DIAGNOSIS AND MANAGEMENT OF THYROID CARCINOMA IN CANINES

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James Elliott discusses methodologies for identifying this often-found disease, and outlines protocols for surgery, chemotherapy and radiotherapy

TUMOURS of the thyroid gland are relatively common in dogs and account for between 1.2 and 3.8 per cent of all canine tumours[1].

The majority of these tumours are unilateral and non-functional (in this article, functionality refers to the ability of the tumour to produce excessive thyroid hormone). Surgery, radiotherapy and chemotherapy can be used solely or in combination to treat this disease, and the prognosis is good with appropriate therapy, with long survival times reported.

Clinical signs, examination and differentials

Dogs usually develop these tumours when they are older, generally at around nine to 10 years of age[2].

Malignant thyroid tumours are frequently large and poorly encapsulated, and may invade into adjacent normal tissues, such as the trachea, larynx, oesophagus, cervical musculature and regional neurovascular structures[2]. Early invasion into the cranial and caudal thyroid veins, with subsequent tumour thrombi formation, is associated with the development of pulmonary metastasis and cranial vena cava syndrome[3,4,5].

The majority of these masses are unilateral, although bilateral disease can occur[2]. Unlike cats, thyroid tumours in dogs are usually non-functional, and it is rare to find dogs with clinical or biochemical evidence of hyperthyroidism.

Hypothyroidism is also possible and may be caused by the neoplastic destruction of normal thyroid tissue, suppression of pituitary thyroid-stimulating hormone (TSH) secretion and subsequent atrophy of normal thyroid tissue[1,2].

The most common presentation is a palpable mass in the ventral or ventrolateral cervical region. Differential diagnoses for masses in this region include abscesses, granulomas, salivary mucoceles, other primary tumours (such as carotid body tumours, soft tissue sarcomas and so on), lymphoma and nodal metastasis from other head and neck tumours. Other clinical signs include coughing, gagging, retching, regurgitation and dysphonia.

Fixed thyroid carcinomas invade into adjacent structures and cause a variety of clinical signs, such as dyspnoea, dysphonia, dysphagia, Horner's syndrome and cranial vena caval syndrome. Severe haemorrhage due to arterial invasion has also been reported[6].

Dogs with functional thyroid tumours have similar clinical signs to hyperthyroid cats, but the symptoms are usually less severe[1,2]. Ectopic thyroid tissue is common in dogs, and thus tumour tissue can occur anywhere from tongue base to thorax[7,8,9].

Physical examination is important to determine the size and degree of fixation of the thyroid mass, assess for metastasis to the regional lymph nodes and determine the presence of concurrent conditions that may affect anaesthetic and surgical management.

Malignant thyroid carcinomas are either freely moveable (approximately 24 to 55 per cent) or fixed and invasive (around two thirds)[1,2]. This is an important distinction, because the treatment options for the primary tumour are determined by the degree of fixation.

Occasionally, determining whether a thyroid tumour is mobile or fixed can be difficult in a conscious dog and, in these cases, palpation under anaesthesia, imaging tests or exploratory surgery are required.

Staging

Staging dogs with thyroid tumours includes haematology, biochemistry, serum TT4 and TSH concentrations, evaluation of the characteristics of the local tumour, assessment of the regional lymph nodes, and three-view thoracic radiographs.

Full staging should also ideally include assessment of the abdomen (such as with ultrasound), but the diagnostic yield of this is likely to be low.

The majority of dogs diagnosed with thyroid tumours are middle aged to old, so it is important to assess their health status with haematology, serum biochemistry, urinalysis and abdominal ultrasonography before embarking on potentially lengthy and expensive treatment.

Palpation and imaging modalities are used to assess the size of the tumour and degree of invasiveness. Ultrasound is a valuable and relatively inexpensive imaging modality to differentiate thyroid tumours from other ventral neck masses, to assess the vascularity and degree of invasion of thyroid masses, to assess the presence of bilateral thyroid disease, and to guide fine-needle aspirates or Tru-cut biopsies[10].

Advanced imaging techniques, using contrast-enhanced CT or MRI, have been described for the diagnosis of thyroid tumours, but their principal indication is for planning radiation treatment of invasive or incompletely resected malignant thyroid tumours. These advanced imaging modalities have also been recommended for evaluating the surgical resectability of these tumours, which seems logical and theoretically may help prevent futile and potentially dangerous surgery in older animals.

However, surgical exploration is often a more accurate, rapid, and cost-effective method of determining tumour invasiveness and respectability[11].

Radionuclide imaging using either technetium-99m pertechnetate or iodine131 has been described for diagnosing thyroid neoplasia in dogs.

