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Distribution of histopathologic types of primary pulmonary neoplasia in dogs and outcome of affected dogs: 340 cases (2010–2019)

Jourdan B. McPhetridge, DVM[1]; Valery F. Scharf, DVM, MS[1*]; Penny J. Regier, DVM, MS[2]; Darby Toth, BA[2]; Max Lorange, DVM[3]; Giovanni Tremolada, DVM, PhD[3]; Josephine A. Dornbusch, DVM[4]; Laura E. Selmic, BvetMed (Hons), MPH[4]; Sohee Bae, DVM, MS[5]; Katy L. Townsend, BVSc, MS[5]; Jack C. McAdoo, BS[6]; Kelley M. Thieman, DVM, MS[6]; Francesca Solari, DVM[7]; Rebecca A. Walton, DVM[7]; Jacob Romeiser, BS[8]; Joanne L. Tuohy, DVM, PhD[8]; Michelle L. Oblak, DVM, DVSc[9]

[1]Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC
[2]Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL
[3]Flint Animal Cancer Center, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO
[4]Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University Columbus, OH
[5]Department of Clinical Sciences, Carlson College of Veterinary Medicine, Oregon State University, Corvallis, OR
[6]Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX
[7]Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Iowa State University, Ames, IA
[8]Department of Small Animal Clinical Sciences, Virginia Maryland College of Veterinary Medicine, Blacksburg, VA
[9]Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, ON, Canada

*Corresponding author: Dr. Scharf (vfscharf@ncsu.edu)

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OBJECTIVE
To provide updated information on the distribution of histopathologic types of primary pulmonary neoplasia in dogs and evaluate the effect of postoperative adjuvant chemotherapy in dogs with pulmonary carcinoma.

ANIMALS
340 dogs.

PROCEDURES
Medical records of dogs that underwent lung lobectomy for removal of a primary pulmonary mass were reviewed, and histopathologic type of lesions was determined. The canine lung carcinoma stage classification system was used to determine clinical stage for dogs with pulmonary carcinoma.

RESULTS
Pulmonary carcinoma was the most frequently encountered tumor type (296/340 [87.1%]), followed by sarcoma (26 [7.6%]), adenoma (11 [3.2%]), and pulmonary neuroendocrine tumor (5 [1.5%]); there was also 1 plasmacytoma and 1 carcinosarcoma. Twenty (5.9%) sarcomas were classified as primary pulmonary histiocytic sarcoma. There was a significant difference in median survival time between dogs with pulmonary carcinomas (399 days), dogs with histiocytic sarcomas (300 days), and dogs with neuroendocrine tumors (498 days). When dogs with pulmonary carcinomas were grouped on the basis of clinical stage, there were no significant differences in median survival time between dogs that did and did not receive adjuvant chemotherapy.

CLINICAL RELEVANCE
Results indicated that pulmonary carcinoma is the most common cause of primary pulmonary neoplasia in dogs; however, nonepithelial tumors can occur. Survival times were significantly different between dogs with pulmonary carcinoma, histiocytic sarcoma, and neuroendocrine tumor, emphasizing the importance of recognizing the relative incidence of these various histologic diagnoses. The therapeutic effect of adjuvant chemotherapy in dogs with pulmonary carcinoma remains unclear and warrants further investigation.

Primary pulmonary neoplasia (PPN) is a relatively uncommon but important cause of pulmonary disease in dogs, representing approximately 1% of all canine tumors.[1–3] Most of these tumors are malignant, with benign lesions such as adenomas, papillomas, hemangiomas, and granulomas rarely reported.[4,5] The distribution of histopathologic types of PPN in dogs was last broadly reviewed in 1989 by Ogilvie et al,[6] who performed a retrospective analysis of medical records for 210 dogs. In that study,[6] 97.1% of tumors were consistent with carcinomas and 2.9% were classified as "other," with no description pro-

vided. Additional tumor types that have since been reported in the veterinary literature include localized histiocytic sarcomas, fibrosarcomas, chondrosarcomas, osteosarcomas, hemangiopericytomas, and mast cell and neuroendocrine tumors,[4,5,7–10] suggesting the need for updated information regarding histopathologic types of PPN in dogs.

The primary treatment of PPN is surgical resection, when possible.[11] The decision of whether to proceed with surgery is influenced by expected long-term survival time and likely perioperative morbidity and mortality rates. Postoperative survival time varies on the basis of histopathologic type, but a median survival time (MST) of approximately 1 year is often referenced.[12] However, this MST is largely based on results of previous retrospective studies conducted between 1975 and 1992 that evaluated prognostic factors in dogs undergoing surgical treatment for PPN in which all of the tumors were classified as carcinomas.[13,14] More contemporary studies evaluating pulmonary carcinoma in dogs have reported MSTs ranging from 60 to 952 days.[15–17] Stage classification also plays an important role in treatment decision-making because it conveys valuable prognostic information.[18] Recently, Lee et al[15] described an updated canine lung carcinoma stage classification (CLCSC) system, adapted from the most recent human lung carcinoma stage classification (HLCSC) system, and found significant differences in MST on the basis of stage. Although the CLCSC system provides much-needed updated prognostic information regarding pulmonary carcinoma in dogs, it was based on a single study of 71 cases; thus, validation with a larger population is warranted. Furthermore, MSTs may vary among types of PPN, further supporting the need for a contemporary assessment of the distribution of histopathological types of PPN in dogs and associated outcomes.

