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# Metastasis to ipsilateral medial retropharyngeal and deep cervical lymph nodes in 22 dogs with thyroid carcinoma

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## Abstract

**Objective:** To determine the rate of nodal metastasis to the medial retropharyngeal (MRP) and deep cervical lymph nodes in dogs surgically treated for thyroid carcinoma.

**Study design:** Retrospective study.

**Animals:** Twenty-two client-owned dogs.

**Methods:** Medical records between July 2015 and October 2019 at the Universities of Missouri and Florida were reviewed. Dogs that underwent thyroidectomy with concurrent elective MRP lymphadenectomy ± deep cervical lymphadenectomy were included. Tumor site, preoperative staging, and histopathological findings were recorded.

**Results:** Twenty-two dogs with 26 total thyroid carcinomas were included. Primary tumors were lateralized in 19 dogs, bilateral in two dogs, and bilateral and midline ectopic in one dog. All dogs underwent ipsilateral MRP resection, including bilateral resection in dogs with bilateral tumors. Three contralateral MRP lymph nodes were excised from dogs with unilateral carcinomas. Four deep cervical lymph nodes and one superficial cervical lymph node were excised. Metastases were identified in 14 lymph nodes in 10 of 22 (45%) dogs. All four excised deep cervical lymph nodes and one contralateral MRP lymph node were identified as metastatic. Size of deposit could be classified in 13 of 14 metastatic lymph nodes. Macrometastasis was detected in seven lymph nodes, micrometastasis was detected in one node, and isolated tumor cells were detected in five lymph nodes.

**Conclusion:** Regional metastasis was common within the lymph nodes sampled in this population of dogs with thyroid carcinoma.

**Clinical significance:** These results provide evidence to justify further exploration of a larger population to verify the rate of regional metastasis and determine the prognostic impact of nodal metastasis.

The results of this study were accepted for presentation at the Veterinary Society of Surgical Oncology conference; May 4-6, 2020; Niagara-on-the-Lake, Ontario Canada (delayed due to COVID-19 protocols).

 

## 1 | INTRODUCTION

Thyroid tumors are the most common endocrine neoplasm in dogs.[1] Thyroid carcinomas are divided into follicular and parafollicular (also known as C-cell or medullary) cell carcinomas. Follicular cell carcinomas are further subclassified as follicular, compact or solid, follicular-compact, papillary, or undifferentiated (small cell or giant cell). Follicular cell carcinomas are most common in dogs, with follicular-compact cellular carcinoma the most common histological subtype.[2-5] C-cell thyroid carcinoma has been reported to comprise up to 36% of thyroid carcinomas in dogs.[5]

Accurate staging is required to guide management and prognostication in dogs with cancer. While metastasis at presentation is uncommonly reported in dogs undergoing surgery for thyroid carcinoma,[6] researchers reporting more general populations of dogs with thyroid carcinoma have documented pulmonary metastasis in 16% to 38% of dogs at the time of diagnosis.[5,7,8] Metastasis has been reported at necropsy in 61% to 80% of dogs with thyroid carcinoma,[9,10] with 51% of dogs with metastasis reported to have lymph node involvement.[9] Because of the risk of regional metastasis, staging of local lymph nodes has been advocated.[11] Despite these considerations, lymph node metastasis has been inconsistently described in the literature detailing canine thyroid carcinoma. Regional lymphadenomegaly is commonly identified by preoperative computed tomography (CT).[12] The clinical significance of these findings is largely unclear, especially because of the poor diagnostic accuracy of CT for detection of medial retropharyngeal (MRP) lymph node metastasis in dogs with tumors of the mouth and nose.[13] Lymph node metastasis is rarely reported in older case series detailing thyroidectomy for thyroid carcinoma.[2,5] Reagan et al[6] and Campos et al[7] reported rates of lymph node metastasis at the time of definitive therapy of 7.1% and 15.7%, respectively, in dogs with thyroid carcinoma; however, methods of staging were not standardized. Broome et al[14] reported lymph node metastasis in 21.4% of their cohort dogs on the basis of thyroid scan data, although these dogs were not part of the main study population and were not reported to undergo any further diagnostic testing.

