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ORIGINAL ARTICLE

Primary pulmonary histiocytic sarcoma in dogs: A retrospective analysis of 37 cases (2000-2015)

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Primary pulmonary histiocytic sarcoma (PHS) has been reported, but is not well characterized. The aim of this retrospective study was to describe clinical characteristics, characterize prognostic factors and report the outcome of a larger group of dogs with primary PHS. Medical records of dogs diagnosed with primary PHS at 11 institutions were retrospectively reviewed. Thirty-seven dogs were included; 13 received CCNU-based chemotherapy alone, 18 received surgery and adjuvant CCNU-based chemotherapy, 3 received medical management alone and 3 dogs received surgery alone. The overall median progression free survival (PFS) and the median survival (overall survival [OS]) were 197 and 237 days, respectively. Measurable responses were noted in dogs receiving only chemotherapy; however, responses were not durable with PFS (91 days) and OS times (131 days) shorter than overall medians. Dogs that received surgery and chemotherapy had significantly prolonged PFS (276 days, $P = 0.001$) and OS (374 days, $P = 0.001$), compared with dogs not receiving surgery. As only three dogs undergoing surgery did not receive chemotherapy, it is not possible to determine the contribution of chemotherapy as an adjuvant to surgery. Dogs without evidence of intra-thoracic metastatic disease were much more likely to undergo surgery (odds ratio = 7.04; $P = 0.018$). While the presence of metastasis or clinical signs at diagnosis negatively impacted PFS, only the former negatively impacted OS. These data imply that dogs presenting with PHS amenable to surgery (ie, no clinical evidence of metastasis) benefit from surgical intervention; however, the lack of a comparable surgery alone group precludes assessment of the efficacy of post-surgical adjuvant chemotherapy.

KEYWORDS

dogs, histiocytic sarcoma, lung neoplasms, oncology

1 | INTRODUCTION

Histiocytic sarcoma (HS) is a malignant neoplasm of dendritic cell origin. It was first recognized as a distinct malignant histiocytic proliferative disorder in Bernese mountain dogs.[1] It is now known to be familiar in this breed, with other breeds reported as predisposed, including golden retrievers, flat-coated retrievers, and rottweilers. HS may present with localized organ involvement or disseminated, multi-organ involvement.[2,3] Localized HS is locally invasive and frequently metastasizes to draining lymph nodes. Reported anatomical sites include liver, spleen, lung, lymph node, stomach, oral cavity, mediastinum, skin/subcutaneous tissue, skeletal muscle, central nervous system, eye, joint/bone and bone marrow.[4–12] HS is known to be an aggressive disease with high metastatic rate, poor response to treatment and short survival times. However, recent publications indicate that dogs with localized HS can experience longer survival times with aggressive treatment, with a reported median survival time of 18.9 months.[4,12] Contrarily, 29% to 46% of disseminated HS cases respond to treatment with chemotherapy, but durable responses are uncommon with a median survival time of only 3.5 months.[12,13]

Primary pulmonary HS (PHS) has been reported, but is not well characterized. Kagawa et al[11] reported 19 cases of PHS in Pembroke

Welsh Corgis in Japan. Median survival time for all dogs in this study was 133 days. No significant improvement in outcome was seen with complete surgical excision or chemotherapy alone. A report of 11 dogs with HS involving the lungs found only one case of primary localized pulmonary involvement, with 10 representing disseminated disease.[2] Dervisis et al described clinical prognostic factors in dogs with HS, 30 of which had pulmonary involvement; however, it is unclear how many represented localized pulmonary disease.[7] More recently, Lenz et al described a series of 14 miniature schnauzers diagnosed with HS. Ten of these dogs had localized disease, and nine of ten were diagnosed with primary pulmonary disease. Treatment varied for the nine dogs, and survival times were poor for those receiving chemotherapy alone, with a median of 19 days. However, one dog who received surgery alone was still alive for 1620 days.[14] Radiographically, PHS is more commonly seen in the right middle and left cranial lung lobes and typically occurs in the periphery rather than the midaspect of the lobe. It is also more likely to involve the entire lobe in comparison to pulmonary carcinomas.[15,16]

Patients with localized HS may have prolonged survival times, and aggressive treatment with surgery, chemotherapy, radiation and combinations of these have suggested improved outcome. In the disseminated form of the disease, palliative treatment and concurrent use of steroids have been identified as negative prognostic factors.[2,3,8,12,17,18] It is currently unknown if patients with localized PHS experience comparable survival times to other localized forms of the disease. The primary aim of this study was to describe clinical characteristics, characterize prognostic factors and report outcome of a larger group of dogs with primary PHS.