There is also a scarcity of information regarding the efficacy of adjuvant chemotherapy for the treatment of pulmonary carcinoma in dogs. Previous studies[13,15,19–21] have evaluated relatively small numbers of cases, limiting the ability to draw meaningful conclusions, and no studies to date have shown a significant benefit of adjuvant chemotherapy for treatment of pulmonary carcinoma. An updated evaluation of the outcome for dogs with pulmonary carcinoma treated with and without adjuvant chemotherapy is warranted to guide postoperative recommendations.

The primary objective of the study reported here was to provide updated information on the distribution of histopathologic types of PPN among a large group of dogs from various institutions and to describe associated outcomes of affected dogs to better aid clinicians and owners in making preoperative decisions regarding treatment. A second objective was to evaluate the effect of postoperative adjuvant chemotherapy on outcome in dogs with pulmonary carcinoma grouped on the basis of clinical stage. We hypothesized that carcinomas would represent the majority of PPNs but that other tumor types, specifically nonepithelial neoplasms, would be identified and associated with variable outcomes, compared with outcomes associated with pulmonary carcinoma. We also hypothesized that adjunctive chemotherapy would improve MST in dogs with primary pulmonary carcinoma when accounting for CLCSC.

Materials and Methods

Case selection

A medical record search was conducted to identify dogs that underwent surgical resection of primary lung tumors at 8 veterinary teaching hospitals between January 1, 2010, and December 31, 2019. Dogs were included if they had undergone surgery for removal of a primary pulmonary mass and a histopathologic diagnosis had been made. Dogs were excluded if histopathologic findings were suggestive of metastatic neoplasia or if the histopathologic appearance of a concurrent or historical extrathoracic primary neoplasm was consistent with histopathologic appearance of the pulmonary mass. Dogs with nonepithelial tumors were considered to have PPN if staging revealed a pulmonary lesion without abdominal involvement on preoperative imaging.

Medical records review

Preoperative data recorded from the medical records of dogs included in the study consisted of age, sex, breed, weight, clinical signs attributable to a pulmonary mass, duration of clinical signs, presence of pleural effusion, history of concurrent or previous neoplasia, and other known comorbidities at the time of diagnosis. Clinical signs attributable to a pulmonary mass included coughing, panting, changes in respiratory pattern or effort, hemoptysis, and lethargy or weight loss; in dogs with no clinical signs at the time of diagnosis, PPN was recorded as an incidental finding. Preoperative diagnostic information that was recorded consisted of results of cytologic examination of fine-needle aspirates or histologic examination of biopsy specimens (if performed), abnormal CBC and serum biochemical results, thoracic imaging modality and findings, abdominal imaging modality and findings, lung lobe involved, presence of abnormal thoracic lymph nodes on CT, and presence of pulmonary and distant metastases. Tumor size was determined from imaging reports when length, width, and height or maximal diameter was documented. All preoperative imaging was interpreted by a board-certified radiologist or a resident under the supervision of a board-certified radiologist.

Intraoperative data obtained from surgical reports included approach, surgical dose (intralesional, marginal, or wide excision), tumor invasion into surrounding structures, lymph node extirpation, additional surgical procedures, and intraoperative complications. Intraoperative complications were scored with the proposed Veterinary Cooperative Oncology Group common terminology criteria for adverse events (VCOG-CTCAE) for intraoperative incidents.[22] Postoperative complications were obtained from the medical records and scored with the VCOG-CTCAE for postoperative incidents.[23]

Histopathologic data that was collected consisted of diagnosis, mitotic count (ie, number of mitoses/10 hpf), grade, surgical margins, and presence of metastatic lymph nodes. Margins were considered complete if no neoplastic cells were identified at ≤ 10 mm from any margin and incomplete if neoplastic cells were identified within 10 mm of any margin.

Outcome was determined from medical records and owner or primary veterinarian interviews. When complete follow-up information was unavailable in the medical record, verbal updates were obtained from the owner or primary veterinarian by telephone. A known outcome was defined as either alive at the time of data collection or deceased, with a date of death documented in the medical record. Overall survival time was defined as time from the date of surgery to the date of death. Tumor-specific survival time was calculated from the date of surgery to the date of death related to PPN. Dogs were considered to have died of tumor-related causes if metastasis or recurrence was confirmed or if clinical signs potentially attributable to recurrence or metastasis were described prior to death or as a reason for euthanasia. Death was considered unrelated to PPN if an alternate cause of death was provided or if no evidence of disease progression or clinical signs attributable to PPN were described prior to death.

Disease progression was defined as recurrence, metastasis, or malignant pleural effusion and was considered to be confirmed if diagnosed on the basis of radiographic, cytologic, or histopathologic findings. The disease-free interval was calculated from the date of surgery to the development of local recurrence, metastasis, or pleural effusion. Perioperative death was defined as death < 15 days after surgery.

The CLCSC system was used to stage all dogs with primary pulmonary carcinomas on the basis of preoperative imaging findings and surgical and histopathologic data **(Appendix)**. For dogs in which lymph node biopsy was not performed, N substage was recorded as N0. Information on postoperative chemotherapy, including drug, dose, and number of doses administered, was recorded. Adverse events were recorded with the VCOG-CTCAE.