In contrast to canine thyroid carcinoma, papillary thyroid carcinomas are the most common subtype in man, with increasing incidence reported in recent years.[15] Lymph node metastasis is reported in approximately 22% to 33% of people with papillary thyroid carcinoma.[15-17] Lymph node metastasis is reported in up to 81% of people with medullary thyroid carcinoma.[18,19] While lymph node metastasis is comparatively uncommon in people with follicular thyroid carcinoma, reported rates of metastasis are variable, ranging from 2% to 17.3% in recent reports.[16,20-22] Although follicular thyroid carcinoma is associated with less frequent nodal metastasis than with papillary thyroid carcinoma, nodal metastasis is still of prognostic importance, with significantly shorter survival times and significantly higher recurrence rates associated with lymph node involvement.[16,20]

Thyroid lymphatic vessels in dogs have been reported to drain primarily to the cranial and caudal deep cervical lymph nodes,[23] while MRP lymph node metastasis has been repeatedly documented at postmortem examination.[9] Deep cervical lymph nodes typically measure up to only a few millimetres in diameter, if they are visible at all.[24] If cranial deep cervical lymph nodes are identifiable, these are expected to lie between the MRP lymph node and the thyroid lobe, close to the carotid sheath.[24] The caudal deep cervical lymph nodes may vary in number and are located at the ventral aspect of the caudal third of the trachea.[24] The MRP lymph nodes act as a collecting center for the head and form the cranial extent of the right and left tracheal trunks.[24] While the MRP lymph node lies deep within the neck, it typically measures approximately 3 to 5 cm in length, and its consistent location allows routine excision in the dog.[13,24,25]

Because of the potential for lymph node metastasis, elective ipsilateral MRP lymphadenectomy with concurrent deep cervical lymphadenectomy has been routinely used by the authors in recent years to support staging of dogs with thyroid cancer. The objective of this study was to retrospectively assess the rate of lymph node metastasis in dogs that underwent thyroidectomy for carcinoma with routine ipsilateral MRP lymphadenectomy ± deep cervical lymphadenectomy.

## 2 | MATERIALS AND METHODS

Medical records of the University of Missouri and the University of Florida between July 2015 and October 2019 were retrospectively reviewed for dogs with thyroid carcinoma and concurrent ipsilateral MRP lymphadenectomy. Data collected included signalment (with age at the time of surgery) and details of preoperative diagnostics, surgery, and histopathology.

Records of preoperative imaging were reviewed. The location, maximum tumor dimension, and presence or absence of gross vascular invasion were recorded. Tumor volume was estimated by using the formula $v = 4/3\ \pi abc$, where a = tumor height / 2, b = tumor length / 2, and w = tumor width / 2. Ipsilateral MRP lymph nodes were noted on preoperative imaging, and their widths were recorded. Total thyroxine (T4) assays were reviewed; dogs were considered to have hyperthyroidism when total T4 exceeded the reference range without concurrent exogenous thyroid supplementation.

Surgery was performed by or under the supervision of American College of Veterinary Surgeons or European College of Veterinary Surgeons board-certified surgeons. Surgery reports were reviewed for evidence of gross vascular invasion or invasion of other surrounding structures. The location of any excised lymph nodes was recorded. Surgery to excise the ipsilateral MRP lymph nodes was routinely performed on an elective basis concurrently with thyroidectomy during the period of case inclusion. Resection of additional lymph nodes was performed at the discretion of the attending surgeon. All dogs in this study with identifiable deep cervical lymph nodes underwent deep cervical lymphadenectomy.

Records of histopathological examination were reviewed. All samples were routinely stained with hematoxylin and eosin, with immunohistochemistry used at the discretion of the attending pathologist or at the request of the clinician managing the case. Immunohistochemistry involved staining with thyroglobulin, thyroid transcription factor-1, or calcitonin, as previously described.[26] Each tumor was classified as follicular or medullary in origin, and the mitotic index was reported. Each lymph node was grossly examined and bisected with a single section taken from the midpoint of the lymph node. Metastatic lesions were reviewed, and their maximum diameter was measured by a board-certified pathologist (D.Y.K) when feasible. Lymph node metastasis was classified as macrometastasis (>2 mm in diameter), micrometastasis (200 μm to 2 mm), and isolated tumor cells (ITC; <200 μm). Because of the small data set, continuous variables (calculated in Prism 8; GraphPad Software, San Diego, California) were reported as median and range.

