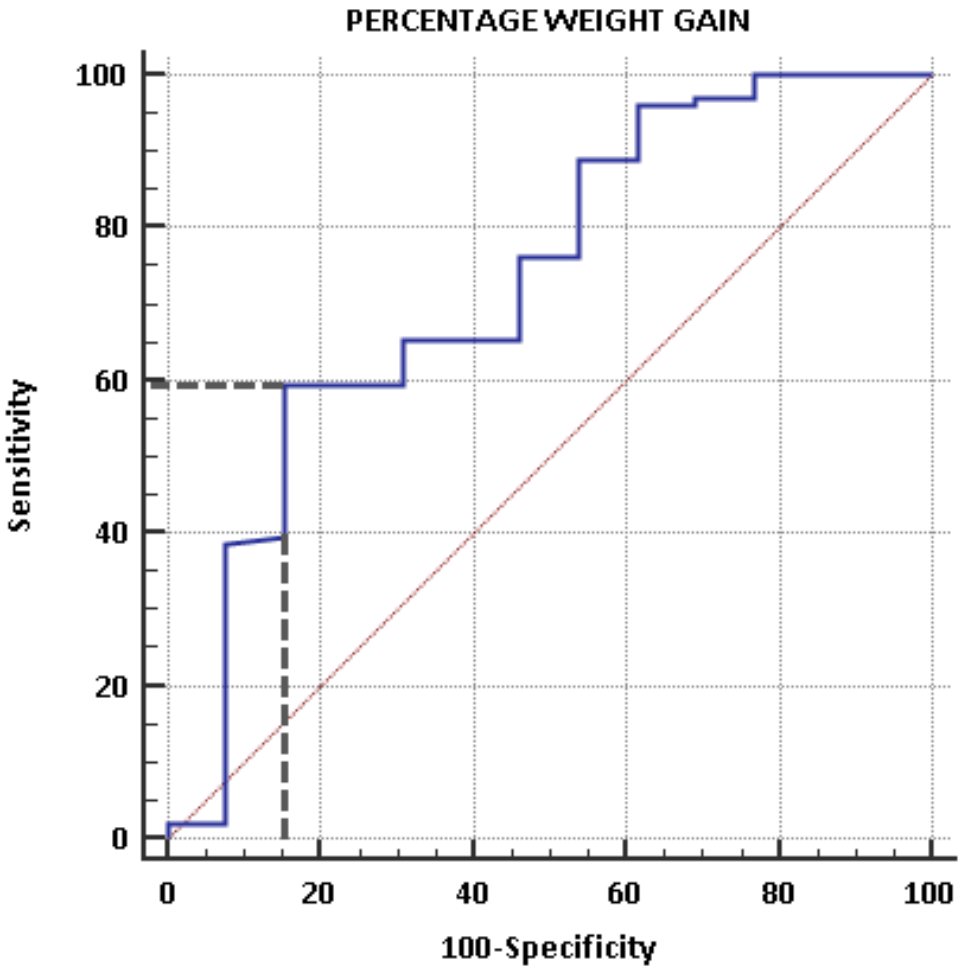

Figure 6. Receiver operating characteristic (ROC) curve for percentage weight gain when used to distinguish between reversal of overt hyperthyroidism and continuation of biochemical hyperthyroidism. The dashed line represents the specific cut-off value of 9.39 % weight gain, creating a sensitivity of 59.41 % and a specificity of 84.62 % for predicting a post-treatment serum T4 concentration ≤ 50 nmol/l.

2.6 Discussion

The data included in this study adds to the current literature that assesses weight gain in hyperthyroid cats following treatment (Boag *et al.*, 2007; Finch *et al.*, 2012; Jaillardon *et al.*, 2012). Although previous studies have documented weight gain following treatment of the feline hyperthyroid state, this is the largest study to date that the author is aware of assessing this in cats treated with I^{131}. The finding that hyperthyroid cats gain weight following treatment with I^{131} is not unexpected given previous study findings both in the human and feline fields (Lönn *et al.*, 1998; Dale *et al.*, 2001; Boag *et al.*, 2007; van Veenendaal & Rivkees, 2011; Finch *et al.*, 2012). However, the results from this study have also shown that cats that remain biochemically hyperthyroid at the three week point following administration of I^{131} gain significantly less weight than cats who become biochemically euthyroid or hypothyroid (proving one of the hypotheses of the study to be correct), and this has not been previously evaluated.

Treatment of hyperthyroidism in humans is commonly associated with excessive weight gain, with the majority of this occurring in the first three months following treatment (Alton & O'Malley, 1985; Pears *et al.*, 1990). This weight gain has been shown to be predominantly due to increases in lean mass, with significant increases in fat-free mass noted on DEXA scans both at the three and 12 month points post I^{131} treatment (De La Rosa *et al.*, 1997; Lönn *et al.*, 1998). Similar findings have also been shown in cats treated with I^{131}, with significant increases in fat-free mass detected three weeks post-treatment (Finch *et al.*, 2012). In that feline study the median and range of percentage increase in fat free mass during the three weeks was 5 % and –5.22 % to 9.08 %, respectively. The 10 cats in that study were also found to gain a median percentage body weight of 9.66 %, with a range of 5.97 % to 32.8 %. This percentage body weight change is similar to the median percentage weight gain of 11.35 % detected in this study.

The weight gain following treatment of hyperthyroidism is thought to be due to multiple reasons. One study that assessed this weight gain following I^{131} treatment in humans concluded that it was not only due to a reduction in the

metabolic rate of the patients secondary to decreased thyroid hormone concentrations but also to an initial increase in food energy intake post-treatment in order to maintain their premorbid weight (Abid *et al.,* 1999). Unfortunately, in this study it was not possible to accurately measure food intake during the isolation period due to radiation safety protocols. Therefore, the weight gain seen in the study cats cannot be specifically attributed to an increase in food intake.

2.6.1 Effect of hypothyroidism on weight gain

In humans, the induction of a biochemical hypothyroid state has been shown to have a significant effect on weight gain when compared to those patients that remain euthyroid (Dale *et al.,* 2001). Hypothyroid patients have been found to have an increased amount of water retention resulting in weight gain due to a reduced capacity to excrete water through the kidneys, an increased extravascular mass of albumin and inadequate lymphatic drainage; however, this excess body water is lost following treatment of hypothyroidism (Parving *et al.,* 1979; Sahun *et al.,* 2001; Karmisholt *et al.,* 2011).

In the current study a significant difference in percentage weight gain was not found between patients that became biochemically euthyroid and those that became biochemically hypothyroid. However, the weight changes were only assessed over a short time period and the sample size of biochemical euthyroid cats was only 16, compared to 85 cases in the biochemical hypothyroid group. This difference in sample sizes may have prevented a statistical significance from being detected. In addition, the 16 biochemically euthyroid cats were not followed over time, potentially resulting in the exclusion of some cases that may have become biochemically hypothyroid.

In humans, they have also found an association between the length of hypothyroidism following treatment and weight gain (Dale *et al.,* 2001). In Dale *et al.,* (2001) the mean weight gain for patients that became transiently hypothyroid was 5.37 kg compared to a mean weight gain of 8.06 kg in patients that became permanently hypothyroid and required treatment with

levothyroxine. These weight gains were compared to a mean weight gain of 4.57 kg in patients that did not become hypothyroid at any point post-treatment.

In the current study there were only six cases that required levothyroxine supplementation and were classified as cases of permanent hypothyroidism, compared to 26 cases in which it was known that the biochemical hypothyroidism reversed. Due to the small number of cases of permanent hypothyroidism it was not possible to directly compare the percentage weight gain of these cases to the percentage weight gain of the cases of transient hypothyroidism. However, should larger studies be carried out in the future, the effect of transient versus permanent hypothyroidism on weight gain could potentially be assessed in more detail.

An association between gender and the incidence of hypothyroidism occurring following I^{131} treatment for toxic nodular goiter in humans has not been noted (Kahraman *et al.,* 2012). In the current study five out of the six cats that remained hypothyroid and required levothyroxine supplementation were female. The predominance of female cats in this group may be a reflection of the overall case load in that ~ 60 % of the study cases were female; however, a possible association between the gender of the cat and the development of hypothyroidism in cats following treatment with I^{131} cannot be completely excluded, and has not been assessed in previous studies on I^{131} (Peterson & Becker, 1995; Nykamp *et al.,* 2005).

The function of normal thyroid tissue is suppressed by the overactive thyroid tissue in hyperthyroidism, resulting in a delay of normal thyroid function occurring following treatment (Peterson, 2006). However, the serum T4 concentration of many cats that are biochemically hypothyroid post-treatment will increase back into the reference interval over the ensuing months, with only a 2.1 % incidence of clinical hypothyroidism noted in a study assessing I^{131} treatment in 524 cats (Peterson & Becker, 1995). In the current study, of the cases that were not lost to follow up long-term, 6/32 cases that were biochemically hypothyroid following treatment remained hypothyroid and required levothyroxine supplementation. The serum T4 concentration of the

other 26 cases returned to within the reference interval during the six-month period post-treatment. Unfortunately, a large number of cases (n = 53) in the biochemical hypothyroid group had insufficient follow up to assess if their biochemical hypothyroidism resolved, which is the most likely reason why the incidence of clinical hypothyroidism in this study was higher than the Peterson & Becker (1995) study at 9.8 %. In the vast majority of cases this loss to follow up in the current study was due to owners failing to bring their cats back for repeat assessment of their serum T4 concentration.

2.6.2 Use of weight gain as a predictor of post-treatment serum T4 concentration

Blood tests are required following I^{131} treatment to assess if the treatment has been successful, as well as for assessing for the development of renal disease.

This study did document that percentage weight gain during the three-week isolation period was significantly higher in cats that obtained either a biochemical euthyroid or hypothyroid state, compared to those cats that continued to remain biochemically hyperthyroid at the 21-day period following treatment. However, it was not possible to identify a clinically relevant cut-off value that produced a high enough specificity for predicting a serum T4 concentration ≤ 50 nmol/l, disproving one of the hypotheses of this study. This was due to the finding that a 100 % probability of a post-treatment serum T4 concentration being ≤ 50 nmol/l was only achieved if a cut-off value of > 37.6 % weight gain was used and this would have only given a definitive result in 1/114 cases in this study. The use of a more relevant cut-off value of > 9.39 % weight gain resulted in an 85 % probability of a cat having a post-treatment serum T4 concentration ≤ 50 nmol/l. Therefore, although percentage weight gain cannot be used as a predictor of a post-treatment serum T4 concentration ≤ 50 nmol/l at the three week point following treatment, it could be used as an indicator of this.

Although percentage weight gain can give an indication of the reversal of overt hyperthyroidism, it cannot differentiate cats that have become biochemically euthyroid post-treatment from cats that have become biochemically

hypothyroid. Induction of a hypothyroid state post-treatment is thought to contribute to the development of azotaemia and therefore should be avoided (Williams *et al.,* 2010). As percentage weight gain cannot be used to identify cases that have become hypothyroid post-treatment, it should not be used in place of the measurement of serum T4 concentration.

2.6.3 Definition of treatment success

Previous studies on feline hyperthyroidism have defined successful treatment using I^{131} as the achievement of a biochemical euthyroid or hypothyroid state post-treatment, where as others have defined it as the achievement of a euthyroid state only (Malik *et al.,* 1993; Mooney, 1994; Theon *et al.,* 1994). However, treatment success in cases treated medically has recently been defined as a serum T4 concentration in the lower half of the reference interval (Daminet *et al.,* 2014). Using the anti-thyroidal medication guidelines, a serum T4 concentration lower than the reference interval would be classified as over-treatment and a serum T4 concentration in the upper half of the reference interval would be classified as suboptimal treatment. For this reason, the cases in this study were divided into four different groups for analysis of post-treatment serum T4 concentration so that these different definitions could be assessed.

This study found that there were no significant differences between the percentage weight gain in groups A (biochemical hypothyroidism), B (biochemical euthyroidism, low normal) or C (biochemical euthyroidism, high normal) but there was a difference between groups A, B and C combined when compared to group D. Therefore, using this data there was a statistical difference in weight gain between treatment failures (using group D as failures) and cases of treatment success when assessing all three different definitions of success. However, not only can percentage weight gain not be used to differentiate between cases of over-treatment (i.e. biochemical hypothyroidism) and biochemical euthyroidism, the study also showed that it cannot differentiate either of these from suboptimal treatment, if using the definition of treatment success according to Daminet *et al.,* (2014).

Although the consensus statement by Daminet *et al.,* (2014) advised that a reduction of the serum T4 concentration into the upper half of the reference interval was not viewed as treatment success, it should be remembered that the treatment modality of I^{131} is different from anti-thyroidal medication in that the full effect can be delayed for up to six months (Peterson & Becker, 1995). Therefore, for I^{131} treatment induction of a biochemical euthyroid state i.e. a low normal or high normal serum T4 concentration should be aimed for at the three-week point post-isolation, in regards to obtaining a treatment success.

2.6.4 Failure to gain weight in cats with post-treatment serum T4 concentration ≤ 50 nmol/l

Of the cats that obtained a biochemical euthyroid or hypothyroid state post-treatment, 10/91 failed to gain weight during the three-week isolation period. Potential reasons for this failure to gain weight include:

1) Stress induced hyporexia.

Stress in cats can result in variability of their appetite and this has been documented previously by Zeiler *et al.,* (2014). That study demonstrated that a marked increase in appetite occurred during the first three days of hospitalization as cats settled into the hospital environment and their stress levels reduced. To try to eliminate this effect of stress on cats presented for I^{131} treatment, they are allowed to acclimatise to the hospital environment within the cat ward for three to four days before transferring them to the isolation unit where they are treated and kept for the following three weeks. However, this acclimatization period may not have eliminated the effect of stress in all treated cats. Therefore, it is still possible that some study cats were stressed and this may have negatively impacted their appetite resulting in a lower amount of weight gain being obtained.

2) Increased activity levels.

Increased activity levels will result in an increase in energy expenditure; however, this factor is unlikely to have caused an effect in this study as the cats were confined to a kennel rather than being in a free-roaming environment.

3) Undiagnosed concurrent disease.

All cats that are admitted for I^{131} treatment of their hyperthyroidism undergo routine haematology, serum biochemistry, testing for the major feline viruses

(FeLV, FIV and feline coronavirus) as well as a full urine analysis being performed. This testing should hopefully reduce the chances of concomitant disease being missed. However, a recent study by Nussbaum *et al.,* (2015) found that 36.1 % of cats referred for I^{131} treatment had evidence of concurrent disease detected by abdominal ultrasonography. This included renal disease in 22.8 % of cases and neoplasia in 2.4 % of cases. Of the cases with renal disease noted on ultrasonography in that study, 96.4 % were classified as stage I according to the International Renal Interest Society (IRIS) guidelines and were therefore non-azotaemic on blood work (IRIS, 2013). Therefore, the presence of concomitant disease as a cause of failure to gain weight could not be definitively excluded in this study, especially as abdominal ultrasonography was not performed.

2.6.5 Assessment for azotaemia

Post-treatment azotaemia is diagnosed by evaluation of the serum renal parameters following treatment. This study did not identify that percentage weight gain was affected by the development of post-treatment azotaemia. Therefore, percentage weight gain would not be useful as an indicator for the development of azotaemia in these cases. The results from this study would support those of van Hoek *et al.,* (2009) that found that the body weight of cats increased between the time of treatment and four weeks post-treatment, regardless of whether they did or did not develop impaired renal function. Despite this lack of effect on early weight changes shown in the current study, van Hoek *et al.,* (2009) showed that long-term weight gain might be affected by renal dysfunction. In the van Hoek *et al.,* (2009) study, only cats that did not develop impaired renal function post-treatment continued to gain weight between one and six months post-treatment. This longer-term effect was not assessed in the current study.