Statistical analysis

Continuous variables were summarized as median and interquartile (25th to 75th percentile) range (IQR), and categorical variables were summarized as frequencies and percentages. A Fisher exact test was used to compare categorical variables between groups. Univariable logistic regression analysis was performed to examine associations between potential prognostic factors and MST. Prognostic factors evaluated included presence of clinical signs or pleural effusion at the time of diagnosis, tumor size (largest diameter ≤ 5 cm or > 5 cm), mitotic count, completeness of surgical margins, local tumor invasion, lymph node metastasis, other metastasis (distant or intrapulmonary), histologic grade (1 to 3), and CLCSC (I to IV). Prognostic variables with a value of $P < 0.05$ were further analyzed with multivariable Cox regression analysis. Disease-free interval, tumor-specific survival time, and overall survival time were estimated with Cox proportional hazards modeling. Patients that were lost to follow up or alive at the time of data collection were right censored for survival analyses. For dogs with pulmonary carcinoma, survival time was compared between dogs treated with adjuvant chemotherapy and dogs treated with surgery alone for each CLCSC by means of log-rank comparisons. The Fisher exact test was used to test for an association between lymph node status (N0 vs N1 or N2) and intrathoracic lymphadenopathy on CT (present vs absent). All analyses were performed by a statistician with commercially available software (R version 4.2; R Foundation for Statistical Computing). Values of $P < 0.05$ were considered significant.

Results

Patient characteristics, diagnostic evaluation, and tumor features

Three hundred fifty-four dogs were considered for inclusion in the study, but 14 were excluded because histopathologic findings were suggestive of metastatic neoplasia. The remaining 340 dogs met the inclusion criteria and were included in statistical analysis.

For the 340 dogs included in the study, median age at the time of surgery was 10.3 years (range, 5 to 16 years) and median body weight was 21.6 kg (range, 2.4 to 62 kg). There were 165 spayed females, 3 sexually intact females, 162 neutered males, and 10 sexually intact males. Mixed-breed dogs (n = 68 [20.0%]) and Labrador Retrievers (44 [12.9%]) were most common, followed by Boxers (14 [4.1%]), Miniature Schnauzers (13 [3.8%]), Golden Retrievers (13 [3.8%]), Bernese Mountain Dogs (11 [3.2%]), and Shih Tzus (11 [3.2%]). The remaining 166 dogs represented a variety of breeds. Clinical signs consisted of coughing (n = 112 [32.9%]), pleural effusion (23 [6.8%]), lethargy (11 [3.2%]), altered appetite (10 [2.9%]), increased respiratory effort (9 [2.6%]), panting (4 [1.2%]), hypertrophic osteopathy (4 [1.2%]), hemoptysis (3 [0.9%]), weight loss (3 [0.9%]), abdominal effusion (3 [0.9%]), and exercise intolerance (2 [0.6%]). All 3 dogs with abdominal effusion had CT evidence of caudal vena cava compression consistent with the Budd-Chiari syndrome secondary to PPN. PPN was identified incidentally in 127 (37.4%) dogs.

Thoracic CT was performed in 327 of the 340 (96.2%) dogs, and abdominal imaging was performed in 276 (81.2%). Evidence of pulmonary metastasis was identified in 60 of the 340 (17.6%) dogs, and evidence of distant metastasis was identified in 3 (0.9%). The primary tumor was located in the right caudal lobe in 103 of the 340 (30.3%) dogs, the left caudal lobe in 90 (26.5%), the left cranial lobe in 47 (14.8%), the right cranial lobe in 44 (12.9%), the right middle lobe in 38 (11.2%), and the accessory lobe in 18 (5.3%). A fine-needle aspirate of the primary lesion was obtained in 193 dogs, and results of cytologic examination of the aspirate were consistent with neoplasia in 146 of the 193 (75.6%). The remaining 47 (24.2%) samples either were not diagnostic or failed to show evidence

Table 1—Intra- and postoperative complications in 340 dogs with primary pulmonary neoplasia (PPN) that underwent surgical excision of the tumor.

Complications	Grade	No. (%) of dogs
Intraoperative		
Minor hemorrhage	1	20 (5.9)
Leakage from bronchus	1	6 (1.8)
Minor iatrogenic trauma to surrounding parenchyma	1	3 (0.9)
Rupture of mass during extirpation	1	2 (0.6)
Iatrogenic trauma to surrounding parenchyma requiring partial lobectomy	2	2 (0.6)
Iatrogenic rib fracture	3	2 (0.6)
Hemorrhage resulting in transfusion	3	3 (0.9)
Unilateral transection of vagal and phrenic nerves	3	1 (0.3)
Progressive hypoxemia and cardiopulmonary arrest	5	1 (0.3)
Postoperative		
Seroma	2	4 (1.2)
Surgical site infection	2	1 (0.3)
Hypoxemia requiring postoperative oxygen supplementation (> 24 h)	3	20 (5.9)
Aspiration pneumonia	3	6 (1.8)
Persistent pneumothorax requiring repeated thoracocentesis or continuous evacuation	4	11 (3.2)
Pleural effusion requiring repeated thoracocentesis	4	2 (0.6)
Hemorrhage requiring revision surgery and transfusion	4	2 (0.6)
Pneumothorax requiring revision surgery	4	1 (0.3)
Aspiration pneumonia requiring mechanical ventilation	4	1 (0.3)
Unknown cause of death	5*	5 (1.5)
Acute respiratory distress syndrome	5*	4 (1.2)
Persistent pleural effusion resulting in euthanasia	5*	2 (0.6)
Pulmonary thromboembolism	5*	2 (0.6)
Poor prognosis resulting in request for euthanasia	5*	2 (0.6)
Refractory seizures	5*	1 (0.3)
Hemothorax	5*	1 (0.3)
Disseminated intravascular coagulation	5*	1 (0.3)
Suspected urosepsis	5*	1 (0.3)
Unresectable tumor resulting in euthanasia	5*	1 (0.3)

*Grade 5 (perioperative death).

of neoplasia. No consistent preoperative hematologic abnormalities were identified.