## 3 | RESULTS

Twenty-two dogs were eligible for inclusion in this study. Breeds included golden retriever (n = 2), dachshund (n = 1), Siberian husky, Welsh corgi, Labrador, Cavalier King Charles spaniel, beagle, boxer, border collie, Yorkshire terrier, Irish terrier, and 10 mixed breed dogs. Median age at surgery was 9 years 1 month (range, 5 years 1 month to 16 years 3 months). Median body weight was 22.5 kg (4.3-47.1). Eight dogs were female, and 14 dogs were male; all dogs were neutered.

### 3.1 | Preoperative staging

All dogs underwent preoperative thoracic imaging (16 with radiographs, 19 with CT, with 13 evaluated with both modalities). No evidence of pulmonary metastasis was identified in any dog. Cervical imaging was performed with CT (21 dogs), ultrasound (four dogs), or with both modalities (three dogs). Median maximum tumor length was 4.5 cm (range, 0.9-11.4). Median (range) primary tumor volume was 15.5 $cm^3$ (0.3-163.9). Cranial deep cervical lymph nodes were identified in four dogs that underwent CT (Figure 1). Preoperative total T4 values were available for 18 of 22 dogs. One dog was receiving treatment with levothyroxine at the time of testing. Among the remaining dogs, median total T4 was 2.7 μg/dL (range, <0.5-9.9); 7 of 17 (41%) dogs were considered hyperthyroid.

### 3.2 | Surgery

Twenty-six thyroid carcinomas were identified in 22 dogs. Eight dogs had right-sided carcinomas, 11 dogs had left-sided carcinomas, two dogs had bilateral thyroid

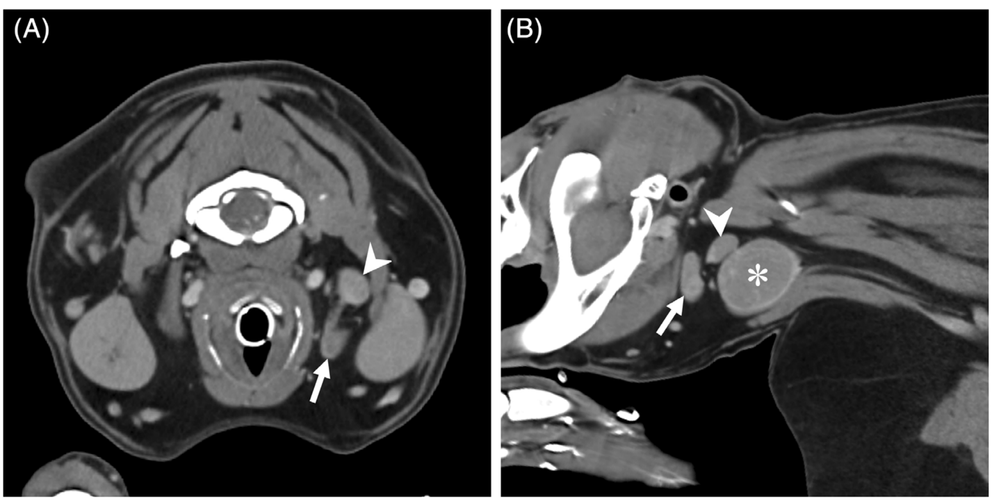


**FIGURE 1** Transverse (A) and sagittal (B) plane reconstructions of contrast-enhanced cervical computed tomography in a dog with thyroid carcinoma. Arrowheads, left cranial deep cervical lymph node; arrows, left medial retropharyngeal lymph node; asterisk, thyroid mass