Previous work by Boag *et al.,* (2007) has shown that the maximal changes to the GFR in cats treated with I^{131} occur four weeks following treatment, therefore suggesting that assessment of serum renal parameters should potentially be delayed until this time-point. Combining these findings with the results of this study, percentage weight gain could be used as an indicator of the reversal of

biochemical hyperthyroidism at the three week point post-treatment and venepuncture for assessment of both serum T4 concentration and renal parameters be delayed until four weeks post-treatment. This would avoid the need for two separate venepunctures to be performed during the first four weeks following I^{131} treatment in these cases. A reduction in the number of blood samples required could also reduce the level of stress experienced by the cats (Zeiler *et al.*, 2014).

Although the frequency of blood sampling could be reduced in the early period post-treatment using this method, repeat assessment for the occurrence of azotaemia should still be continued past the one-month period even if azotaemia is not detected at that time point. This is because the serum creatinine concentration in these cats has been shown to continue to increase up to three months following treatment with I^{131} and in some cases even up to six months (Boag *et al.*, 2007).

2.6.6 Pre-referral treatment for hyperthyroidism

Original analysis found that cats that had been treated surgically or with a combination of surgery and anti-thyroidal treatment prior to referral were found to gain significantly less weight than those cats that had been treated medically or had received no treatment at all. However, this finding is likely a confounding factor due to the small number of cases in both the surgery and combination treatment groups.

When the study population was split into those cats that had received pre-referral treatment for hyperthyroidism and those cats that had not, no statistical difference in weight gain between the two groups was seen. This lack of significance was despite the median pre-treatment serum T4 concentration being 234 nmol/l in the former group and 148 nmol/l in the latter group, suggesting that the former group may have been more severely affected by their hyperthyroidism.

Due to these different findings, definitive conclusions regarding specific pre-referral treatment and weight gain cannot be currently made.

This lack of definitive significance between specific pre-referral treatment and weight gain is also likely to have been influenced by the type of hyperthyroid cats seen at the SAH. The vast majority of cats that are referred to the SAH are referred due to an inability to control their serum T4 concentrations, whether that is due to difficulties in medicating the cat consistently on a daily basis or due to poor control of hyperthyroidism despite treatment. Due to this, most cats that are seen at the SAH have never been successfully treated, which is the most likely reason why the weight gain of those cats that had not received any management prior to referral was not significantly different from those cats that had received treatment.

In humans, weight gain following treatment of hyperthyroidism appears to occur regardless of the treatment modality used. Significant differences in the amount of weight gained by patients between treatment modalities (carbimazole, surgical thyroidectomy and I^{131}) were not found by Pears *et al.,* (1990); however, the sample size in that study was small with only 65 cases. Later studies have shown that treatment modality could have an effect on weight gain in these patients, with Dale *et al.,* (2001) finding that more weight gain was seen in patients that underwent thyroidectomy than in those patients treated with I^{131} or anti-thyroidal medication.

A study assessing weight gain in hyperthyroid cats treated with different treatment modalities has not yet been performed as it has been in humans (Pears *et al.,* 1990; Dale *et al.,* 2001). Therefore, conclusions on whether treatment modality could affect weight gain cannot be drawn.

In humans, it has also been shown that patients that undergo a surgical thyroidectomy are less likely to gain weight when compared to those patients that first undergo I^{131} and then have a surgical thyroidectomy performed (Schneider *et al.,* 2014).

In this study there was no definitive effect of sequential treatments e.g. surgical thyroidectomy then I^{131} on weight gain, as weight gain between pre-referral treatments was not significant; however, only weight changes over the three

week period were assessed rather than weight changes since diagnosis and the start of treatment in cats, which may have affected this finding.

The vast majority of cases in this study that had received pre-referral treatment had been treated with anti-thyroidal medication (n = 58). Ideally, the findings from this study assessing weight changes in patients treated first with anti-thyroidal medication and then I^{131} would be compared to findings in the human field. However, permanent remission using anti-thyroidal drugs is rarely achieved in toxic nodular goiter in humans, so surgery or I^{131} treatment are the preferred treatment modalities, unless there are contraindications to their use (van Soestbergen *et al.*, 1992; De Leo *et al.*, 2016). Due to this there are not many studies assessing the use of anti-thyroidal treatment prior to the use of I^{131} in humans and those that have, have not assessed weight changes (Kartamihardja & Massora, 2016). Therefore, comparisons between this study and the human field cannot be made.

2.7 Limitations

2.7.1 Case exclusions

The main limitation to this study was due to its retrospective nature. Lack of post isolation weight recording resulted in 15.4 % of the originally identified cases having to be excluded. Further investigations into this suggested it was likely these cats were weighed following treatment but unfortunately at the time of discharge the weight was not recorded.

2.7.2 Appetite variability

The cats' appetites were variable within the unit on a daily basis and therefore appetite was not a consistent parameter in the statistical analysis and this may have acted as a limitation. In order to limit the nurses' exposure to radiation the cats were only fed once daily; however, large quantities of food were offered at this point. The food fed was a mixture of dry and wet food, which was dependent on the individual cat's preference.

As discussed previously, the variability in appetite may have been an indicator of stress in the study cats; however, an attempt was made to negate this by hospitalizing them prior to administration of I^{131}. Due to the radiation health and safety concerns regarding limiting the nurses' exposure to radiation, provision of more frequent meals to the cats while they were in the isolation unit was not possible. Should fresh wet food have been offered more frequently, it is possible that some cats may have eaten larger amounts each day, which could have resulted in further weight gain.

2.7.3 Previous control and severity of hyperthyroidism

Another limitation in this study was the variability in the study population's length of hyperthyroidism control if they were pre-treated, as well as the severity of disease. A previously well-controlled hyperthyroid cat with mild disease would not be expected to have lost as much weight as a severely affected cat that had been poorly stabilised. In the study population only 28 cats were injected with a dose of I^{131} > 150 MBq, suggesting that most of the study cats were only mildly to moderately affected by hyperthyroidism and therefore may have had less weight to gain. However, statistical analysis did not identify the dose of I^{131} to have a significant effect on the weight gained by the study cats, demonstrating that the severity of hyperthyroidism was unlikely to have had a major effect. Unfortunately, regulating the length and control of hyperthyroidism in the study population before referral was not possible and therefore this effect could not be avoided.

2.7.4 Azotaemia

Development of azotaemia was not identified to have a significant effect on weight gain in this study. However, only eight of the study cats were detected to be azotaemic post-treatment and this number of cases may have been too small to enable a significant effect to be identified.

The definition of azotaemia in this study was a post-treatment serum creatinine concentration > 180 μmol/l, which is the upper limit of the laboratory reference interval. Although serum creatinine is a crude marker of renal dysfunction this

was a retrospective study and this value provided a clear cut-off point for identification of cases with potential post-treatment renal disease. However, this definition may have resulted in cases that had developed renal insufficiency being missed, as cats with chronic kidney disease can have serum creatinine concentrations < 180 μmol/l, as per the IRIS guidelines (IRIS, 2013). Previous studies have reported incidence rates of renal disease post-treatment of 28-63 % which is markedly higher than in this study and the definition used to identify cases of renal disease may be the cause of this (Rogers *et al.,* 2000; Milner *et al.,* 2006).

Unfortunately, post-treatment analysis of urine is not routinely performed in treated cats, partly due to the concern of radiation levels in the urine following treatment (Lamb *et al.,* 2013). Therefore, it was not possible to evaluate if some of the study cats had developed a reduced urine concentrating ability during the isolation period nor was it possible to completely exclude a pre-renal cause of the azotaemia in cases included in the azotaemic group. To avoid this limitation in future studies a post-treatment urine analysis could be obtained in all cases to further assess the azotaemia but this should be postponed until four weeks following administration due to concerns of radiation levels in the urine (Lamb *et al.,* 2013).

An alternative method to assess for the development of renal dysfunction would be to measure the GFR pre- and post-treatment in these cases as was performed in van Hoek *et al.,* (2009); however, as iohexol can decrease the absorbed dose of I^{131} if given within 24 hours of its administration, this should be taken into consideration (Peremans *et al.,* 2008). Measurement of serum symmetric dimethylarginine could also be considered; however this was not commercially available at the time of the study dates (Braff *et al.,* 2014; Hall *et al.,* 2014).

2.7.5 Method of defining weight changes

Percentage body weight change was used as the marker for changes in weight in this study population, whilst in human studies they have also assessed changes in absolute body weight (kg) and body mass index (De La Rosa *et al.,* 1997). Unfortunately, body condition scores were not recorded in the study population

and so they could not also be evaluated. Although absolute body weight changes were recorded in this study, percentage body weight changes were used instead. This was because this value was less likely to be impacted by the variation in the different body statures and builds of the study cats, as previous studies have shown a marked variation in the body weights of hyperthyroid cats, with a weight range from two to seven kg (Slater *et al.,* 2001).

Another potential method to assess the weight changes of hyperthyroid patients undergoing treatment is with the use of DEXA scans (Lönn *et al.,* 1998; Finch *et al.,* 2012). These scans assess if weight changes are due to alterations in the fat mass or the fat-free mass and they have already been used within the human field for this purpose (Lönn *et al.,* 1998). Recently, DEXA scans have also been used in a small number of cats with hyperthyroidism (Finch *et al.,* 2012). Unfortunately, DEXA scans are not available at the SAH and therefore could not be used in this study.

2.8 Further studies

This study only evaluated weight gain in hyperthyroid cats treated with I^{131} but in human medicine weight gain between patients treated either with anti-thyroidal medication, thyroidectomy or with I^{131} have been compared (Pears *et al.,* 1990; Dale *et al.,* 2001). Future studies could therefore evaluate the weight gain in hyperthyroid cats treated medically, surgically, with I^{131} or with iodine-restricted diets to assess if the use of different treatment modalities has an effect on the amount of weight gained. It would also enable the assessment of whether weight gain can be used as an indicator of the reversal of the hyperthyroid state in other treatment modalities, as has been shown in the use of I^{131} in this study.

The weight gain following achievement of a euthyroid state in humans has been documented to last for many years following treatment (Dale *et al.,* 2001). Although Boag *et al.,* (2007) previously documented the longer-term weight changes in cats treated with I^{131} by assessing the weight changes at six-months post-treatment, a longitudinal study assessing weight changes over the first

year, including the short-term weight changes has not yet been performed in cats.

Future studies on weight changes in hyperthyroidism could also include the use of DEXA scans given the findings of the small study by Finch *et al.*, (2012). These scans would enable the weight changes seen in these patients to be directly attributed to changes in fat or fat-free mass. It would be interesting to compare these findings in hyperthyroid cats treated with the different treatment modalities currently available to assess if differences exist. In the human field of hyperthyroidism, DEXA scans have also been used to document the long-term changes in body composition of these patients (Lönn et al., 1998). This is an area that could also be explored in cats.

2.9 Conclusions

The findings of this study show that hyperthyroid cats treated with subcutaneous I^{131} that become biochemically euthyroid or hypothyroid three weeks following treatment gain significantly more weight than those cats that remain biochemically hyperthyroid. However, percentage weight gain cannot be used as a replacement for measurement of serum T4 or serum creatinine concentrations as it cannot differentiate cats with biochemical euthyroidism from those cats with biochemical hypothyroidism, nor can it be used to differentiate cats that have developed post-treatment azotaemia from those that have not.

CHAPTER 3

3 GAMMA (γ) RADIATION EMISSIONS DURING THE THREE-WEEK ISOLATION PERIOD FOLLOWING ADMINISTRATION OF I^{131} IN CATS WITH HYPERTHYROIDISM

3.1 Introduction

Hyperthyroid cats treated with I^{131} remain in isolation for a variable time period following I^{131} administration, dependent on the centre at which they are treated and the local radiation legislation (Puille & Peremans, 2011; Lamb *et al.,* 2013; Boland *et al.,* 2014). In some centres this isolation period varies on a case-by-case basis, depending on the individual cat and the radiation levels they are emitting (Meric *et al.,* 1986). However, at other centres the isolation period is fixed, regardless of the dose of I^{131} that is administered (Boland *et al.,* 2014).

The original isolation period of hyperthyroid cats treated with I^{131} at the SAH was 28 days in length. This was based on unpublished work carried out at the SAH in the 1990's under the guidance of the Scottish Environment Protection Agency. This isolation period was subsequently reduced to 21 days for cases administered doses of $I^{131} \leq 200$ MBq, following the results of the study performed by Lamb *et al.,* (2013).

Within the UK there are legal dose limits of ionising radiation in place that members of the public can be exposed to, to prevent members of the public being placed at undue risk (Ionising radiations regulations, 1999). Therefore, it is important that the level of ionising radiation that is emitted by people or cats treated with I^{131} be measured, to ensure that these limits are not exceeded. In the UK the legal dose limit is currently one mSv (1000 microsieverts (μSv))/year, which is averaged over a five-year period (Ionising radiations regulations, 1999; Environment Agency, 2012). There is also a constraint for a single new source of ionising radiation, which is limited to 0.3 mSv (300 μSv) (Environment Agency, 2012).

Despite these limits, there is some room for flexibility by regulating bodies for ionising radiation in that they can allow a public dose commitment of 20 μSv, which is $1/50^{th}$ of the annual dose commitment for members of the public, without having to impose major restrictions (Environment Agency, 2012). Recommendations by the International Commission on Radiological Protection (ICRP) in 2005 also advised that a public dose commitment of 100 μSv, which is

1/10th of the annual limit for members of the public, should be the minimal dose constraint of an effective dose of ionising radiation that should be considered for application in any situation (ICRP, 2005). Taking this information a dose commitment < 100 μSv could therefore be allowed, as long as there are certain restrictions in place. These restrictions include:

1) The radiation exposure is a one-off.
2) The dose commitment is restricted to a small group of the public.
3) That the as low as reasonably practical (ALARP) procedures are followed.

The γ radiation emitted by treated hyperthyroid cats has been previously assessed using surface exposure at the level of the thyroid gland itself (Feeney *et al.*, 2003). Feeney *et al.*, (2003) assessed surface emissions from treated cats at several time points during their isolation period using a calibrated Geiger-Müller counter, as well as measuring the radioactivity of the urine from the same cats. That study found that surface emission rates from treated cats were useful in determining upper thresholds of urine radioactivity. The conclusion from the study was that the use of surface emission rates was a valid method of assessing whether the level of γ radiation emitted from the cats was low enough to enable exit from isolation. Therefore, due to these study findings this methodology is used at some institutions to dictate when cats can be released from isolation following treatment of hyperthyroidism using I^{131}, which allows a variable isolation period to be used. However, a potential concern of using this methodology for radiation monitoring is that it requires staff to be in close proximity to the treated cats to allow the surface emission to be measured at the level of the thyroid gland, increasing their exposure to radiation. This methodology is also operator dependent and could therefore be affected by the orientation of the counter towards the thyroid gland and also by the variability in the location of the thyroid gland itself between individual cats.

In the human field of radiation, EPDs are used by workers in medical laboratories, nuclear power plants and nuclear research facilities to monitor their exposure to radiation (Mirion Technologies, 2010). These dosimeters monitor workers exposure to ionising radiation, which includes γ, β and neutron radiation, as well as x-ray radiation in real-time. The dosimeters can have both

audible and visual alarms that are activated when a dose rate level of radiation is exceeded. These alarms act to alert the personnel wearing them, so that appropriate action can be taken. These dosimeters are capable of not only detecting a specific dose rate level but also of recording radiation exposure over time.