2 | MATERIALS AND METHODS

Medical records of dogs diagnosed with primary PHS between the years of 2000 and 2015 were retrospectively reviewed at 11 institutions. Data were collected by participants at each institution by review of medical records. Follow-up calls to owners and referring veterinarians were performed when necessary. The information gathered included signalment, presenting clinical signs, diagnostic findings, gross lesion description, cytology and/or histopathology reports, immunohistochemistry results, evidence of metastasis at diagnosis, date of clinical onset, date of diagnosis, treatment pursued, response to treatment, date of progressive disease, date of death, cause of death and necropsy results. Dogs with either a cytological or histopathological diagnosis of primary PHS were included. Primary HS for the purpose of inclusion in this study was defined as the presence of intra-thoracic disease without abdominal involvement. Dogs were excluded if they were determined to have pulmonary involvement as a component of disseminated histiocytic disease based on abdominal imaging at diagnosis. Treatment response was defined according to Veterinary Cooperative Oncology Group (VCOG v1.1) RECIST criteria.[19] A minimum response duration of 21 days was required to determine response (complete response and partial response) and dogs that died before their first reevaluation were considered to have progressive disease.

Temporal outcomes were assessed by progression free survival (PFS) and overall survival (OS). PFS was calculated from the date of diagnosis to the date of local tumour recurrence/progression, metastasis or death from any cause. PFS for dogs alive without progression or lost to follow-up at the completion of the study was censored at the last date of follow-up. OS time was calculated from the date of diagnosis to the date of death from any cause. Survival times for dogs alive at the completion of the study or lost to follow-up were censored at the date they were last known to be alive. The Kaplan-Meier survival analysis method was used to estimate median PFS and OS curves. The Log-rank test was used to compare potential risk factors, including the presence of clinical signs at diagnosis, the presence of metastasis as diagnosis, size of pulmonary mass (longest diameter) and treatment options (chemotherapy, surgery, combination of chemotherapy and surgery and medical management). The likelihood (odds ratio) of dogs receiving surgical intervention in the presence or absence of intra-thoracic metastatic disease as well as the likelihood of dogs with metastatic disease to have clinical signs was analysed using Fisher's exact test. Multivariate analysis using the Cox proportional hazards model was performed on variables identified as prognostic in univariate analysis; a full model with all meaningful variables was formulated followed by backwards step elimination until only significantly associated variables were left in the model. Univariate and Fisher's statistical analyses were performed using standard software (Prism GraphPad 4.0, La Jolla, California), and multivariate analysis was performed using open source R (https://www.r-project.org, version 3.3.3). Two-sided *P*-values are reported, with values of $P < 0.05$ considered significant.

3 | RESULTS

The medical records of 37 dogs diagnosed with primary PHS were reviewed between 2000 and 2015. Eleven institutions submitted patient data: University of Minnesota ($n = 9$); University of Wisconsin ($n = 7$); University of Georgia ($n = 6$); Oregon State University ($n = 1$); The Oncology Service, Richmond, Virginia ($n = 1$); Blue Pearl Veterinary Partners, Atlanta, Georgia ($n = 2$); Royal Veterinary College ($n = 4$); Centre Veterinaire Laval ($n = 2$); Wheat Ridge Animal Hospital, Denver, Colorado ($n = 2$); Blue Pearl Veterinary Partners, New York, New York ($n = 2$) and East Bay Veterinary Specialists and Emergency, Walnut Creek, California ($n = 1$). Signalment, tumour characteristics and presenting clinical signs are summarized in Table 1. Presenting clinical signs included coughing ($n = 14$, 37.8%), lethargy ($n = 9$, 24.3%), inappetence ($n = 10$, 27.0%), dyspnea ($n = 4$, 9.3%), vomiting ($n = 2$, 5.4%), pyrexia ($n = 2$, 4.6%), lameness ($n = 2$, 4.6%), polyuria/polydipsia ($n = 2$, 4.6%), hemoptysis ($n = 1$, 2.3%), weight loss ($n = 1$, 2.3%), fatigue ($n = 1$, 2.3%) and shaking ($n = 1$, 2.3%). The pulmonary mass was an incidental finding in 11 dogs (25.5%).

