Comparison of results of computed tomography and radiography with histopathologic findings in tracheobronchial lymph nodes in dogs with primary lung tumors: 14 cases (1999–2002)

Melissa C. Paoloni, DVM, DACVIM; William M. Adams, DVM, DACVIM; Richard R. Dubielzig, DVM, DACVP; Ilene Kurzman, MA, MS, EdD; David M. Vail, DVM, DACVIM; Robert J. Hardie, DVM, DACVS

**Objective**—To compare results of computed tomography (CT) and radiography with histopathologic findings in tracheobronchial lymph nodes (TBLNs) in dogs with primary lung tumors.

**Design**—Retrospective case series.

**Animals**—14 client-owned dogs.

**Procedures**—Criteria for inclusion were diagnosis of primary lung tumor, use of thoracic radiography and CT, and histologic confirmation of TBLN status. Medical records were reviewed for signalment; history; and physical examination, clinicopathologic, radiographic, CT, surgical, and histopathologic findings.

**Results**—Tracheobronchial lymphadenopathy was not identified via radiography in any dogs. Tracheobronchial lymphadenopathy was diagnosed in 5 dogs via CT. Six dogs had histologic confirmation of metastasis to TBLNs. Radiographic diagnosis yielded 6 false-negative and no false-positive results for tracheobronchial lymphadenopathy. Computed tomography yielded 1 false-negative and no false-positive results. Sensitivity of CT for correctly assessing TBLN status was 83%, and specificity was 100%. Positive predictive value was 100%, and negative predictive value was 89%. Dogs with lymphadenopathy via CT, histologic confirmation of TBLN metastasis, or primary tumors with a histologic grade >1 had significantly shorter survival times than their counterparts.

**Conclusions and Clinical Relevance**—Results of CT evaluation of TBLN status were in agreement with histopathologic findings and more accurate than use of thoracic radiography for evaluating TBLNs in dogs with primary lung tumors. Computed tomography imaging should be considered as part of the staging process to more accurately assess the TBLNs in dogs with primary lung tumors. (J Am Vet Med Assoc 2006; 228:1718–1722)

**Abbreviations**

TBLN Tracheobronchial lymph node
CT Computed tomography
PET Positron emission tomography

Primary lung tumors represent approximately 1% of newly diagnosed tumors in dogs. Although the exact mechanism is not known, it has been suggested that the incidence of primary lung tumors in dogs may be increasing because of environmental carcinogens as well as advances in diagnostic imaging and increased longevity.

The most common histopathologic diagnosis for primary lung tumors in dogs is adenocarcinoma of either bronchial, alveolar, or mixed bronchoalveolar origin. Other tumor types that have been reported include squamous cell carcinoma, sarcoma, and anaplastic tumors. Caudal lung lobes are the most common sites for primary tumors, although any lung lobe can be affected.

Primary lung tumors typically occur in older dogs; however, no breed or sex predilection has been reported. Clinical signs are often vague and variable in duration and may include coughing, exercise intolerance, or, more rarely, acute respiratory signs (ie, tachypnea or dyspnea) caused by hemothorax, pleuritis, or pleural effusion. Dogs may also have nonspecific signs including inappetance, weakness, or weight loss, and in some cases, the primary tumor may be diagnosed incidentally during evaluation for another problem.

Several prognostic factors have been reported for dogs with primary lung tumors. A study by McNiel et al. found that dogs with small (<5 cm3), well-differentiated, peripheral tumors had longer mean survival times, compared with dogs with larger, poorly differentiated or more centrally located tumors. Two subsequent studies have established more specific prognostic factors. Ogilvie et al. reported the importance of tracheobronchial lymphadenopathy, pulmonary metastasis, and evaluation of tumor size in determining disease-free interval and overall survival. In a more recent study by McNiel et al., the presence of clinical signs at the time of diagnosis, clinical stage, TBLN status, and histologic score of the primary tumor were identified as prognostic factors for dogs with primary lung tumors. Dogs with metastasis to the TBLNs had significantly shorter median survival times than dogs without metastasis.

