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Swedish University of Agricultural Sciences

**Fakulteten för veterinärmedicin
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Thyroid carcinomas in dogs – a literature review and retrospective study on the outcome of treatment for dogs treated at the Swedish University Animal Hospital (UDS), Uppsala 2008-2018

Tyroideakarcinom – en litteraturstudie och retrospektiv studie av överlevnadstid hos hundar behandlade på Universitetsdjursjukhuset, Uppsala 2008-2018

Lisa Ekström

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Lisa Ekström

***Supervisor**: Henrik Rönnberg, Department of Clinical sciences Uppsala*

***Examiner**: Jens Häggström, Department of Clinical sciences, Uppsala*

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SUMMARY

Thyroid carcinomas is not the most common canine neoplasm, but since it is more common than the benign thyroid adenoma it is still an important disease to recognize. Most commonly it affects older dogs, with a mean age of about 10 years. No predilection for gender is seen, but it seems to be more common in certain breeds like Golden retriever, Beagle and Boxer.

The etiology of thyroid carcinomas is still unknown. There are several theories, but no proven facts. This makes it difficult to treat the condition medically, as we are not sure what to direct the treatment at. The most successful treatment seems to be surgery, surgery combined with chemotherapy or surgery combined with external radiation therapy. There are a few studies on the subject which do not all agree with each other. They do however all agree that treatment improves survival time.

The most common clinical sign of thyroid carcinoma is a lump in the ventral throat region. Dyspnea, difficulties to swallow, cough or signs of hyper-/hypothyroidism are other reported symptoms.

Small studies on thyroid carcinoma and the outcome of treatment have been published abroad, but none on the dogs treated at the Swedish University Animal Hospital in Uppsala (UDS). The aim of this study was therefore to increase the knowledge of thyroid carcinomas by writing a literature review, and also to investigate the prognosis of treatment by comparing different treatment methods with no treatment. In addition, the study also investigated methods of diagnosis and tried to identify factors which increase/decrease survival time. The foremost goal was to give veterinarian clinicians more information about the diagnosis, ways of treatment and the prognosis of thyroid carcinomas. The hypothesis was that treatment (surgical, medical and/or radiation) increased survival time in dogs diagnosed with thyroid carcinomas.

In agreement with previous studies, both groups of treated dogs showed a longer survival time than the dogs not treated. However, this difference could not be shown to be statistically significant. As for the factors increasing/decreasing survival time, the only significant result was that neoplastic ectopic thyroid tissue decreased survival time. All other analyzed factors such as clinical attachment to underlying tissue, presence of metastasis, tumor volume and hyperthyroid VS euthyroid dog showed a logical trend, but had no statistically significant impact. Further research on bigger study populations need to be performed to decide if these factors affect the survival time. The survival analysis for grade of tumor did not show a logical result. FNA biopsy was proved to provide a conclusive diagnosis in significantly less cases than tissue biopsy.

CONTENTS

INTRODUCTION

Thyroid carcinomas are not the most common neoplastic diagnosis in dogs, only 1-2% are affected. (Brodery & Kelly, 1968; Wucherer & Wilkes, 2010). However, it is more often reported than the benign thyroid neoplasm; thyroid adenoma. In dogs, carcinomas make up for 90% of thyroid neoplasms detected during life (Wucherer & Wilkes, 2010). Usually, only one of the thyroid lobes is affected (Taeymans *et al.,* 2013; Deitz *et al.,* 2014).

The etiology of thyroid tumors in dogs remains unknown. In humans, scientists have found that extensive external radiation to the cervical region in young age is linked to the development of thyroid neoplasms (Ron *et al.,* 1995). Internal radiation alone (examination with ^{131}I for diagnostic purposes) does not propose an increased risk for developing thyroid neoplasms in adulthood (Dickman *et al.,* 2003). The hypothesis is that in papillary carcinoma tyrosine receptor kinases like RET and TRK are activated; in follicular carcinoma activating mutations in RAS are common to find, and in anaplastic carcinomas inactivation of p53 is common (Kondo *et al.* 2006). As the growth factor for follicular cells is TSH, the hormones binding to the TSH-receptor are well studied in thyroid neoplasms. It seems to be able to bind to the TSH-receptors on the tumor-cells to the same extent as in normal thyroid tissue (Verschueren *et al.,* 1991). A study from 1996 shows that TSH can stimulate excess release of VEGF (vascular endothelial growth factor) in a thyroid neoplasm. VEGF is secreted by some tumor cells to increase the blood supply to the tumor and hence, make it grow (Soh *et al.,* 1996). This could explain why most thyroid tumors are found to be rich in blood supply (Mitchell *et al.,* 1979).

In several studies the breeds Boxer, Beagle and Golden Retriever seem to be predisposed for thyroid carcinomas. No statistical significance in sex-predilection has been proven, but it is more common in elderly dogs with a mean age of about 10 years (Brodery & Kelly, 1968; Leav *et al.,* 1976). A fairly recent study by Wurcherer & Wilkes (2010) showed that Golden retrievers and Beagles were more predisposed than Boxers. Neither this study showed a sex-predilection, but the results revealed an older age of between 10-15 years at discovery of the thyroid carcinoma.

This study will mainly focus on the outcome of treatment in 18 dogs treated for thyroid carcinomas at the veterinary university hospital in Uppsala, Sweden. The dogs were divided into three groups; not treated, surgical treatment only, and treated both with surgery and chemotherapy. They were then compared for survival time using a Kaplan Meier curve. Metastatic spread, attachment to underlying tissue, hyperthyroidism and grade 1 VS grade 2 tumor was also analyzed as potential prognostic factors. Potential predilection factors like sex, age and breed was also compared to previous research.

The aim of this study is to increase the knowledge of thyroid carcinomas by writing a literature review, and also investigate the prognosis of treatment by comparing different treatment methods with no treatment. In addition to this, the study also investigates methods of diagnosis and try to identify factors increasing/decreasing survival time. The goal is to give veterinarian clinicians more information about the diagnosis, ways of treatment and the prognosis of thyroid carcinomas. The hypothesis is that treatment (surgical, medical and/or radiation) increases survival time in dogs diagnosed with thyroid carcinomas.

LITERATURE REVIEW

Anatomy

The thyroid is the largest organ that functions exclusively as an endocrine gland. In dogs it consists of two lobes, one on each side of the cranial part of the trachea. The right lobe is situated slightly cranial to the left lobe (Zachary & McGavin, 2012).

Accessory thyroid glands are usually located close to the main organ, but can also be found around the hyoid apparatus, along the trachea, in the mediastinum and/or adjacent to the aorta (Konig & Liebich, 2014; Swartz *et al.,* 1911).

Blood is mainly supplied from the common carotid artery branching into the cranial thyroid artery, and the caudal thyroid artery. Venous drainage goes through the cranial and middle thyroid veins which drain into the internal jugular vein. Lymph drains to the deep cervical lymph nodes or directly to the tracheal trunk. Adjacent nerves are the cranial and caudal laryngeal nerves, as well as the sympathetic nerve fibers which originate from the cranial cervical ganglion (Konig & Liebish, 2014).

Histology

Microscopically a normal thyroid gland consists of follicles in varying sizes. These follicles contain colloid produced by the follicular cells (epithelial cells) surrounding them. The cells are cuboidal to columnar in shape. The secretory pole of the cells is positioned towards the lumen of the follicle. Interfollicular and intrafollicular capillaries supply the follicular cells with blood.

The thyroid gland also contains C-cells, or parafollicular cells, which are responsible for the secretion of calcitonin. C-cells are found either in the follicular wall or between the follicular cells. They do not secret calcitonin to the follicular lumen but directly to the blood through the interfollicular capillaries. C-cells contain numerous cytoplasmic secretory granules that are immunoreactive for calcitonin.

As the thyroid gland must produce large amounts of protein hormones, the follicular cells contain large amounts of RER (rough endoplasmic reticulum) and have a substantial golgi apparatus for packaging of these hormones (Zachary & McGavin, 2012).

Physiology

The hypothalamus releases TRH (thyroid releasing hormone) which activates the secretory cells, called basophils, in the pars distalis of the adenohypophysis. These cells produce and release TSH (thyroid stimulating hormone) (Zachary & McGavin, 2012).

When TSH binds to the cells of the thyroid gland it releases T3 (tri-iodothyronine) and T4 (thyroxine), two hormones that control metabolic rate, growth, body temperature, carbohydrate metabolism and calcium blood levels (Konig & Liebish, 2014).

Thyroglobulin is a precursor to T3 and T4, and it is produced in the thyroid gland by the follicular cells. It is then transported over the cell membrane to the follicular lumen where it is

assembled into T3 and T4. When there is a high concentration of T3 and T4 in the blood circulation the hormones act as a negative feedback mechanism on the hypothalamus and adenohypophysis. This results in less TRH and TSH production, decreasing the amount of T3 and T4 being released from the thyroid gland (Zachary & McGavin, 2012).

C-cells secrete calcitonin when the serum concentration of calcium is too high. When lowered the secretion ceases. Calcitonin works by interacting with target cells in the kidneys and bone, making the osteoclasts in bone more inactive, and the renal tubules to reabsorb less calcium, see figure 1 (Kallio *et al.,* 1972; Cochran *et al.,* 1970).

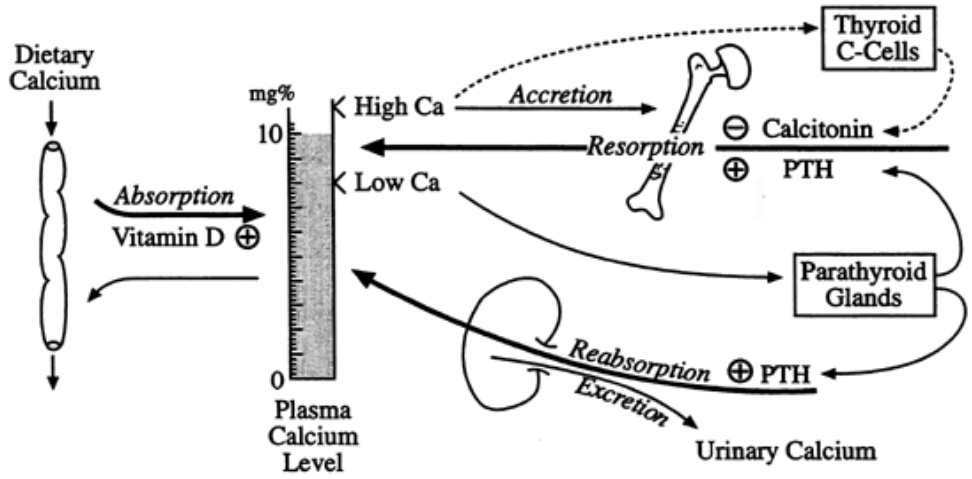

Figure 1. *Description of calcium metabolism. Source of picture: http://www2.csudh.edu/nsturm/CHE452/20_Calcium%20Homeostasis16.htm*

Classification of Thyroid carcinomas

Neoplasms arising from follicular cell-types are divided into follicular-, compact-, papillary- or anaplastic thyroid carcinomas. The other type; medullary carcinoma, derives from C-cells. In order to test whether the tumor is of follicular- or C-cell origin, immunohistochemistry is used by raising antibodies against thyroglobulin and calcitonin. If the cells are positive for thyroglobulin, the neoplasm is derived from follicular cells, if the cells are positive for calcitonin, the neoplasm is derived from C-cells (Leblanc *et al.*, 1991; Ramos-Vara *et al.*, 2002).

Ramos-Vara *et al.*, (2002) found another way to determine if the tumor was of thyroid tissue origin by using a protein called Thyroid Transcription Factor-1 (TTF-1). TTF-1 was only found in thyroid and lung tissue. However, this protein was both a less sensitive and less specific marker than thyroglobulin and calcitonin. In combination with thyroglobulin, TTF-1 increased the sensitivity for finding follicular thyroid carcinomas though. Leblanc *et al.* (1991) also investigated alternative markers for identifying and classifying thyroid carcinomas. They found that the calcitonin-gene-related peptide (CGRP) was even more sensitive than calcitonin in finding medullary carcinomas.

In a study by Leav *et al.* (1976) the authors divided the carcinomas from 97 dogs into seven groups based on macroscopical and microscopical appearance. The classification was based on the system by Meissner and Warren (1969).

Follicular carcinoma

The follicular carcinomas are amongst the more common types of thyroid carcinoma in the dog. Fifteen of the 97 dogs in a study by Leav *et al.* (1976) had a follicular carcinoma, making it the third most common malignant thyroid neoplasm in that study. They typically had a firm nodular external surface with softer parts focally. The inner core was irregular and contained a soft, dark-red caseous material surrounded by firm cream-colored tissue. Hard, gritty spicules are recorded to be common in and around the soft central regions. Metastatic foci sometimes lacked these spicules (Leav *et al.,* 1976; Leblanc *et al.,* 1991).