**TABLE 1** Data for dogs with confirmed lymph node metastasis

| Case | Tumor location | Excised lymph nodes | Metastatic lymph nodes, n | Location of metastatic lymph nodes |
|---|---|---|---|---|
| 1 | Left | $R_I$ | 1 | $R_I$ |
| 2 | Left | $R_I$ | 1 | $R_I$ |
| 3 | Left | $R_I$ $C_I$ | 2 | $R_I$ $C_I$ |
| 4 | Right | $R_I$ $C_I$ | 1 | $C_I$ |
| 5 | Left | $R_I$ | 1 | $R_I$ |
| 6 | Left | $R_I$ | 1 | $R_I$ |
| 7 | Bilateral and hyoid | $M_B$ $R_B$ $C_I$ (right) | 2 | $R_I$ (left) $C_I$ (right) |
| 8 | Left | $R_I$ $C_I$ | 2 | $R_I$ $C_I$ |
| 9 | Right | $R_B$ $S_I$ | 2 | $R_I$ $R_C$ |
| 10 | Bilateral | $M_B$ $R_B$ | 1 | $R_I$ (right) |

Abbreviations: C, cranial deep cervical lymph nodes; M, mandibular lymph nodes; R, medial retropharyngeal lymph nodes; S, superficial cervical lymph nodes; subscript I, ipsilateral; subscript C, contralateral; subscript B, bilateral.

carcinomas, and one dog had bilateral conventionally located thyroid carcinomas and an ectopic thyroid carcinoma at the hyoid. Two tumors were fixed, while the remaining 24 tumors were variably mobile. Eight (31%) tumors were identified with gross vascular invasion, while one dog was suspected to have gross lymphatic vessel thickening at surgery. Four thyroid carcinomas exhibited gross, extravascular infiltration into surrounding tissues at surgery. Median (range) width of ipsilateral and contralateral MRP lymph nodes was 7 mm (3-10) and 6 mm (3-18), respectively. Twenty-five ipsilateral MRP lymph nodes were excised (including three in dogs with bilateral tumors). Three contralateral MRP lymph nodes were excised from dogs with unilateral carcinomas. Four deep cervical lymph nodes and one superficial cervical lymph node were excised. The deep cervical lymph nodes ranged in size from $1 \times 0.6 \times 0.3$ to $2.6 \times 1.3 \times 1.1$ cm. Bilateral mandibular lymphadenectomy was performed in one dog with concurrent mandibular osteosarcoma, one dog with bilateral thyroid carcinomas, and the dog with three synchronous thyroid carcinomas. The dog with bilateral thyroid carcinomas had mild bilateral mandibular lymphadenomegaly (up to 10 mm) reported at preoperative CT, while mandibular lymph nodes were excised in the dog with three synchronous thyroid carcinomas because of concern that mandibular lymph nodes may be more likely to drain the hyoid thyroid carcinoma.

### 3.3 | Histopathology

Twenty-four thyroid carcinomas were follicular in origin, and two tumors were diagnosed to be of C-cell origin. Median mitotic index was 2.5 figures per 10 high-power fields (range, <1-35). Lymphatic invasion was described in 3 of 26 thyroid carcinomas, while vascular invasion was described in 10 of 26 thyroid carcinomas, and capsular invasion was described in 9 of 26 thyroid carcinomas.

Lymph node metastasis was identified in 10 of 22 (45%) dogs, with 14 metastatic lymph nodes identified (Table 1). All four deep cervical lymph nodes excised were metastatic. One contralateral MRP lymph node was identified as metastatic. Sufficient information was available to allow categorization of the size of deposit in 13 of 14 metastatic lymph nodes. Macrometastasis was detected in seven lymph nodes, micrometastasis was detected in one lymph node, and ITCs were detected in five lymph nodes. Immunohistochemistry was used in 14 of 22 cases, including thyroid transcription factor (nine dogs), thyroglobulin (six dogs), and calcitonin (five dogs). Immunohistochemistry was required for identification of metastasis in all five lymph nodes with ITC. Median (range) primary tumor volume was 15 $cm^3$ (1.9-163.8) for tumors associated with lymph node metastasis and 15.5 $cm^3$ (0.3-82.9) for tumors not associated with lymph node metastasis.