Laboratory abnormalities at the time of diagnosis were mild and non-specific, and included thrombocytosis ($n = 4$, 9.3%), thrombocytopenia ($n = 3$, 6.9%), anaemia ($n = 3$, 6.9%), lymphopenia ($n = 2$, 4.6%), neutrophilia ($n = 2$, 4.6%), elevated ALP ($n = 7$, 18.9%), elevated ALT ($n = 6$, 13.9%), hypoalbuminemia ($n = 3$, 8.1%), hypocalcemia ($n = 3$, 6.9%), hyperglobulinemia ($n = 3$, 6.9%), elevated AST

TABLE 1 Summary of results in all dogs (%)

Breeds	**Bernese mountain dog, *n* = 9 (24.3) Labrador retriever, *n* = 7 (18.9) Miniature schnauzer, *n* = 3 (8.1) Shar pei, *n* = 3 (8.1) Other, *n* = 15 (40.5)[a]**
Mean age	8.8 years (range: 4.0-14.4 years)
Mean weight	31.1 kg (range: 5.5-57.0 kg)
Sex	Spayed female, *n* = 21 (56.7)
	Castrated male, *n* = 11 (29.7)
	Intact male, *n* = 3 (8.1)
	Intact female, *n* = 2 (5.4)
Mean tumour size	6.7 cm (range: 1.2-15)
Tumour location	Right middle lung lobe, *n* = 10 (27.0)
	Right caudal lung lobe, *n* = 8 (21.6)
	Right cranial lung lobe, *n* = 6 (1.6)
	Other, *n* = 13 (35.1)[b]
Most common clinical signs	Coughing, *n* = 14 (37.8)
	Lethargy, *n* = 9 (24.3)
	Inappetence, *n* = 10 (27.0)

[a] See text for list of other breeds.
[b] See text for list of other tumours sites.

(*n* = 2, 4.6%), hypocholesterolemia (*n* = 1, 2.7%), hyperbilirubinemia (*n* = 2, 4.6%), elevated CK (*n* = 2, 4.6%), hypokalemia (*n* = 1, 2.3%), decreased BUN (*n* = 1, 2.3%), increased BUN (*n* = 2, 4.6%), increased creatinine (*n* = 1, 2.3%), hypertriglyceridemia (*n* = 1, 2.3%), hyperlipidemia (*n* = 1, 2.3%), hypercalcemia (*n* = 2, 4.6%), hypoproteinemia (*n* = 1, 2.3%) and hyponatremia (*n* = 1, 2.3%).

Twenty-four dogs were diagnosed via histopathology. Immunohistochemical staining with an anti-CD18 antibody was performed on 17 of these dogs, all of which showed positive staining. Cytology alone was used to diagnose 13 dogs. None of these dogs had immunocytochemistry performed. The primary tumour location was available in 32 dogs (Table 1). Four dogs had tumours in more than one lung lobe at diagnosis, and the affected lung lobe was not reported in one dog.

Thirty dogs had thoracic radiographs performed, and 28 dogs had a thoracic computed tomography (CT) scan. Nineteen dogs had no evidence of metastasis at diagnosis. This finding was based mainly on imaging. However, dogs that had surgery performed had enlarged lymph nodes and other pulmonary nodules biopsied at the time of surgery. In cases where surgery was not performed, suspected metastatic lesions were often not sampled, therefore metastasis was suspected but could not be confirmed. However, intra-thoracic nodal disease met criteria for metastatic disease established by Paoloni et al.[20] Eleven dogs had evidence of metastasis to the regional lymph nodes (ie, tracheobronchial or cranial mediastinal). Two dogs had mildly enlarged intra-thoracic lymph nodes seen on CT scan that were suspected to be reactive, but metastasis could not be ruled out. Two dogs had evidence of pulmonary metastasis. Four dogs had evidence of metastasis to both the local lymph nodes and lungs.

Abdominal imaging was performed in all dogs; 8 had an abdominal CT, 28 had an abdominal ultrasound and 1 dog had abdominal radiographs performed at the time of diagnosis. One dog with suspected pulmonary and lymph node metastasis had nodules in the liver and spleen that showed contrast enhancement on abdominal CT scan. All of these abnormalities were suspected to represent metastatic disease, but lesions were not sampled, and therefore could not be confirmed. No other dogs had evidence of metastasis within the abdomen. Only three dogs had a bone marrow aspirate performed, and none revealed evidence of neoplastic infiltration.