There are many companies that currently manufacture and supply EPDs for radiation workers. One particular company, Mirion Technologies, Berkshire, manufacture a battery operated EPD used by radiation workers (Mirion Technologies, 2010). One of the EPD models used, the MGP DM2000X, is an energy compensated silicon diode detector. It has flat energy responses to x-ray and γ-rays from 50 keV to 6 megaelectronvolts (MeV) and linear responses to dose-rate fields from natural background up to more than 10 Sv/hour. These monitors are front facing with an accuracy better than ± 20 % over an angular range of −75° to +75° (Mirion Technologies, 2010). These EPDs are calibrated with caesium (Cs^{137}), which has been shown to have a similar energy range to the isotope I^{131} that is used for radioactive iodine treatment in hyperthyroid cats (Delacroix *et al.,* 1998).

Within the human field of radiation EPDs are commonly used and studies have been performed using them to assess the radiation exposure of caregivers and family members of people with hyperthyroidism treated with I^{131} (Barrington *et al.,* 1999; Marriott *et al.,* 2007). However, they have only recently been evaluated in the field of feline hyperthyroidism (Roberts *et al.,* 2015).

A pilot study assessing the use of an EPD in the monitoring of γ radiation in feline hyperthyroidism has already been performed at the SAH between December 2011 and September 2014 (Roberts *et al.,* 2015). However, as this study only assessed the γ radiation emissions from 12 cats treated with I^{131}, it was decided to expand the study to include more cases, whilst keeping the original aims the same for this part of the thesis.

3.2 Aims and hypotheses

1) To assess if an EPD could be used to measure the γ radiation emitted from hyperthyroid cats treated with radioactive iodine at the SAH, by assessing if it could be used to determine the effective half-life of the radioisotope used (I^{131}). It was hypothesized that the EPD could be used to measure the γ radiation.
2) To assess if an EPD could be used to determine the release time of treated hyperthyroid cats, as well as ascertain if a fixed isolation period could be used for these cats treated with I^{131}. It was hypothesized that the EPD could be used to determine the release time of treated hyperthyroid cats.

3.3 Materials and methods

This prospective study was carried out at the SAH of the University of Glasgow between December 2011 and April 2016 and involved cats that had been referred to the SAH for the treatment of feline hyperthyroidism using I^{131}. This study included cases that had previously been part of the pilot study (Roberts *et al.*, 2015).

Cats referred for I^{131} have been previously diagnosed with hyperthyroidism in general practice. Dependent on the individual case, previous treatment for hyperthyroidism using anti-thyroidal medication (methimazole or carbimazole), surgery (thyroidectomy) or an iodine-restricted diet may have been trialed.

3.3.1 Inclusion criteria

Any cat that had been referred to the SAH for I^{131} treatment of their previously diagnosed hyperthyroidism and remained in the isolation unit for three weeks following I^{131} administration was eligible for inclusion into this study.

3.3.2 Exclusion criteria

1) Any cat that was due to receive a dose of I^{131} > 200 MBq and therefore be required to remain in the isolation unit for more than the standard 21-day period.
2) Any cat that had an incomplete data set recorded by the EPD i.e. did not have full data recorded for all days they were in the isolation unit for.

3.3.3 Standard protocol for cases referred for I^{131}

This protocol is the same as described in chapter 2.3.3 of this thesis. See chapter 2.3.3 for details.

3.3.4 The monitor kennel

Within the I^{131} unit there are eight available kennels for treated cats. During this study all cats that were enrolled were placed in the same kennel during their isolation period, which was designated as the monitoring kennel. This particular kennel was chosen because it was the furthest kennel from the lead lined radioactive waste bin, which housed used sharps and previously emptied vials that had contained/been contaminated with I^{131}, in the I^{131} unit. The dimensions of the monitoring kennel were: height 86 cm, width 86 cm and depth 71 cm. To minimize the impact of other treated cats in the unit on readings from the monitor kennel and to standardize the methodology, the three kennels surrounding the monitor kennel were kept empty (Figure 7). Due to this the minimum possible distance between a cat in the monitor kennel and the next treated cat was 133 cm.

The EPD (model MGP DM2000X) used for this study was clipped onto the monitor kennel door in exactly the same position for all cats included in the study, which was 42 cm above the kennel floor. Whilst in the isolation unit the daily position of the cat within the monitor kennel was observed subjectively when the veterinary nurses cleaned them out. Each cat was cleaned out on a daily basis and this involved the removal of the cats' faeces and urine. This meant that

data recorded by the EPD was not affected by the previous days urine and faecal waste, as excreted faeces and urine from treated cats have previously been shown to act as sources of radiation exposure (Lamb *et al.*, 2013).

MONITORING KENNEL	EMPTY KENNEL	OTHER TREATED CAT	OTHER TREATED CAT
EMPTY KENNEL	EMPTY KENNEL	OTHER TREATED CAT	OTHER TREATED CAT

Figure 7. A diagrammatic representation of the eight kennels in the I^{131} isolation unit, illustrating which kennel was used as the monitoring kennel for cats enrolled in this study and had the EPD attached to the kennel door, which kennels were kept empty and which kennels were available to be used by other cats undergoing treatment that were not enrolled in the study.

3.3.5 Data recorded by the electronic personal dosimeter (EPD)

The EPD recorded radiation exposure events, which were measured in Sieverts. This data was downloaded onto a computer database system (Dosimass Software; Mirion Technologies, Berkshire) at the end of the isolation period once the cat had been removed from the I^{131} isolation unit (Mirion Technologies, 2010). The EPD was then reset and placed back onto the monitor kennel when the next cat in the study was placed into the monitor kennel. The downloaded data was then transferred into a separate database (Microsoft Excel), to enable the dose of γ radiation that was emitted by the monitored cat each day to be calculated. This was then converted into grays so that radiation exposure could be evaluated. This was performed by using the calculation that one Sievert is the equivalent of one gray.

As there were other potential sources of radiation within the isolation unit, which included other treated cats and the bins used for radioactive waste, a second MGP DM2000X EPD was placed into the isolation unit to take these factors into account. This EPD was placed in two separate locations within the unit during the study. Location one was the ledge of the viewing window into the unit, which was 252 cm away from the monitor kennel and location two, which was 346 cm from the monitor kennel, was the windowsill of the isolation unit. These specific locations were chosen as they were locations where the EPD would not be interfered with and therefore the monitor would not be moved by accident. Background daily radiation was recorded from one of the two locations, for the same 21-day period that the cats were being monitored for. The location of the second EPD alternated between the two locations during the study period. For odd case numbers e.g. one, three, five and seven, it was placed in location one, and for even case numbers e.g. two, four, six and eight, it was placed into location two. The recorded readings from these two locations were then used to calculate an average background radiation level/day. This background radiation was then subtracted from the daily monitor kennel readings so that these background variables, which would not be present in the home of the treated cats, could be taken into account.

3.4 Statistical analysis

The Pearson correlation coefficients of the measured half-lives against exponential models were calculated and expressed as r^2. The effective half-life of I^{131} for all cats was calculated using the equation $t_{1/2} = t \times \ln(2)/\ln(Sv_{first}/Sv_{last})$ where $t_{1/2}$ = calculated effective half-life, t = number of days from the first full day of readings to the last day of detectable radiation, Sv_{first} is the radiation measured on the first full day of readings and Sv_{last} is the radiation measured on the last day of detectable readings (Roberts *et al.*, 2015).

The potential additional γ radiation exposure emitted by the cats was then calculated had they left the isolation unit earlier than the current 21-day period. This was assessed at three separate time points: after seven, 14 or 17 days of isolation. The daily γ radiation emission of the cats involved in the study was then assessed using a multilevel linear regression model. This was performed to assess if the daily γ radiation emissions were associated with the dose of I^{131} administered. Dose, which was a categorical variable and days since administration, which was used as a continuous variable, were both entered into the multivariable model. A cat identifier was included as a random effect to account for clustering within each cat. Explanatory variables were retained if their respective P-values were < 0.05. These analyses were conducted using STATA/SE V.12.1 (STATA, College Station, Texas, USA) (Roberts *et al.*, 2015).

Due to the dose constraints discussed previously, the data obtained in this study was also analysed in regards to both the 20 μSv and 100 μSv dose commitments, to assess how many cats would be emitting radiation levels within these dose constraints had they been released following seven, 14 or 17 days of isolation. To enable this to be done the radiation data for dose equivalent was changed into dose exposure. This was done using the calculation that one microgray (μGy) of radiation exposure is approximately equal to one μSv of radiation dose equivalent.

3.5 Results

3.5.1 Exclusions

When the study was first started several cases were excluded. This was due to either the alarm of the dosimeter being triggered or poor battery life of the EPD. As the EPD is manufactured for use by radiation workers it comes with a preset alarm of 10 μSv/hour, which alerts the workers when this level has been reached due to safety concerns of radiation levels higher than this. The dosimeter alarm was triggered in the first four cases in this study shortly after the I^{131} was injected and resulted in incomplete data being recorded. As the alarm was not necessary for this study it was subsequently disabled. Once the alarm had been disabled no further cases were excluded due to this issue. In an additional two cases, incomplete data sets were recorded due to a battery failure during the monitoring period and these cases were also excluded.

One of the cases that had been included in the pilot study did not have data recorded for the first two days of isolation due to the dosimeter not being placed on the kennel door. Due to the incomplete data set it was elected to remove this case from the expanded study. This resulted in 11/12 cases that had been used in the pilot study being included in the expanded study.

One further case was excluded from the study as another treated cat was accidentally placed into the kennel next to the monitor kennel during the monitoring period. This resulted in a sudden increase in the level of γ radiation recorded by the dosimeter on day 13 of the isolation period onwards.

3.5.2 Study cats

Following these eight case exclusions, 20 cats that were treated with I^{131} and had their daily γ radiation emissions recorded during the 21-day isolation period were used in this study. The age of the cats in the study ranged from seven years of age up to 16 years of age, with a mean age of 12.5 years. There were

eight male neutered cats and 12 female neutered cats and they were all domestic shorthaired cats. The dose of I^{131} injected in these cases was 80 MBq (n = 5), 120 MBq (n = 7), 150 MBq (n = 4), 175 MBq (n = 1) and 200 MBq (n = 3) (Table 5).

None of the cats included in this study were found to be azotaemic, defined as a serum creatinine concentration greater than the laboratory reference interval of 91-180 µmol/l, on their pre-treatment blood work (Table 5), nor were they known to have concurrent illnesses e.g. congestive heart failure.

Eleven of the 20 cats were biochemically hypothyroid three weeks following their treatment with I^{131}, with post-isolation serum T4 concentrations < 15 nmol/l and six of the 20 cats were biochemically euthyroid with post-isolation serum T4 concentrations ≥ 15 nmol/l and ≤ 50 nmol/l. Three of the 20 cats had post-isolation serum T4 concentrations > 50 nmol/l at the three week point post-treatment and were classified as biochemically hyperthyroid (Table 5).

Case (MBq)	Serum creatinine concentration pre-treatment	Serum creatinine concentration post-treatment	Serum T4 concentration post-treatment
1 (80)	135	164	14.9
2 (120)	85	109	33.5
3 (175)	65	91	104
4 (120)	82	59	459
5 (120)	84	121	27.9
6 (200)	143	158	6.5
7 (80)	100	167	< 3.2
8 (150)	67	103	7.04
9 (80)	66	98	17.6
10 (120)	80	113	7.6
11 (200)	95	81	144
12 (120)	143	201	3.37
13 (120)	117	128	44.1
14 (200)	66	117	11.9
15 (150)	78	87	12.6
16 (150)	105	130	24.3
17 (80)	102	148	15.1
18 (150)	90	142	5.8
19 (120)	79	154	6.7
20 (80)	101	116	8.3

Table 5. The dose of I^{131} used in each case in MBq, the serum creatinine concentration (in μmol/l) before and three weeks after treatment with I^{131} (laboratory reference interval 91 – 180 μmol/l) and the serum T4 concentration (in nmol/l) three weeks post-treatment.

3.5.3 EPDs

The EPDs were attached to the monitor kennel cage door with ease. Once attached to the cage door, using the clip on the back of the dosimeter, the EPD remained in place during the whole monitoring period for each cat. The dosimeters were not noted to be interfered with by any of the cats during the study period.

During the three-week isolation period the cats were subjectively noted to move around the monitor kennel freely. They were therefore at variable distances from the dosimeter during the period of study. Due to this variable movement within the monitor kennel, the average distance of the study cats from the EPD was presumed to be ~50 cm. However, cats could have been as far as 100 cm away from the dosimeter.

3.5.4 Effective half-life of I^{131}

The first aim of this study was to ascertain if the EPD could be used to measure the γ radiation emitted by the hyperthyroid cats following administration of I^{131}.

It was found that the rate of decrease in radioactivity of the study cats was found to follow an exponential decay pattern very closely, with correlation coefficients (r^2) of more than 0.93 in 19 of the cats and 0.84 in the remaining cat (Table 6) (Figures 8-27).

Following this, the effective half-lives of I^{131} were calculated and the mean value was found to be 2.60 ± 0.65 days with a range of 1.40 to 4.16 days (Table 6). The mean effective half-life of I^{131} was very similar to the data previously described by Puille *et al.,* (2002), which found the effective half-life of I^{131} to be 2.5 ± 0.7 days. The similarity between the effective half-life of I^{131} in the Puille *et al.,* (2002) study and the effective half-life in this study, suggested that the data could be used to assess the γ radiation emissions from the cats in this study, which was the second aim.

Case (MBq)	$t_{1/2}$	t	r2	7-Day	14-Day	17-Day
1 (80)	2.22	15	0.99	74	3	0
2 (120)	3.08	19	0.97	354	79	32
3 (175)	4.16	19	0.97	542	115	41
4 (120)	3.27	19	0.95	236	34	12
5 (120)	2.91	18	0.99	403	69	24
6 (200)	2.20	19	0.97	393	33	7
7 (80)	1.85	15	0.97	207	6	0
8 (150)	2.18	18	0.97	318	22	5
9 (80)	3.08	19	0.98	149	31	11
10 (120)	2.15	18	0.98	264	29	6
11 (200)	2.97	19	0.96	271	65	27
12 (120)	2.64	19	0.95	380	34	16
13 (120)	2.81	19	0.95	240	34	12
14 (200)	2.72	19	0.96	951	89	34
15 (150)	3.24	19	0.99	617	110	43
16 (150)	2.45	19	0.97	442	36	8
17 (80)	2.74	19	0.96	86	18	9
18 (150)	1.40	7	0.93	28	0	0
19 (120)	1.53	11	0.84	86	0	0
20 (80)	2.47	12	0.97	150	0	0

Table 6. The dose of I^{131} administered (in MBq), the effective half-life of I^{131} ($t_{1/2}$), the number of days from the first full day of readings to the last day of detectable radiation (t) and the Pearson correlation coefficients of the measured half-lives against exponential models (r^2) in each case. Also shown is the potential additional dose exposure in micrograys (μGy) to owners if the treated cats had left the isolation unit following a seven, 14 or 17-day isolation period after administration of I^{131}.