Complete lobectomy of 1 or more affected lobes was performed in 294 of the 340 (86.5%) dogs, partial lobectomy was performed in 35 (10.3%), and a combination of complete and partial lobectomies was performed in 8 (2.4%); the extent of resection in the remaining 3 dogs was not documented. Intraoperative complications occurred in 40 (11.8%) dogs **(Table 1)**, and postoperative complications occurred in 70 (20.6%). The perioperative mortality rate (ie, percentage of dogs that died within 14 days of surgery) was 5.9% (20/340). Excluding dogs that died while hospitalized, median time from extubation to discharge was 48 hours (IQR, 24 to 52 hours).

Pulmonary carcinoma was the most frequently encountered tumor type, accounting for 87.1% (296/340) of cases **(Table 2)**. Sarcomas and pulmonary neuroendocrine tumors represented 7.6% (26/340) and 1.5% (5/340) of cases, respectively. All 20 dogs with a histopathologic diagnosis of primary pulmonary HS (PPHS) had no reported evidence of abdominal disease on preoperative CT (n = 8) or ultrasonography (12). Of the 20 dogs with PPHS, 7 were Bernese Mountain Dogs and 6 were Miniature Schnauzers. The primary tumor was located in the right hemithorax in 19 of these 20 dogs (right middle lobe, n = 7; right cranial lobe, 7; right caudal lobe,

Table 2—Distribution of histopathologic types for 340 dogs with PPN that underwent surgical excision of the tumor.

Tumor type	No. (%) of dogs
Carcinoma	296 (87.1)
Unclassified carcinoma	38 (11.2)
Adenocarcinoma	
Unclassified adenocarcinoma	59 (17.4)
Papillary	109 (32.1)
Bronchoalveolar	44 (12.9)
Tubulopapillary	6 (1.8)
Mixed	6 (1.8)
Minimally invasive	2 (0.6)
Lepidic	2 (0.6)
Solid	1 (0.3)
Acinar	1 (0.3)
Epithelial other than adenocarcinoma	
Adenosquamous	15 (4.4)
Squamous	6 (1.8)
Bronchial	3 (0.9)
Anaplastic	3 (0.9)
Clear cell	1 (0.3)
Sarcoma	26 (7.6)
Primary pulmonary histiocytic sarcoma	20 (5.9)
Poorly differentiated	3 (0.9)
Fibrosarcoma	1 (0.3)
Angiosarcoma	1 (0.3)
Chondrosarcoma	1 (0.3)
Neuroendocrine (carcinoid)	5 (1.5)
Adenoma	11 (3.2)
Other	
Plasmacytoma	1 (0.3)
Carcinosarcoma	1 (0.3)

3; and accessory lobe, 2) and in the left hemithorax in 1 (left cranial lobe). None of the 5 dogs with a neuroendocrine tumor had any reported evidence of abdominal disease on preoperative CT (n = 2) or ultrasonography (3). Malignant lesions were present in 329 of the 340 (96.8%) dogs. Pulmonary adenoma was the sole benign lesion reported and was identified in 11 (3.2%) dogs. Histologic grading was performed in 78 of the 296 (26.4%) dogs with pulmonary carcinoma, with tumors in 31, 44, and 3 dogs classified as grades 1, 2, and 3, respectively.

Thoracic CT and lymph node status

Intrathoracic lymphadenopathy was documented in 94 of the 327 (28.7%) dogs in which CT was performed. Lymph node biopsy was performed in 47 of these 94 (50.0%) dogs, and 25 of the 47 (53.2%) samples had histologic evidence of metastasis. Of the 233 dogs in which thoracic CT was performed and lymph nodes appeared normal, 89 (38.2%) had lymph node biopsy performed and 25 of the 89 (28.1%) samples had histologic evidence of metastasis.

Outcome

One- and 2-year survival rates for all dogs with PPN surviving the perioperative period were 46.0% (147/320) and 20.9% (67/320), respectively. Dogs that were lost to follow-up (n = 51) or alive at the time of data collection (n = 59) were right censored for survival analyses; median follow-up time for these 110 dogs was 494 days (range, 2 to 3,040 days). Median overall survival time for the 320 dogs surviving the perioperative period was 399 days (range, 18 to 3,040 days). Median tumor-specific survival time for the 320 dogs included in the survival analysis was 242 days (range, 18 to 1,808 days). Dogs that died of PPN-related causes had a significantly ($P < 0.001$) shorter survival time (median, 242 days; IQR, 85 to 550 days) than did dogs that died of causes unrelated to PPN (median, 620 days; IQR, 230 to 875 days; **Table 3**). Of the 106 dogs that died of local recurrence, metastatic disease, or suspected tumor-related causes, 3 of 4 (75%), 40 of 68 (59%), and 13 of 34 (38%), respectively, received adjuvant chemotherapy.

Three hundred twenty dogs survived the perioperative period (≥ 15 days after surgery). Of these, 168 of 278 (60.4%) with a pulmonary carcinoma, 18 of 19 (94.7%) with a PPHS, and 1 of 5 with a neuroendocrine tumor were dead at the time of data collection. MST was 399 days (IQR, 161 to 711 days) for the 278 dogs with a pulmonary carcinoma, 300 days (IQR, 128 to 528 days) for the 19 dogs with a PPHS, and 498 days (IQR, 159 to 1,273 days) for the 5 dogs with a neuroendocrine tumor. There was a significant ($P = 0.02$) difference in MST between dogs with carcinomas, dogs with PPHS, and dogs with neuroendocrine tumors **(Figure 1)**.

Immunohistochemistry was performed in 3 of the 5 dogs with neuroendocrine tumors. Of the 5 dogs with neuroendocrine tumors, 1 died of pulmonary thromboembolism 50 days postoperatively, 2 were alive at the time of data collection with follow-up periods of 2,688 and 801 days, and 2 were lost to follow-up at 2 and 493 days.