Treatment protocols varied within the population. Of 37 dogs, 13 received chemotherapy alone. All of these dogs received Lomustine (CCNU) as part of their chemotherapy protocol, with 8 of 13 receiving CCNU alone. One dog received an alternating CCNU and vinorelbine protocol; 3 of 13 dogs received an alternating CCNU and doxorubicin protocol; and 1 of 13 received an alternating CCNU and cyclophosphamide protocol. Of 13 dogs, 6 received prednisone as part of their chemotherapy protocol. Three dogs were medically managed with prednisone alone (*n* = 2) or not treated (*n* = 1).

Twenty-one dogs underwent surgery. Surgery was the sole treatment modality in three dogs, and 18/21 received adjuvant chemotherapy in addition to surgery. Of the 21 dogs who received chemotherapy after surgery, 12 dogs received CCNU alone, 3 received an alternating CCNU and doxorubicin protocol, 1 received an alternating CCNU and vinorelbine protocol, 1 received maintenance metronomic chlorambucil after five doses of CCNU, and 1 received an alternating toceranib and metronomic cyclophosphamide maintenance protocol after five doses of CCNU.

Of the 13 dogs that received chemotherapy alone in the macroscopic disease setting, RECIST response could be evaluated in 9 dogs; 3 of 9 had stable disease (33.3%), 3 of 9 had a partial response (33.35%), 1 of 9 had a complete response (11.1%) and 2 of 9 had progressive disease (22.2%). The one dog who achieved a complete response received CCNU and prednisone. The complete response was documented via thoracic radiographs on the first recheck at 43 days; the dog was lost to follow-up at 92 days.

Only two dogs were known to still be alive at the end of the study period. Progression of disease was suspected in most dogs; however, the extent and characterization of "progression" could not be accurately ascertained from retrospective review of records in 16 dogs. Where characterization of progression was documented (*n* = 17), 3 of 17 dogs had local recurrence/progressive local disease, 10 of 17 had evidence of metastasis to either intra-thoracic lymph nodes, lungs or distant locations, and 4 of 17 had evidence of both local progression and metastasis. Four dogs had no evidence of progressive disease or metastasis.

Temporal outcome data are summarized in Table 2. The overall median PFS and OS of the entire cohort were 197 and 237 days, respectively (Figure 1A,B). Dogs that received both surgery and chemotherapy had prolonged PFS (276 days vs 79 days, $P = 0.001$) and OS (374 days vs 131 days, $P = 0.001$) compared with those that were not treated with the combination of surgery and chemotherapy (Figure 2A,B). A meaningful statistical comparison of dogs undergoing surgery with or without adjuvant chemotherapy was not possible owing to the small number of dogs receiving surgery without chemotherapy (*n* = 3; PFS of 69, 281, 219 days; OS of 69, 281, 237 days), and the Kaplan-Meier curves were virtually superimposable to those generated for surgery and chemotherapy. Dogs receiving only

TABLE 2 Prognostic factors found to effect outcome

Group	Median PFS in days (95% CI)	*P*-value	Median OS in days (95% CI)	*P*-value
All patients	197 (110-267)		237 (187-307)	
Surgery + chemotherapy		0.001[a]		0.001[a]
YES	276 (199-357)		374 (237-558)	
NO	79 (42-124)		131 (57-213)	
Chemotherapy alone	91 (41-123)	0.003[b]	131 (41-214)	0.005[b]
Metastasis				0.043
YES	123 (51-263)	0.031	214 (57-288)	
NO	265 (101-490)		261 (185-679)	
Clinical signs		0.022		0.251
YES	123 (50-203)		185 (70-281)	
NO	276 (101-556)		298 (205-557)	

Abbreviations: OS, overall survival; PFS, progression free survival.
[a] Patients who received the combination of surgery and chemotherapy compared with those receiving chemotherapy alone, surgery alone, supportive care or no treatment.
[b] Compared with dogs receiving surgery and chemotherapy.