Microscopically the neoplastic cells formed follicles, although a minor part may have contained compact tissue. Both micro- and macrofollicular patterns could be observed. Foamy, vacuolated colloid was found in the lumen of larger neoplastic follicles but not in the microfollicles. The uptake of radioiodine was most profound in the follicular parts of the neoplasm and less in the compact areas (Leav *et al.,* 1976; Leblanc *et al.,* 1991).

In humans the follicular carcinomas seem to be more uncommon. Only 2 of 80 patients had follicular carcinomas in a study by Russel *et al.* (1963).

Compact cellular carcinomas

The external texture of compact cellular carcinomas was firm and smooth. The cut surface was described to have a creamy color and a fine lobulation.

Microscopically compact cellular carcinomas had randomly arranged cells in densely packed sheets, divided into lobules by thin strands of connective tissue and small blood vessels. A minor follicular component was sometimes present. The staining for immunoreactive calcitonin was usually negative, meaning the C-cells were not involved (Leav *et al.,* 1976). A study in dogs by Brodery and Kelly (1968) showed the compact thyroid carcinomas were the most common type of thyroid carcinomas - 14 out of 22 dogs were affected.

Mixed follicular-compact cellular carcinomas

Mixed follicular-compact cellular carcinomas were considered to be the most common thyroid carcinoma found in the dog (Leav *et al.,* 1976). Up to 58% of dogs with thyroid carcinoma had a mixed follicular-compact cellular pattern.

These neoplasms had a firm surface and an inner core similar to the one found in the follicular carcinoma. Microscopically they contained both the follicular carcinoma and compact cellular carcinoma. Connective tissue in cribiform patterns separated the follicular and compact cellular regions (Leav *et al.,* 1976; Leblanc *et al.,* 1991).

Mixed papillary-follicular carcinoma

Mixed papillary-follicular carcinoma was described to be very unusual in dogs. Only one of the 97 dogs with carcinomas in the study by Leav *et al.* (1976) had a mixed papillary-follicular carcinoma.

Macroscopically these tumors were firm and multi-lobulated. The inside had a creamy color and a nodular structure. Microscopically the cell nuclei were pleomorphic and lack polarity. Some were vesicular, and sometimes had a prominent nucleoli (Leav *et al.*, 1976).

Metastases were not found in the study by Leav *et al.*, but invasion of the connective tissue capsule surrounding the thyroid gland and vessels was seen. However, histologically, mitoses were not present.

In a study by Russel *et al.* (1963) mixed papillary-follicular carcinoma was reported to be the most common type of thyroid carcinomas in humans.

Anaplastic thyroid carcinomas

Anaplastic thyroid carcinomas were according to Thomas and Buckwalter, (1973) relatively common in humans - 15-20% of the thyroid carcinomas were anaplastic. In dogs however, this type of carcinoma was shown to be rare (Mason & Wells 1929).

Spindle cell carcinoma

Only one spindle cell carcinoma was found in the dogs examined by Leav *et al.* (1976). It had a firm surface with a cream-colored, homogenous inner texture. Microscopically most of the cells were spindle shaped and arranged in small, poorly defined lobules. Mitotic figures were numerous and abnormal. Metastasis to the retropharyngeal lymph node was observed. Follicles were rarely seen.

Giant cell carcinoma

Two of the dogs in the study by Leav *et al.* (1976) were diagnosed to have an anaplastic giant cell carcinoma in the thyroid gland. They both differed macroscopically and microscopically, but were prone to metastasize and invade surrounding tissues, like the sternocephalic muscles, carotid sheath, and the lateral surface of the esophagus. One of these tumors contained osteosarcomatous parts.

Diffuse small cell carcinoma

The diffuse small cell carcinoma was described by Leav *et al.* (1976) to be a firm neoplasm. It was adherent to the esophagus and showed metastasis to the lungs, kidneys, the adrenal gland, mesentery and the diaphragm. Only one of the dogs in the referred study was considered to have a diffuse small cell carcinoma.

Microscopically, it consisted of loosely aggregated uniform small, round cells with an oval, vesicular nucleus. Mitosis was rare. In a few areas, the small cells might have created structures resembling follicles (Leav *et al.*, 1976).

Aldinger *et al.* (1978) discussed that small cell carcinoma was in fact a type of lymphoma which should not be part of the classification of thyroid carcinomas. A clinicopathologic study performed by Rayfield *et al.* (1971) indicated that even though small cell carcinoma resembled a thyroid carcinoma histologically, none of the small cell carcinomas had thyroid epithelial origin.

Medullary carcinoma

Medullary carcinomas, also called C-cell carcinomas, arise from C-cells and in humans they are usually associated with excess secretion of calcitonin. Despite the abnormal secretion of calcitonin, human patients usually did not show hypocalcemia or hypophosphatemia (Tashjian *et al.*, 1974). However, in dogs with medullary carcinoma, hypocalcemia had been observed (Leav *et al.*, 1976).

Both of the medullary carcinomas in the study by Leav *et al.* (1976) were unilateral and involved the right thyroid lobe. Macroscopically, the medullary carcinomas were firm and about 4 cm in diameter and had nodular external surfaces. The inside differed between the two tumors, but they both showed vascular and capsular invasiveness and were positive in immunoperoxidase staining for calcitonin.

In the study by Leblanc *et al.* (1991) no mitosis was seen in the canine medullary carcinomas.

Some studies showed that medullary carcinomas in dogs may be more common than previous research studies had shown, as they were easily mistaken for compact follicular carcinomas. In order to know for certain, immunoperoxidase staining with calcitonin must be performed (Lee *et al.*, 2006; Carver *et al.*, 1995).

In a recent study medullary carcinomas were found in a family of dogs which implied clinical similarity to the familial form of medullary thyroid carcinoma (FMTC) in humans (Lee *et al.*, 2006). However, the RET-mutation present in 95% of the human cases of FMTC could not be confirmed in these dogs. The clinical findings still indicated that some thyroid carcinomas may have been hereditary.

Adenomas

Leav *et al.* (1976) also writes about adenomas of the thyroid in canines. Adenomas are the benign type of neoplasm in the thyroid, and in contrary to carcinomas they do not metastasize, nor grow fast. There are two types of adenomas; follicular and papillary. Clinically adenomas are described to be more uncommon in dogs than carcinomas are, but after post-mortem examinations it is found to be more common than previously known. About 30% (44 of 141) of the dogs with a thyroid neoplasia has an adenoma. Only seven of these are large enough to be detected during life. Dogs with adenomas show no evidence of hypo- or hyperthyroidism.

As this review focuses on carcinomas, adenomas will not be discussed further.

Ectopic thyroid tumors

Ectopic thyroid tissue may be found in healthy dogs but similar to the original thyroid gland it can become neoplastic. The ectopic thyroid tissue was usually located along the cervical region, hyoid region or adjacent to the aorta (Swartz *et al.*, 1911).

Aortic body carcinoma and ectopic thyroid carcinoma can arise from the same location in the thoracic cavity. They are similar in that both are vascular, invasive and have tendencies to grow within lymphatics. Even histologically they are fairly similar (Cheville, 1972). Leav *et al.* (1976) differed the two tumors by looking for follicles, or structures similar to follicles which

were found in most ectopic thyroid tumors. He also studied the cells closely, the cells in aortic body carcinomas differed more in size and shape than did the cells in ectopic thyroid carcinomas. Also, PAS-staining droplets are found in ectopic thyroid carcinomas, and an argyrophilic network of fibers surrounding nests of cells is noted in aortic body carcinomas, but not in the ectopic thyroid carcinomas.

Staging of thyroid neoplasms

In one review from 2000, the scientists suggest that all use one staging system to make the staging easier. They suggest the TNM-staging, (tumor, lymph nodes and metastases), (table 1-4) as it considers several factors, works for all types of thyroid neoplasms and is universally available (Brierley *et al.*, 2000).

Table 1. *T; primary tumor*

Stage	**Size**
T0	No evidence of tumor (microscopic residual disease)
T1	<2 cm
T2	2-5 cm
T3	>5 cm
Substage a	Freely movable tumor
Substage b	Tumor fixed to surrounding tissue

Table 2. *N; regional lymph nodes*

N0	No evidence of lymph node involvement
N1	Ipsilateral lymph node involvement
N2	Bilateral lymph node involvement
Substage a	Lymph node freely movable
Substage b	Lymph node fixed

Table 3. *Metastases*

M0	No evidence of distant metastasis
M1	Distant metastasis detected

Owen, 1980. TNM classification of tumors in domestic animals, Geneva, World Health organization.

Table 4. *Staging*

Stage	Primary tumor	Regional lymph nodes	Distant metastases
1	T1 a, b	N0	M0
2	T0	N1	M0
	T1 a, b	N1	M0
	T2 a, b	N0 or N1 a	M0
3	T3	Any N	M0
	Any T	N1 b or N2 b	M0
4	Any T	Any N	M1

Owen, 1980. TNM classification of tumors in domestic animals, Geneva, World Health organization.

Clinical signs

Several articles describes clinical symptoms of thyroid carcinomas. In table 5 there is a compilation of the most common symptoms reported in dogs with thyroid carcinoma.

Table 5. *Clinical signs of thyroid carcinomas*

Study	**Swelling in ventral throat region**	**Coughing**	**Dyspnea**	**Dysphonia**	**Edema**
R.S Brodey *et al.*	+		+		+
I. Leav *et al.*	+		+		
J.R Carver *et al.*	+	+	+	+	
J. Harari *et al.*	+	+	+		
O. Taeymans *et al.*	+		+	+	
K. Deitz *et al.*	+	+			

As stated from table 5, a swelling in the ventral throat region and dyspnea are the most common symptoms, but also coughing, edema, dysphonia and dysphagia occurs. Clinical movability of the mass does not seem to correlate with malignancy or type of tumor (Deitz *et al.*, 2014).

Another characteristics of thyroid carcinomas in dogs may be signs of hypo- or hyperthyroidism. These carcinomas are in veterinary medicine called functional thyroid carcinomas and can consist of either ectopic thyroid tissue or origin thyroid tissue (Deitz *et al.*, 2014). In a case report, symptoms like weight loss, increased heart rate, hyperactivity, anxiety and excessive panting are described, as well as a swelling in the throat region. The dog is diagnosed with a thyroid carcinoma causing hyperthyroidism (Bezzola, 2002). However, not

all dogs show signs of hyperthyroidism even though they have a high concentration of thyroxine in the blood. (Carver *et al.*, 1995; Fukui *et al.*, 2015). Rijnberk (1971), see Leav *et al.* (1976), studied 57 dogs with thyroid carcinomas, 13 of these also had hyperthyroidism with symptoms similar to the ones mentioned above; polyuria, polydipsia, weight loss despite increased appetite, restlessness, tachycardia and heat intolerance.

The hypothesis of thyroid carcinoma causing hyperthyroidism is uncontrollable tumor production of T3 and T4. TRH and TSH secretion is inhibited because of the high levels of T3 and T4 in the blood, making the contralateral normal thyroid gland regress. After surgical removal of the thyroid carcinoma, the symptoms of hyperthyroidism disappear (Rijnberk 1971: see Leav *et al.*, 1976)

In a study by Benjamin *et al.* (1996) beagles with hypothyroidism and lymphocytic thyroiditis were examined postmortem. A significant correlation between the hypothyroid dogs and thyroid neoplasms was found. The clinical signs consisted of weight gain, obesity, lethargy, epidermal scale, hyperpigmentation, and bilateral symmetrical alopecia.

The hypothesis of the linked hypothyroidism and thyroid neoplasia is that the low blood concentration of T3 and T4, which persists during hypothyroidism, causes overstimulation of the adenohypophysis and an excess production of TSH. TSH then promotes cell proliferation in the thyroid gland, thus leading to increased neoplasia of follicular cells (Benjamin *et al.*, 1996).

A case report from 1996 described a dog with hyperthyroidism and a large thyroid carcinoma. This dog also presented symptoms consistent with Horner's syndrome. The authors discussed that tumors in the cervical region invading the vago-sympathetic nerve trunk had been suggested to cause Horner's syndrome. They drew the conclusion that thyroid carcinomas should be able to do so as well, and could thus be the reason for the symptoms of Horner's syndrome in this dog (Melián *et al.*, 1996).