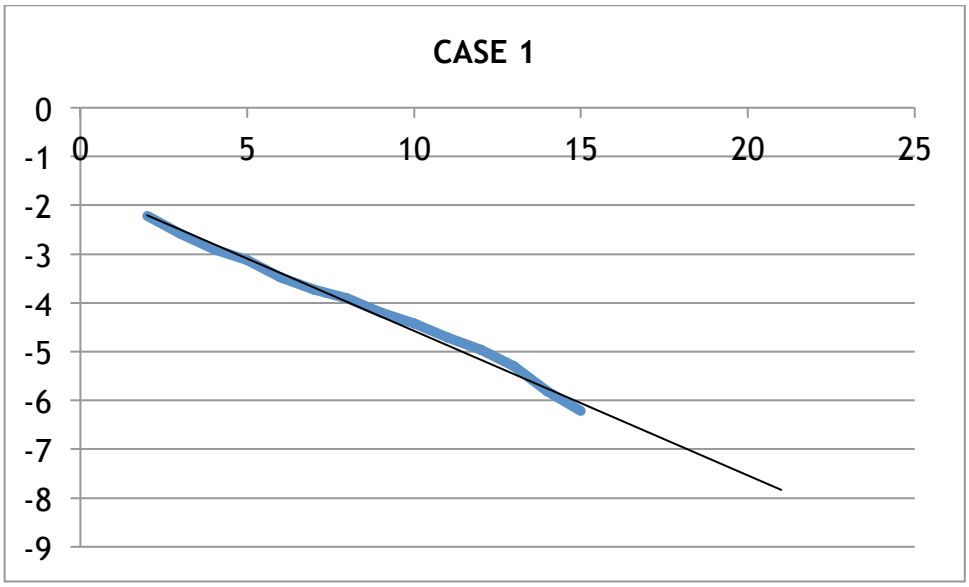

Figure 8. $r^2 = 0.99$, $t_{1/2} = 2.22$

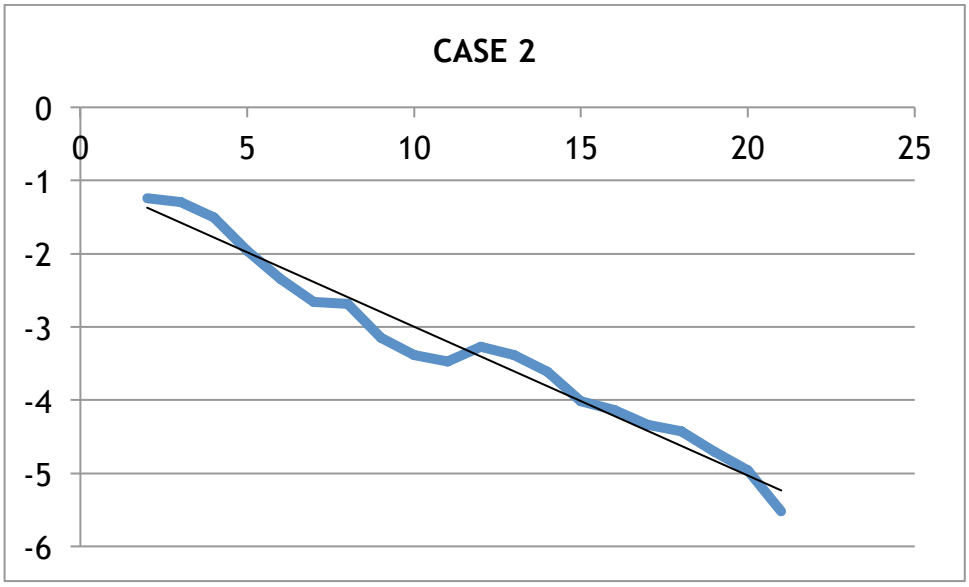

Figure 9. $r^2 = 0.97$, $t_{1/2} = 3.08$

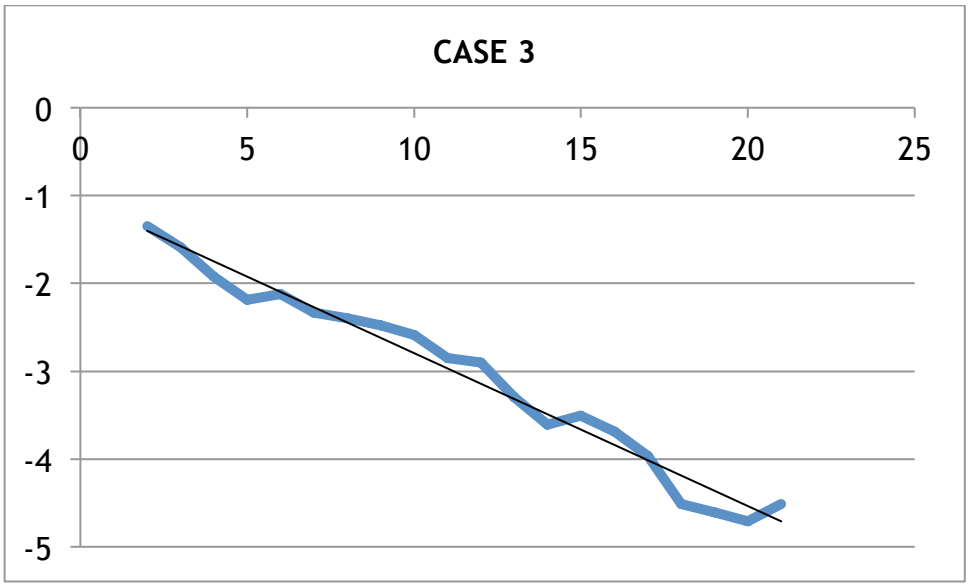

Figure 10. $r^2 = 0.97$, $t_{1/2} = 4.16$

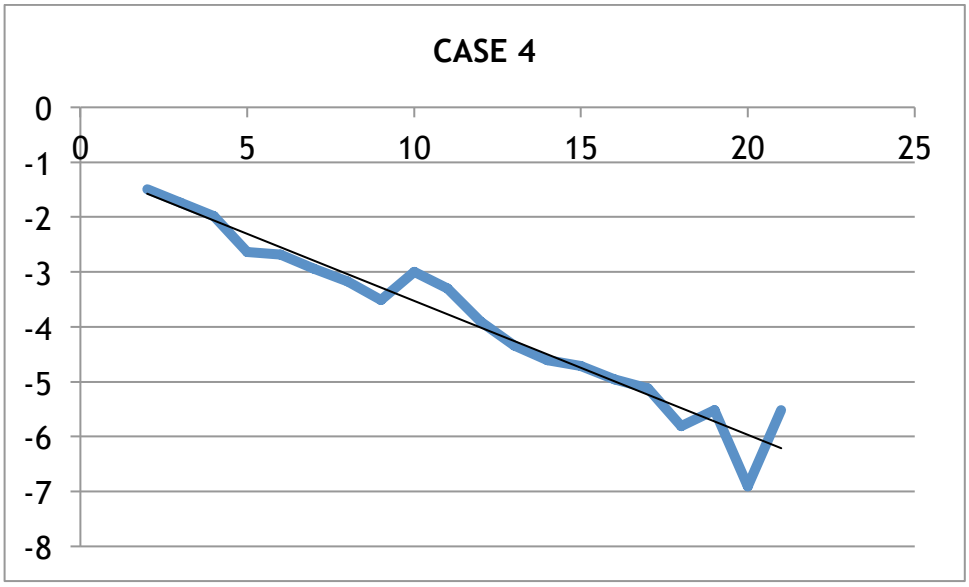

Figure 11. $r^2 = 0.95$, $t_{1/2} = 3.27$

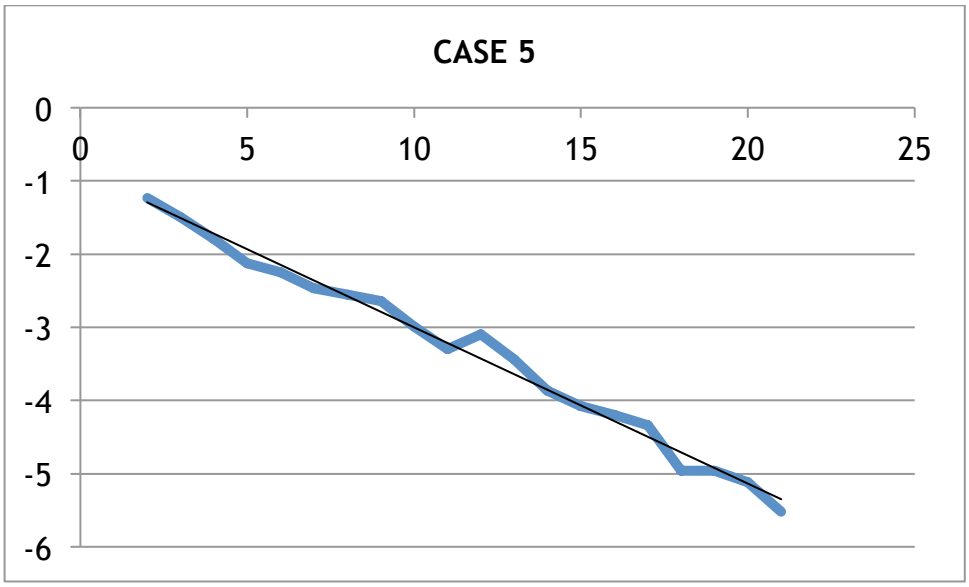

Figure 12. $r^2 = 0.99$, $t_{1/2} = 2.91$

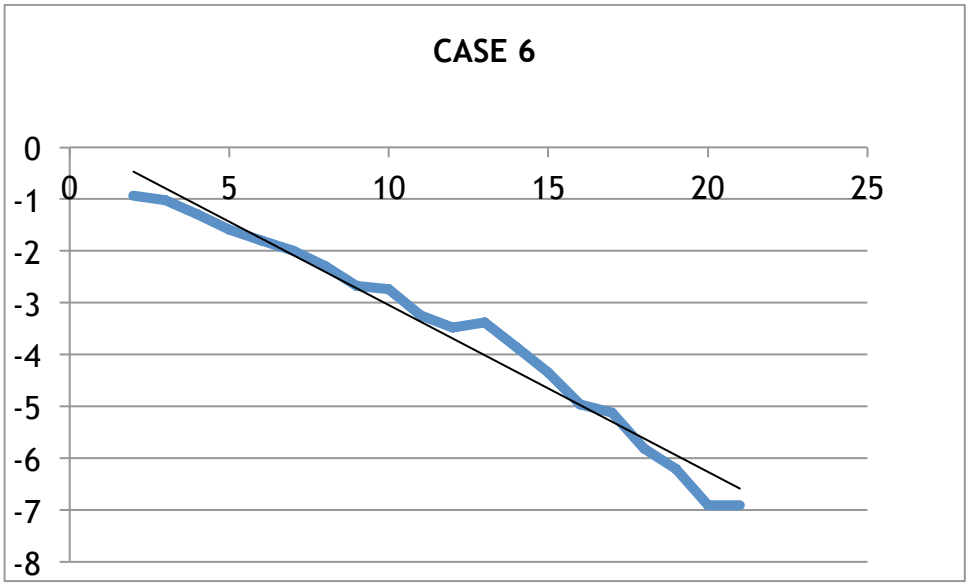

Figure 13. $r^2 = 0.97$, $t_{1/2} = 2.20$

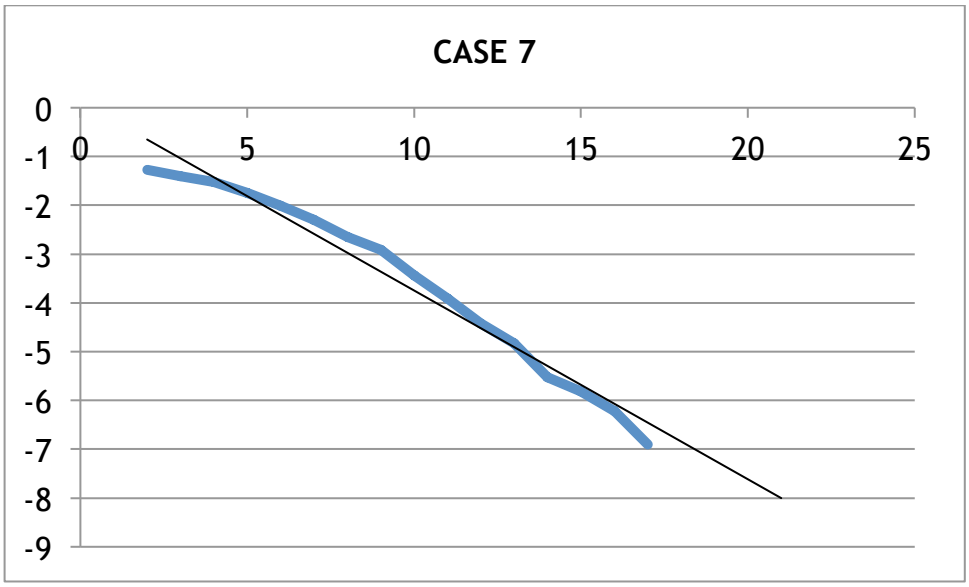

Figure 14. $r^2 = 0.97$, $t_{1/2} = 1.85$

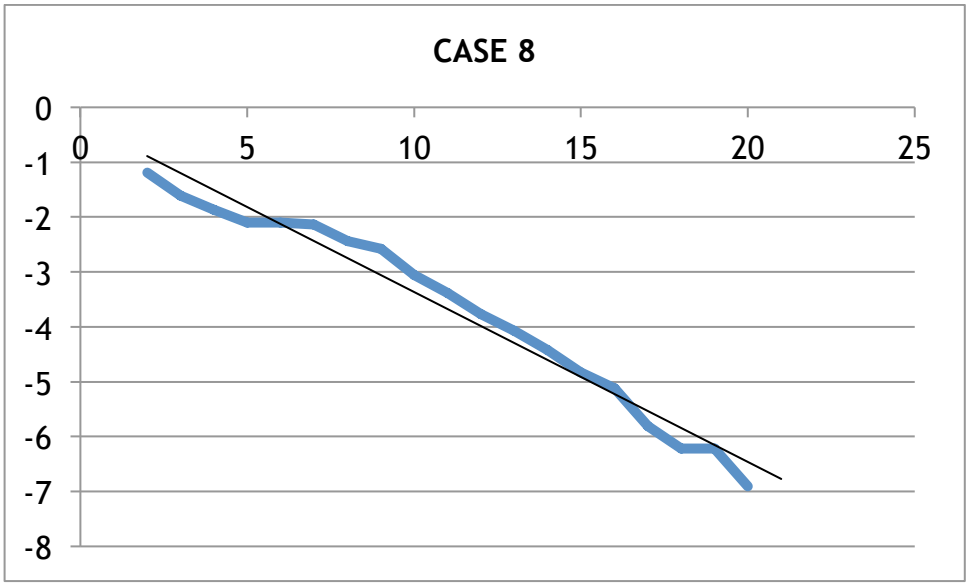

Figure 15. $r^2 = 0.97$, $t_{1/2} = 2.18$

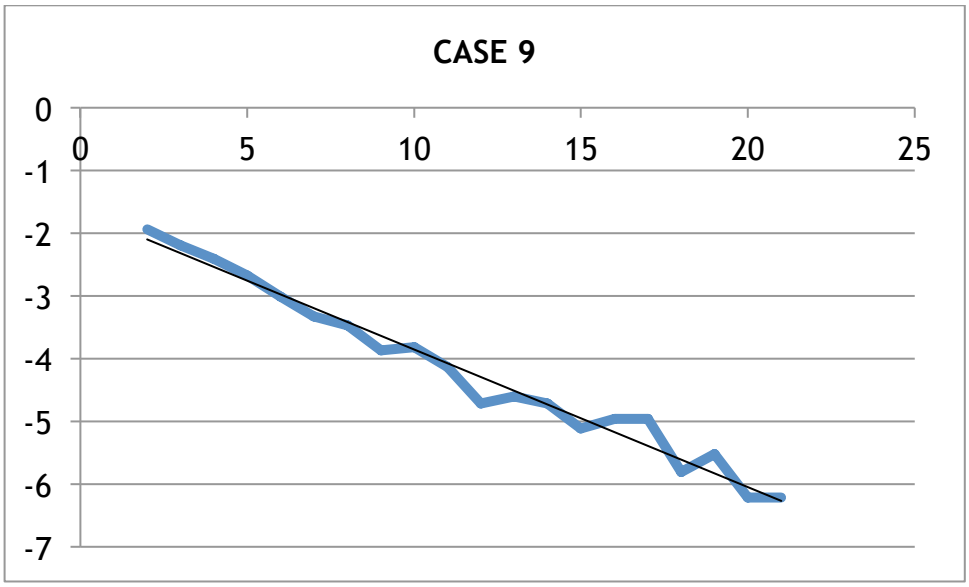

Figure 16. $r^2 = 0.98$, $t_{1/2} = 3.08$

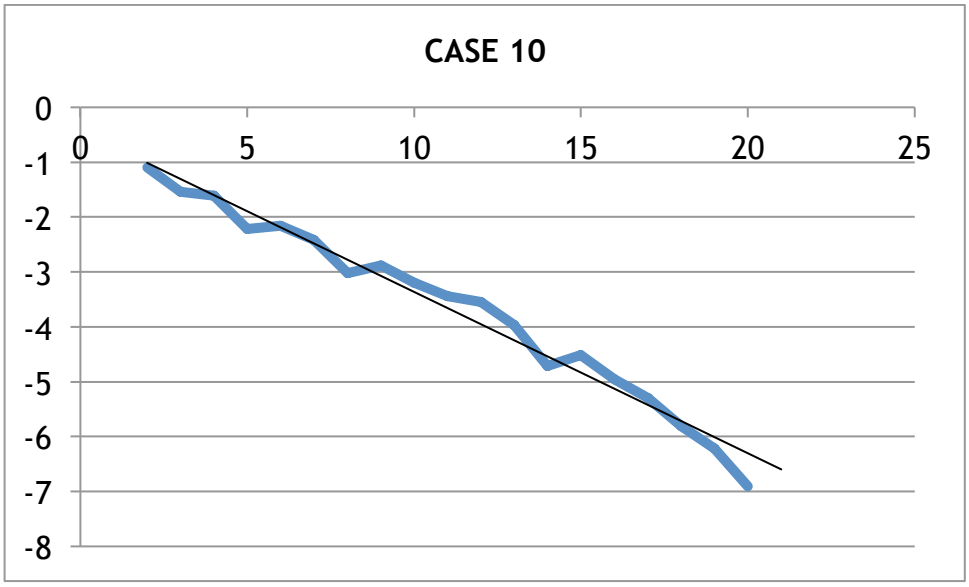

Figure 17. $r^2 = 0.98$, $t_{1/2} = 2.15$

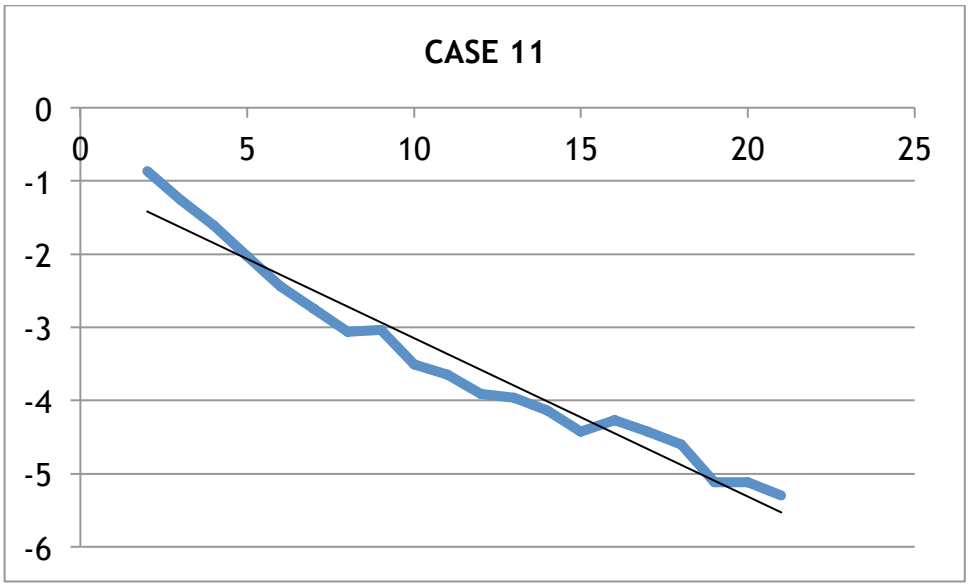

Figure 18. $r^2 = 0.96$, $t_{1/2} = 2.97$

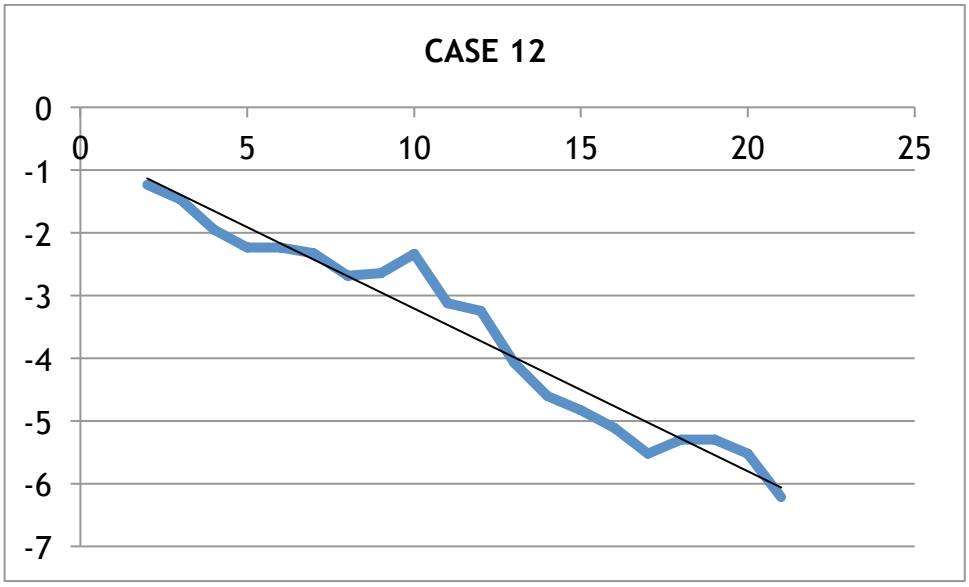

Figure 19. $r^2 = 0.95$, $t_{1/2} = 2.64$

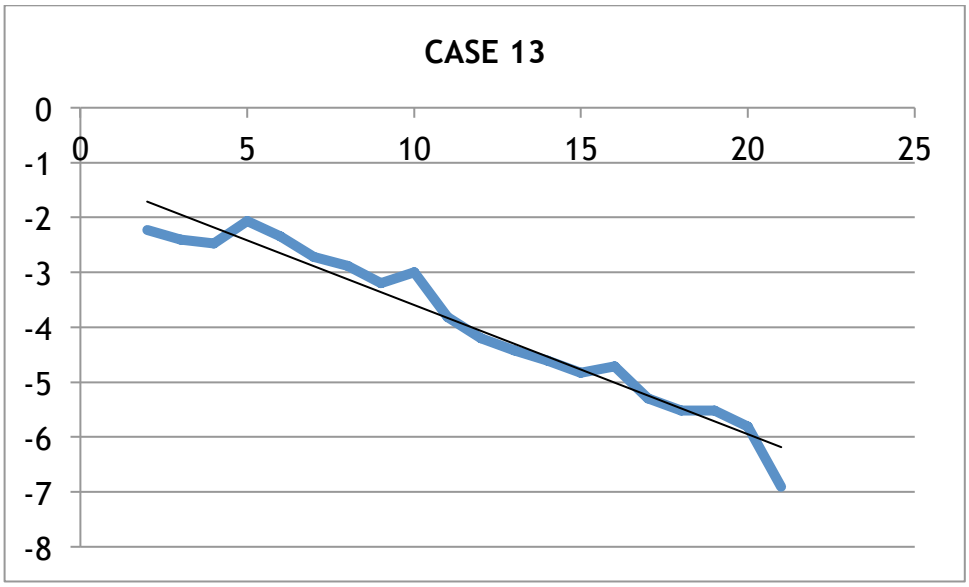

Figure 20. $r^2 = 0.95$, $t_{1/2} = 2.81$

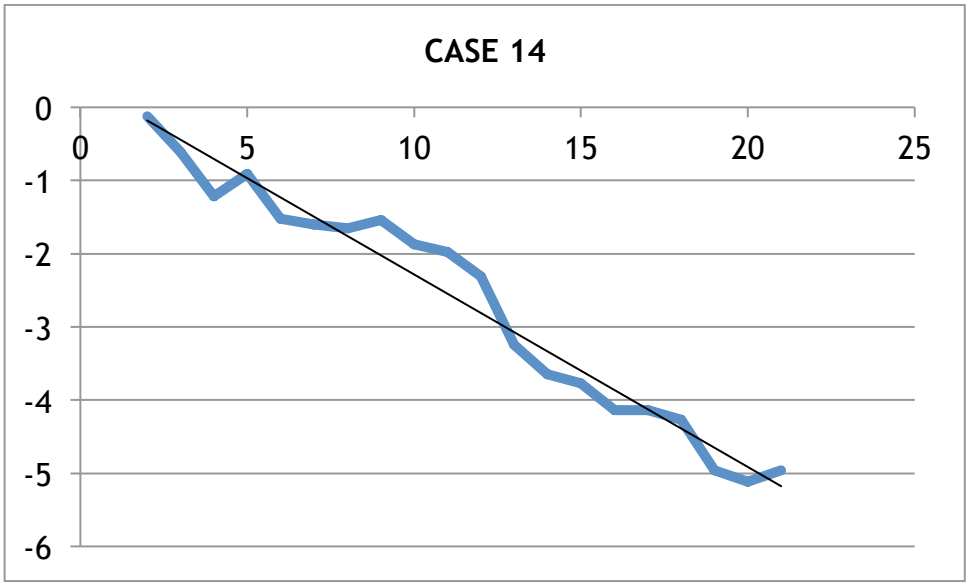

Figure 21. $r^2 = 0.96$, $t_{1/2} = 2.72$

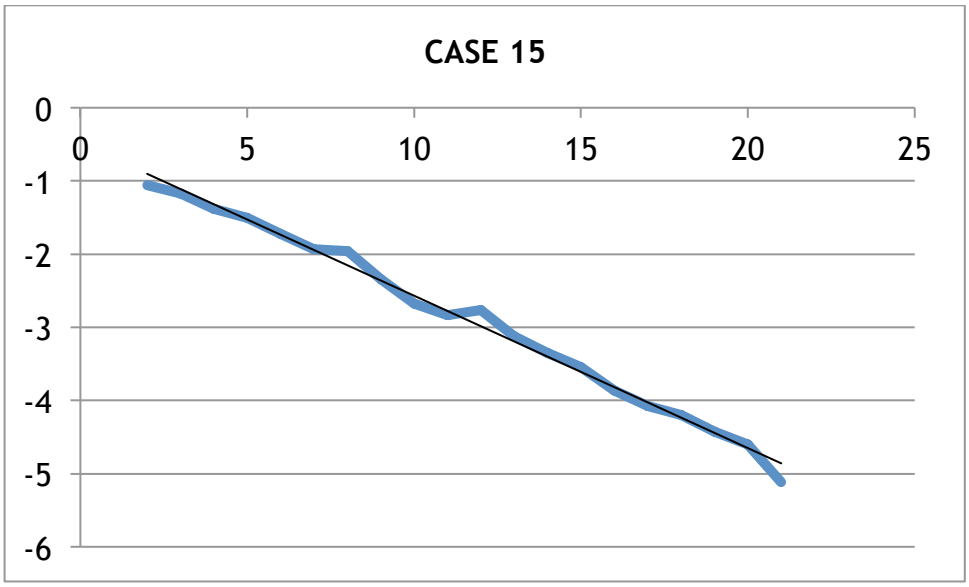

Figure 22. $r^2 = 0.99$, $t_{1/2} = 3.24$

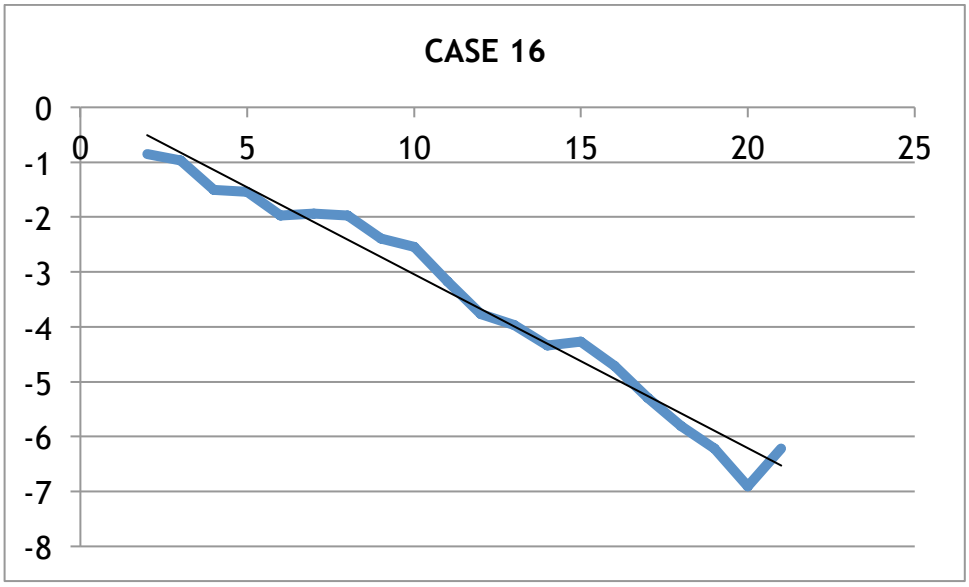

Figure 23. $r^2 = 0.97$, $t_{1/2} = 2.45$

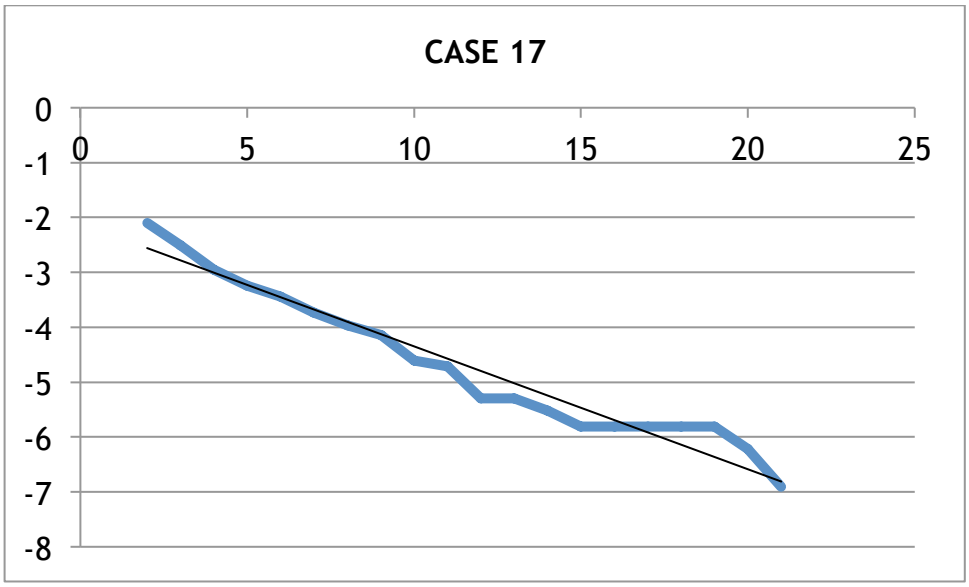

Figure 24. $r^2 = 0.96$, $t_{1/2} = 2.74$

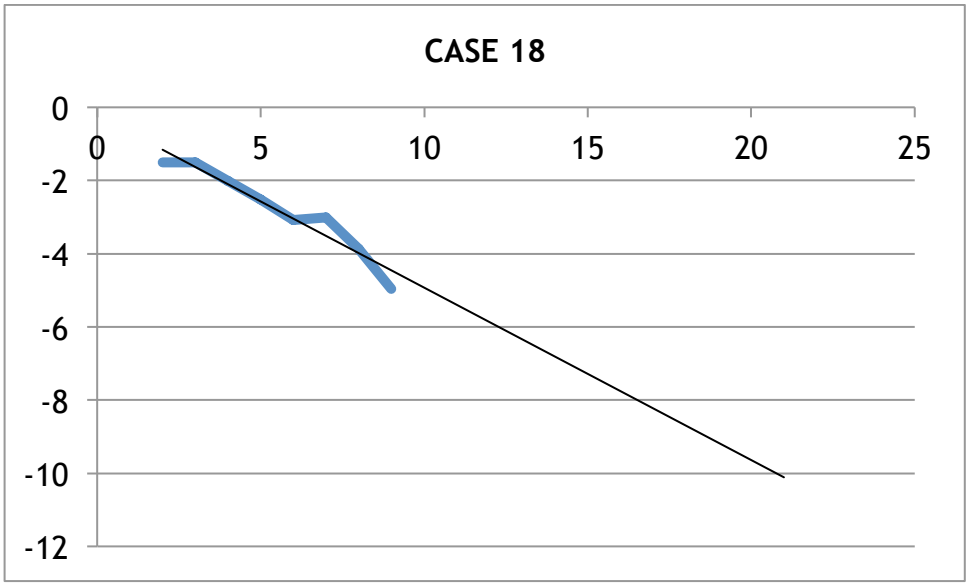

Figure 25. $r^2 = 0.93$, $t_{1/2} = 1.40$

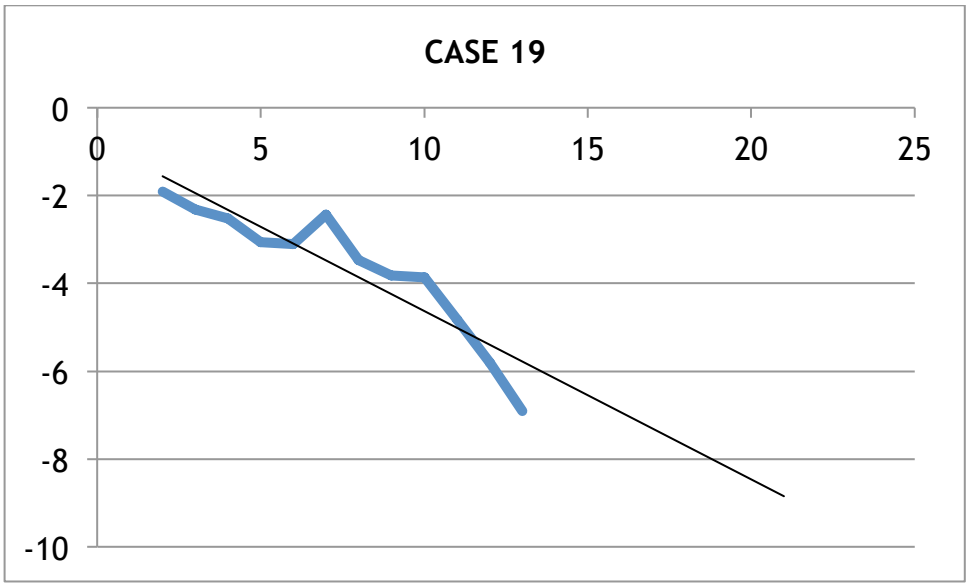

Figure 26. $r^2 = 0.84$, $t_{1/2} = 1.53$

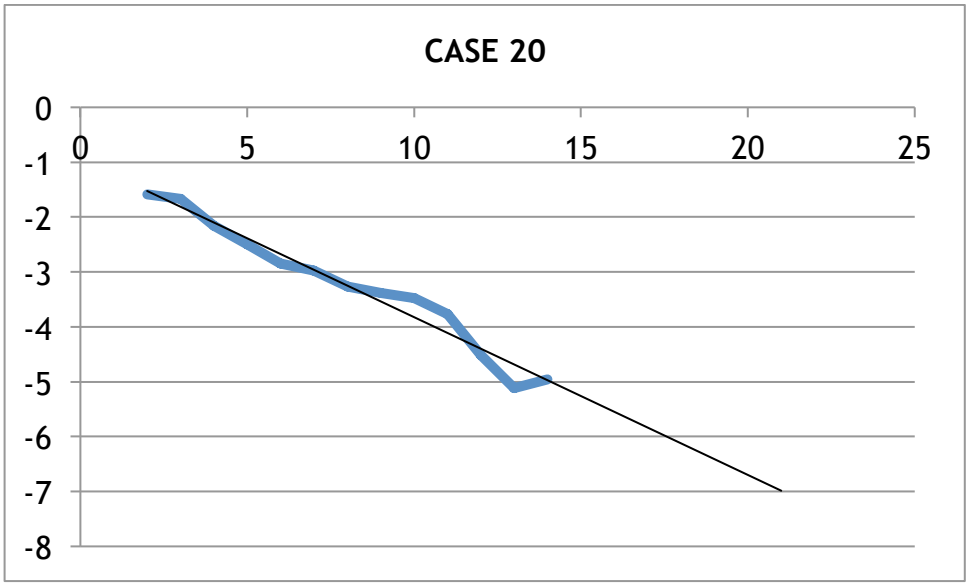

Figure 27. $r^2 = 0.97$, $t_{1/2} = 2.47$

Figures 8-27. These figures show the logarithmic regression line for each of the 20 cases in the study. The blue line in each graph represents the logarithmic regression line and the black line shows the trend line. r^2 is displayed for each graph and represents the Pearson correlation coefficient of the measured half-lives against exponential models. $t_{1/2}$ is displayed for each graph and shows the effective half-life of I^{131} in each case. The x-axis shows the days of isolation and the y-axis the decrease in radioactivity.

3.5.5 Background radiation exposure

The EPD recorded background daily radiation exposure readings in the range of 1-9 µGy from the first location (location one) and 1-8 µGy from the second location (location two). The daily background radiation readings from the two locations used for the background exposure were then combined and averaged to calculate the mean daily background radiation reading, which was 5 µGy. To remove the effect of background radiation on the cage-side data, this value (5 µGy), was then subtracted from all daily cage-side readings.

3.5.6 Cage-side radiation exposure readings

Once the subtraction of background radiation exposure from the cage-side radiation exposure readings was performed, the potential additional radiation exposures that owners may have been exposed to, had the study cats been released at an earlier period than 21 days were calculated. Three new isolation lengths in this study were assessed: seven days, 14 days and 17 days (Table 6). To give an example of the calculations:

- For an isolation period reduction to seven days, the daily radiation exposures from days eight to 21 were added together for each study cat. This calculated value was the total additional radiation exposure that the owners would hypothetically have been exposed to over that time period, assuming they were constantly in close contact with their cat.

From the data collected, the additional radiation dose exposure to owners following a reduction of the isolation period to seven days would have had a mean value of 310 µGy, with a range of 28-951 µGy. Had the isolation period been shortened to 14 days, the mean value of the additional radiation dose exposure to owners would have been 40 µGy, with a range of 0 to 115 µGy and following a 17 day isolation period the mean additional radiation dose exposure would have been 14 µGy, with a range of 0-43 µGy (Table 6). On the 21st (final) day of the isolation period, the mean radiation exposure recorded by the EPD was 3 µGy/day, with a range of 0 to 11 µGy.

Had a 17-day isolation period been used, all cats would have emitted < 100 µGy over the remainder of the 21-day isolation period but only 14/20 cats would have emitted < 20 µGy. Had the isolation period been reduced to 14 days, 18/20 (90%) cats would have emitted < 100 µGy and 5/20 cats would have emitted < 20 µGy over the remainder of the isolation period. However had a seven day isolation period been used, only 4/20 cats would have emitted < 100 µGy and none of the study cats would have emitted < 20 µGy over the following 14 days.