In humans with primary lung tumors, TBLN status is strongly associated with survival. Computed tomography of the thorax is commonly used to evaluate the TBLNs for more accurate preoperative staging and surgi-
Thoracic CT scans were obtained for all dogs by use of an bronchial lymphadenopathy, and pleural effusion. Mary tumor, evidence of pulmonary metastases, tracheobronchial radiographs of the thorax were obtained for all dogs. procedures and accuracy were calculated for thoracic radiography and CT as part of the diagnostic workup and histologic examination of TBLNs and the primary lung tumor.

Criteria for Selection of Cases

A retrospective analysis of dogs evaluated at the University of Wisconsin-Madison Veterinary Medical Teaching Hospital from January 1999 to December 2002 with a diagnosis of a primary lung tumor was conducted. Criteria for inclusion required that all dogs had thoracic radiography and CT as part of the diagnostic workup and histologic examination of TBLNs and the primary lung tumor.

Procedures

Medical records were reviewed for signalment; history; and physical examination, hematologic, serum biochemical, radiographic, surgical, and histopathologic findings. Ventrodorsal and left and right lateral recumbent radiographs of the thorax were obtained for all dogs. Radiographs were evaluated for the location of the primary tumor, evidence of pulmonary metastases, tracheobronchial lymphadenopathy, and pleural effusion. Thoracic CT scans were obtained for all dogs by use of an axial CT unit. All dogs were positioned in ventral recumbency, and general anesthesia was used. Transverse slices were obtained at 1-cm intervals. Contrast and noncontrast images were obtained for each dog. Meglumine diatrizoate was administered through a catheter placed in the cephalic vein at a dose of 2 mL/kg (0.91 mL/lb). IV, up to a maximum of 60 mL. Images were evaluated for the characteristics of the primary tumor, tracheobronchial lymphadenopathy, and pulmonary metastases. Normal TBLNs have neither enlargement nor appreciable contrast enhancement. Lymphadenopathy of the TBLNs was defined as lymph node enlargement or irregularity with or without contrast enhancement. Subjective radiographic and CT assessment of the TBLNs as reported by the radiologist during diagnostic evaluation were used for this study. However, 1 author (WMA) reviewed all CT scans to verify their quality and conclusions.

All dogs were treated via surgical removal of the primary lung tumor and biopsy of the TBLN through a lateral intercostal thoracotomy. Gross appearance of the TBLNs was not recorded in all dogs and therefore was not specifically analyzed in this study. Tissue samples were preserved in neutral-buffered 10% formalin, processed routinely, and stained with H&E.

The same pathologist (RRD) reviewed the histology specimens of all dogs. The TBLNs were evaluated for evidence of metastasis, degree of inflammation, and grade of primary tumor, tracheobronchial lymphadenopathy, and pulmonary metastases. Histologic characteristics were scored on a scale of 0 to 10 (0 = no inflammation, 1 = mild inflammation, 2 = moderate inflammation, and 3 = severe inflammation). The primary tumor was evaluated and graded for degree of nuclear pleomorphism, number of mitotic figures per high-powered field (objective lens, 100X), nucleolar size, differentiation, fibrosis, inflammation, necrosis, and completeness of excision. Histologic scoring was applied to each tumor as defined by McNeil et al. Histologic characteristics were scored on a scale of 0 to 10 (0 = not present; 10 = the most evident example). An overall grade was determined by summation of the individual scores from the described 8 characteristics (grade 1, score < 9; grade 2, score = 9 to 14.0; and grade 3, score > 14.0). Tumors with higher scores represented more anaplastic or aggressive variants.