Metastasis

The risk of metastasis seemed to be correlated with the size of the tumor. If the tumor was 1-20 cm^3 the risk of metastasis was 14%, if the tumor was 21-100 cm^3 the risk was 74%. A tumor with a volume more than 101 cm^3 had a 100% chance of metastasis (Leav *et al.*, 1976).

The lungs, regional lymph nodes and adjacent tissues were the most common site of metastasis (Brodey & Kelly, 1968; Leav *et al.*, 1976).

Diagnosis

In order to diagnose, classify and stage the thyroid carcinomas clinical examination, radiography of the thorax, endoscopy and radio-isotope scanning must be performed. There must also be histological examination (Owen, 1980).

According to a study which compared ultrasound, MRI (magnetic resonance imaging) and CT (computed tomography) regarding sensitivity and specificity, MRI was the most sensitive (93%) method for detecting thyroid carcinomas compared to CT, with a sensitivity of 85%.

However, CT was a more specific (100%) method, compared to MRI, with a specificity of 67% (Taeymans *et al.*, 2013).

At the University animal hospital in Uppsala (UDS), blood samples, ultrasound with/without FNA biopsy, CT followed by thyroidectomy is the most common approach when diagnosing a thyroid carcinoma. After surgery the removed thyroid is usually sent for a histological examination, which confirms the diagnosis and determines classification of the carcinoma.

Examination and Blood samples

A thorough clinical examination should always be performed, followed by blood samples; hematology, clinical chemical panel, TSH and T4, to study the values and determine whether the thyroid is hyperfunctional, hypofunctional or euthyroid. Sometimes kidney- and liver values are also valuable (Nadeau & Kitchell, 2011).

Ultrasound

Ultrasound is a common way to examine nodules or swellings in the thyroid region (Tuohy *et al.*, 2012). It can assess size, volume, and shape of the neoplasm/thyroid gland as well as echogenicity and homogeneity. The larynx, trachea and the common carotid artery are nearby structures commonly used as hallmarks (Brömel *et al.*, 2005).

In addition to the thyroid gland and possible carcinoma, identification of the adjacent lymph nodes, blood vessels, the esophagus and trachea can be performed with ultrasound. This way it is possible to find signs of metastasis in the lymph nodes, to assess how invasive and vascularized (using Doppler technique) -the tumor is and whether it is operable or not. Ultrasound can also help in determining where the mass originates, and with a color doppler technique it is possible to distinguish veins from arteries. Ultrasound is also helpful when guiding a fine needle aspiration from a thyroid neoplasm as they can be extensively vascularized. With the assistance of an ultrasound it is possible to avoid the largest vessels. A thyroid carcinoma is typically hypoechoic and nonhomogeneous compared to normal thyroid tissue (Wisner *et al.*, 1993).

Ultrasound is a quick and fairly easy examination compared to MRI and CT. No anesthetics are necessary, unless the neoplasm is pressing on to the larynx/trachea giving symptoms of dyspnea (Wisner *et al.*, 1993; 1998).

FNA

In a FNA (fine needle aspiration) biopsy a thin needle and a syringe is used. The needle is inserted into the neoplasm and the syringe is used to carefully aspirate cellular material. Excess aspiration results in blood dilution of the thyroid cells. If the mass is big, repositioning during aspiration may be favorable, as long as no blood vessel is punctured. The content is then transferred to a microscopy slide, stained and studied in a microscope. Cellularity, cell-size, cell-type and shape, adhesiveness of cells, nuclear and chromosomal features, nucleolar abnormalities and mitotic activity are assessed (Thompson *et al.*, 1980).

In a study by Thompson *et al.* (1980) the authors show that FNA can be used to diagnose thyroid carcinomas. Menard *et al.* (1986) show that FNA correctly diagnose the malignant neoplasms in 71% of the dogs. They hence suggest to use it as a concluding but not excluding method to diagnose malignant tumors. If three FNA biopsies fails to conclude cytological changes, a surgical biopsy should be made. The authors also points out that FNA is faster, well tolerated by the dogs and cheaper than tissue biopsy.

As mentioned above, an ultrasound guided FNA can help in avoiding blood vessels and hence decrease the risk of bleeding and increases the diagnostic value by avoiding taking a FNA containing blood.

Biopsy

Because of the rich blood supplement to a thyroid carcinoma, tissue biopsies are not taken in the clinic. They are only performed with incision, or after surgical removal of the thyroid, to get a definite diagnosis and help the veterinarian in making a post-surgical plan and decide further treatment (Carver *et al.*, 1995).

MR imaging

Size, volume, surrounding structures, shape and intensity can be assessed with an MRI. However, MRI has a better sensitivity and specificity than ultrasound when it comes to diagnosing thyroid carcinomas. MRI is also the best method for visualizing capsule disruption (Taeymans *et al.*, 2008a; 2013).

The disadvantages of MR imaging is the need for anesthesia, making it time consuming. The technique is also expensive.

In humans, scientists have found a way to differ between papillary carcinomas and benign nodules by using MRI. They have done this by comparing T2 SIR (signal intensity ratio) and ADC (apparent diffusion coefficient) values. If the mass has a papillary carcinoma the values are lower than if it is a benign nodule (Noda *et al.,* 2015). No studies comparing the most common thyroid neoplasms in dogs, follicular carcinoma and follicular adenoma, could be found in the literature.

Scintigraphy

Scintigraphy is used to examine the thyroid glands, regional lymph nodes and the lungs for size, position and abnormal uptake of radionuclides (Mitchell *et al.*, 1979). However, the assessment of lung metastasis is limited in scintigraphy compared to x-ray or CT because the metastases may not have the same uptake of radionuclides as the original tumor (Silverman *et al.,* 1983; Adams *et al.,* 1995; Taeymans *et al.,* 2007).

Three different radionuclides have been used in scintigraphy; ^{131}I, ^{123}I and 99m-Tc pertechnetate. In a case report the authors tried both ^{123}I and 99m-Tc pertechnetate on a dog with a thyroid carcinoma. It showed that some parts of the carcinoma was not detected with 99m-Tc pertechnetetate. They therefore suggested that if scintigraphy with 99m-Tc pertechnetate was negative, one with ^{123}I should also be performed (Broome & Donner, 1992).

99m-Tc pertechnetate was preferred in the study by Bähre *et al.* (1988) since it was less expensive and more available than ^{123}I. Arnold and Pinsky (1975) came to the same conclusion in their study, and added that scintigraphy could be performed sooner if pertechnetate was injected (20 minutes) than with ^{123}I (4-24 hours).

By studying the uptake of the administered radionuclide the technician can distinguish functional from non-functional thyroid carcinomas with a scintigraphic examination. In a hypothyroid carcinoma, the uptake of the administered radionuclide is less than in normal thyroid tissue, usually these carcinomas are of the non-differentiated kind (Espineira *et al.*, 2007). Not many studies has been performed on dogs with hyperthyroidism and scintigraphy, but one case report show that one hyperthyroid dog has an increase in uptake of 99m-Tc pertechnetate both in the thyroid tissue and the thyroid carcinoma (Petersen *et al.*, 1989).

To perform a scintigraphy, the dog needs to lie still for a longer period of time, and so general anesthesia or sedation is necessary. 99m-Tc pertechnetate is injected intravenously and the dog is placed in ventral position over a large field-of-view gamma camera. The uptake peak in the thyroid glands happens after 2-3 hours, although after 20 min up to 1 hour after injection the ratio of salivary gland uptake and thyroid gland uptake is closest to one in a healthy dog, which is why this is the best time to perform the study (Adams *et al.*, 1997).

CT

Taeymans *et al.*, (2008b) performed a study on the normal appearance of the thyroid gland on CT. Just as the above imaging techniques CT could assess thyroid size, shape, homogeneity, location of thyroid tissue and blood vessels. They came to the conclusion that due to the thyroid having a high attenuation value compared to surrounding tissue, CT could also distinguish thyroid masses from non-thyroid masses, and be helpful in diagnosing suspected thyroid neoplasms. They also thought it could aid in staging of the neoplasm and planning of the surgery. After injection of iodine the thyroid gland increased in volume.

A study in dogs from 2017 show that CT is of help in diagnosing thyroid carcinomas. CT make it possible to assess shape, volume, invasiveness to surrounding soft tissue, homogeneity, mineralization, intratumoral vasculature, regional lymph node size and distant metastases of the thyroid carcinoma (Bertolini *et al.*, 2017). It is more likely that lung metastases are detected with CT compared to plain radiographs (Deitz *et al.*, 2014).

In a study of human thyroids, CT iss compared to scintigraphy. CT is better at identifying retrotracheal- and substernal thyroid tissue. It provides more information when it comes to both the primary tumor and the ectopic thyroid tissue. For example the extent of them in relation to the other adjacent- or mediastinal structures, invasiveness and blood supply. CT can also detect calcified tissue, scintigraphy cannot. Metastases to the lymph nodes are detected with CT - and not with scintigraphy (Silverman *et al.*, 1983).

As the animal needs to lie still in a spinal position, general anesthesia or heavy sedation is required. This makes CT more time consuming, more expensive and more risky than ultrasound or x-ray (Taeymans *et al.*, 2008b).

Treatment and prognosis

Surgical treatment

If the tumor is movable, relatively small and not too invasive, it is considered surgically operable. In a study by Carver *et al* (1995) 10 out of 12 dogs with medullary thyroid carcinomas are assessed to have surgically operable tumors. None of the dogs has evidence of metastasis to the lungs at the point of surgery. Eleven of the 21 dogs with thyroid adenocarcinoma in the above referred study, are considered to have a surgically operable tumor. Three of these presented with metastasis to the lungs.

Prior to surgery, hematological testing, biochemical analysis, resting thyroxine concentration or TSH-response test, and thoracic x-ray should be performed. (Carver *et al.,* 1995; Tuohy *et al.,* 2012).

An extracapsular technique is used for removal of the thyroid carcinoma, to prevent seeding of the tumor cells. It is important that at least one of the parathyroid glands remains, even though extensive surgery has to be done to remove the tumor. If either parathyroid glands or their blood vessels are invaded by tumor tissue, the healthy parathyroid tissue can be minced into 1 mm cubes and implanted into muscle. These dogs will likely need calcium supplement for a few weeks after surgery. If the parathyroid glands are removed the dog will be hypocalcemic and need oral calcium gluconate and vitamin D for the rest of its life (Fukui *et al.,* 2015).

If the thyroid carcinoma is not removed with clean margins, radiation therapy is recommended post-operatively (Fukui *et al.,* 2015).

Complications may include hemorrhage, seroma, transient hypocalcemia, hypothyroidism, temporary upper airway obstruction, aspiration pneumonia and damage to the laryngeal nerve (Nadeau & Kitchell, 2011; Tuohy *et al.,* 2012).

Prognosis after surgery is not good in a study by Carver *et al.* (1995). A few of the dogs lived for at least 12 months after surgery (both dogs with medullary carcinoma and adenocarcinoma), but so did the dogs with tumors which did not have surgery. In the study by Fukui *et al.* (2015) the mean survival time is 30 months after surgery, however, the study only includes 6 dogs. Tuohy *et al.* (2012) show a mean survival time of 38.3 months after surgery, in a study on fifteen dogs. No recurrence is found at follow up in any of the studies.

Campos *et al.* (2014) show that size, volume, histologic type and the amount of expressed Ki-67 is associated with a macroscopically invasive tumor and a more negative prognosis. Size, volume, tumor localization and bilateral vs unilateral tumor is associated with patients having distant metastasis, and hence a less favorable diagnosis. Tumor diameter, localization, unilateral vs bilateral tumor, ectopic thyroid tissue and tumor mobility is correlated to histological invasion. They also show that there is no significant difference in survival after surgery between a dog with medullary thyroid carcinoma and a dog with follicular thyroid carcinoma.

Radiotherapy with ^{131}I

In a study by Simpson (1975) seven human patients received therapeutic doses of ^{131}I, three of these were cured and no recurrence could be shown at check-up 12 years later (patient no 1) or 17 years later (patient no 2). One patient died of other causes 3.5 years later, without clinical signs of recurrence. Three other patients had a relief of symptoms and lived several years after treatment, but were not cured of the disease. The last patient did not respond to treatment, neither was any sign of ^{131}I uptake by the tumor seen.

A few studies on animals have been performed. A dog with hyperthyroidism and an inoperable thyroid carcinoma was treated with a dose of 2220-2770 MBq ^{131}I on three occasions with an interval of 5 to 7 months. However, the symptoms recurred 5 months after the last treatment and the dog was euthanized. The authors of the study speculated that dogs with hyperthyroidism should be the best candidates in treatment with ^{131}I as their uptake of radionuclides was higher than in euthyroid dogs. They also pointed out that treatment of dogs with ^{131}I was problematic because of the long hospitalization period due to the need of collecting radioactive feces and urine in radiation isolation facilities afterwards (Peterson *et al.*, 1989). ^{131}I may also be used as adjunctive treatment to surgery, or alone if the tumor was inoperable because of metastasis and/or invasiveness, and if the tumor showed uptake of ^{131}I. In the last case it was considered to be prolonging of life rather than curative (Worth *et al.,* 2005).