Thyroid tumours do not need to be functional for an abnormal scintigraphic study, although hyperthyroid dogs have a more intense uptake than euthyroid dogs. This imaging modality is particularly useful for identifying malignant ectopic tissue – which can be difficult to detect using conventional imaging modalities – and regional lymph node metastasis, but not pulmonary metastasis[11]. These modalities are not used routinely in the diagnostic work-up of canine thyroid tumour patients.

The regional lymph nodes and lungs are the two most common metastatic sites in dogs with thyroid carcinomas.

Careful attention to regional nodes is, thus, important in managing these dogs. Lymph drains cranially from the thyroid glands – therefore, the regional lymph nodes for dogs with thyroid tumours are the mandibular, parotid and medial retropharyngeal lymph nodes[1,12,13]-[14]. Studies in cats and dogs with oral tumours suggest we may miss discovering nodal metastases if we only assess the submandibular nodes.

Perhaps, then, we should make more effort to aspirate each of these lymph nodes under ultrasound guidance for clinical staging purposes[13,14].

Three-view, inflated thoracic radiographs are recommended for evaluating pulmonary metastasis[5]. Following these staging tests, dogs with thyroid tumours are clinically staged according to the World Health Organization's TNM staging system ([Table 1]).

A biopsy is required for definitive diagnosis. Fine-needle aspiration (FNA) should be performed initially because it is minimally invasive and does not require sedation or general anaesthesia. However, the diagnostic accuracy of this technique is low because of frequent blood contamination[15].

Ultrasound guidance of fineneedle aspirates or needle-core biopsies may improve the diagnostic accuracy by reducing the risk of blood contamination.

Incisional biopsies are recommended for definitive diagnosis of fixed and invasive thyroid masses, but are rarely indicated for mobile thyroid tumours because the surgical approach for this biopsy is the same as for thyroidectomy.

Furthermore, because of the highly vasculature nature of thyroid tumours, surgical biopsy procedures are also associated with a high risk of haemorrhage – this complication should be considered when deciding whether to perform a biopsy of a thyroid mass[1].

FNA cytology of thyroid masses yields cells of neuroendocrine appearance, with typically minimal criteria of malignancy[15]. Therefore, cytological appearance cannot be used to predict biological behaviour, and one should remember that, in contrast to the cat, almost all thyroid masses diagnosed in practice are malignant.

Treatment

• Surgery[1] [3] [5] [16] [17]

Surgery is recommended for dogs with mobile thyroid tumours or thyroid tumours with invasion limited to the superficial tissues. Surgical exploration may be necessary to determine the level of invasion if this distinction is unable to be made preoperatively.

Surgical resection is not indicated for dogs with deeply invasive and fixed thyroid carcinomas. If the thyroid carcinoma is invasive into adjacent neurovascular structures, then the ipsilateral jugular vein, carotid artery and vagosympathetic trunk can be sacrificed with minimal morbidity. There are no vascular consequences following this procedure, but the dog will be likely to develop unilateral Horner's syndrome.

Thyroidectomy also involves removal of the ipsilateral internal and external parathyroid glands. Preservation of the ipsilateral external parathyroid gland is not necessary because this may increase the risk of local tumour recurrence, and calcium homeostasis will not be

disrupted – providing the contralateral parathyroid glands are not compromised.

• **Radiotherapy**[1][2][3] -[4] ,[16]

Radiation therapy is recommended for dogs with fixed and invasive thyroid carcinomas that are not surgical candidates.

A number of different protocols have been described, including a hypofractionated protocol (9Gy once weekly for four weeks, for a total dose of 36Gy) and fractionated protocols (4Gy per fraction on a Monday– Wednesday-Friday basis for 12 fractions and a total dose of 48Gy). Acute radiation effects include oesophageal, tracheal, and laryngeal mucositis, resulting in mild and self-limiting dysphagia, dysphonia and coughing.

Hypothyroidism is a rare potential late effect following irradiation of thyroid tumours. Most dogs cope with these schedules extremely well.

The outcome following treatment with either hypofractionated or fractionated radiation therapy is very encouraging. The majority of tumours will respond to radiation therapy, with complete responses observed in eight per cent of dogs (such as resolution of palpable tumour) and partial responses in 69 per cent of dogs (such as tumour volume decreases in size by more than 50 per cent). However, it can take between six to 22 months to achieve the maximal reduction in tumour size. Importantly, the duration of this response is excellent, with no tumour progression in 80 per cent of dogs at one year and 72 per cent at three years after irradiation.

Radiation therapy can be used to downstage large invasive thyroid carcinomas and make them more amenable to surgical excision. Although this has not been investigated, surgical removal or de-bulking of residual tumour burden following irradiation may provide a survival benefit, because local tumour progression accounts for a significant proportion of mortality in dogs treated with radiation therapy.

The role of adjuvant radiotherapy following surgical de-bulking/incomplete tumour margins has not been defined in the veterinary literature.

• **Chemotherapy**

Chemotherapy's role in treating dogs with thyroid tumours remains to be defined.