Therefore, using these results of γ radiation emission, 14/20 cats would be within the $1/50^{th}$ of the annual limit criteria i.e. < 20 µSv if using a 17-day isolation period but this would reduce to no cats if using a seven day isolation period. However, all cats would be within the $1/10^{th}$ of the annual limit criteria using a 17-day isolation period i.e. < 100 µSv, compared to only 4/20 (20 %) cats if using a seven day isolation period.

Due to insufficient statistical power in the pilot study it was not possible to assess if the dose of I^{131} had a significant effect on the additional dose exposures to owners using a seven, 14 or 17-day isolation period. An expansion of the study population from 12 cases to 20 cases did enable this to be assessed; however, no statistical significance was found (P-values > 0.05).

In regards to the dose of I^{131} administered, the EPD measured 53.2 µGy of γ radiation/day more from cats injected with 200 MBq compared to cats who had been injected with doses < 200 MBq. This difference was found to be statistically significant (P = 0.002). However, there were no significant differences found between the daily γ radiation emitted by cats treated with doses of 80, 120, 150 or 175 MBq.

3.5.7 Renal disease

Previous studies have shown that I^{131} is excreted through the kidneys of treated cats, as the urine from these cats has been found to emit radiation (Feeney *et al.*, 2003; Lamb *et al.*, 2013). It was therefore possible that renal disease in the study cats may have affected the rate of excretion of I^{131} in their urine. Due to

this the study group was evaluated to assess for the development of overt renal disease following I^{131} treatment. The study cats were followed up for varying time periods, ranging from zero to 24 months.

Of the 20 cats in the study only three were known to develop renal disease following treatment; however, only one of these cases had renal disease unmasked immediately following resolution of their hyperthyroidism. As only one case developed renal disease during the three week isolation period post-treatment, the statistical evaluation of the impact of renal disease on the excretion of I^{131} in urine was underpowered and therefore not performed.

Of the three cases that developed renal azotaemia in the follow up period, the first case had persistent increases in their serum creatinine concentration, with values consistently > 200 µmol/l (laboratory reference interval 91-180 µmol/l) following I^{131} treatment. These increases in serum creatinine concentrations were in the absence of known pre-renal or post-renal causes of azotaemia and the cat had a USG of 1.017, indicating a reduced concentrating ability. This cat had been administered 120 MBq of I^{131} and was calculated to have had radiation emissions of < 100 µGy at both the 14-day and 17-day isolation points (Case 12, Tables 5 and 6).

The second cat was diagnosed with renal disease five months following treatment with I^{131} when it was found to have persistent increases in its serum creatinine concentration > 180 µmol/l and a USG of 1.026 in the absence of pre- and post-renal causes. This cat had been injected with 80 MBq of I^{131} and also had total radiation emissions < 100 µGy at both the 14-day and 17-day isolation points (Case 7, Tables 5 and 6). This cat was also found to remain hypothyroid following treatment with a low serum T4 concentration and a high serum cTSH concentration and was subsequently started on levothyroxine supplementation. Despite the start of levothyroxine supplementation the cat remained azotaemic.

The third cat was diagnosed with renal disease 21 months following I^{131} treatment. The diagnosis of renal disease at its referring veterinary practice was based on an azotaemia (blood urea nitrogen concentration 33.2 mmol/l, serum

creatinine concentration 316 µmol/l) and hyperphosphataemia (3.09 mmol/l); however, a USG was not recorded. This cat had received 200 MBq of I^{131} and had total radiation exposures of < 100 µGy at both the 14-day and 17-day isolation points (Case 11, Tables 5 and 6). This cat was euthanized 10 weeks after the detection of its renal azotaemia due to deterioration in quality of life secondary to renal disease.

3.5.8 Continuation of hyperthyroidism following I^{131}

Three of the 20 cats in this study continued to be biochemically ± clinically hyperthyroid following I^{131} treatment. The first case was originally treated with 120 MBq of I^{131} and had a higher post-isolation serum T4 concentration (459 nmol/l) than pre-treatment (210 nmol/l) (Case 4, Table 5). This cat was subsequently treated again with I^{131} two months later using a higher dose of 250 MBq. This resulted in resolution of the hyperthyroidism; however, the cat became persistently biochemically hypothyroid and was started on levothyroxine supplementation.

The second case that had a serum T4 concentration still above the reference interval following treatment received 175 MBq of I^{131}. The serum T4 concentration had reduced from 278 nmol/l pre-treatment to 104 nmol/l post-treatment (Case 3, Table 5). On follow-up this cat's serum T4 concentration was found to have normalized four months post-treatment.