In a study by Worth *et al.* (2005) 32 dogs were given a subcutaneous injection with ^{131}I, another group was not treated at all, a third was treated with surgery alone and the fourth was both surgically treated and given ^{131}I. The group with the longest mean survival time (34 months) was the one treated both surgically and with ^{131}I. The group treated with surgery alone had a mean survival time of 30 months. In a study published in 1995 the authors treated seven dogs diagnosed with thyroid carcinomas with a variety of surgery, chemotherapy and ^{131}I radiotherapy. The four dogs which received only ^{131}I and thyroid hormones did not have a significant reduction in tumor size. The mean survival time for the seven dogs was 25 months (Adams *et al.*, 1995).

As pointed out earlier, metastases may not have the same uptake of radionuclides as the hyperfunctional thyroid/thyroid carcinoma, and thus the treatment may not be as effective towards metastases as towards the original tumor (Silverman *et al.*, 1983; Adams *et al.*, 1995; Taeymans *et al.*, 2007).

Reported side effects were pancytopenia, bone marrow megakaryocytic, erythroid and myeloid hypoplasia, hypothyroidism and diarrhea (Adams *et al.*, 1995; Worth *et al.*, 2005).

External radiation therapy

In a study of human thyroid carcinomas, external radiation was used on follicular, papillary, medullary and thyroid anaplastic carcinomas. In all tumor types it diminished the amount of people who had reoccurrence. The patients with anaplastic tumors were the ones with highest recurrence frequency. The author concluded that external radiation may be an effective way of treatment in any kind of thyroid carcinoma. It should be used after surgery if there was even

slight doubt that some tumor tissue remained, in combination with ^{131}I if the tumor was inoperable, or alone for undifferentiated tumors which did not concentrate ^{131}I (Simpson, 1975).

25 dogs with non-operable thyroid carcinomas participated in a study to evaluate external radiation (megavoltage) as a therapy and determine duration of progression free survival. The dose given was 12 fractions of 4 Gy/fraction over a period of 4 weeks. In the dogs that had metastases the disease progressed even after treatment. However, three years after treatment the progression free survival was 72%, indicating that irradiation prolonged life in dogs with non-operable thyroid carcinomas (Theon *et al.,* 2000). Another study published in 2001, studied megavoltage radiation therapy in 8 dogs with the same protocol as above. The mean survival time was 24.5 months (Pack *et al.,* 2001). Earlier studies agree with these results. Brearley *et al.* (1999), treated 13 dogs with non-operable thyroid carcinomas with external radiation and found that their mean survival time was 24 months. They all agreed radiation therapy was a good palliative treatment.

Side effects from radiation has been seen in some dogs; tracheal, esophageal or laryngeal mucositis for example. This led to hoarseness, mild dysphagia and cough. Skin fibrosis, alopecia and chronic tracheitis creating a dry cough has been shown to be the chronic side effects of radiation therapy. Cases of hypothyroidism after treatment have also been described (Brearley *et al*., 1999; Theon *et al.*, 2000; Pack *et al.*, 2001). In one study, 21 dogs were treated with megavoltage radiation, 47.6% (10) of them were hypothyroid 1-13 months afterwards. The dose received did not seem to be related to the risk of developing hypothyroidism. No risk factors were identified, but several of these dogs had both had surgery and chemotherapy before/during radiation (Amores-Fuster *et al.*, 2015).

Chemotherapy

Chemotherapy is rarely used alone in treatment of thyroid carcinomas, but more often in conjunction with another therapy. In the study by Nadeau & Kitchell (2011) one group of dogs are only surgically treated (28 dogs), and the other both surgically treated and receiving chemotherapy (16 dogs) with one or a combination of carboplatin, doxorubicin and gemcitabin. Only one complete remission is seen in a dog who received doxorubicin. The other dogs show partial remissions. The median survival time is almost the same between the two groups, 510 VS 518 days.

Another study performed in 13 dogs given cisplatin showed a mean survival time of 6.3 months. Seven of the thirteen dogs had had previous treatment with surgery or doxorubicin. Only 54% of the dogs responded to the chemotherapy. Two of the dogs that had partial remission had previously been treated with doxorubicin without any success. The authors speculated that cisplatin might be effective even when doxorubicin is not (Fineman *et al.*, 1998). In an earlier study published in 1988, 36 dogs were evaluated for survival time after treatment with cisplatin. The response rate in this study was much lower than in the one above. Only 19% of the dogs responded to treatment. However, two of the dogs in this study with partial regression were candidates for surgical removal after chemotherapy (Knapp *et al.*, 1988).

Side effects noted from cisplatin treatment was vomiting, azotemia, anorexia, hemorrhagic diarrhea, thrombocytopenia, granulocytopenia, neutropenia and seizures. (Knapp *et al.*, 1988;

Fineman *et al.,* 1998). In a study by Knapp *et al.* (1988) two of the 41 treated dogs died. One due to seizure and one because of hemorrhagic diarrhea.

The effect of Toceranib in dogs was studied by London *et al.* (2011). Ten of the fifteen dogs had had previous treatment with surgery, radiation or other chemotherapy. Four of the dogs had partial regression, while eight were seen to have stable disease after treatment. Two of the dogs with partial remission also had lung metastasis. One and five months respectively after treatment with toceranib the lung metastasis had resolved. No data on survival time was reported in the study (London *et al.,* 2011).

Side effects noted after toceranib treatment was diarrhea, anorexia, vomiting, musculoskeletal pain and/or weakness, weight loss, positive hemocult, lethargy, neutropenia, skin disorder (depigmentation) and neutropenia (London *et al.,* 2011).

Local (inhalation) treatment of lung metastasis with doxorubicin and paclitaxel was evaluated in one study. The authors included lung metastases from two thyroid carcinomas but neither of these responded to treatment (Hershey *et al.*, 1999).

Thyroid hormone supplement

Post-operatively it is common to treat dogs with levothyroxine, especially dogs that have undergone extensive thyroidectomy and may develop hypothyroidism. In a study by Fukui *et al.* (2015) the dogs are given levothyroxine post-operatively and thereafter showed normal thyroxine concentration.

Thyroid hormones are not merely given as post-operative treatment but also to suppress the endogenous production of TSH and so decrease the risk of making the tumor grow (Simpson, 1975). In a study by Adams *et al.* (1995) it is used for this purpose during treatment with ^{131}I.

MATERIAL AND METHODS

Literature review

Data for the literature review was obtained by searching the databases “Web of Science”, “PubMed” and “Google Scholar” for scientific articles. The SLU-library service “Primo” was also used. Search words were; “Thyroid carcinoma”, “Canine”, “Ectopic thyroid”, “Dog”, “Human thyroid carcinoma”, “Staging thyroid carcinoma” “Diagnosis”, “Ultrasound”, “MR imaging”, “Computed tomography”, “Scintigraphy”, “Fine-needle aspiration”, “Biopsy”, “Treatment”, “Chemotherapy”, “Surgical”, “External radiation” and “^{131}I radiation”.

Student literature was used for the chapters “Anatomy”, “Physiology” and “Histology” where the information was regarded to be common knowledge.

Collection of data

A list of 23 dogs treated for thyroid carcinoma at the University Animal Hospital in Uppsala, Sweden between years 2008-2018 was created from medical records. Five of the dogs were excluded because the medical records lacked data essential to the study (three dogs because there was no confirmed diagnosis, and the other two were lacking information concerning time of death/euthanasia). To collect missing data concerning date of death/euthanasia or if the dog was still alive, 11 owners were first texted and then called. To be included the dogs had to have a diagnosis determined by cytology or histology and a date of death, or information on the fact that the dog was alive. FNA biopsy indicating thyroid carcinoma was considered enough to include the patient in the study.

All data was collected retrospectively from the medical records (software; Trofast) or animal owners. Data collected was: Age at diagnosis, date when the tumor was discovered, date of death/euthanasia, breed, sex, type of tumor, suspected metastases, ectopic thyroid tissue or not, treated or not, diagnostic methods, side effects of surgery, tumor volume, movability of the tumor, performed treatment and time of survival from date of discovery. The tumors were divided into two groups depending on high or low malignancy.

Classification

The 18 dogs were divided into two groups depending on if they had a confirmed histological diagnosis saying follicular thyroid carcinoma. The other group was named “Thyroid carcinoma, not further classified”. The dogs were placed in this group if there was any question marks concerning the type of thyroid carcinoma, or if the histological diagnosis just said thyroid carcinoma.

Grading

Survival time was compared for dogs with tumors graded with “low malignancy” and tumors graded as “highly malignant”. A highly malignant tumor was a tumor that: broke through the connective tissue capsule surrounding the thyroid, had large areas of necrosis, high mitotic activity (>5/10 HPF) and/or had metastatic foci. A low malignancy tumor was a tumor that: had a low-moderate mitotic activity (<5/10 HPF), lacked large areas of necrosis, had no metastases and did not break through the connective tissue capsule surrounding the thyroid.

Two of the original 18 dogs in this study were excluded in this particular part of the analysis due to lack of data.

Degree of attachment to underlying tissue

Sixteen of the dogs were divided into two groups “movable mass” or “not movable mass” based on the information in their medical records. Two of the original eighteen dogs were excluded from this part of the analysis because of lack of data. The survival time was then compared between the two groups. For details, see below the subtitle “treatment”.

Metastases

To be included, an examination regarding metastatic status had to be in the records. Three of the original 18 dogs were excluded in this particular part of the analysis because of lack of data. The 15 dogs were divided into two groups; “metastases” and “no metastases” and survival time was then compared. For details, see below the subtitle “treatment”.

To correlate the volume of the tumor to metastasis, similar to what the scientists in the study by Leav *et al.* (1976) did, the CT-reports in the medical records were scanned for information regarding tumor volume. For 11 of the dogs, the volume of the tumor was calculated based on the measurements obtained at CT-examination. The other seven dogs were excluded because of no CT scan providing a 3D-picture, no/too little information in the medical records regarding metastasis, or lack of information in the CT-report.

Blood analyzes

For the analysis regarding blood tests the dogs had to have information about TT4, TSH and/or calcium levels noted in the journal to be included. If for example, the surgical removal of the thyroid carcinoma was performed at another clinic but the follow-up was performed at SLU, the test results may have been included in the post-surgical group, but not appear for the same dog in the pre-surgery group because of lack of data.

A Kaplan-Meier analysis was performed based on the information prior to surgery. Fifteen dogs were included in the Kaplan Meier analysis for hyperthyroidism VS euthyroidism. See below the subtitle “treatment” for details.

Diagnosis

Diagnostic methods used to search for metastases were also included in table 6, showing the different diagnostic methods used for each patient. Complementary to the diagnostic methods brought up in table 6, all dogs went through a thorough clinical examination and had blood tests (hematology, CRP, electrolytes) taken, some also had TSH and TT4 tested.

Most of the biopsies were taken and sent post-operatively. Only two were performed before surgery. One with the assistance of ultrasound and one with incision. One of them could not differ between a benign and a malignant thyroid neoplasm.

Table 6. *Table overlooking the different diagnostic methods used on the patients with thyroid carcinoma. M check = metastasis check, only lnn = only lymphnodes*

	X-ray	**Ultrasound**	**CT**	**Scintigraphy**	**Biopsy**	**FNAB**
Dog 1		X	X			X
Dog 2		X, only lnn	X		X	X, only lnn
Dog 3		X, only lnn	X		X	X, only lnn
Dog 4	X				X	X
Dog 5	X		X			X
Dog 6	X, thorax M check	X			X	X
Dog 7	X, thorax M check	X	X		X	X, only lnn
Dog 8		X	X		X	X
Dog 9	X					X
Dog 10		X	X		X	X
Dog 11			X		X	
Dog 12		X	X		X	X
Dog 13				X	X	
Dog 14	X, thorax M check	X			X	X
Dog 15	X, thorax M check	X			X	X
Dog 16	X, thorax M check	X		X	X	X
Dog 17		X	X			X
Dog 18	X, thorax M check	X	X			X

The difference between biopsy and FNAB as a diagnostic tool was analyzed using Fisher's exact test.

Treatment

The dogs were divided into three groups depending on whether they received no treatment, only surgical treatment or surgical treatment and chemotherapy.