The use of either doxorubicin[18] or cisplatin[19] results in response rates of 30 to 50 per cent in dogs with measurable thyroid carcinomas, which suggests that chemotherapy may have a role in managing canine thyroid carcinomas.

Individual responses have also been noted with mitoxantrone[20][21] -[22] and actinomycin D23.

Chemotherapy should probably be recommended following either surgery or radiation therapy in dogs with a high risk for developing metastatic disease, such as large or bilateral tumours, those with histological evidence of lymphatic/vascular invasion or documented nodal metastases.

In dogs with small, unilateral and perhaps medullary thyroid carcinomas (possibly less aggressive), the choice to proceed with chemotherapy should be dependent on an informed discussion with the owners about the risks and benefits of treatment.

• **Iodine**[24,25,26,27]**-**

Radioactive iodine is the preferred treatment for cats with thyroid lesions and, either as an adjunct to surgery or as a primary treatment for non-resectable malignant thyroid tumours, in people. Thyroid tumours do not need to be functional to respond to radioactive iodine therapy. Pretreatment radionuclide scans are recommended, as it has been suggested that tumours that do not adequately concentrate the radioisotopes are less likely to respond to radioactive iodine therapy.

Radioactive iodine is not effective for treating large tumours, which limits its clinical applicability in many dogs with thyroid tumours. However, a study of 43 dogs treated with one to three doses of iodine-131, either alone (n = 32) or as an adjunct to surgery (n = 11), to a total dose of 555MBq to 1,850MBq, resulted in very encouraging median survival times (MSTs) of 30 and 34 months, respectively. The major disadvantages of radioactive iodine therapy in dogs are the need for very high doses (compared to cats) and prolonged hospitalisation. This limits its availability in the UK.

Prognosis

The prognosis for dogs with malignant thyroid carcinomas is good to excellent with appropriate treatment.

The MST for untreated dogs with thyroid carcinomas is only three months. The MST for dogs with mobile thyroid carcinomas treated with surgery alone is greater than 36 months, with one and two-year survival rates of 75 and 70 per cent, respectively. In contrast, the MST for dogs with fixed thyroid carcinomas treated with surgery alone is only 10 months, with one and two-year survival rates of 25 and 10 per cent, respectively.

Radiation therapy is recommended for treating dogs with fixed thyroid carcinomas, because survival outcome is superior to surgery alone, with a MST of 24.5 to greater than 45 months and one and two-year progression-free survival rates of 80 and 72 per cent, respectively. The MST of 32 dogs treated with iodine-131 alone is 30 months. In 13 dogs treated with a hypofractionated protocol, there was no difference in survival time for dogs with (n = five) and without (n = eight) metastasis at the time of radiation therapy, but this is only a small number.

Tumour thrombi extending into the cranial thyroid vein is associated with a high risk of metastasis. Local recurrence or progression is reported in up to 30 per cent of dogs following thyroidectomy and 24 per cent after radiation therapy.

The metastatic rate for dogs with treated thyroid carcinomas is less than 40 per cent. The risk of metastasis increases in dogs, with tumour volume greater than $20cm^3$ or a diameter greater than 5cm, bilateral thyroid tumours and perhaps follicular thyroid carcinomas (possibly behaviourally more aggressive than medullary thyroid carcinomas).

Dogs with thyroid tumours smaller than $20cm^3$ have a metastatic rate of less than 20 per cent, whereas almost all dogs with tumours larger than $100cm^3$ develop metastases. Dogs with bilateral thyroid carcinomas have a 16 times greater risk of developing metastatic disease than dogs with unilateral tumours.

The risk of metastatic disease is significantly decreased with good local tumour control, as dogs with no evidence of tumour progression have a 15 times decreased risk of developing metastasis[1,2,3,5,16,24,27].

Conclusion

A variety of treatment options are available for dogs with thyroid carcinomas, and even dogs that are not surgical candidates can still enjoy long survival times when treated appropriately.

References

- 1. Liptak J M (2007). Canine thyroid carcinoma, *Clin Tech Small Anim Pract* **22**: 75-81.
- 2. Barber L G (2007). Thyroid tumors in dogs and cats, *Vet Clin North Am Small Anim Pract* **37**: 755-773, vii.
- 3. Brearley M J, Hayes A M and Murphy S (1999). Hypofractionated radiation therapy for invasive thyroid carcinoma in dogs: a retrospective analysis of survival, *J Small Anim Pract* **40**: 206-210.
- 4. Brearley M J (2000). Radiation therapy for unresectable thyroid carcinomas, *J Am Vet Med Assoc* **217**: 466-467.
- 5. Theon A P, Marks S L, Feldman E S and Griffey S (2000). Prognostic factors and patterns of treatment failure in dogs with unresectable differentiated thyroid carcinomas treated with megavoltage irradiation, *J Am Vet Med Assoc* **216**: 1,775-1,779.
- 6. Slensky K A, Volk S W and Schwarz T et al (2003). Acute severe hemorrhage secondary to arterial invasion in a dog with thyroid carcinoma, *J Am Vet Med Assoc* **223**: 636, 649-653.
- 7. Liptak J M, Kamstock D A, Dernell W S et al (2008). Cranial mediastinal carcinomas in nine dogs, *Vet Comp Oncol* **6**: 19-30.
- 8. Lantz G C and Salisbury S K (1989). Surgical excision of ectopic thyroid carcinoma