## 4 | DISCUSSION

The main finding of this study was the high rate of lymph node metastasis identified in 10 of 22 dogs that underwent thyroidectomy for thyroid carcinoma. The small study sample and retrospective nature of this study require that caution be exercised in interpreting these results; however, this study provides sufficient evidence to warrant additional prospective research to assess the rate and prognostic significance of lymph node metastasis in dogs with thyroid carcinoma. While contralateral lymphadenectomy was performed in only three dogs with unilateral carcinoma, contralateral metastasis was identified in one dog. This potential for contralateral metastasis is in keeping with findings for both oral cancer in dogs and for thyroid carcinoma in man.[27,28]

Although lymph node metastasis has not been commonly reported in dogs at the time of thyroidectomy, metastasis may not be readily apparent at presentation. Furthermore, distinguishing local and regional recurrence at reevaluation could be highly challenging, particularly without advanced imaging or revision surgery, options that may be out of reach for some owners in the context of recurrent disease. Lymph node metastasis has been reported in just over half of dogs with metastatic thyroid carcinoma at postmortem examination.[9] In addition, approximately 12% of dogs in which follicular carcinoma had been diagnosed and 14% of dogs in which medullary carcinoma had been diagnosed in one retrospective study were known to develop regional disease at a later date.[7] These data and the results of this study provide evidence that lymph node metastasis in dogs may be underreported in the current clinical veterinary literature.

Cervical lymph nodes in man tend to be small and distributed throughout regions of tissue, whereas dogs exhibit low numbers of larger lymph nodes.[24,29] Although direct comparisons between human nodal levels and canine lymph nodes are challenging, the cranial deep cervical lymph nodes may best correspond to level III, while the caudal deep cervical lymph nodes correspond roughly to level VI and likely provide the closest analog to the central compartment.[18,30] Cranial deep cervical lymph nodes were noted at preoperative CT in four dogs. These lymph nodes are not readily apparent on CT images in nondiseased dogs, and these lymph nodes were confirmed as metastatic for all four dogs. While a larger data set is required to fully assess the impact of identifiable cranial deep cervical lymph nodes, the results of this study provide evidence to suggest that surgeons actively look for deep cervical lymph nodes on preoperative imaging because of the potential for metastasis.

Intraoperative sensitivity and specificity for detection of metastatic lymph nodes have been shown to be low in man,[18] thus underscoring the importance of careful preoperative staging. Varying approaches are used for preoperative staging of thyroid carcinoma in dogs. While some surgeons rely on cervical ultrasound for local staging of mobile thyroid masses, ultrasound has been reported to have lower sensitivity and specificity than CT for identification of thyroid carcinoma, with lower accuracy regarding capsular invasion and size.[31] Cervical ultrasound is also highly operator dependent, and deeper structures of the neck may be challenging to image. Ultrasound-guided aspirates of the MRP lymph nodes have been reported to be of low diagnostic yield,[32] while fine needle aspirates of lymph nodes collectively have been reported to be only 66% sensitive for metastasis.[33] In addition, small, atypical lymph nodes or limited areas of gross vascular invasion could be challenging for some ultrasonographers to identify. While contrast-enhanced CT provides more complete assessment for preoperative evaluation,[31] it does provide a substantial iodine load, which precludes the use of radioactive iodine for 4 to 6 weeks after imaging.[34,35] Thyroid scintigraphy may provide a useful adjunct to CT or ultrasound for regional staging of dogs with tumors of follicular origin because of its capacity to identify areas of atypical radionuclide uptake associated with lymph nodes.[14] This technique, however, depends on ion trapping, which is not uncommonly lost by canine thyroid tumors. The clinical utility of differing imaging techniques for the detection of lymph node metastasis and their effects on survival have not been evaluated in dogs; however, the documented limitations of existing techniques in veterinary medicine provide evidence that some form of lymphadenectomy may be required to maximize sensitivity.

Kim et al[36] evaluated the diagnostic utility of CT compared to cervical ultrasound in people with clinically node-negative papillary thyroid carcinoma. Computed tomography was significantly more sensitive and accurate than ultrasound for detecting lymph node metastasis in the central compartment of the neck. Although no difference in locoregional recurrence was noted in that population between matched patients assessed with CT or ultrasound, more than 80% of patients received adjuvant radioactive iodine, which may have ablated residual neoplastic disease.[36]

The incidence of bilateral or contralateral lymph node metastasis cannot be determined from this study; however, the potential for contralateral metastasis has been confirmed. Variable rates of contralateral metastasis have been reported in man, including 22% in high-risk differentiated carcinoma,[37] 24% in papillary carcinoma,[28] and 44% for medullary carcinoma.[18] No researchers have specifically evaluated rates of contralateral lymph node metastasis in dogs with thyroid carcinoma. This question must be addressed specifically in dogs to guide any potential intervention because the differences in histologic type and behavior between dogs and man preclude direct extrapolation.