Survival times were calculated, and rounded off to the nearest month. Entry date was defined by the date when the thyroid carcinoma was discovered as a lump in the throat region, no matter the treatment. Although, only dogs treated for thyroid carcinomas after 2008-09-06 were included. The termination date was the date the last search for medical records was done – 2018-09-06.

All survival distributions in this study were analyzed with the non-parametrical Kaplan Meier-method. P-values and mean survival time were calculated using the log-rank test. The calculations were performed in Excel and MedCalc. The symbols in the graphs (circles, triangles and squares) without a following vertical drop is censored data. Censored data is data from dogs who are still alive at the end of the study.

RESULTS

Breed

Breed distribution of the dogs included in the study is shown in table 7.

Table 7. *Number and breed distribution of the dogs in this study (a), with consideration of the number of dogs registered in Sweden (b) (Jordbruksverket, 2017-12-31). The calculated ratio is also shown.*

Breed distribution	**No of dogs**	**% of study (a)**	**% in Sweden (b)**	**Ratio (a/b)**
Mixed breed	3	17%	27,05%	0,62
Golden retriever	2	11%	2,68%	4,15
Alaskan Husky	1	6%	0,07%	74,70
Am. Staffordshire terrier	1	6%	0,94%	5,90
Border collie	1	6%	1,31%	4,24
Labrador retriever	1	6%	3,15%	1,77
Papillon	1	6%	0,75%	7,44
Stabyhoun	1	6%	0,08%	70,86
Siberian husky	1	6%	0,57%	9,68
Poodle	1	6%	0,55%	10,07
Tibetan spaniel	1	6%	0,41%	13,45
Nova Scotia Duck Tolling Retriever	1	6%	0,46%	12,11
Weimaranier shorthaired	1	6%	0,08%	70,08
West Highland White Terrier	1	6%	0,34%	16,28
Whippet	1	6%	0,40%	13,89
Total	18			

Sex and Age

Sex and age of the participating dogs are shown in table 8.

Table 8. *Number and percentage of each sex of dogs participating in the study*

Sex distribution	Number of dogs	% of dogs
Female	6	33%
Male	7	39%
Neutered female	3	17%
Neutered male	2	11%
Total	18	

No statistical significant difference between male/female, nor amongst neutered females/males were found.

Age distribution of the dogs in the study is shown in figure 2.

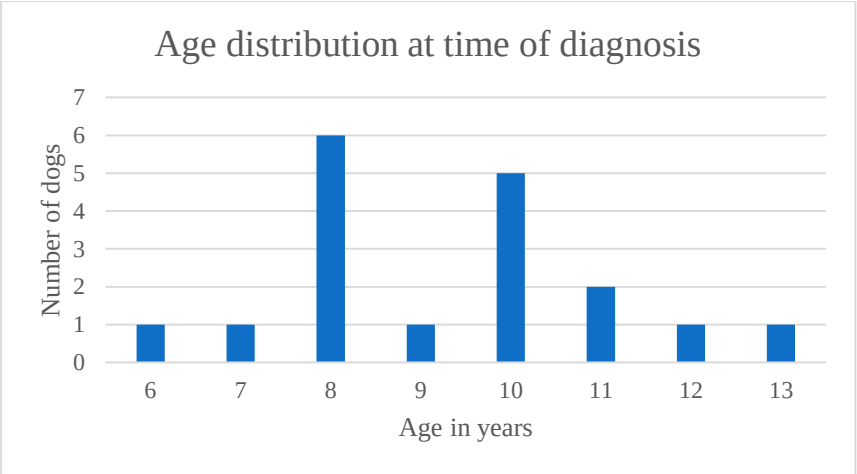

Figure 2. *A diagram showing the age of the dogs participating in the study, at the time of diagnosis.*

Thyroid carcinoma was most common in older dogs. In this study the mean age of the dogs at diagnosis was 9.28 years and the median age was 9.5 years (range 6-13).

Classification

Ten of the dogs included in the study were diagnosed with follicular thyroid carcinoma. Eight of the dogs had carcinomas which were not further classified.

Grading

Based on the information in the medical records the tumors were divided into “highly malignant tumor” and “low malignant tumor”. A survival analysis, shown in figure 3, was made to compare survival time between the two groups.

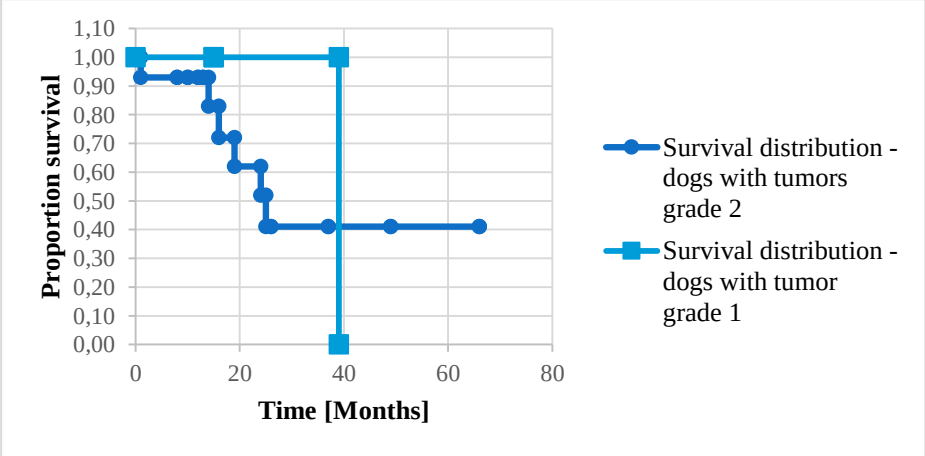

Figure 3. *Kaplan Meier curve showing the survival time of dogs with highly malignant tumors (14 dogs) VS low malignant tumors (2 dogs). No statistically significant P-value was obtained (P=0.8488).*

The mean survival time of dogs with a grade 2 tumor was 37 months. The mean survival time of dogs with a grade 1 tumor was 39 months.

Clinical signs, Metastases and Ectopic thyroid tissue

All dogs examined for thyroid carcinoma at The Veterinary Animal Hospital, UDS had a swelling in the ventral throat region (18 dogs). Other clinical signs reported was PU/PD (2 dogs), increased appetite (2 dogs), weight loss (2 dogs), cough (1 dog) and dysphagia (1 dog).

Based on ultrasound or/and CT-scan, three of the 18 dogs were suspected to have metastases in the right retropharyngeal lymph node. No metastases to the lungs could be detected in any of the dogs.

Survival time dependent on attachment to underlying tissue

A survival analysis (shown in figure 4) was performed to compare survival time depending on how attached the tumor was to underlying tissue.

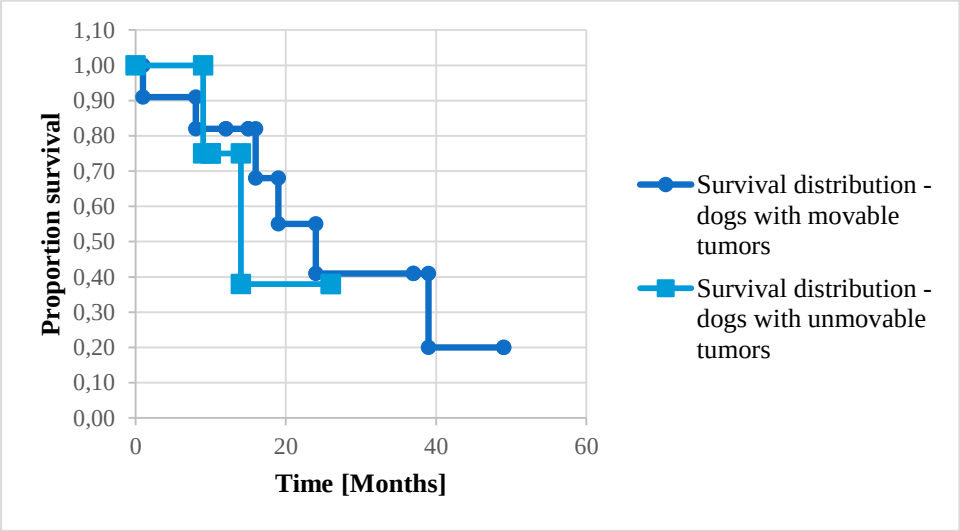

Figure 4. *Survival distribution showing the difference in survival time for dogs with tumors that at the time for examination was assessed as movable (10 dogs) VS not movable (4 dogs). No significant P-value was obtained (P = 0.9798)*

The mean survival time of dogs with movable tumors was 23 months, and for the dogs with unmovable tumors 17 months.

To investigate whether the movability of the tumor correlated with grade of tumor the data was incorporated in table 9.

Table 9. *Distribution of dogs having a grade 2 tumor correlated with clinical movability*

Grade 2 + Movable	8
Grade 2 + Not movable	4
Grade 1 + Movable	2
Grade 1 + Not movable	0

Metastasis

Survival time was compared between dogs with metastases and those without. The result was shown in figure 5.

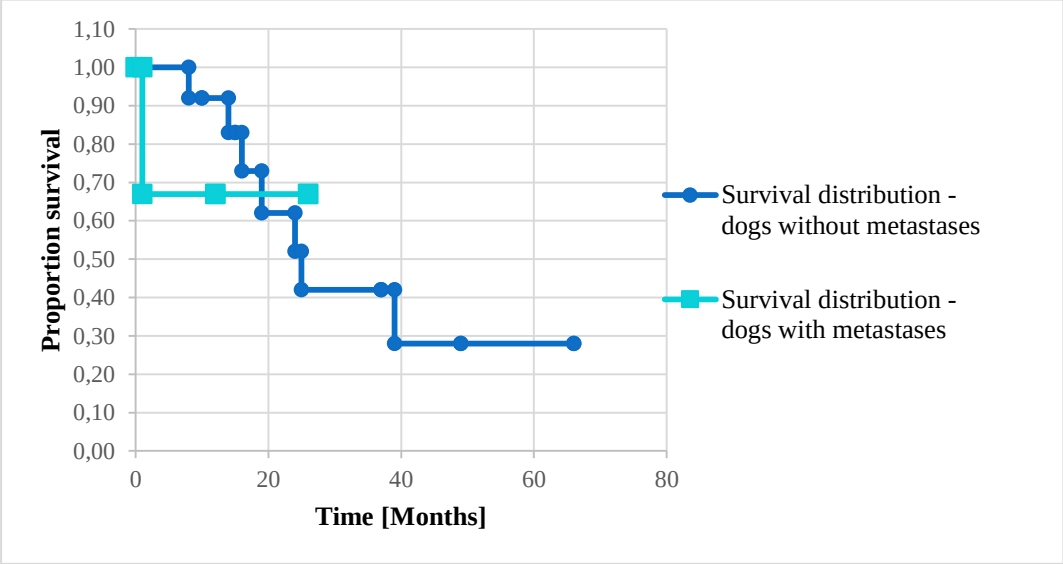

Figure 5. *A Kaplan Meier curve showing survival time depending on whether metastases were evident (3 dogs) or not evident (12 dogs). However, the P-value showed no statistical significance. (P=0.9820)*

The mean survival time of dogs without metastases was 34 months, while the mean survival time for dogs with metastases was 18 months.

Tumor volume and correlation to metastasis

Tumor volume was divided into the same range as in the study by Leav *et al.* (1976) to investigate correlation to metastasis. The result is shown in table 10.

Table 10. *The volume of the tumor was divided into the same range as in the study by Leav et al. (1976)*

Tumor volume	Number of tumors	Metastasis
1-20 cm^3	1	Not known
21-100 cm^3	10	Yes, 3 cases
>100 cm^3	0	0

The chance of metastasis in dogs with a tumor of 21-100 cm3 in this study was approximately 33%.

Ectopic thyroid carcinomas

Ectopic thyroid carcinoma was suspected in two of the dogs as their tumors showed involvement of the hyoid bone. None of these two were autopsied, or had a definite diagnosis though. The survival analysis is shown in figure 6.