The final cat was treated with 200 MBq of I^{131} and had a serum T4 concentration pre-treatment of 257 nmol/l that reduced to 144 nmol/l post-treatment (Case 11, Table 5). This cat was followed up and similar to case three, the serum T4 concentration returned to within the reference interval by four months post-treatment.

Due to insufficient statistical power it was not possible to assess if the mean radiation emissions of the three cats that remained biochemically hyperthyroid were significantly different from the 17 cats that became biochemically

euthyroid/hypothyroid, had they been discharged following a seven-day, 14-day or 17-day period of isolation.

3.6 Discussion

There are currently several institutions within the UK that offer I^{131} as a treatment option for feline hyperthyroidism. However, following administration of I^{131} the isolation period of treated cats varies between them (Lamb *et al.*, 2013; Boland *et al.*, 2014). This variability in isolation periods is due to a combination of factors. These include local radiation rules and radiation legislation and the dose of I^{131} that is administered, as some centres use a variable dose of I^{131} dependent on the severity of hyperthyroidism, where as other centres use a fixed dose of I^{131} (Boland *et al.*, 2014).

This study has shown that EPDs can be used as a monitoring option for measuring the γ radiation emitted from hyperthyroid cats treated with I^{131}, proving the first hypothesis of this study to be correct. These dosimeters also offer an advantage over other monitoring options as they continuously monitor radiation emissions. This is compared to other modalities that only assess spot sample radiation emissions e.g. Geiger-Müller counters.

As these monitors can be clipped onto the cage door and be easily removed and therefore do not involve holding the monitoring equipment whilst readings are taken, they could also reduce the γ radiation levels that staff are exposed to and are less operator dependent. This is in comparison to other methods such as the Geiger-Müller counter, which require a staff member to hold the counter at a set distance from the treated cat to obtain readings (Feeney *et al.*, 2003).

3.6.1 Length of isolation following treatment with I^{131}

As discussed, there are dose limits put in place to limit the radiation exposure that members of the public are exposed to; however, regulating bodies can allow public dose commitments of 20 μSv and 100 μSv (ICRP, 2005; Environment Agency, 2012). For a public dose commitment of 100 μSv, restrictions must be

put in place including the dose commitment being restricted to a small group of the public, which for the use of I^{131} in cats would be the restriction of this to the owners of the cats.

This study found that none of the cats were within the $1/50^{th}$ of the annual limit criteria had a seven day isolation period been used, only 25 % (5/20) cats were within it had a 14-day isolation period been used but 70 % (14/20) cats were within it had a 17-day isolation period been used. In comparison, 20 % (4/20) cats were within the $1/10^{th}$ of the annual limit criteria with a seven day isolation period, 90 % (18/20) cats with a 14-day isolation period and 100 % (20/20) cats were within this limit using a 17-day isolation period. These results would suggest that the isolation period of hyperthyroid cats be reduced from the current 21-day period at the SAH, to at least 17 days following treatment with I^{131}. However, this would only apply to cats treated with doses ≤ 200 MBq of I^{131}. These findings also support the second hypothesis of this study, as they show that the EPD can be used to determine the release time of treated hyperthyroid cats.

In this study, 35 % (7/20) of the cats were no longer emitting detectable γ radiation by the time of exit from the isolation unit, with one cat no longer emitting radiation as early as day nine of isolation. After day 14 of isolation three cats were no longer emitting radiation and after day 17, five cats were no longer emitting radiation. The last two cats in this group were no longer emitting radiation on the last day of isolation i.e. day 21.

The radiation data recorded by the EPD, which was located ~ 50 cm away from the study cats, was dependent on the cats' precise location within the kennel at any point. The γ radiation that was recorded would have included both external and internal radiation hazards from the treated cats. This was due to the fact that the EPD will have recorded γ radiation emissions from the treated cats as well as from their urine, faeces and saliva. Therefore, the radiation exposure that owners of the treated cats would have been exposed to, as documented in this study, took both of these factors into consideration.