Two of 3 dogs with a poorly differentiated sarcoma survived to discharge; one of these dogs died of unknown causes 1,885 days after surgery, and the other was alive 1,907 days after surgery with no evidence of disease progression. The single dog with an angiosarcoma developed pulmonary metastases 425 days after surgery and died of progressive disease at 447 days. The single dog with pulmonary chondrosarcoma survived 72 days postoperatively; cause of death was unknown because the dog died at home and the owner could not be reached. The single dog with carcinosarcoma developed pulmonary metastases 252 days postoperatively and was euthanized because of progressive disease 312 days postoperatively. The single dog with a plasmacytoma was lost to follow-up at 227 days, and the single dog with a fibrosarcoma was lost to follow-up at 27 days. No evidence of disease progression had been documented in the medical record of either dog.

MST of the 106 dogs with preoperative pulmonary, nodal, or distant metastasis was 222 days

Table 3—Outcome and median survival times (MSTs; days) for 340 dogs with PPN that underwent surgical excision of the tumor.

Outcome	No. of dogs	MST (IQR)
Known	289	546 (160–748)
Alive[a]	59	568 (370–1203)
Died or euthanized	230	328 (121–692)
Tumor-related death	109	242 (86–550)
Local recurrence	4	467 (183–681)
Metastatic disease	68	218 (186–589)
Local recurrence and metastatic disease	3	128 (99–152)
Suspected tumor related[b]	34	NA
Unrelated cause of death	82	620 (230–875)
Perioperative death (< 15 days of surgery)	20	NA
Unknown cause of death	119	NA
Unknown (lost to follow-up)[c]	51	NA

NA = Not available or not applicable. IQR = Interquartile (25th to 75th percentile) range.

[a]Median follow-up time was 472 days (range, 141 to 3,040 days). [b]Death was suspected to be related to PPN, but confirmatory diagnostic testing was not performed. [c]Median follow-up time was 191 days (range, 16 to 882 days).

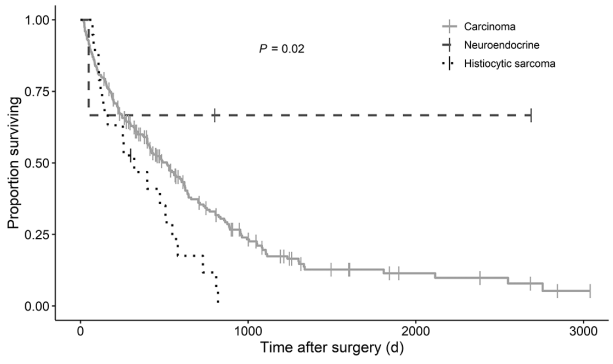

Figure 1—Overall survival time curves for dogs with primary pulmonary neoplasia that underwent surgery and in which the tumor was classified as a carcinoma (n = 278), primary pulmonary histiocytic sarcoma (19), or neuroendocrine tumor (5).

(range, 12 to 2,040 dogs), and dogs with preoperative metastasis had worse outcomes than did dogs without preoperative metastasis (hazard ratio, 2.29; $P < 0.001$). In univariable analyses, tumor size, mitotic count, intrathoracic lymph node metastasis, distant metastasis, and presence of pleural effusion at diagnosis were negative prognostic indicators **(Table 4)**. Dogs with complete surgical margins had significantly ($P = 0.027$) longer survival times than dogs with incomplete margins; however, there was no significant association between completeness of surgical margins and local recurrence ($P = 0.99$) or development of metastatic disease ($P = 0.562$). Mitotic count, intrathoracic lymph node metastasis, distant metastasis, and presence of pleural effusion at diagnosis remained significant on multivariable analysis.

Outcome following disease progression

Median disease-free interval for the 309 dogs with malignant tumors was 302 days (range, 17 to 1,394), and median times to disease progression were 344, 253, and 347 days, respectively, for dogs with pulmonary carcinoma (n = 95), PPHS (9), and neuroendocrine tumors (3). Time to disease progression not significantly ($P = 0.395$) different among these 3 groups.

Of the 278 dogs with pulmonary carcinoma that survived the perioperative period, 75 (27.0%) developed pulmonary metastases and 17 (6.1%) developed a local recurrence. Chemotherapy was initiated in 38 of the 75 (50.7%) dogs that developed pulmonary metastases; however, no significant ($P = 0.509$) association was detected between dogs that received chemotherapy and survival time. Nine of the 17 (52.9%) dogs with local recurrence received chemotherapy, and the remaining 8 received no additional treatment. Survival time following disease progression was significantly ($P = 0.021$) shorter for dogs that received chemotherapy (MST, 306 days) than for dogs that did not receive any additional treatment (MST, 419 days).

Of the 19 dogs with PPHS that survived the perioperative period, 2 developed a local recurrence and 10 developed metastatic disease. MST following disease progression in these 12 dogs was 119 days (range, 23 to 635 days).

Two of the 5 dogs with neuroendocrine tumors developed radiographic lesions suggestive of pulmonary metastasis 347 and 458 days after surgery. Both dogs were treated with toceranib and were alive at the time of data collection 801 and 2,688 days after surgery.