Univariate analysis was performed to evaluate associations between outcome (survival [No. of days]) and age, weight, sex, breed, clinical signs prior to diagnosis, location, histopathologic diagnosis, histologic score of primary tumor, tracheobronchial lymphadenopathy on radiographs or CT images, histologically confirmed metastasis to TBLNs, and chemotherapy. Survival curves were generated by the Kaplan-Meier method and compared by use of the Breslow and Mantel-Cox tests of significance between survival curves. These statistical tests adjust for dogs still alive or lost to follow-up at the time of analysis. A P value < 0.05 was considered significant. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated for thoracic radiography and CT as follows:

Sensitivity (% [percentage of true-positive results]) = TP / (TP + FN) × 100
Specificity (% [percentage of true-negative results]) = TN / (TN + FP) × 100
Positive predictive value (% [percentage of dogs with a positive test result that had metastasis to TBLNs]) = TP / (TP + FP) × 100
Negative predictive value (% [percentage of dogs with a negative test result that did not have metastasis to TBLNs]) = TN / (TN + FN) × 100
Accuracy (% [percentage of dogs with correct results from test]) = TP + TN / (TP + TN + FN + FP)

where TP is true-positive results, FN is false-negative results, TN is true-negative results, and FP is false-positive results.

Results

Records of 14 dogs met the inclusion criteria for this study. There were 5 males and 9 females. Median age was 11 years (range, 9 to 16 years), and median weight was 18 kg (39.6 lb; range, 6.8 to 46.8 kg [15 to 103 lb]). There was no breed predilection; however, Labrador Retrievers, Bichon Frises, and Cocker Spaniels were each represented twice. Ten dogs had clinical signs at diagnosis. Cough was the most common clinical sign (10/14 dogs). Other
Clinical signs included exercise intolerance, dyspnea, inappetance, and lethargy. None of the dogs had severe respiratory distress at initial evaluation.

A pulmonary mass consistent with a primary lung tumor was identified on thoracic radiographs in all 14 dogs; however, tracheobronchial lymphadenopathy, pulmonary metastasis, or pleural effusion was not identified in any dog. A contrast-enhancing pulmonary mass consistent with a primary lung tumor was identified via CT in all dogs. Smaller lesions consistent with pulmonary metastasis in other lung lobes were identified in 5 dogs. Nine dogs had normal CT findings for TBLNs (Figure 1), whereas enlargement, contrast enhancement, or both of the TBLNs was identified in 5 dogs (Figure 2). The transaxial size range for measurable nodes was 5 to 15 mm. Three of these dogs had contrast enhancement of the TBLNs with minimal lymph node enlargement. This contrast enhancement was described as uniform in 2 dogs and as rim enhancement in another (Figure 3). Two of the 5 dogs with lymphadenopathy also had lesions consistent with pulmonary metastasis on CT images. Via CT, none of the dogs had evidence of pleural effusion.

All dogs recovered from surgery and were discharged from the hospital. The most common location for the primary tumor was the right caudal lung lobe (5/14 dogs). The only lung lobe that was not affected was the left cranial lung lobe. Complete surgical excision was obtained in 11 dogs.

Histologic examination of the primary tumors revealed carcinomas in all 14 dogs including 9 papillary carcinomas (bronchoalveolar), 2 squamous cell carcinomas, and 1 each of solid carcinoma (bronchial), acinar carcinoma (bronchial), and mucoepidermal carcinoma (combined squamous cell and adenocarcinoma). Histologic scoring revealed 5 grade 1 tumors, 9 grade 2 tumors, and no grade 3 tumors. Histologic examination of the TBLNs confirmed metastasis in 6 dogs. Inflammation of the TBLN was graded as 0 in 4 dogs, grade 1 in 3 dogs, grade 2 in 5 dogs, and grade 3 in 2 dogs. There was no significant association between inflammation and TBLN metastasis and no relationship between degree of inflammation and CT appearance. No TBLNs with severe inflammation were erroneously misclassified as having metastases. Pneumoconiosis was found in 9 dogs in various degrees and was not associated with metastatic disease. Pneumoconiosis also was not related to the degree of inflammation in TBLNs.

Accuracy of CT for detecting metastasis to TBLNs was 93%, compared with 57% for thoracic radiography. Sensitivity of CT for detecting lymph node metastasis was 83%, compared with 0% for radiographs. Specificity for both CT and radiography was 100% because no false-positive results were identified with either imaging technique. Positive predictive value for CT was 100%, compared with 0% for radiography, and the negative predictive value for CT was 89%, compared with 57% for radiography (Table 1).