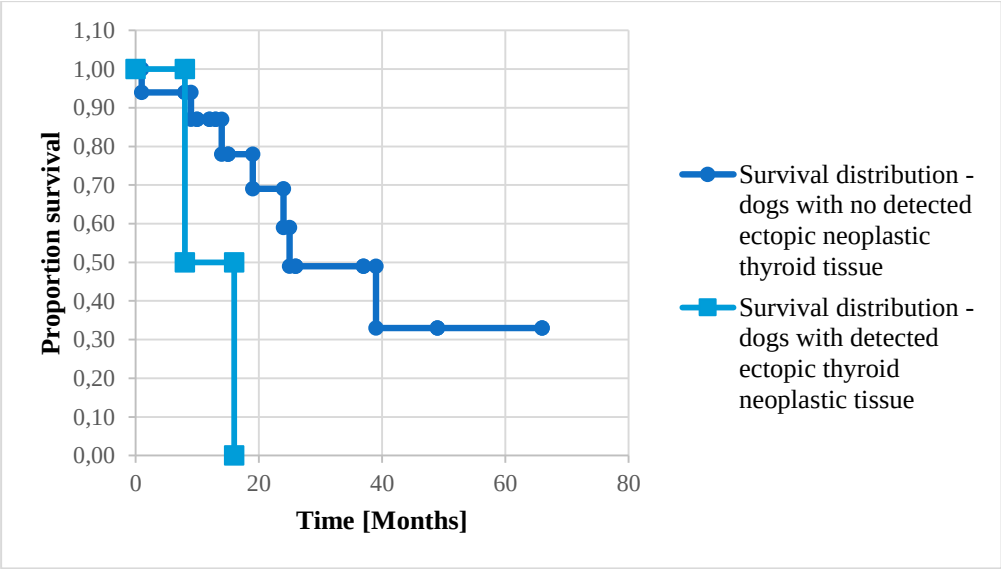

Figure 6. *Survival distribution comparing dogs with detected ectopic thyroid carcinomas (2) to dogs with no detected ectopic thyroid carcinoma (16). P-value = 0.0245.*

The mean survival time of dogs with no detected ectopic thyroid tissue was 36 months. The mean survival time of dogs with detected ectopic thyroid tissue was 12 months.

Blood analyzes

Pre-treatment

Six of the 15 tested dogs were hyperthyroid before treatment. The remaining nine dogs were euthyroid. Calcium levels were normal in all 10 dogs tested prior to treatment.

Post-treatment

After treatment test results showed that four dogs had become hypothyroid due to the surgery. Three of these were hyperthyroid prior to surgery. The other two tested dogs were euthyroid. All 10 dogs tested for calcium post-treatment had normal values.

In figure 7 survival distribution comparing functional thyroid carcinomas and euthyroid dogs with thyroid carcinoma is presented.

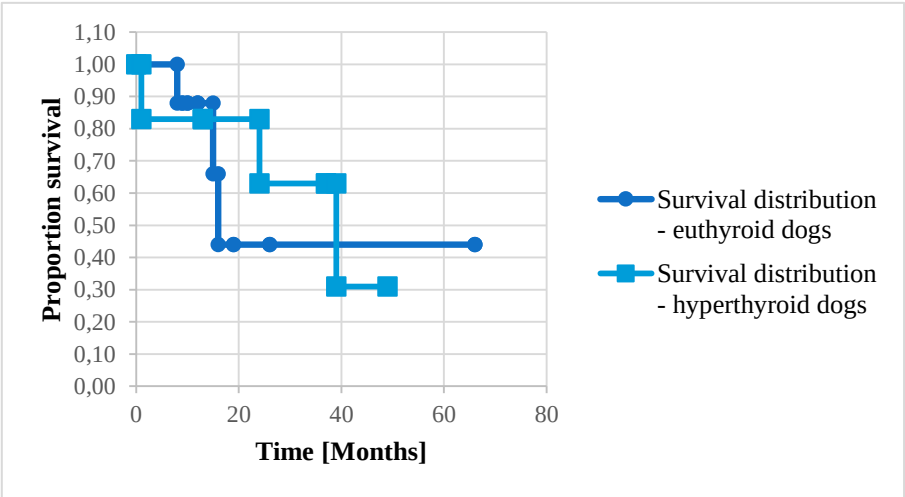

Figure 7. *Difference in survival time between the groups; hyperthyroid dogs (6) vs euthyroid dogs (9). P-value = 0.8736 and thus not statistically significant.*

The mean survival time of hyperthyroid dogs was 38 months. For euthyroid dogs the mean survival time was 33 months.

Diagnosis

FNA iss compared with biopsy to determine the most successful way to diagnose thyroid carcinomas. The data distribution is shown in table 11.

Table 11. *The use of FNA vs Biopsy as a diagnostic method*

	Diagnostic	**Not diagnostic**
FNA	4	8
Biopsy	14	0

The P-value was calculated using Fisher's exact test. There was a significant difference at $P < 0.05$. Thus, in comparison with FNA, biopsy was more likely to be diagnostic.

Treatment

Nine of the dogs were only treated surgically with thyroidectomy. One of these nine dogs had partial thyroidectomy of both thyroid lobes. Four other dogs were treated with both thyroidectomy and chemotherapy (three with carboplatin and one with toceranib phosphate). The remaining five dogs included in the study did not have any treatment of the thyroid carcinoma.

Fourteen of the 18 dogs had tumors which were considered surgically operable. The remaining four were too large and/or too invasive.

Hypothyroidism (4 dogs) and seroma (1 dog) were reported complications to surgery.

One of the dogs treated with thyroidectomy and adjunctive chemotherapy was presented with an infected wound on the paw after the first carboplatin-treatment. This developed into sepsis and treatment with carboplatin was therefore terminated.

Ten of the dogs who had surgical treatment had unilateral thyroid carcinomas. Five of these were left-sided and four were right-sided. The medical record of the tenth dog was lacking information about which thyroid lobe the tumor was occupying. One of the 18 dogs had bilateral thyroidectomy.

Three of the dogs were treated with levothyroxine post-surgery. One of them was euthanized in 2014 and was on medication until then. The other two are still alive, and on medication.

Survival time in months is compared between the three groups "not treated", "surgery and chemotherapy" and "only surgery". The results are shown in figure 8.

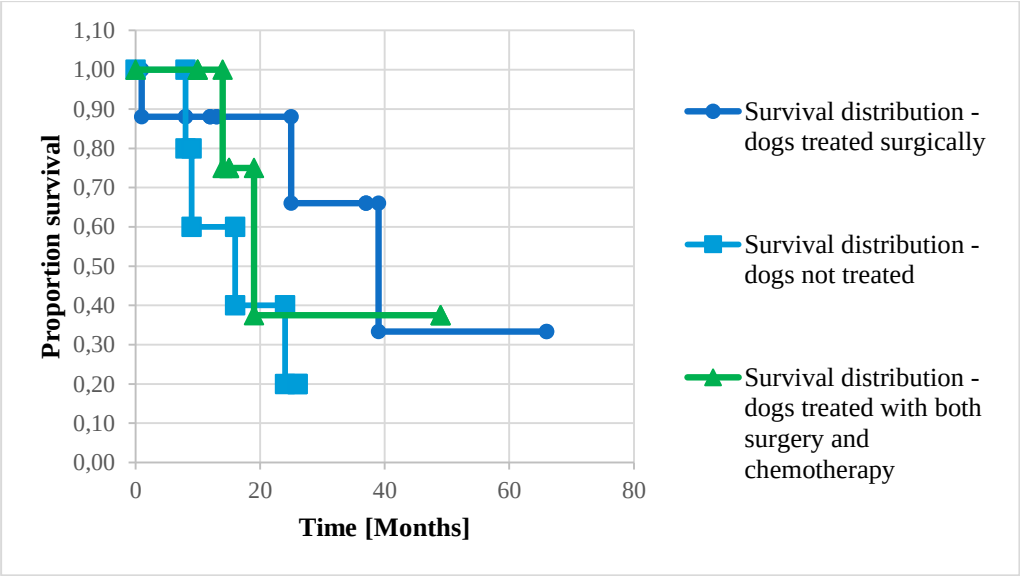

Figure 8. *A Kaplan Meier curve showing the correlation between survival time and treatment method. Surgically treated: 9 dogs, not treated: 5 dogs, treated both with chemotherapy and surgery: 4 dogs. Survival is measured from the day of diagnosis.*

Neither of the groups had a statistically significant difference in survival time. See table 12.

Table 12. *Table showing groups compared and the P-value obtained by a log-rank test*

Groups compared	**P-Value**
Surgically treated VS Not treated	0,1135
Surgically treated VS Treated both with surgery and chemotherapy	0,8118
Treated both with surgery and chemotherapy VS Not treated	0,4756

The mean survival time of dogs treated surgically was 40 months, while the dogs treated with both surgery and chemotherapy had a mean survival time of 29 months. The dogs not treated had a mean survival time of 17 months.

Six of the 18 dogs were euthanized because of their thyroid carcinoma. Four of these dogs did not have any treatment.

Survival

At the end of the study, 9 dogs were still alive and according to their owners, had no signs of recurrence of the thyroid carcinoma. Two of the 9 dogs were on treatment with levothyroxine.

DISCUSSION

Thyroid carcinoma is an important diagnosis. It is not the most common neoplasm among dogs, but it is malignant and more common than the benign thyroid neoplasm, thyroid adenoma. (Wurcherer and Wilkes, 2010). Thyroid adenomas are smaller and the dogs usually do not show any clinical symptoms because of them. In the study by Leav *et al.* (1976) adenomas are found post-mortem in 30% of the dogs with a thyroid neoplasia, only seven of these are big enough to be noticed clinically. Hence, it is not difficult to make the assumption that thyroid adenomas are rarely found and diagnosed.

In humans, medullary thyroid carcinoma has a genetic form. This was explored in a family of dogs which seemed to inherit the disease. The scientists could not find the same mutation involved in the neoplasm in humans, but the family tree clearly showed the trait was inherited (Lee *et al.*, 2006). To know for sure more studies would need to be done to find the mutation causing the neoplasm in dogs. Maybe this would be a step closer to find out at least part of the etiology.

Limitations to the study

This is a retrospective study with a small study population, due to the fact that thyroid carcinomas are relatively uncommon. Like all retrospective studies it depends on the medical records to be correct. Another factor of uncertainty is that many of these dogs lived and died years ago. Even though the owners remember much, specific dates are difficult to recall.

Dogs with both follicular thyroid carcinomas and not further classified thyroid carcinomas are included in the same survival distribution calculations. This may cause a source of error as there can be multiple kinds of thyroid carcinomas in the group “not further classified”. The optimal situation would is if there had been enough dogs to make one survival analysis for dogs with “follicular thyroid carcinomas” and one for “not further classified thyroid carcinomas” but in this case the study population is too small.

Also, there is no data to compare mean survival time of healthy individuals of the same breeds at the time of writing. This makes it difficult to say that the dogs did not die of old age.

Breed, sex and age

The literature mentions Boxer, Golden retriever and Beagle as overrepresented breeds to receive the diagnosis thyroid carcinoma (Brodery & Kelly, 1968; Leav *et al.*, 1976; Wurcherer & Wilkes, 2010). In this study the most common breed is mixed breed (3/18) and Golden retriever (2/18). The rest of the affected dogs are one breed each, therefore when comparing with Sweden’s dog population in total, the most uncommon breeds shows to be predisposed. These breeds are not considered to be more likely to be diagnosed with a thyroid carcinoma, but rather to be a result of statistical fluctuation.

In accordance to previous studies, no predilection for gender was found, nor amongst neutered dogs, if taking into consideration that every fifth dog in Sweden is neutered (Svenska kennelklubben, 2012).

Thyroid carcinomas is shown to be more common in older dogs with a mean age of about 10 years (Brodery & Kelly, 1968; Leav *et al.*, 1976). This is true also for the current study. The mean age is 9.28 years and the median age is 9.5 years. The fact that older dogs are more commonly affected, contradict that thyroid carcinomas in dogs have the same etiology as thyroid carcinomas in young humans exposed to radiation. Studies in young dogs and the effect of high radiation doses can not be found though, probably due to ethical reasons of performing such a study. Tumor development in the thyroid at an older age may rather imply errors in cell division as an etiology, but no articles could be found to support this.

Sometimes it may be difficult to determine the reason for euthanasia in an old dog, especially when reading a study. Even though the study may be about thyroid carcinomas, the dog could have another disease not linked to the neoplastic thyroid and die of other causes not known to the author. Six of the 18 dogs in this current study are euthanized because of the thyroid carcinoma, three due to other causes. The remaining nine dogs are still alive.

Classification and grading

According to Lee *et al.* (2006) and Carver *et al.* (1995) immunohistochemistry needs to be done to distinguish a medullary thyroid carcinoma from a compact follicular thyroid carcinoma. This gives reason to believe that medullary carcinomas may be more common than we think. There is no information in the journals studied for this paper saying that UDSs lab, "Klinisk kemi" use immunohistochemistry to distinguish medullary carcinomas from the follicular thyroid carcinomas. Thus, we cannot be sure that there is no medullary thyroid carcinomas amongst the dogs diagnosed with follicular thyroid carcinoma.