Outcome for dogs with pulmonary carcinoma

Staging with the CLCSC system was possible for 227 dogs that had pulmonary carcinomas, with 50 dogs classified as stage 1 (MST, 663 days; IQR, 295 to 1,037 days), 90 classified as stage 2 (MST, 389 days; IQR, 168 to 779 days), 58 classified as stage 3 (MST, 361 days; IQR, 103 to 510 days), and 29 classified as stage 4 (MST, 273 days; IQR, 141 to 419 days). For the remaining 70 dogs with pulmonary carcinoma, information in the medical record regarding the primary tumor was insufficient for staging. MST decreased significantly ($P < 0.001$) as stage increased, with a mean decrease of 136 days for each increase in stage **(Figure 2)**. The hazard of death was increased by 1.4 for each increase in stage ($P < 0.001$). Owing to the known significance of lymph node metastasis on survival time, an additional analysis by CLCSC stage was performed including only those dogs in which lymph node extirpation was performed, and similar results were obtained.

Table 4—Results of univariable analysis of potential prognostic factors for MST (days) in 340 dogs PPN that underwent surgical excision of the tumor.

Factor	No. of dogs	MST (IQR)	*P* value
Preoperative clinical signs			0.07
Yes	213	345 (123–634)	
No	127	464 (218–822)	
Pleural effusion present	15	274 (120–399)	0.015
Primary tumor size			0.015
≤ 5 cm	140	525 (221–914)	
> 5 cm	121	321 (316–529)	
Histologic grade			0.263
1	31	404 (282–779)	
2	44	386 (177–661)	
3	3	170 (124–260)	
Mitotic count (per 10 hpf)			< 0.001
≤ 10	188	477 (218–859)	
> 10 to ≤ 20	52	388 (83–448)	
> 20 to ≤ 30	20	244 (173–523)	
> 30	24	89 (28–222)	
Surgical margins			0.027
Incomplete	31	300 (104–554)	
Complete	48	324 (172–893)	
Tumor invasion present	44	282 (84–552)	0.264
Lymph node metastasis present	43	147 (71–318)	< 0.001
Distant metastasis present	3	206 (103–259)	0.017
Pulmonary metastasis present	60	387 (289–546)	0.914

IQR = Interquartile (25th to 75th percentile) range.

Chemotherapy

Of the 227 dogs with pulmonary carcinoma for which staging with the CLCSC system was possible, 83 received adjuvant chemotherapy postoperatively. Chemotherapy was discontinued in 3 dogs owing to grade 2 VCOG-CTCAE (gastrointestinal signs in all 3), and 2 dogs were lost to follow-up before completing the intended course of chemotherapy. Thus, 78 dogs that received adjuvant chemotherapy were included in this survival analysis. Dogs were treated with single-agent vinorelbine (n = 38), carboplatin (21), toceranib (5), cyclophosphamide (2), doxorubicin (1), lomustine (1), or chlorambucil (1). Alternating or combination chemotherapy included carboplatin and vinorelbine (n = 5); carboplatin, vinorelbine, and toceranib (3); and vinorelbine and lomustine (1). Dogs treated with adjuvant chemotherapy had significantly (P = 0.008) shorter survival times (MST, 237 days; range, 22 to 2,756 days) than did dogs treated with surgery alone (MST, 432 days; range, 18 to 3,040 days; **Figure 3**). When dogs were grouped on the basis of stage with the CLCSC system, there were no significant differences in MST between dogs that did and did not receive adjuvant chemotherapy **(Table 5)**. In addition, disease-free interval was not significantly (P = 0.12) different between dogs that received adjuvant chemotherapy and those treated with surgery alone.

Eighteen dogs with PPHS received adjuvant chemotherapy, with all 18 receiving lomustine as a single agent. Meaningful analysis of the effect of adjuvant chemotherapy on survival time was not possible, because information on survival time was available for only 1 dog that underwent surgery alone.

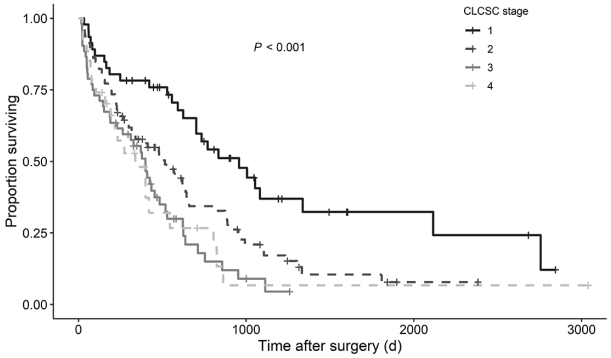

Figure 2—Overall survival time curves for 227 dogs with primary pulmonary carcinoma grouped on the basis of stage as determined by the canine lung carcinoma stage classification system as stage 1 (n = 50), 2 (90), 3 (58), or 4 (29). CLCSC = Canine lung carcinoma stage classification.

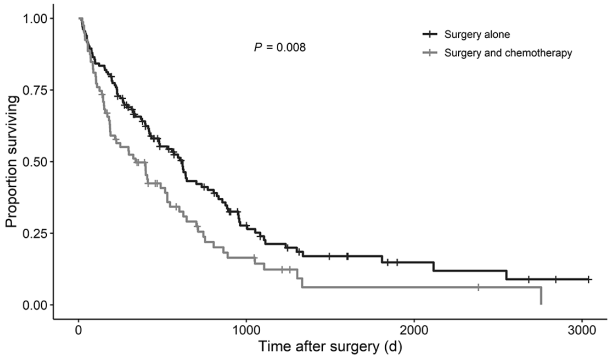

Figure 3—Overall survival time curves for 222 dogs with primary pulmonary carcinoma treated with surgery and adjuvant chemotherapy (n = 78) or with surgery alone (144).

Discussion

Results of the present study supported our hypothesis that pulmonary carcinoma is the most common cause of PPN in dogs. However, nonepithelial tumors (sarcomas and neuroendocrine tumors) comprised almost 10% (31/340) of the pulmonary tumors in the present study and occurred more frequently than previously reported. Survival times were significantly different among dogs with pulmonary carcinoma versus PPHS versus neuroendocrine tumor, emphasizing the importance of recognizing the relative incidence of these various histologic diagnoses.