Follow-up information was obtained on all dogs. Overall median survival time was 414 days (range, 19 to 876 days). Five dogs were alive at the end of the study; however, 2 had evidence of progressive disease on follow-up thoracic radiographs. One of these dogs did not have TBLN metastasis, and the other dog had metastasis to TBLNs that was not detected via CT (false-negative results). The other 3 dogs that were still alive had no evidence of pulmonary metastasis on thoracic radiographs. Of the 9 dogs that died, 2 died of other forms of neoplasia (lymphoma and a perianal tumor). Neither dog had evi-
idence of recurrence of their primary lung tumor. Two dogs were euthanized for decreased quality of life believed to be unrelated to the original diagnosis of primary lung tumor, and 5 died or were euthanized because of progressive pulmonary metastasis. Four of the 6 dogs with TBLN metastasis at the time of surgery died of progressive disease (pulmonary metastasis) detected on follow-up thoracic radiographs. In 1 dog, a necropsy was performed and confirmed pulmonary metastasis via histologic examination. Factors negatively associated with survival by statistical analysis were lymph node enlargement (n = 2) or CT contrast enhancement, TBLN metastasis, and histologic grade of the primary tumor (grade 1 vs 2). Dogs with lymph node enlargement, contrast enhancement via CT, or both had a median survival time of 126 days versus a median that has not yet been reached for the 9 dogs without lymphadenopathy (P = 0.001; Figure 4). Dogs with histologic confirmation of metastasis to the TBLN had a median survival time of 131 days, whereas the median for the 8 dogs without metastasis had not been reached at the end of the study (P = 0.003; Figure 5). Histologic score of the primary tumor was also associated with duration of survival.

Table 1—Comparison of the accuracy of CT versus thoracic radiography for assessment of metastasis to TBLNs in 14 dogs with primary lung tumors.

<table>
<thead>
<tr>
<th>Variable (%)</th>
<th>CT Radiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>83 0</td>
</tr>
<tr>
<td>Specificity</td>
<td>100 100</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>100 0</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>89 57</td>
</tr>
<tr>
<td>Accuracy</td>
<td>93 57</td>
</tr>
</tbody>
</table>

Figure 4—Kaplan-Meier survival curve for 14 dogs detected with (CT positive) or without (CT negative) abnormalities of the TBLNs (lymphadenopathy, contrast enhancement, or both) via CT.

Figure 5—Kaplan-Meier survival curve for 14 dogs detected with (LN positive) or without (LN negative) metastasis to the TBLNs via histologic examination.

Dogs with grade 1 tumors (median not yet reached) lived longer than those with grade 2 tumors (median survival time: 208 days; P = 0.034).

Four dogs were given adjuvant chemotherapy. Each dog received cisplatin, carboplatin, or vinorelbine. Two of the 4 had histologic confirmation of TBLN metastasis, and 2 had evidence of pulmonary metastasis via CT. There was no significant difference in duration of survival for dogs receiving chemotherapy, compared with those that did not, although this represented a very small sample size for appropriate statistical comparison.

Discussion

Results of this study indicated that CT was more accurate than radiography for assessing TBLN in dogs with primary lung tumors. The sensitivity, specificity, positive predictive value, and negative predictive values were all high (> 82%), and with the exception of specificity, the values were all higher than with thoracic radiography. The strong association between metastasis to TBLNs and shorter duration of survival for dogs with primary lung tumors highlights the importance of using CT as part of the diagnostic evaluation so that more informed decisions can be made regarding treatment for these dogs.

In humans, the current American Thoracic Surgery Guidelines state that thoracic CT should be considered a standard part of the diagnostic investigation for patients with lung cancer. It is used to better define the location of the primary tumor, determine the extent of mediastinal and lymph node involvement and detect pulmonary metastases prior to further intervention such as surgery, radiation, or chemotherapy. Standard criteria used to assess TBLN include size, shape, and presence of contrast enhancement. Metastasis is considered when lymph node diameter is > 10 mm, the shape is no longer uniformly rounded, or enhancement with contrast media is detected. However, use of these variables for assessment of TBLN in humans with primary lung tumors is controversial because of the wide variation in accuracy for correctly determining TBLN status. Sensitivities ranging from 25% to 95% and specificities ranging from 40% to 100% have been reported.