The TNM-system is usually used to grade the thyroid tumors in the literature. However, at UDS it is not routine procedure to classify the thyroid carcinomas according to TNM. Therefore, to get an overview of how malignant the tumors in this study are, the information in the medical records is used to grade the tumors into two groups, one with low malignant thyroid tumors and one with highly malignant tumors. Most tumors are grouped together in the second group with highly malignant tumors. This is concurrent with earlier studies concluding that thyroid carcinomas are likely to invade nearby tissue and anatomic structures, grow fast and commonly metastasize.

When analyzing the survival rate using the Kaplan-Meier method the group with a grade 1 tumor actually lived for a shorter time than the dogs with a grade 2 tumor. This is probably due to source of errors, such as a too small number of dogs in the group "Grade 1 tumor". Looking individually at these two dogs the prognosis looks fairly good. The dog with a grade 1 tumor and a survival time of 39 months is not euthanized because of the thyroid tumor. According to the owner of this dog the thyroid carcinoma did not reappear after surgery. The second dog with a grade 1 tumor is still alive 13 months after surgery with no signs of recurrence. No significant statistical difference can be shown between the two groups.

Clinical signs, Metastases and Ectopic thyroid tissue

Clinical signs

The most commonly noted clinical feature described in the literature is a swelling in the ventral throat region. All the patients treated at UDS had this symptom, although in most of them this was the only symptom. The literature also describes dyspnea, coughing and dysphonia to be relatively common symptoms. This difference might be explained by the fact that most of the dogs participating in the previous studies had a progressed thyroid carcinoma. Several of the studies were performed on dogs which had been through several treatments already, and where the treatment, subject to the study was the last option left. At UDS the dogs may have been referred from another animal hospital, but rarely unsuccessfully treated previously, and thus the tumor could be assumed to not be as progressed as the ones in the previous studies.

Another explanation could be that in Sweden, due to cultural differences, dog owners might be more prone to consult the veterinarian early and get their dog examined for a lump, than in other countries.

Movability of the mass

The Kaplan Meier analysis in this dissertation show that the survival time for the dogs with an unmovable tumor is shorter than for the dogs with a movable tumor. It should however be noted that the P-value is high and the result therefore not conclusive. Previous studies on this cannot be found. To explore this further, studies with a bigger study population needs to be done.

The study by Deitz *et al.* (2014) saying clinical movability cannot be seen to correlate with the degree of malignancy or invasion into surrounding tissue, agree with this current study. Both are small studies which limit the probative, but as the dogs with a grade 2 tumor has double the amount movable tumors than not movable tumors it seems likely that clinical movability has little to do with the invasiveness of the tumor. To assess that, a CT needs to be done.

Metastases

The survival distribution of dogs in this study with metastases VS dogs without metastases shows a longer survival time for dogs without metastases. As metastasis of the tumor is a well-known factor for a less favorable prognosis this is not surprising. Although, the difference is not statistically significant.

All tumors in this current study have the volume of 1-20 cm^3 or 21-100 cm^3. According to Leav *et al.* (1976) the volume of the tumor correlates with the risk of metastasis. Tumors with a volume higher than 100 cm^3 have a 100% risk of metastasis, while tumors between 21-100 cm^3 have 74% risk. The calculated risk in the current study, is as low as 33% when the tumor is between 21-100 cm^3. However, two of the three tumors with metastases are in the top three tumors with largest volume.

Ectopic thyroid tissue

Ectopic thyroid tissue could be found along the cervical region, adjacent to the aorta and/or along the hyoid apparatus (Konig & Liebich, 2014; Swartz *et al.*, 1911). Two of the dogs participating in this study had an ectopic thyroid carcinoma invading the hyoid bone. This was

diagnosed by FNAB, ultrasound and CT, however, no post-mortem examination or histology was performed to confirm the diagnosis. The current study showed FNA was a fairly limited tool when it came to diagnosing thyroid carcinomas, this uncertainty should be kept in mind when interpreting the results.

When the groups "Dogs with ectopic thyroid carcinoma" and "Dogs with no detected ectopic thyroid carcinoma" was compared, a statistical significant difference was obtained in survival time. This meant that dogs with an ectopic thyroid carcinoma in the hyoid region had a worse prognosis than a dog with a thyroid carcinoma in the normal anatomic location for the thyroid. However, these two cases had very invasive types of tumors, both were invading the hyoid bone, and one was also invading the linguofacial vein. Thus, their prognosis was obviously not good. As there were only two such tumors, one should still be careful to draw conclusions and not say that all dogs with ectopic thyroid tumors had a worse prognosis than a dog with a thyroid carcinoma. Especially not since the ectopic thyroid tissue can be located in such a variety of anatomic locations.

Blood analyses

TSH and T4 values are used to determine if the tumor is functional or not. A low TSH- and high T4 value indicates hyperthyroidism, while a high TSH- and a low T4 value indicates hypothyroidism. It is important to know before surgery as it has an effect on the metabolism. The author considers it important to follow up on TSH and T4 values after surgery as several thyroidectomies have led to hypothyroidism (Nadeau & Kitchell, 2011; Tuohy *et al.*, 2012).

Four dogs in this current study are hyperthyroid prior to surgery, three of them are hypothyroid after surgery. This supports the hypothesis of uncontrollable tumor production of T3 and T4, with the consequence of a regression in the contralateral thyroid lobe. When removing the thyroid lobe containing the tumor, there is almost no tissue left to produce T3 and T4, making the dog hypothyroid instead. One of these dogs recovered from the hypothyroidism in time, but the other two remained on the same dose of levothyroxine.

All tested dogs were normal in calcium-levels, indicating that the parathyroid remained after surgery. If the parathyroid glands are both invaded by the tumor, Fukui *et al.* (2015) suggests a method where they mince the parathyroid gland into small cubes and then implant them into muscles. This seems like a clever way to keep the body's natural way of regulating calcium as long as no tumor cells are left in the body and start to grow. The dog in the study by Fukui *et al.* (2015) with the implanted parathyroid gland needed calcium supplement for 110 days, after that it was discontinued. Recurrence was suspected at the last follow up (at 42 months post-surgery), but not confirmed.

The survival distribution of euthyroid dogs compared to hyperthyroid dogs (before surgery) showed a longer survival time for the euthyroid dogs in this study. This could be due to the metabolic stress to which the body is exposed by being hyperthyroid, but most dogs are "cured" from the hyperthyroidism after surgery. As noted above, three of the hyperthyroid dogs in this study became hypothyroid after surgery. Maybe this abrupt change in hormone concentration was tough for the body to adjust to. No previous studies comparing this could be found in the

literature, and so it was difficult to draw any conclusions based on these relatively few dogs, especially as the P-value was high.

Diagnosis

Owen (1980) declared five examinations necessary for the diagnosis of thyroid carcinomas. However, the diagnostic methods have developed since then. Today it is more common to use ultrasound and CT to diagnose the thyroid carcinomas than x-ray and scintigraphy. CT can in theory replace ultrasound, the clinician get more information about the tumor from a CT-scan than from an ultrasound, especially if the tumor is of substantial size. However, ultrasound is cheaper and faster, and even though most dog owners have their dogs insured, this is not true for all cases. Ultrasound is also helpful when taking an FNAB to avoid puncturing a blood vessel.

Scintigraphy is used when the clinician has a suspicion of a functional thyroid carcinoma. At UDS the radionuclide 99m-Tc pertechnetate is used. It is more available than the other radionuclides, cheaper, and the examination can start after 20 minutes, instead of 4-24 hours as in a dog who has been injected with ^{123}I. The only drawback of 99m-Tc pertechnetate seems to be the uncertainty of it detecting metastases (Bähre *et al.*, 1988; Arnold & Pinsky, 1975). Considering the advantages of 99m-Tc pertechnetate it is logical that it is the most used radionuclide at UDS. The dogs in this current study, diagnosed with scintigraphy, are scanned with 99m-Tc pertechnetate. None of them are proven to have metastases. This might mean that there are none with metastasis, but according to the literature (Silverman *et al.*, 1983; Adams *et al.*, 1995; Taeymans *et al.*, 2007) the metastases might not have increased uptake, even though the original tumor has, and therefore not show on the scintigraphy. No autopsies were performed, which makes it difficult to know for sure.

It is not common to use MR imaging on the patients with a thyroid carcinoma, despite the fact that it is proven to be the best method for visualizing capsule disruption (Taeymans *et al.*, 2008a; 2013). One reason may be that it is more expensive than CT, but it is also safer for both animal and personnel without the exposure of the large dose of radiation by a CT-scan. There are descriptions in the literature (human medicine) of MRI being used for guidance of FNA biopsies as well, but a few obvious things makes an MRI-guided FNA difficult to perform, such as the design of the MRI apparatus. It is not easy to access the patient while going through an MR-scan. The systems have developed though, but far from all MRI-systems are possible to use for taking biopsies (Weiss *et al.*, 2008).

Research in human medicine has shown a way to differ between human papillary carcinomas and benign nodules with the help of MRI (Noda *et al.*, 2015). No studies are found on dogs with thyroid carcinomas regarding this, but it would be interesting to know if this fact is true even for dogs with thyroid adenoma/carcinoma. If so, this would be an additional reason to explore the use of MRI as a diagnostic tool for suspected thyroid neoplasms instead of CT.

Histological examination was one of Owens (1980) criteria for diagnosing a thyroid carcinoma. This still needs to be done to confirm the diagnosis. Many clinicians use FNA biopsy as a first step in treatment. Thompson *et al.* (1980) did research to find out whether FNA could be used

in the diagnosis for thyroid carcinomas. They showed that it could, but when looking more closely at their results, FNA, in contrast to tissue biopsy and histology, almost never provided a definitive diagnosis but rather a step on the way to diagnosis.

In this current study, biopsy is needed to confirm the diagnosis in most cases, even after a FNA biopsy. The author therefore questions FNA biopsy as a tool in the diagnosis of thyroid carcinomas. It is an easy method, but can still lead to hemorrhage and discomfort for the dog, and is rarely of much use. Furthermore, if this is the only reason for an ultrasound (hence, the patient is still going through a CT before surgery) this is one more reason not to do an FNAB before surgery. There are articles describing CT-guided FNA biopsies, but these take a long time to perform (about 22 minutes) compared to the ultrasound-guided biopsies. However, an important positive aspect of the use of an FNAB is that it is useful in ruling out differential diagnoses.

Treatment

Compared to previous studies (Carver *et al.*, 1995) many of the tumors in this current study were operable. In a study by Carver *et al.* (1995) the percentage of operable tumors was 64%. Of the 18 dogs in this study, 78% were considered removable. As noted before, this might be due to less progressed tumors in the current study. To support this, three of the dogs with an adenocarcinoma had metastasis to the lungs in the study by Carver *et al.*, indicating a more progressed neoplasm.

The dogs studied at UDS had a low frequency of complications during/after surgery compared to the dogs in the literature. This may be because their surgeons performing the thyroidectomies are well qualified, the tumors were observed early by the owners, the owners were not good at reporting the complications, the complications were not incorporated in the journals, or a combination of those reasons.

When comparing survival distribution, the group with dogs treated solemnly with surgery was the one with the longest survival time. Mean survival time was calculated to 40 months. Even though there was an obvious difference in the group “not treated” and “treated surgically” the result of the P-value showed it was not statistically significant. The P-value was however low enough to not ignore the results showing the increase in survival time. The mean survival time of the dogs not treated was 17 months. More studies on bigger populations needs to be performed. However, one should take into consideration that the dogs with thyroid carcinomas usually were above middle age. To prolong their life with approximately 40 months was in many cases a lot, and maybe all we could ask for. These results are similar to the ones in the study by Tuohy *et al.* (2012) where the mean survival time was 38.3 months. In many aspects Tuohy’s study was similar to the current study, the study population was almost the same size and the survival time was analyzed using the Kaplan-Meier method. It differs in that Tuohy *et al.* had the groups “dogs treated both surgically and with chemotherapy”, and “dogs treated only with surgery” mixed together though.

The five dogs treated both with surgery and chemotherapy unexpectedly had a lower mean survival time than the dogs treated only with surgery. The mean survival time for this group

was 29 months. An explanation could be that the dogs in this group had a worse prognosis even from the start, and that may also be the reason for treating them with adjuvant chemotherapy. This was partly true, they all had a bad prognosis; one had a very invasive tumor with high mitotic activity, one had dirty margins after surgery, one had an anaplastic thyroid carcinoma and the last one had infiltrative growth into surrounding tissue. However, so did most of the dogs treated only with surgery. Another reason for the bad prognosis could be that the tumor was more progressed in these five dogs. The two of these tumors measured at the CT-scan were amongst the ones with largest volume. A previous study comparing a group of dogs treated only surgically, with a group treated with both chemotherapy and surgery showed almost no difference in mean survival time (510 VS 518 days) (Nadeau & Kitchell, 2011). There was a study showing a lower survival time, with an average of 191.8 days, but these scientists did not differ between dogs who had previous treatment with surgery and dogs that did not. Six of the thirteen dogs did not have any previous treatment, which reasonably lowers the survival time. The authors of the same study found an interesting fact; two of the dogs who had been unresponsive to doxorubicin responded with partial remission when given cisplatin (Fineman *et al.,* 1998). The two cytotoxic drugs both bind to the DNA to inhibit the replication. Cisplatin had been reported to be a bit less cell cycle specific than Doxorubicin, that fact may play a part in why it was more effective on thyroid carcinomas.