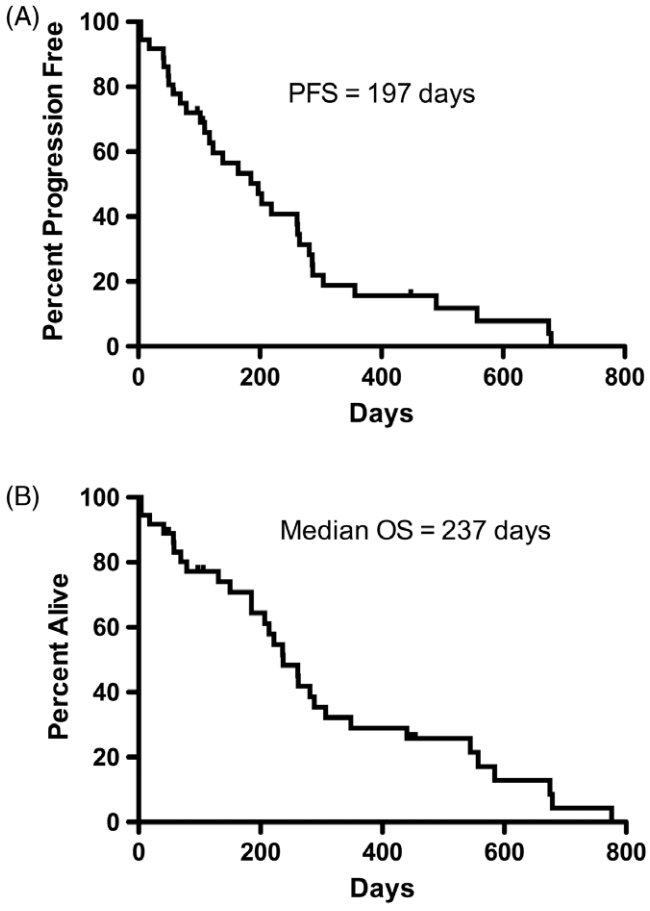

FIGURE 1 A, Kaplan-Meier survival curve estimating PFS of entire cohort. Tick marks represent censored cases. B, Kaplan-Meier survival curve estimating OS of entire cohort. Tick marks represent censored cases. OS, overall survival; PFS, progression free survival

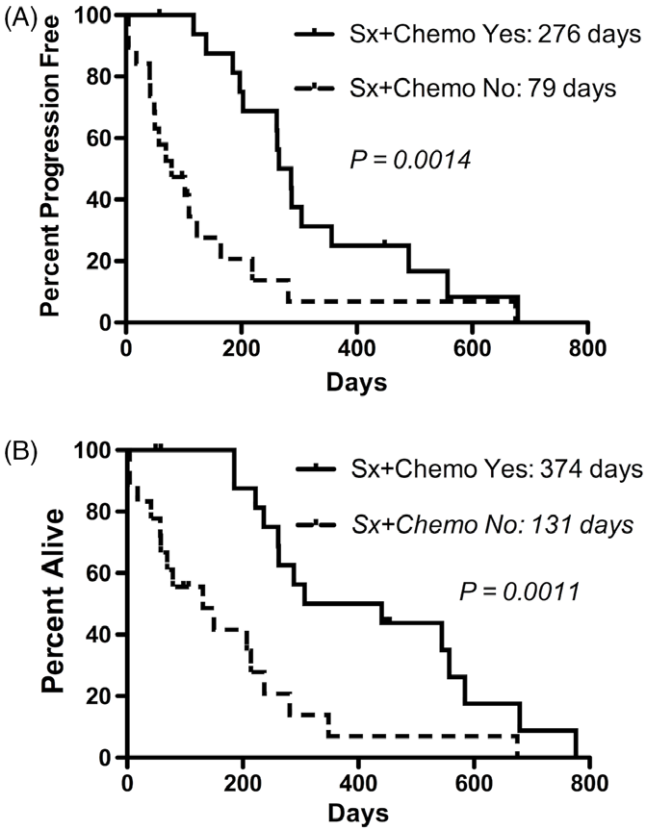

FIGURE 2 A, Kaplan-Meier survival curves estimating median progression free survival in dogs receiving surgery and chemotherapy compared with dogs that were treated with any other therapeutic modality (surgery alone, chemotherapy alone, supportive care or no treatment). Tick marks represent censored cases. B, Kaplan-Meier survival curves estimating median overall survival in dogs receiving surgery and chemotherapy compared with dogs that were treated with and other treatment modality (surgery alone, chemotherapy alone, supportive care, or no treatment). Tick marks represent censored cases