Despite these findings, it is very unlikely that owners are going to be 50 cm away from their cats at all times following the cats discharge from the hospital, especially as it is currently recommended by the SAH that there be limited contact between the owner and treated cat for a two week period following discharge. However, to assess this further, by averaging the daily γ radiation emissions from all the study cats during days 15 to 21 of isolation, the additional dose exposure to the owner would have been 1.84 µGy/hour. Due to this level of dose exposure, combined with the fact that only 20 % of the cats emitted potential additional dose commitments to the owners > 100 µSv following day 14 of isolation, a reduction of the SAH isolation period to 14 days is also feasible. It would still be advised that owners limit contact with their treated cat post-treatment with this new isolation length; however, this period of limited contact could be shortened to one week.

A reduction of the isolation period following injection of I^{131} at the SAH, to lower than 14 days is not recommended. This is due to the findings from a previous study, which was also based at the SAH that assessed the radioactivity of the faeces and urine excreted by cats treated with I^{131}. In that study it was found that the faeces and urine of the cats treated with doses of $I^{131} \leq 200$ MBq were only able to be designated for disposal as 'very low level waste' two weeks following administration of I^{131} (Lamb *et al.*, 2013). Due to the concerns highlighted by that study regarding the disposal of the urine and faeces from treated cats in the home environment for the immediate 14 days following treatment, isolation periods should not be reduced to a shorter time period than two weeks.

Reducing the current length of hospitalization for hyperthyroid cats following treatment with I^{131} could result in this treatment modality being more commonly utilized, as well as making it potentially more affordable for some owners. Previous work assessing factors that may influence owners decisions when choosing a treatment option for their hyperthyroid cat, has found that owners do have concerns regarding the length of hospitalization following treatment with I^{131} and this factor could actually deter some owners from pursuing this option (Boland *et al.*, 2014). Costs associated with I^{131} treatment have also been shown

to effect the frequency with which practitioners consider this as their preferred treatment option for hyperthyroid cats in the UK (Higgs *et al.*, 2014). A reduction of the isolation period and therefore the costs associated with this treatment may negate some of these concerns.

A previous study identified that the only factor that could be used to determine isolation duration following administration of I^{131} was the dose administered (Weichselbaum *et al.*, 2003). It was therefore suggested that the lowest dose of I^{131} should be used in each case. Although in the current study it was found that cats treated with the highest doses of I^{131} i.e. 200 MBq, emitted more γ radiation/day than other doses, all three cats treated with this dose emitted < 100 µGy over days 15-21 of isolation. This would suggest that the dose of I^{131} used does not appear to have such a marked effect on isolation times. This was shown even further in this study by the finding that the dose of I^{131} administered did not affect the total additional dose exposures at any of the three proposed time frames of a seven-day, 14-day or a 17-day isolation period. However, the difference in findings between this study and the Weichselbaum *et al.*, (2003) study may have been due to the difference in sample size included in each study at 20 cases and 149 cases, respectively.

In the current expanded study it was found that cats injected with 200 MBq emitted 10 times the amount of γ radiation/day than was detected in the pilot study (Roberts *et al.*, 2015). A definitive cause for this difference was not apparent; however, a possible contributing cause may have been the exclusion of one of the cases used in the pilot study. The excluded case had incomplete data recorded at the beginning of the isolation period, which is the time when the highest radiation exposures are recorded as the I^{131} has only recently been administered. In order to explore this difference in daily γ radiation emissions further, the γ radiation emissions of more cats treated with 200 MBq would need to be assessed in a future study.

3.6.2 Effect of renal disease on I^{131} excretion

One of the main routes of I^{131} excretion in cats has previously been shown to be via the urine (Lamb *et al.,* 2013). It has also been shown that following treatment with I^{131}, the GFR of the kidneys decreases, with the maximum drop in GFR being detected at four weeks post-treatment (Boag *et al.,* 2007; van Hoek *et al.,* 2009). Due to this there is a possibility that the unmasking of, or development of, renal disease in these cats during the isolation period may affect the excretion rate of the γ radiation. In this study there was only one cat that developed overt renal azotaemia during the isolation period so it was not possible to draw conclusions on the impact of this on the study results. This cat had γ radiation emissions of < 100 µGy at both the 14-day and 17-day isolation points, which would suggest that the excretion of radiation had not been significantly affected by the development of azotaemia. However, to draw more definitive conclusions, larger numbers of cats with immediate unmasking of renal disease following treatment would need to be included in a future study.

3.7 Limitations

3.7.1 Lack of comparison

In this study only the data collected from the EPD was evaluated and a direct comparison of this data with another radiation recording modality e.g. a Geiger-Müller counter was not performed. However, as the data recorded by the EPD resulted in the calculation of similar effective half-lives of I^{131} when compared to Puille *et al.,* (2002), it was concluded that the EPD could reliably assess the γ radiation emitted by the cats in the study. Although it would have been ideal to perform a direct comparison of the data collected by the EPD to data collected using an alternative technique, it was not possible to do this. The original unpublished data collected at the SAH in the 1990's, which forms the basis of the current local radiation rules at the SAH, can no longer be accessed. The studies performed for the Scottish Environment Protection Agency in the 1990's were performed to address their concerns regarding environmental

contamination from urine and faeces from treated cats; however, no assessment was made of the radiation hazards posed to the owners of treated cats.

The current local radiation rules at the SAH reduce the exposure of staff to radiation by reducing the need for monitoring of radiation emissions. Therefore, for the purposes of this study, the exposure rate of staff to radiation could not be increased by starting to monitor the cats in a more intensive manner i.e. by use of a Geiger-Müller counter. This combination of factors resulted in it not being possible to obtain radiation data using other radiation monitoring methodology to compare the data collected from the EPD to.

3.7.2 Case numbers

Although this was an expansion of a previously published study, a main limitation of this study was still the sample size (Roberts *et al.*, 2015). Unfortunately, the small sample size included in this study, despite the study being carried out over several years, was in part due to the hyperthyroid case load at the hospital, combined with the fact that only one cat could be included every three weeks due to the need for them to be in a specific monitoring kennel. A further expansion of the study group may have allowed additional statistical analyses to be performed e.g. evaluation of the development of renal disease on the excretion of radiation.

3.7.3 Assessment of renal insufficiency

Whilst considering the topic of renal azotaemia, it is possible that cats with early IRIS stage renal disease i.e. stages I or II may have been overlooked in this study. This was because urine samples were not routinely collected post-treatment to assess the USG nor did assessment of GFR occur before or after treatment. Therefore, this is also a limitation of this study.

Of the 20 cats included in the study, seven cases had post-treatment serum creatinine concentrations > 140 μmol/l, which is the current lower reference

limit for IRIS stage II chronic renal disease (IRIS, 2013). Unfortunately, only two of these cases had post-treatment urine samples collected following isolation, with one of these cases being the case diagnosed with renal azotaemia. The other case had a USG of 1.046, suggesting sufficient renal concentrating ability.

Ideally, in future studies, the GFR ± serum symmetric dimethylarginine would be assessed before and after I^{131} treatment to correctly identify cases that may have renal disease unmasked, rather than solely relying on the development of overt azotaemia as this may miss cases of early renal disease i.e. IRIS stage I and II cases (Hall *et al.*, 2014).

3.7.4 Battery life of the EPD

The other main limitation of this study, which was only relevant at the start, was the battery life of the dosimeter. A battery failure during the recording period resulted in four cases having data incompletely recorded and these cases were therefore excluded from the study group. However, following these case exclusions, it was found that complete data sets would be obtained as long as the battery in the EPD was replaced after every third cat in the monitoring kennel and that the battery was also removed when the dosimeter was not in use.

3.7.5 Location of the monitor kennel dosimeter

One further possible limitation in this study was the placement height of the dosimeter on the kennel door, when compared to the height of the cat's thyroid gland, as well as the distance of the cat from the dosimeter. The dosimeter was placed in the same place on the cage door for all cases in this study, as this position was the most secure and easiest place for its attachment. This position was 42 cm above the floor of the kennel, which would have been above the height of the cats' thyroid. However, due to the directionality of the monitor, which is linear over a 150° cone area, combined with the fact that there were no objects in the kennel that would allow the cats to climb onto higher surfaces, it

is unlikely that this would have had a substantial effect on the results obtained (Roberts *et al.*, 2015).

As the position of the dosimeter was fixed but the monitored cats position would vary each day, there is a potential that this may have affected the data collected in this study. This is due to the fact that radiation exposure obeys the inverse square law i.e. a doubling of the distance results in a reduction in the radiation exposure by a factor of four. However, as the monitored cats would move around the kennel daily and be noted to be in variable positions within the kennel, the variation in the distance from the dosimeter would likely even out each day and therefore minimize the effect on the data collected (Roberts *et al.*, 2015).

3.8 Conclusion

The results of this study have shown that the EPD, model MGP DM2000X, can be used to monitor the γ radiation emitted from hyperthyroid cats treated with I^{131}. The data obtained in this study is suggestive that the current isolation period of 21 days following administration of I^{131} could be safely reduced to a maximum period of 17 days at the SAH. The data also suggests that the isolation period could be further shortened to 14 days, which would be within both current UK and ICRP guidelines. However, should a 14-day isolation period be used, it is important that the time owners spend in close contact with their cats post-treatment be limited for the following week. A shortening of the isolation period for cats treated with I^{131} could result in this treatment option being chosen more frequently by owners of hyperthyroid cats.

It is advised that additional assessment of this method of radiation monitoring be performed at other centres that currently offer I^{131} as a treatment option for feline hyperthyroidism, as well as at centres that use doses > 200 MBq, to assess if this method would assist radiation monitoring in their cases as well.

CHAPTER 4

4 CONCLUSIONS

4.1 I^{131} as a treatment modality

Feline hyperthyroidism has become the most common endocrine disease in cats and, therefore, it is a relatively frequent condition seen by veterinarians in general practice (Peterson, 2012). Multiple treatment options exist for this condition, including anti-thyroidal medication, surgery, an iodine-restricted diet and I^{131}. According to a survey of general practitioners, the preferred treatment options currently within the UK are those of anti-thyroidal medication and surgery (Higgs *et al.,* 2014). This preference is most likely influenced by the costs associated with I^{131} treatment and also the lack of inclusion of an iodine-restricted diet as an option in the survey, due to the diet only just being launched prior to the time of the survey in 2012 (Higgs *et al.,* 2014).

Although I^{131} is not currently the preferred treatment option of general practitioners in the UK, it is viewed as the gold standard treatment option for this condition (Mooney, 1994; Higgs *et al.,* 2014). Unfortunately, the availability of this treatment option is limited within the UK to University environments and some private referral practices and this may contribute to the reasons why it is not opted for as a first-line treatment, as has been shown in Australia (Kopecny *et al.,* 2016).

There is a notable difference between Australia and the UK in regards to the preference of practitioners opting to use I^{131} for treatment of hyperthyroidism in cats. In Australia, I^{131} is the preferred treatment choice of 38 % of general practitioners, compared to only 5.5 % in the UK and this difference has been partly shown to be due to the increased availability of I^{131} in Australia (Higgs *et al.,* 2014; Kopecny *et al.,* 2016). In the Kopecny *et al.,* (2016) study it was identified that a greater number of facilities offering I^{131} treatment were available in Australia compared to the UK. It was also found that the availability of centres providing I^{131} and therefore the time needed to travel to the centre had an effect on how often I^{131} was offered; if the centre was less than two hours away 87 % of general practitioners were likely to offer it, compared to only 64 % if the centre was more than two hours away. This concern regarding distance to a treatment centre was highlighted even further in the same study,

by the finding that 48 % of participants marked this factor as a great concern caused to owners of hyperthyroid cats (Kopecny *et al.,* 2016). The findings of the Kopecny *et al.,* (2016) study would suggest that the availability of I^{131} treatment does have an effect on the frequency that it is utilized. Should more centres capable of providing I^{131} treatment be available, then more cats could be treated with this modality in the UK.

Treatment with I^{131} in the short-term is a more expensive option when compared to the costs associated with anti-thyroidal medication. However, for cost-effectiveness in the long-term, I^{131} treatment is superior to anti-thyroidal medication where the costs of medication combined with associated blood monitoring are spread out over many months to years (Trepanier, 2007; Daminet *et al.,* 2014). Costs of I^{131} treatment have been shown to have an effect when choosing a treatment option for hyperthyroidism, both by general practitioners and owners and it is one of the main reasons why anti-thyroidal treatment is preferred in the UK (Boland *et al.,* 2014; Higgs *et al.,* 2014).

In both the Higgs *et al.,* (2014) and Kopecny *et al.,* (2016) studies, the preference of utilizing I^{131} as a treatment option by general practitioners was shown to be influenced by costs. In both studies when costs were eliminated as a consideration factor, the utilization of I^{131} as the preferred treatment option was found to increase by 40 % (Higgs *et al.,* 2014; Kopecny *et al.,* 2016). Costs associated with I^{131} are also thought to be a great concern for 82 % of owners when deciding on treatment options, as viewed by general practitioners (Kopecny *et al.,* 2016). Despite the findings in Kopecny *et al.,* (2016), an owners decision was not found to be impacted by costs in 51.3 % of cases when the views of owners were directly assessed, but this may have been influenced by whether or not their cat was insured (Boland *et al.,* 2014).

The study by Boland *et al.,* (2014) specifically set out to identify factors that may affect owners' treatment choices when deciding on what option to choose for their cats' hyperthyroidism. They also assessed the owners' experiences of I^{131} treatment, which were found to be very good, with > 90 % of owners being happy in their decision to pursue I^{131} treatment in their cat. The study also

showed that owners perceived a marked improvement in the quality of life of their cat following treatment with I^{131} (Boland *et al.*, 2014). The study highlighted that one of the main factors as to why I^{131} is not chosen by some owners, is due to the fact that many owners are not made aware of this as a treatment option. The finding that owners are not made aware of all the possible treatment options for their hyperthyroid cat has also been corroborated by the findings of other studies (Caney, 2013; Kopecny *et al.*, 2016). In Caney (2013), owners of cats receiving anti-thyroidal medication were surveyed and ~ 30 % of owners had only been made aware of anti-thyroidal medication as a treatment option for their cat. In Kopecny *et al.*, (2016), only 39 % of practitioners were found to routinely offer I^{131} to owners of hyperthyroid cats. These study findings would suggest that I^{131} could become a more popular treatment option in the UK, if owners are made more aware of it. They also highlight the point that veterinary surgeons should be making owners aware of all possible treatment options available for the treatment of hyperthyroidism in their cat.

Boland *et al.*, (2014) also found that owners do have concerns about the length of hospitalization associated with I^{131} treatment. Those concerns (in decreasing frequency) included their cat being unhappy, the owner missing the cat, the cat developing inappetance, other pets missing the cat, the development of co-morbid disease, and side effects caused by the treatment (Boland *et al.*, 2014). In Australia, where hospitalization times are generally shorter than the UK at five to seven days, I^{131} is also a more popular option (Kopecny *et al.*, 2016). As there is no requirement for hospitalization for sustained periods of time with the use of anti-thyroidal medication, an iodine-restricted diet or surgery (unless hypocalcaemia occurs post-thyroidectomy), this factor will contribute to reasons why these treatment options are preferentially pursued over I^{131} in the UK (Boland *et al.*, 2014). This combination of findings would suggest that more owners in the UK would opt for I^{131} treatment in their cat, if hospitalization periods associated with the treatment were reduced.