Mixed-breed dogs and Labrador Retrievers represented 20.0% and 12.9% of dogs in the present report, respectively, and most of the dogs were older, similar to previous studies. Bernese Mountain Dogs have a known predisposition to develop histiocytic sarcoma; however, 2 reports[8,24] have suggested that Miniature Schnauzers may also be overrepresented among dogs with histiocytic sarcoma, which was supported by our study's findings. Reports describing PPHS in dogs are limited.[8] Reports describing

Table 5—MSTs (days) for 222 dogs (grouped on the basis of the canine lung carcinoma stage classification system) with primary pulmonary carcinoma that underwent surgical excision of the tumor and did or did not receive adjuvant chemotherapy.

Stage	Group	No. of dogs	MST (IQR)	*P* value
1	Surgery and chemotherapy	11	426 (182–875)	0.564
	Surgery alone	39	734 (422–1,005)	
2	Surgery and chemotherapy	32	263 (132–496)	0.824
	Surgery alone	55	465 (229–885)	
3	Surgery and chemotherapy	20	207 (115–484)	0.879
	Surgery alone	36	379 (128–548)	
4	Surgery and chemotherapy	15	274 (123–473)	0.802
	Surgery alone	14	254 (193–399)	

IQR = Interquartile (25th to 75th percentile) range.

PPHS in dogs are limited.[8,24,25] A recent study by Marlowe et al[8] described 37 cases of PPHS and reported median progression-free survival and overall survival times of 276 and 374 days, respectively, among dogs treated with surgery and adjuvant chemotherapy. Similar results were obtained in the present study, with a median disease-free interval of 253 days and MST of 300 days.

Pulmonary neuroendocrine tumors are rarely reported in veterinary species. To the authors' knowledge, only 4 case reports[26–29] involving dogs have been published and only 1 provided follow-up information; thus, limited information regarding survival time is available for this population. In humans, pulmonary neuroendocrine tumors (also termed carcinoids) have variable prognoses and are classified as low-grade, intermediate-grade atypical, high-grade small-cell, or high-grade large-cell carcinoid.[30] For the 5 dogs with pulmonary neuroendocrine tumors in the present study, MST was 498 days. The 2 dogs that were still alive at the time of data collection developed progressive disease postoperatively and both were treated with toceranib, surviving 801 and 2,688 days. Despite the small number of cases examined in our study, these results suggested that prolonged survival times and a durable response to intervention is possible in this population.

Dogs with pulmonary carcinoma in the present study had an MST (399 days; IQR, 161 to 711 days) similar to that described in previous reports. Importantly, the CLCSC system described by Lee et al[15] was prognostic for survival time in this large population, supporting the use of the CLCSC system in the clinical management of pulmonary carcinoma in dogs. The distribution of histopathologic types among dogs with pulmonary carcinoma highlighted the lack of standardized nomenclature in the veterinary literature regarding classification of primary pulmonary adenocarcinomas. Since the last consensus updating the classification system in veterinary species in 1999, there have been 2 significant revisions regarding classification of pulmonary carcinomas in humans to better correlate histopathologic features with clinical behavior.[31,32] Most notably, the term bronchoalveolar has been abandoned, and configurations of tumor growth, specifically lepidic and papillary patterns, are emphasized. Although pulmonary carcinomas in dogs appear to display similar features, to the authors' knowledge, formal investigation into the prognostic importance of an updated classification scheme in veterinary species is lacking. The abundance of terms describing pulmonary adenocarcinomas identified in the present study and the improved prognostic capacity of the updated classification of human pulmonary adenocarcinoma suggest a similarly updated classification scheme for use in small animals may be beneficial in more precisely conveying prognostic information to clinicians and owners.

Several prognostic factors were identified in the present study and were generally consistent with findings in previous reports. Primary tumor size (largest diameter > 5 cm), presence of pleural effusion, increasing mitotic count, distant metastasis, and lymph node status (N1 or N2) were independently associated with shorter survival times, consistent with results of previous studies.[13–15] Completeness of surgical margins and primary tumor size were not found to have prognostic importance in the multivariable analysis; however, incomplete surgical margins occurred most frequently in dogs with large (> 5 cm) tumors, and many of these dogs also had pulmonary or nodal metastasis. Thus, the lack of association in the multivariable analysis may have been due to the presence of residual disease in dogs with larger tumors and incomplete surgical margins. Interestingly, there was no association between the completeness of surgical margins and local recurrence. This was suspected to be due to the lack of standardized follow-up of dogs in the present study, limiting the ability to reliably identify dogs with recurrence versus other forms of disease progression. Tumor size and location within the lung lobe (hilar vs peripheral) may have also confounded these results because both factors can impact the ability to achieve complete resection; unfortunately, tumor location within the lung lobe was not analyzed in our study.

Histologic grade was not significantly associated with survival time in the present study; however, grading was not standardized or performed in all cases. Furthermore, histologic samples were not reviewed by an independent pathologist, thus limiting the interpretation of this finding. Similarly, local tumor invasion was not associated with survival time, although this is a negative prognostic indicator in humans. Identification of this feature was dependent on a clear description of the grossly visible extent of invasion in operative reports, which may have resulted in underestimation of the number of dogs in which local tumor invasion was present. Furthermore, in the authors' experience, PPNs rarely have gross evidence of invasion of surrounding structures intraoperatively, and invasion may be better determined histologically.