chemotherapy had PFS and OS durations of 91 days (95% confidence interval [CI]: 41-123) and 131 days (95% CI: 41-214), respectively, which was significantly less than if surgery was included in the treatment received (P = 0.003 for PFS, P = 0.005 for OS). The presence/suspicion of intra-thoracic metastasis at diagnosis negatively impacted PFS (123 days vs 265 days, P = 0.031), and OS (214 days vs 261 days, P = 0.043). Based on this result, the data were analysed to determine if the presence of intra-thoracic metastasis had an effect on whether dogs had surgery. Of 21 dogs that had surgery as part of their

treatment, 8 had metastatic disease at presentation and 13 did not. Of 16 dogs that did not undergo surgery, 13 had metastatic disease at presentation and 3 did not. Therefore, dogs that were deemed to be free of intra-thoracic metastatic disease at presentation were significantly more likely to undergo surgery as part of their therapy (odds ratio = 7.04; P = 0.018; 95% CI: 1.5-32.7).

The presence of clinical signs at diagnosis negatively impacted PFS (123 days vs 276 days, P = 0.022), but did not impact OS. The dogs that presented with evidence of intra-thoracic metastasis were more likely to present with clinical signs (odds ratio = 7.24; P = 0.025; 95% CI: 1.5-35.3). The size of the tumour at diagnosis had no significant impact on PFS or OS. As the data suggested the presence of metastasis likely impacted the decision to pursue surgery, we performed multivariate analysis of factors shown to be prognostic by univariate analysis post hoc (surgery yes/no, intra-thoracic metastasis yes/no and clinical signs yes/no) and as suspected, no factor was shown to independently predict outcome (data not shown).

4 | DISCUSSION

Canine HS has an aggressive biologic behaviour, and most dogs have evidence of metastasis or disseminated disease at diagnosis. However, recent literature indicates that dogs with localized disease can experience prolonged survival. Klahn and colleagues found dogs with localized periarticular HS had significantly longer survival times compared with dogs with HS of other anatomic locations and particularly dogs with widespread disease.[4] Similarly, Skorupski and colleagues reported long-term survival in dogs with localized HS treated with surgery and chemotherapy, with the median OS extending to 18.9 months. Five of the 16 dogs in Skorupski's study had primary PHS.[12] Other reports of primary PHS exist; however, this is the first descriptive study performed with the intent of documenting a larger cohort of patients with primary PHS and identifying prognostic factors associated with this disease.

Bernese mountain dogs and Labradors, which have previously been identified as breeds predisposed to developing HS, appear overrepresented in this study. Miniature schnauzers accounted for 9% of the breeds in this study and may represent another breed predisposed to HS. Unlike the study performed by Kagawa et al,[11] describing primary PHS in Japan, no Pembroke Welsh Corgis were identified in this study. This may indicate a difference in genetic background in corgis in North America compared with Japan, or may be due to the popularity of the breed in Japan. The most common clinical signs in this study population included coughing (37.8%), lethargy (24.3%) and inappetance (27.0%). However, 25.5% of cases were diagnosed incidentally on thoracic radiographs taken for unrelated reasons. This is similar to other pulmonary tumours where up to 30% of cases do not have clinical signs at the time of diagnosis. Clinical signs at diagnosis were associated with a shorter PFS, similar to primary lung tumours of other histologic types.[21] However, the presence of clinical signs was not associated with a decrease in OS. This may be due to the small case number or retrospective nature of the study. Anaemia, thrombocytopenia and hypocholesterolemia have been associated with the hemophagocytic form of HS, and previously identified negative prognostic factors in dogs with HS.[16,22] In this study, three dogs presented with hypoalbuminemia, three with anaemia, three with thrombocytopenia and one with hypocholesterolemia; such small numbers precluded meaningful statistical comparisons. Intra-thoracic metastasis was present in 45.9% of patients, and significantly impacted PFS and OS, mirroring primary lung tumours of other histologic types.[21] The fact that dogs with intra-thoracic metastatic disease were much less likely to go to surgery likely impacted outcome. Unlike previous reports of primary lung tumours, size of the lung mass did not affect survival in this study.