These previous studies highlight several concerns associated with the use of I^{131} as a treatment option in cats with hyperthyroidism, including the concerns

associated with cost and length of hospitalization (Boland *et al.,* 2014; Higgs *et al.,* 2014; Kopecny *et al.,* 2016). The length of hospitalization following I^{131} treatment in the UK is quite variable, from as little as five days up to six weeks (Lamb *et al.,* 2013; The Hyperthyroid Cat Centre, 2015). This is due to local radiation rules and legislation, as well as the dose of I^{131} that is administered. The longest periods of hospitalization following treatment i.e. six weeks, are used when high doses of I^{131} (1100 MBq) are administered in cases of thyroid carcinoma (Hibbert *et al.,* 2009; Lamb *et al.,* 2013). The costs associated with I^{131} treatment, which in part are due to the costs associated with hospitalization times, can have a marked effect on the decision as to whether I^{131} is pursued (Higgs *et al.,* 2014; Kopecny *et al.,* 2016). Therefore, if a shorter isolation period could be used following administration of I^{131}, this could result in a reduction of associated costs. If this was achieved it could make I^{131} a more popular treatment option, as this would negate two of the concerns voiced by general practitioners and owners.

For some diseases in veterinary medicine, direct comparisons can be drawn from similar diseases in human medicine and this can aid the understanding and treatment of such conditions. Feline hyperthyroidism has been shown to be one of these conditions, as it has been compared to the condition toxic nodular goiter in humans (Peterson, 2014). Anti-thyroidal medication is the most popular treatment choice in cats with hyperthyroidism (Higgs *et al.,* 2014). In contrast, in humans with toxic nodular goiter, it is actually advised not to use this treatment option long-term and instead they advise surgery or the use of I^{131} (De Leo et al., 2016). Therefore, if these two conditions are seen as being similar, then this would suggest that I^{131} as a treatment option in cats should be pursued more often.

Hyperthyroidism in cats has been shown to be a progressive disease, with increases in disease severity, tumour size, prevalence of multifocal disease and thyroid carcinomas seen with increasing disease duration (Peterson *et al.,* 2016a). The use of I^{131} in the treatment for feline hyperthyroidism has been shown to be associated with longer survival times post-treatment, when compared to the use of methimazole alone (Milner *et al.,* 2006). These findings

would suggest that definitive treatment of this condition with I^{131} should be pursued at the earliest time point in cats with hyperthyroidism, to prevent progression of the disease and also result in longer survival times when compared to anti-thyroidal medication. This may be an easier task to achieve if hospitalization periods are shorter and therefore associated costs are lower as well.

4.2 Ionising radiation

The main reason why isolation periods exist following treatment with I^{131} is due to the concerns regarding the γ radiation emitted by the treated cats and the risks that this radiation poses to humans. However, this study has shown that the level of γ radiation that owners would be exposed to, should the treated cats be released from the isolation unit one week earlier i.e. following 14 days of isolation, is within an acceptable limit, as long as certain precautions are taken.

Humans are exposed to ionising radiation on a daily basis from many natural and man-made sources. These sources include exposure from cosmic radiation, terrestrial radiation from sources in the earths crusts e.g. uranium, exposure through inhalation e.g. inhalation of radon from soil/bedrock, exposure through ingestion of radiation sources, x-rays and working or living with people that are being medically treated with radiation. These ionising radiation sources also come in different forms including alpha (α) radiation, β radiation, γ radiation, x-rays and neutron radiation and the penetration of these types of radiation also differ (Canadian Nuclear Safety Commission, 2015).

Ionising radiation can cause radiation damage to human tissues, depending on the amount of radiation that they are exposed to, the time period over which it occurs and the individual tissue/organ sensitivity to radiation. There is also a concern that exposure to ionising radiation, depending on the dose and dose rate, can result in cancer in the long-term, as voiced by the World Health Organization (World Health Organization, 2016).

Due to this, there are legal limits in place for members of the public in regards to the level of ionising radiation that they can be exposed to. These limits include a yearly exposure of one mSv and a one-off exposure of 300 μSv (Ionising radiations regulations, 1999; Environment Agency, 2012). Therefore, there is a requirement and duty of care to ensure that humans are not put at undue risk by exposing them to levels of ionising radiation that are higher than legal levels.

Exposure of owners to ionising radiation above these levels should therefore be avoided. By shortening the current isolation time post-treatment for hyperthyroid cats treated with I^{131}, it was important to ensure that this would not result in owners being unnecessarily exposed to unacceptable levels of ionising radiation. The EPD used in this study documented that the level of potential ionising radiation that owners would be exposed to, should the isolation period be shortened to 14 days, was within an acceptable level. This was as long as certain precautions were put in place for the following week after the cat was discharged from hospital, which are already part of the standard practice at the SAH. These precautions include:

- Owners being asked to limit their contact with the treated cat to short periods of time, i.e. < 10 minutes/day.
- Owners avoiding face-to-face contact with their cat.
- Owners not allowing the cat to sleep on their bed.
- Owners washing their hands after handling the cat and using non-absorbable, disposable gloves to dispose of the cats' urine and faeces.
- Keeping the cat indoors for the week following discharge from the hospital. This precaution prevents other members of the public from being exposed to ionising radiation from the treated cat.
- Keeping the cat away from food preparation areas.
- Using litter tray liners for the first week and placing these and the used litter they contain into a black plastic bin bag which is then placed into a shed/garage. In the second week following the cats' discharge from hospital, the black bin bag can be sealed and disposed of in the normal dustbins.

Studies have been performed in the human field that have documented and measured the external radiation exposure that family members, members of the public, caregivers and even pets are exposed to following I^{131} treatment in humans (Grigsby *et al.*, 2000; Pant *et al.*, 2006; Marriott *et al.*, 2007; Ostinelli *et al.*, 2015). In particular, the study by Grigsby *et al.*, (2000) assessed the radiation exposure to household members and household pets during the 10-day period following administration of I^{131} to a family member. The average radiation dose to household members was 240 μSv and to household pets was 370 μSv and these doses were deemed to be safe according to the local radiation legislation. Those mean values were much higher than the radiation exposure owners would be exposed to should a 14-day isolation period be used at the SAH, as documented by the data recorded by the EPD.

In humans, to ensure that the dose of radiation that family members are exposed to remains less than one mSv following treatment with I^{131}, it is advised that a time period of 15 days be put in place during which in contact time with family members should be restricted (IAEA, 2009). This includes the requirement that the treated patient sleep apart from their partner, which is defined as equal or greater than one metre apart, for up to eight hours. These recommendations are specific for when doses of 200 MBq are used. This is also the maximum dose that is usually administered to cats at the SAH, unless a cat is being specifically treated for a thyroid carcinoma (Hibbert *et al.*, 2009). Therefore, the proposed reduction of the post-isolation period to 14 days in cats treated with ≤ 200 MBq of I^{131} at the SAH, combined with the advised precautions that are put in place for the week following discharge, would result in owners being exposed to levels of radiation that are within the radiation safety limits currently advised by the IAEA and ICRP.

The isolation period of treated cats would ideally be reduced to the shortest time possible. Although data from this study has shown that the current isolation period of 21 days can be reduced to 14 days, it would not be feasible to reduce this isolation period any further. This is due to the levels of γ radiation present in the excreted faeces and urine of these cats during the first two weeks of the isolation period, following injection of I^{131} (Lamb *et al.*, 2013).

The results of this study have allowed the current isolation period at the SAH to be reduced, whilst ensuring that this reduction will not lead to owners being exposed to levels of ionising radiation above that allowed by radiation legislation.

4.3 Weight changes in hyperthyroidism

There are similarities drawn between hyperthyroidism in cats and hyperthyroidism in humans (Peterson, 2014). The overall prevalence of hyperthyroidism in humans is 0.8 to 1.3 %, dependent on geographical location, compared to an even higher prevalence in cats of 3 % and in both species this prevalence has been found to increase with age (Garmendia Madariaga *et al.,* 2014; O'Neill *et al.,* 2014; De Leo *et al.,* 2016). One of the main concerns voiced by human patients undergoing treatment for hyperthyroidism is the weight gain that may ensue (Dale *et al.,* 2001).

This weight gain can be excessive, with a prevalence of obesity as high as 32 % documented in some cases (Brunova *et al.,* 2003). It has been found that the amount of weight that is gained by patients following treatment for hyperthyroidism can be affected by a multitude of different factors, including the treatment modality used, gender, ethnicity and age of the patient, as well as the amount of weight loss experienced by the patient prior to treatment (Dale *et al.,* 2001; Ariza *et al.,* 2010; Lang *et al.,* 2016).

Although weight gain is commonly seen in hyperthyroid cats following treatment, there are only a limited number of studies that document the actual values seen in their study findings (Boag *et al.,* 2007; Jaillardon *et al.,* 2012). In contrast, there are several studies in the human field that have broached this subject more extensively (Ariza *et al.,* 2010; van Veenendaal & Rivkees, 2011; Lang *et al.,* 2016). Therefore, one of the aims of this study was to add to the current literature on this topic in cats, by specifically assessing the weight changes in a feline hyperthyroid population when treated with I^{131}.

The results of the study concurred with previous studies findings that weight gain does occur following treatment and subsequent reversal of hyperthyroidism (Finch *et al.,* 2012; Jaillardon *et al.,* 2012). Although the weight changes of cats over the three-week period following I^{131} treatment had already been documented by Finch *et al.,* (2012), their study had only included a very small number of cases (n = 10), compared to the larger study size of 114 cases in this study.

This study also specifically assessed whether factors such as age or gender of the cat had an effect on the weight changes seen in this population of treated cats. These factors had not been previously assessed in studies on feline hyperthyroidism, despite these factors being examined in the human field (Ariza *et al.,* 2010; Lang *et al.,* 2016).

The cats included in this study were all treated with I^{131} and weight changes using other treatment modalities were not assessed. Due to this it cannot be ascertained whether the weight changes of cats treated with other modalities (e.g. anti-thyroidal medication) may be similar to those seen in this study, especially given the findings from studies assessing iodine-restricted diets that have shown minimal weight gain to occur (Hui *et al.,* 2015; Scott-Moncrieff *et al.,* 2015). The preferred treatment of choice for hyperthyroidism by general practitioners in the UK is currently anti-thyroidal medication (Jaillardon *et al.,* 2012; Higgs *et al.,* 2014). Therefore, future studies should be performed to assess the weight changes seen in cats treated this way in more detail.

This study also only assessed the weight changes over a short-time frame following treatment for hyperthyroidism in cats; however, the main amount of weight gain in humans has been shown to occur over a longer time period (Brunova *et al.,* 2003). Although Boag *et al.,* (2007) and van Hoek *et al.,* (2009) have assessed the weight changes in cats treated with I^{131} up until the six month period post-treatment, there have yet to be any studies assessing the weight changes of cats treated with I^{131} past this point. Should the assessment of longer-term weight changes be investigated in cats, the impact of comorbid disease on this would also need to be evaluated due to the previous findings that

many hyperthyroid cats develop renal disease or neoplasia on follow-up (Slater *et al.,* 1994).

4.4 Is assessment of serum T4 concentration all that is needed to assess the control of hyperthyroidism?

Although assessment of serum T4 concentration is the gold standard for assessing control of hyperthyroidism in cats, one of the study aims was to assess whether percentage weight gain could be used as a predictor of the achievement of reversal of overt hyperthyroidism (Daminet *et al.,* 2014). The results of this study have shown that percentage weight gain can be used as an indicator of the serum T4 concentration reducing to either within or below the reference interval, therefore showing that it could be used as an additional factor when assessing the efficacy of treatment for hyperthyroidism using I^{131}. The advantages of using percentage weight gain include the ease with which this information can be collected and the lack of cost associated with it. However, as the study identified that percentage weight gain could not differentiate between the achievement of biochemical euthyroidism and biochemical hypothyroidism, the measurement of serum T4 concentration should still be performed.

4.4.1 Subclinical/physiological hyperthyroidism

A recent study has also supported the need to assess weight gain when assessing a cats' response to treatment for hyperthyroidism, as well as the serum T4 concentration (Hui *et al.,* 2015). The study by Hui *et al.,* (2015) showed contrasting findings when assessing control of hyperthyroidism in a hyperthyroid population treated with an iodine-restricted diet. Although the serum T4 concentration reduced to within the reference interval in 83 % of cats treated with the specific diet, their body weight did not significantly increase (nor did their heart rate significantly decrease), which was unexpected. Two reasons were proposed for this lack of weight gain, the first of which was the presence of undetected concurrent illnesses. The second proposed reason was that some of these cats were actually still physiologically hyperthyroid despite having a

normal serum T4 concentration. This reason would also support the lack of evidence of the cats' heart rates decreasing despite effective treatment.

This syndrome of subclinical/physiological hyperthyroidism has been described in humans and is classified by a low or undetectable serum TSH concentration in the face of normal serum fT4 and fT3 concentrations (Biondi & Cooper, 2008). This syndrome has also been associated with an increased heart rate and weight loss, as well as having a potential association with increased cardiovascular and skeletal risks in humans (Biondi *et al.,* 1999; Santos Palacios *et al.,* 2012; Biondi *et al.,* 2015).

Unfortunately, the use of serum cTSH concentration in cats with thyroid disease is limited in that the current assay of serum cTSH concentration cannot distinguish low-normal values from low or suppressed values (Peterson *et al.,* 2015). Due to this, the use of serum TSH concentration cannot be relied on for detecting subclinical hyperthyroidism in cats to the same degree that it is in humans (Biondi *et al.,* 2015).

There could be potential concerns of subclinical hyperthyroidism occurring in cats despite apparently effective treatment being reported given the findings in humans (Biondi *et al.,* 1999; Hui *et al.,* 2015). However, due to the inability of serum cTSH concentration to definitively differentiate low-normal from suppressed values, a definitive diagnosis of subclinical hyperthyroidism is difficult to obtain in cats and it highlights the need to consider more than just blood tests when assessing control of hyperthyroidism in this species (Peterson *et al.,* 2015). Indeed in the current study, 10/101 (9.9 %) cases that became biochemically euthyroid/hypothyroid did not gain weight during the three-week isolation period, raising suspicion as to whether these cases could have still been physiologically hyperthyroid as proposed by Hui *et al.,* (2015).

This concern regarding physiological hyperthyroidism opens up the possibilities for further research in this field. Potential future studies could involve assessing weight changes both in the short and long-term in hyperthyroid cats being treated with the different treatment modalities-surgery, anti-thyroidal

medication, I^{131} and an iodine-restricted diet, as well as assessing the control of hyperthyroidism in more detail. This would include not only measurement of their serum T4 concentration but also of their serum fT4, fT3 and cTSH concentrations (taking into account the caveats associated with measurement of serum cTSH concentration), and physical examination findings such as heart rate (Hui *et al.*, 2015; Peterson *et al.*, 2015).

4.5 Concluding thoughts

The findings of the two studies in this thesis add to the current literature on I^{131} treatment in hyperthyroid cats. They have illustrated the weight changes that occur in the three-week isolation period following the administration of I^{131} on a larger scale than previously documented. They have also shown that these changes can be used as an additional factor when assessing the efficacy of treatment of the cats' hyperthyroid state; however, they do not replace the requirement for assessment of serum T4 concentration.

The studies have also shown that the level of γ radiation emitted by these treated cats can be detected using EPDs. This method of detecting γ radiation allows for a more continuous recording of data from these treated cats, which has now enabled the current isolation period at the SAH to be reduced. The reduction in hospitalization time could result in I^{131} treatment being more commonly used.

The findings of the γ radiation study in this thesis will also directly benefit future studies on the weight changes in hyperthyroid cats treated with I^{131}. The isolation period for cats injected with I^{131} is now to be reduced to two weeks at the SAH. This will permit the weight changes that occur in this population over the first two weeks following treatment to be assessed and compared to the weight changes seen at the three week point post-treatment documented in this study. This will add further data to the current literature on weight changes in hyperthyroid cats, improving our knowledge and understanding of this disease in cats.

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