Potential reasons for variations in assessment of TBLN metastasis with CT include the subjectivity of individual radiologists, very small nodes, microscopic metastasis, inflammation, hyperplasia, other intercurrent disease, and superimposition of structures in the mediastinum. In humans, false-negative results have been reported when nodes are < 1 cm in diameter or when large primary tumors (> 40 mm) obscure the adjacent lymph nodes. Similarly, false-positive results have been reported as a result of overinterpretation of lymph nodes superimposed over centrally located tumors or when lymph nodes are enlarged because of inflammation or hyperplasia rather than metastasis.

The 1 false-negative diagnosis made with CT (sensitivity: 83%) in this study was most likely attributable to the fact that micrometastasis had not yet affected the node’s size or contrast enhancement; therefore, these
variables were not considered abnormal. The 6 false-negative diagnoses made with thoracic radiography (sensitivity, 0%) were attributable to the fact that the affected TBLNs were still relatively small (< 15 mm in diameter) and therefore obscured because of superimposition of adjacent structures. Also complicating radiographic detection was the fact that the primary tumor was superimposed over the hilar region in some of these dogs, possibly obscuring the TBLN. Generally, results of CT of TBLN and histopathologic findings were in agreement in this study; however, the potential for incorrect assessment still exists, highlighting the need for improving the accuracy of CT diagnosis. A recommendation for improving accuracy of CT is to develop objective criteria for assessment of TBLNs, taking into account variations in body weight, size, and body conformation as well as identifying anatomic structures (ie, adjacent ribs) to which the TBLNs could be consistently and accurately compared. Measurements of TBLNs in dogs with pulmonary neoplasia and non-neoplastic thoracic disease (ie, fungal pneumonia or pyothorax) would potentially aid in the development of criteria specific to metastatic disease and further improve the sensitivity of CT assessment.

In addition, because 10 of 14 dogs had concurrent inflammation of the TBLN, the effect of this variable on contrast enhancement and lymph node enlargement should be further evaluated in a larger series of dogs. Another interesting finding in this study was pneumonicosis in 9 dogs. Although the importance of this was unknown, the potential for a cause-and-effect relationship between exposure to inhaled particles and the development of primary lung tumors warrants further investigation.

In humans, it is common to combine several diagnostic techniques to improve overall accuracy in identifying lymph node metastasis in patients with primary lung tumors. Mediastinoscopy is often performed after CT to substantiate the status of the lymph nodes and as a means for sampling abnormal-appearing sites. CT of mediastinal and hilar lymph nodes as well as providing a means for sampling abnormal-appearing sites. Computed tomography is also often combined with PET to more thoroughly evaluate patients with lung cancer. Positron emission tomography may reveal increased tumor metabolism even in normal-sized nodes, whereas CT helps define the size, location, and characteristics of lymph nodes, which is lacking with PET. Transesophageal ultrasonography has also been used in the staging of lung cancer patients. When combined with fine-needle aspiration, transesophageal ultrasonography may be used to detect and sample lymph nodes as small as 3 to 5 mm, further improving the ability to accurately diagnose TBLN metastasis. The high female-to-male ratio of dogs in this series is likely not clinically important. This overrepresentation of female dogs was likely attributable to the small number of cases. Although chemotherapy was not associated with survival in this small series of dogs, the efficacy of adjuvant chemotherapy for dogs with metastatic primary lung tumors warrants further study. A prospective analysis of dogs with metastatic disease receiving chemotherapy and those with metastases that do not receive chemotherapy is needed.

Results of the present study indicated that CT interpretation of TBLNs was in agreement with histologic findings and was superior to radiography for assessment of TBLN in dogs with primary lung tumors. In agreement with previous reports, significantly lower survival duration was detected for dogs with high-grade tumors and metastasis to TBLN, compared with their counterparts. The importance of biopsy of the TBLNs at surgery in dogs with primary lung tumors was also evident because biopsy provides the most accurate means of identifying metastasis.

References