involving the base of the tongue in dogs: three cases (1980-1987), *J Am Vet Med Assoc* **195**: 1,606-1,608.
- 9. Bracha S, Caron I, Holmberg D L et al (2009). Ectopic thyroid carcinoma causing right ventricular outflow tract obstruction in a dog, *J Am Anim Hosp Assoc* **45**: 138-141.
- 10. Wisner E R and Nyland T G (1998). Ultrasonography of the thyroid and parathyroid glands, *Vet Clin North Am Small Anim Pract* **28**: 973-991.
- 11. Taeymans O, Peremans K and Saunders J H (2007). Thyroid imaging in the dog: current status and future directions, *J Vet Intern Med* **21**: 673-684.
- 12. Smith M M (1995). Surgical approach for lymph node staging of oral and maxillofacial neoplasms in dogs, *J Am Anim Hosp Assoc* **31**: 514-518.
- 13. Smith M M (2002). Surgical approach for lymph node staging of oral and maxillofacial neoplasms in dogs, *J Vet Dent* **19**: 170-174.
- 14. Herring E S, Smith M M and Robertson J L (2002). Lymph node staging of oral and maxillofacial neoplasms in 31 dogs and cats, *J Vet Dent* **19**: 122-126.
- 15. Thompson E J, Stirtzinger T, Lumsden J H and Little P B (1980). Fine-needle aspiration cytology in the diagnosis of canine thyroid-carcinoma, *Canadian Veterinary Journal-Revue Veterinaire Canadienne* **21**: 186-188.
- 16. Pack L, Roberts R E, Dawson S D and Dookwah H D (2001). Definitive radiation therapy for infiltrative thyroid carcinoma in dogs, *Vet Radiol Ultrasound* **42**: 471-474.
- 17. Klein M K, Powers B E, Withrow S J et al (1995). Treatment of thyroid carcinoma in dogs by surgical resection alone: 20 cases (1981-1989), *J Am Vet Med Assoc* **206**: 1,007-1,009.
- 18. Susaneck S J (1983). Doxorubicin therapy in the dog, *J Am Vet Med Assoc* **182**: 70-72.
- 19. Fineman L S, Hamilton T A, de Gortari A and Bonney P (1998). Cisplatin chemotherapy for treatment of thyroid carcinoma in dogs: 13 cases, *J Am Anim Hosp Assoc* **34**: 109-112.
- 20. Ogilvie G K, Obradovich J E, Elmslie R E et al (1991). Efficacy of mitoxantrone against various neoplasms in dogs, *J Am Vet Med Assoc* **198**: 1,618-1,621.
- 21. Ogilvie G K, Obradovich J E, Elmslie R E et al (1991). Toxicoses associated with administration of mitoxantrone to dogs with malignant tumors, *J Am Vet Med Assoc* **198**: 1,613-1,617.
- 22. Ogilvie G K, Moore A S, Chen C et al (1994). Toxicoses associated with the administration of mitoxantrone to dogs with malignant tumors: a dose escalation study, *J Am Vet Med Assoc* **205**: 570-573.
- 23. Hammer A S, Couto C G, Ayl R D and Shank K A (1994). Treatment of tumor-bearing dogs with actinomycin-D, *Journal of Veterinary Internal Medicine* **8**: 236-239.
- 24. Turrel J M, McEntee M C, Burke B P and Page R L (2006). Sodium iodide I 131 treatment of dogs with nonresectable thyroid tumors: 39 cases (1990-2003), *J Am Vet Med Assoc* **229**: 542-548.
- 25. Turrel J M, Feldman E C, Nelson R W and Cain G R (1988). Thyroid carcinoma causing hyperthyroidism in cats: 14 cases (1981-1986), *J Am Vet Med Assoc* **193**: 359-364.
- 26. Peterson M E, Kintzer P P, Hurley J R and Becker D V (1989). Radioactive iodine treatment of a functional thyroid carcinoma producing hyperthyroidism in a dog, *J Vet Intern*

Med **3**: 20-25.
- 27. Worth A J, Zuber R M and Hocking M (2005). Radioiodide (131I) therapy for the treatment of canine thyroid carcinoma, *Aust Vet J* **83**: 208-214.