Overall, response to treatment with chemotherapy is low. One study reports 54% (Fineman *et al.,* 1998), another 19% (Knapp *et al.,* 1988). This is probably due to that we know too little about thyroid carcinomas. Without an etiology it is difficult to find effective treatment as we do not know what to direct the treatment at, on a cellular level. Many cytotoxic drugs have effect on more than one part of the cell cycle, but since none have been found which seems to help substantially, the author of this dissertation thinks there is still much we do not know about the upcoming of thyroid carcinomas.

Four of the five dogs treated at UDS were given carboplatin, and the fifth toceranib. Toceranib is a drug inhibiting the enzyme protein kinase. London *et al.* (2011) studied toceranib given to 15 dogs with a thyroid carcinoma. Ten of the dogs were previously treated. The study showed positive results of treating the dogs with toceranib, and also, it resolved the lung metastases evident in two of the dogs. In conclusion; toceranib might be more close to inhibiting the reason for the upcoming of thyroid carcinomas than carboplatin or doxorubicin. At the very least, it could have a better effect on the metastases of these neoplasms.

Campos *et al.* (2014) showed that there was no significant difference in survival between a dog with medullary thyroid carcinoma and a dog with follicular thyroid carcinoma. As previously noted, these two types of thyroid carcinomas are easy to mistake for each other. Therefore if one is only interested in survival time, maybe it is not essential to differ them.

Radiotherapy with ^{131}I may work if the tumor is hyperfunctional and shows an increased uptake of ^{131}I (Peterson *et al.,* 1989). Not many studies are performed on dogs, but one indicates that radiotherapy is a good adjunctive treatment to surgery. The dogs treated with both ^{131}I and surgery has the longest mean survival time (4 months longer than the group treated only with surgery) (Worth *et al.*, 2005). On the contrary, a study published in 1995 reported no significant reduction in tumor size (Adams *et al.,* 1995). Only one of the seven dogs in Adams study has

a hyperfunctional thyroid. These results indicate that the conclusions Peterson *et al.* (1989) draws in their study may be correct. Peterson *et al.* (1989) also points out the problem with treating a dog with ^{131}I – there is a long period of hospitalization in special radiation safe facilities after treatment to collect the radioactive waste (urine, feces). No such facilities exists for animals in Sweden, making treatment (especially of large dogs) difficult. Another problem to treatment with ^{131}I is that metastases can have a lower or no uptake of the radionuclide. Thus, if the dog has metastatic spread, another treatment method, for example chemotherapy may be a better option.

External radiation therapy is considered a good palliative treatment, but with the presence of metastases, evidence shows that the disease progresses even after treatment (Theon *et al.*, 2000). Both the study by Pack *et al.* (2001) and Brearley *et al.* (1999) were small and had few dogs with metastases. This explains why both of them has a lower survival time than the dogs in the study by Theon *et al.* Theon *et al.* (2000) presents a mean survival time of 45 months, a lot more than the mean survival time of 24, respectively 24,5 months presented in the other studies. Although, in the study by Theon *et al.* (2000) 14 of the 25 dogs are treated surgically before referral for external radiation. To summarize; external radiation alone may increase survival time with a few months (mean survival time 24 months, compared to the untreated group in this current study with a mean survival time of 17 months). Dogs treated with external radiation as adjunctive treatment to surgery may have a longer mean survival time than dogs treated only surgically (45 months in the study by Theon *et al.*, compared to the current study with a mean survival time of 40 months in dogs treated solemnly with surgery).

CONCLUSION

In conclusion, the results in this dissertation cannot confirm the hypothesis that treatment increases survival time in dogs with thyroid carcinoma, as no significant difference was found between dogs not treated, and the dogs that were treated. However, the P-value was relatively low, and so maybe with a bigger study population it could be possible to prove that treatment prolongs time of survival.

The only factor which significantly worsened the prognosis was if the dog had neoplastic ectopic thyroid tissue. Although, as previously discussed, this conclusion had a few sources of errors.

Further studies are needed to investigate the following potential prognostic factors; grade of tumor, hyperthyroidism VS euthyroidism, attachment to underlying tissue and metastases.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Elakartad cancer i sköldkörteln är inte den vanligaste diagnosen bland hundar, endast 1-2% av alla hundar som får cancer drabbas av just sköldkörtelcancer. Det är ändå en viktig sjukdom att uppmärksamma då den elakartade typen är vanligare än den godartade. Diagnos i tidigt skede är viktigt för att hinna operera innan tumören växt in alltför mycket i omkringliggande vävnad eller spridit sig till någon annan del av kroppen. Ju större tumören hunnit bli, desto större är risken för att den ska ha spridit sig. Resultaten i denna studie visar att ju mer fast tumören sitter i omkringliggande vävnad, desto sämre prognos. Detta resultat skulle dock kunna bero på slumpen då skillnaden inte är tillräckligt stor för att säga att den är statistiskt signifikant.

Målet med det här examensarbetet var bland annat att uppmärksamma sköldkörtelcancer hos hund, samla in information från tidskrifter för att öka kunskapen om tecken på sjukdomen, för- och nackdelar med olika sätt att diagnostisera, behandlingsalternativ och prognos för dem. Studien på de 18 hundar som behandlats för sköldkörtelcancer på universitetsdjursjukhuset i Uppsala de senaste 10 åren var tänkt att ge en indikation på om behandlingen ökar hundarnas livslängd. Enligt överlevnadskurvan (se figur 2 i arbetet) är resultaten positiva. Både gruppen där sköldkörteln med cancer i tagits bort, och i gruppen där sköldkörteln tagits bort och hunden sedan hade behandlats med cellgifter levde längre än hundarna i gruppen som inte fått någon behandling. Gruppen var dock för liten för att dra några slutsatser till en större population, som t.ex. alla hundar inom europa med sköldkörtelcancer. Resultatet av borttagandet av sköldkörteln berodde dessutom på ett flertal olika faktorer, som hur duktig den opererande veterinären var, hur långt gången cancern var och hur gammal hunden var. Det verkade ändå vara så att borttagning av tumören var den mest effektiva metoden för att öka överlevnadstiden hos hunden. Resultaten gav en konkret grund att stå på när man som veterinär rekommenderade behandlingsalternativ till en patient på UDS i Sverige. Det skulle också kunna vara till hjälp vid diagnos och val av behandling av vilken hund som helst med elakartad sköldkörtelcancer under förutsättning att det inte är den enda källan till information.

Det finns två huvudsakliga grupper man delar in elakartad sköldkörtelcancer i; gruppen där tumören utvecklas från en celltyp (C-celler) som bland annat har hand om kalciumomsättningen i kroppen – medullär sköldkörtelcancer, och en typ som utgår ifrån sköldkörtelns epitelceller, de som bland annat tillverkar hormonen som till stor del styr vår ämnesomsättning – follikulär sköldkörtelcancer. Den follikulära typen är vanligast hos hund. Några studier visar dock att en särskild typ av follikulär sköldkörtelcancer är lätt att blanda ihop med medullär och att mörkertalet därför är stort. Vissa av de follikulära sköldkörteltumörerna producerar för mycket av dessa hormoner, de kallas då funktionella sköldkörteltumörer. Resultaten i den pågående studien visar att hundarna med en överfunktionell sköldkörteltumör har en sämre prognos än en hund med en sköldkörtel som trots sin tumör, fungerar normalt.

Den medullära typen är hos människa associerad med en ökad frisläppning av hormonet calcitonin, som reglerar kalciumnivåerna i blodet. Trots detta verkar inte kalciumnivåerna påverkas hos människa, det har dem dock visats göra hos hund. Hos människa finns också en ärftlig variant av medullär sköldkörtelcancer. Lee *et al* (2006) rapporterar om en familj av hundar som uppvisar liknande sjukdomsbild som denna typ. Däremot saknas en av mutationerna som ses hos människa med den typen av medullär sköldkörtelcancer.

Gradering av sköldkörtelcancer förekommer. Det vanligaste använda systemet är TNM (tumour, nodes, metastases). Där används siffror för att tala om hur stor tumören är, om den har spridit sig till närliggande lymfknuta/lymfknutor och om metastaser har hittats eller inte. I denna studie visade sig överlevnadstiden vara kortare om hunden hade en metastas. På universitetsdjursjukhuset i Uppsala är det inte rutin att gradera sköldkörtelcancern efter TNM-systemet. Inför denna studie delades därför tumörerna upp i grad 1 och grad 2, baserat på informationen i journalerna. Överlevnadstiden för hundarna med grad 1 var lägre, men gruppen bestod bara av två hundar, varav en lever och en avlivades på grund av andra orsaker än sköldkörtelcancern, resultatet bör därför tas med en nypa salt då det var såpass få hundar i gruppen.

Det är inte helt klarlagt hur sköldkörtelcancer hos hund uppstår. På människa är det visat att en hög dos strålning i ung ålder ger upphov till sköldkörtelcancer, men något liknande har inte bevisats hos hund. Teorier finns om att det har med ett hormon som heter TSH (Thyroid stimulating hormone) att göra eftersom det binder till epitelcellerna i sköldkörtel och aktiverar dem. Inom humanmedicin har det även gjorts studier på cellnivå och konstaterats olika förändringar i cellens beteende och uttryck beroende på typ av sköldkörteltumör.

Litteraturen anger att sköldkörtelcancer är vanligare hos vissa hundraser; golden retriever, boxer och beagle är tre av dessa. På grund av att denna studie innehåller så få patienter kan ingen pålitlig slutsats dras baserat på de raserna. Ingen studie bland de som hittats under litteratursökningen har kunnat visa att sköldkörtelcancer hos hund är vanligare hos något av könen. Även i denna studie, trots de få patienterna, är det ungefär lika många av varje kön. Det är i regel äldre hundar över 10 år som får sköldkörtelcancer, vilket även stämmer bra med resultaten i denna studie.

Det allra vanligaste tecknet på att din hund fått sköldkörtelcancer är en knöl på undersidan av halsen. Ibland kan de också få svårt att svälja och/eller andas. Hos veterinären tas inledningsvis oftast ett prov från sköldkörteln med en tunn nål som sticks in i knölen. Ibland använder man ultraljud för att guida nålen rätt, eftersom tumören kan vara mycket blodförsörjd och därmed lätt börja blöda. Från det provet kan man ibland sedan hitta tumörcellerna när man tittar på det i mikroskop. Pågående studie visar dock att denna metod (finnålsaspiration) är mycket osäker i jämförelse med att göra en undersökning på den tumöromvandlade vävnaden efter att den blivit borttagen, ett så kallat vävnadsprov. Däremot kan ett FNA vara bra att ta för att utesluta att knölen är något annat än en sköldkörteltumör.

Oftast görs också en så kallad datortomografi på halsen, en slags röntgenteknik där man får ut flera röntgenbilder i en lång sekvens, för att kunna studera tumören i flera lager. På så sätt kan man se om den går att operera, eller om den någonstans växt in för mycket i omkringliggande vävnad/strukturer. Har tumören växt in för mycket i den omkringliggande vävnaden rekommenderas inte operation, utan hunden får leva så länge den mår bra och inte störs av knölen. Man kan behandla för att förlänga livstiden, med tillexempel radioaktiv strålning som har visat sig tillfälligt minska tumörens storlek.

Om tumören är möjlig att ta bort rekommenderas oftast det, med reservation för att prognosen är osäker. Man kan också välja att behandla med cellgifter efter operationen för att få bort

eventuella rester av tumören. Enligt resultaten i den här studien ökar inte det överlevnadstiden, men det finns studier som visar på en längre överlevnadstid vid operation följt av cellgiftsbehandling.

Studien utfördes genom att göra en sökning i journalsystemet Trofast efter journaler på alla hundar som fått diagnosen sköldkörtelcancer på universitetsdjursjukhuset i Uppsala 20080906-20180906. Journalerna gicks sedan igenom och data från dem samlades in. Några djurägare kontaktades via telefon för att samla in kompletterande information. Litteratursökningen gjordes i databaserna ”Web of science”, ”Pubmed” och ”Google Scholar”.

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