The most common clinical sign at presentation in our study was coughing (32.9%); however, the presence of clinical signs was not significantly associated with survival time. The presence of clinical signs has previously been identified as a negative prognostic indicator, but a more contemporary study[15] also found a lack of association between clinical signs and survival time. Certain factors evaluated for prognostic importance may have been influenced by selection bias because only dogs that underwent surgery were included in our study, limiting the ability to identify prognostic information for all dogs with PPN.

The use of CT to better delineate features of pulmonary tumors and identify intrathoracic metastasis has increased dramatically over the past decade. Because regional lymph node involvement is a known negative prognostic indicator in dogs with PPN, preoperative CT may provide prognostic information. There is limited information, however, regarding the sensitivity and specificity of preoperative CT for the evaluation of regional lymph node metastasis in dogs with PPN. A retrospective case series[33] of 14 dogs with PPN comparing CT evidence of tracheobronchial lymphadenopathy with histopathologic confir-

mation of metastasis found that 5 of 14 dogs had tracheobronchial lymphadenopathy and 6 of 14 had histopathologic evidence of lymph node metastasis, resulting in positive and negative predictive values of 100% and 89%, respectively, for preoperative CT. In the present study, metastasis was identified histologically in 25 of the 89 (28.1%) dogs in which lymph node biopsy was performed despite normal-appearing lymph nodes on preoperative CT. Given the importance of accurately determining lymph node status for staging and prognostication, extirpation or biopsy is strongly recommended regardless of lymph node appearance on preoperative CT.

An additional aim of the present study was to evaluate the effect of adjuvant chemotherapy in dogs with pulmonary carcinoma. Treatment protocols varied; however, dogs treated with adjuvant chemotherapy had significantly shorter survival times (MST, 237 days) than did dogs treated with surgery alone (MST, 432 days). Dogs with advanced stages of disease were more likely to receive chemotherapy; thus, treatment bias and unmeasured variables such as vascular or lymphatic invasion may have affected our results. To account for the effect of stage, outcomes for dogs that did and did not receive adjuvant chemotherapy were compared for each CLCSC stage; however, no significant differences in survival time were detected between groups. The results of our study do not provide convincing evidence to support or refute the use of adjuvant chemotherapy in dogs with pulmonary carcinoma; thus, the therapeutic benefit in this population remains uncertain. The large number of dogs included in the present study and the inability of previous investigators to demonstrate a significant survival benefit call into question the validity of chemotherapeutic treatment in dogs with pulmonary carcinoma, especially given the morbidity associated with chemotherapy. Further investigations in the form of prospective, randomized clinical trials are needed to determine the effect of adjuvant chemotherapy for dogs with pulmonary carcinoma.

Limitations of the present study included the retrospective nature of data collection and limited sample size used to draw conclusions for some groups, such as dogs with PPHS or neuroendocrine tumors. Because the objective of the present study was to report the distribution of histopathologic types and associated outcomes, information on outcomes for dogs with rare tumors was limited by inherently low case numbers. Given the paucity of data available regarding long-term outcome in dogs with these rare tumors, reporting such information is warranted but our results should be interpreted in light of the low sample sizes. The CLCSC system was prognostic in this population of dogs, although information used for staging was derived from preoperative imaging and operative and pathology reports, which were not written in a standardized manner. Preoperative imaging and abdominal staging were variable, which may have led to inconsistent staging, the effect of which was unknown. Because 96 dogs without lymph node extirpation were staged as N0, our survival time analysis was repeated only for those dogs with lymph node biopsy results, and similar findings were obtained. Follow-up was also inconsistent in our study, limiting our ability to interpret endpoints such as disease-free interval and overall survival time. Similarly, we attempted to evaluate the effect of adjuvant chemotherapy on outcome in dogs with pulmonary carcinoma; however, the lack of standardized treatment protocols, case selection bias, and inconsistent follow-up confounded our ability to interpret the results. More rigorous prospective investigation to determine the effect of adjuvant chemotherapy in dogs with surgically excised pulmonary carcinoma is warranted.

In conclusion, carcinoma represented the most common cause of PPN in dogs in the present study; however, nonepithelial tumors occurred more frequently than previously reported. Because survival times differed between dogs with pulmonary carcinoma and dogs with nonepithelial pulmonary neoplasms, PPHS and other rare tumors reported here should be considered in the differential diagnosis for dogs with PPN. The effect of adjuvant chemotherapy for the treatment of pulmonary carcinoma remains unknown, and future prospective studies are needed to investigate its impact on survival time.

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Appendix

Canine lung carcinoma stage classification scheme adapted from Lee et al.[15]

T Classification	Criteria
T1	≤ 3 cm in diameter; solitary nodule; no organ invasion
T2	> 3 to ≤ 5 cm in diameter; solitary nodule; invasion of visceral pleura or main bronchi (not carina)
T3	> 5 to ≤ 7 cm in diameter; separate nodules in same lobe; invasion of thoracic wall, pericardium, or phrenic nerve
T4	> 7 cm in diameter; separate nodules in ipsilateral lung lobes; invasion of mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, or spine

N Classification	Criteria
N0	No lymph node metastasis
N1	Ipsilateral tracheobronchial lymph node metastasis
N2	Distant lymph node metastasis

M Classification	Criteria
M0	No distant metastasis
M1	Malignant effusion, contralateral lung lobe metastasis, or extrathoracic metastasis

Stage	Criteria
1	T1, N0, M0
2	T2, N0, M0; T3, N0, M0; and T1 or T2, N1, M0
3	T4, N0, M0; T3 or T4, N1, M0; and T1 to T4, N2, M0
4	T1 to T4, N1 or N2, M1