Although retrospective studies cannot be directly compared, the dogs in this study with primary PHS had less durable outcomes than previous studies reporting dogs with localized disease in other locations.[12] Both PFS and OS were shorter, at 197 and 237 days, respectively. However, patients that received surgery and adjuvant chemotherapy did significantly better (Table 2, Figure 2) than dogs that did not receive the combination. Patients who received chemotherapy without surgery had the shortest temporal outcomes. These data imply that surgery is a beneficial therapeutic modality for primary PHS; however, it is likely that presence of metastatic disease, which was shown to negatively impact outcome, influenced the decision to perform surgery and is supported by the greater likelihood of surgery (odds ratio = 7.04) in dogs without documented intra-thoracic metastatic disease and the lack of independence found on multivariate analysis. The question remains, what impact does adjuvant chemotherapy have on survival in cases that can be taken to surgery? In our data set, nearly all dogs receiving surgery also received chemotherapy, precluding a direct comparison. Of the nine dogs where response to chemotherapy in the macroscopic setting could be evaluated, the overall response rate was 44.4%. Including cases with stable disease, the overall biologic activity was 77.7%, although responses were not durable. Current dogma states that cytotoxic chemotherapy should be more efficacious in the microscopic, post-surgical adjuvant setting. While the combination of surgery and chemotherapy greatly outperformed our group receiving only chemotherapy, any comparison is again biased as cases with intra-thoracic metastatic disease at presentation were much less likely to undergo surgery, either because of practical surgical concerns or client decision based on perceptions of poor outcome in the presence of metastatic disease. It could also be argued, that since we do not have a group of dogs without intra-thoracic metastatic PHS that did not undergo surgery for comparison, the true natural history of early stage PHS is unknown and therefore the benefit of surgery, while suggested, is not clearly established.

Limitations of this study include those common to retrospective analyses; limited case numbers, lack of histologic and immunohistochemical diagnosis for every patient, variable staging, and lack of standardized treatment protocols. Because of the rarity of the disease process, we included cases from multiple institutions which allowed for different chemotherapy protocols and follow-up was sometimes limited. As with any retrospective data set, findings should raise questions to be tested in more rigorous prospective studies. For this study, cases were included with either a cytologic or histopathologic diagnosis of HS. Cytologic features of HS include numerous pleomorphic, large, discrete mononuclear cells with abundant, lightly basophilic, vacuolated, granular cytoplasm and marked anisocytosis and anisokaryosis.[23] While a diagnosis can be made off of cytology, recent work has shown histopathology with immunohistochemistry (IHC) to be more accurate and should be performed whenever possible.[8] In this

study, the patients with a histopathologic diagnosis of HS were patients that had tissue submitted following surgery. Many dogs with enlarged intra-thoracic lymph nodes or other pulmonary nodules that did not go to surgery did not have those lesions sampled because of inaccessibility. Therefore, the metastatic rate at diagnosis in this population may be over or under represented. Finally, we included one case with suspected metastasis to the liver and spleen based on lesions seen on CT scan. This dog had a single pulmonary mass measuring 10 cm and had metastasis to local lymph nodes. Because of the presentation, we highly suspect this case represents a primary PHS with metastasis to the abdomen, and we wanted to report this case as such. However, we cannot definitively rule out a disseminated HS.

In conclusion, we described clinical characteristics of a series of primary PHS cases to characterize potential prognostic factors and report outcome. While the combination of local therapy with surgery and chemotherapy does appear to improve outcome, these data do not provide information as to the relative contribution of each. While dogs receiving only chemotherapy had the shortest survivals, this result, while intuitive, is likely biased as dogs with intra-thoracic metastatic disease at presentation were much more likely to receive chemotherapy without surgery. In general, patients with primary PHS appear to have shorter temporal outcomes than dogs with other localized anatomic sites; however, dogs whose disease is amenable to surgery and adjuvant chemotherapy can have durable (≈1 year) survival outcomes. As with any retrospective study, controlled prospective studies would be necessary to confirm these preliminary findings.

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Conflict of interest

The authors declare no conflicts of interest.