The paucity of evidence available regarding lymph node management for canine thyroid carcinoma precludes formulation of strong recommendations. Approaches to diagnosis and management of regional disease are variable. Extensive data sets in man allow more effective stratification than is feasible in dogs. This stratification can allow for standardized protocols based on available evidence. Sentinel lymph node mapping for thyroid carcinoma in man was pioneered by using vital dyes for identification of draining nodes;[38] however, protocols that include lymphoscintigraphy have become more common in recent years.[39] While interest in sentinel lymph node techniques has developed for papillary carcinoma, the clinical utility of this approach is still a topic of debate, with false negative rates reported as high as 40%.[39] Furthermore, when a sentinel lymph node is positive, that typically raises the question of whether further lymph node extirpation beyond the sentinel node is required. The American Thyroid Association guidelines for management of medullary carcinoma advocate for dissection of all required compartments during the initial thyroidectomy because of the complications associated with repeat surgery.[40] As such, some form of elective node dissection is often recommended in patients with medullary carcinoma or locally advanced differentiated thyroid carcinoma.[40,41] While sentinel lymph node techniques in dogs may identify typical draining lymph nodes, the concern for complications with repeat neck surgery as well as the financial challenges of multiple referral level surgeries may provide a greater indication for elective node dissection in higher risk dogs, with either sentinel node mapping or monitoring for dogs that are deemed low risk. Although the risk of MRP and deep cervical lymphadenectomy in dogs anecdotally appears low, the morbidity of these techniques has not been robustly assessed. It is possible that dogs at low risk may not benefit sufficiently from lymph node excision to justify lymphadenectomy. Such determinations, however, require research with a large cohort of dogs to determine whether risk for lymph node metastasis can be adequately predicted on the basis of case factors, such as tumor size and behavior, and to establish some form of clinical benefit vs risk assessment.

A high proportion of functional tumors was identified in this study. Recent reports have described variable proportions of functional follicular carcinomas. While Reagan et al[6] reported that 9.6% of 156 dogs with unilateral thyroid carcinoma had functional lesions, it is unclear how many dogs underwent endocrine testing. Campos et al[7] reported that 28% of dogs with follicular carcinoma and endocrine testing had hyperthyroidism. Most dogs in this series were treated at the University of Missouri, where T4 and thyroid-stimulating hormone testing is routinely performed. Recurrence of hyperthyroidism due to lymph node metastasis has been recently reported, supporting further investigation into management of regional disease in this population.[42] Ultimately, prospective evaluation of the prevalence of hyperthyroidism among dogs with thyroid carcinoma is required.

The main limitations of this study stem from its retrospective design and limited data set. While most of the dogs included in this study underwent elective lymphadenectomy, there was inevitably a degree of bias in the selection of dogs that were considered surgical candidates. Furthermore, lymphadenectomy was not routinely performed at the University of Florida; however, the first author (O.T.S.) began electively performing MRP ± deep cervical lymphadenectomy for all thyroid carcinomas during this time and continued this practice at the University of Missouri. While this variation will introduce a degree of selection bias, no obvious difference in metastatic rate was noted between sites. Sites of drainage from thyroid carcinoma are likely variable, and this study could not control for this variation or reliably assess drainage patterns. Immunohistochemistry was not routinely applied for all lymph nodes and all cases, so it is possible that the rate of micrometastasis or isolated tumor cells may be higher in this population than reported.

In conclusion, lymph node metastasis was a frequent finding in this retrospective study. Additional research in a large, prospective cohort is required to evaluate the frequency of lymph node metastasis as well as the prognostic and therapeutic significance of regional metastasis. Deep cervical lymph nodes should be considered during imaging review of canine thyroid carcinoma and extirpation should be considere, if visible.


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## CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this report.


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