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REFERENCES

1. Moore PF, Rosin A. Malignant histiocytosis of Bernese mountain dogs. *Vet Pathol*. 1986;23:1-10.
2. Affolter VK, Moore PF. Localized and disseminated histiocytic sarcoma of dendritic cell origin in dogs. *Vet Pathol*. 2002;39:74-83.
3. Fulmer AK, Mauldin GE. Canine histiocytic neoplasia: an overview. *Can Vet J*. 2007;48:1041-1050.
4. Klahn SL, Kitchell BE, Dervisis NG. Evaluation and comparison of outcomes in dogs with periarticular and nonperiarticular histiocytic sarcoma. *J Am Vet Med Assoc*. 2011;239:90-96.
5. Naranjo C, Dubielzig RR, Friedrichs KR. Canine ocular histiocytic sarcoma. *Vet Ophthalmol*. 2007;10(3):179-185.
6. Fant P, Caldin M, Furlanello T, De Lorenzi D, Bertolini G, Morini M. Primary gastric histiocytic sarcoma in a dog—a case report. *J Vet Med*. 2004;51:358-362.
7. Craig LE, Jullian ME, Ferracone JD. The diagnosis and prognosis of synovial tumors in dogs: 35 cases. *Vet Pathol*. 2002;39:66-73.
8. Dervisis NG, Kiupel M, Qin Q, Cesario L. Clinical prognostic factors in canine histiocytic sarcoma. *Vet Comp Oncol*. 2017;15(4):1171-1180.
9. Mariana CL, Jennings MK, Olby NJ, et al. Histiocytic sarcoma with central nervous system involvement in dogs: 19 cases (2006-2012). *J Vet Intern Med*. 2015;29:607-613.
10. Kumagai K, Makino T, Maejima T, Manabe S, Teranishi M. Pulmonary histiocytic sarcoma in two aged dogs of a beagle colony. *J Toxicol Pathol*. 2006;19:143-146.
11. Kagawa Y, Nakano Y, Kobayashi T, Asano K, Takagi S. Localized pulmonary histiocytic sarcomas in Pembroke Welsh Corgi. *J Vet Med Sci*. 2015;77(12):1659-1661.
12. Skorupski KA, Rodriguez CO, Krick EL, Clifford CA, Ward R, Kent MS. Long-term survival in dogs with localized histiocytic sarcoma treated with CCNU as an adjuvant to local therapy. *Vet Comp Oncol*. 2009;7(2):139-144.
13. Rassnick KM, Moore AS, Russell DS, et al. Phase II, open-label trial of single-agent CCNU in dogs with previously untreated histiocytic sarcoma. *J Vet Intern Med*. 2010;24:1528-1531.
14. Lenz JA, Furrow E, Craig LE, Cannon CM. Histiocytic sarcoma in 14 miniature schnauzers – a new breed predisposition? *J Small Anim Pract*. 2017;58:461-467.
15. Barrett LE, Pollard RE, Zwingenberger A, Zierenberg-Ripoll A, Skorupski KA. Radiographic characterization of primary lung tumors in 74 dogs. *Vet Radiol Ultrasound*. 2014;55(5):480-487.
16. Tsai S, Sutherland-Smith J, Burgess K, Ruthazer R, Sato A. Imaging characteristics of intrathoracic histiocytic sarcoma in dogs. *Vet Radiol Ultrasound*. 2012;53(1):21-27.
17. Skorupski KA, Clifford CA, Paoloni MC, et al. CCNU for the treatment of dogs with histiocytic sarcoma. *J Vet Intern Med*. 2007;21:121-126.
18. Wouda RM, Miller ME, Chon E, Stein TJ. Clinical effects of vinorelbine administration in the management of various malignant tumor types in dogs: 58 cases (1997-2012). *J Am Vet Med Assoc*. 2015;246:1230-1237.
19. Nguyen SM, Thamm DH, Vail DM, London CA. Response evaluation criteria for solid tumours in dogs (v1.0): a Veterinary Cooperative Oncology Group (VCOG) consensus document. *Vet Comp Oncol*. 2015;13(3):176-183.
20. Paoloni MC, Adams WM, Dubielzig RR, Kurzman I, Vail DM, Hardie RJ. 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). *J Am Vet Med Assoc*. 2006;228(11):1718-1722.
21. McNiel EA, Oglivie GK, Powers BE, Hutchinson JM, Salman MD, Withrow SJ. Evaluation of prognostic factors for dogs with primary lung tumors: 67 cases (1985-1992). *J Am Vet Med Assoc*. 1997;211(11):1422-1427.
22. Moore PF, Affolter VJ, Venrau W. Canine hemophagocytic histiocytic sarcoma: a proliferative disorder of CD11d+ macrophages. *Vet Pathol*. 2006;43:632-645.
23. Brown DE, Thrall MA, Getzy DM, Weiser MG, Ogilvie GK. Cytology of canine malignant histiocytosis. *Vet Clin Path*. 1994;23(4):118-122.

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