Veterinary Dermatology

Vet Dermatol 2017 DOI: 10.1111/vde.12504

Clinical outcome and prognosis of dogs with histopathological features consistent with epitheliotropic lymphoma: a retrospective study of 148 cases (2003–2015)

Catherine M. Chan*, Angela E. Frimberger† and Antony S. Moore†

*Animal Referral Hospital, 250 Parramatta Road, Homebush West, Sydney, New South Wales 2140, Australia
†Veterinary Oncology Consultants, 379 Lake Innes Drive, Wauchope, New South Wales 2446, Australia

Correspondence: Catherine Chan, Queensland Veterinary Specialists, 53 Flinders Parade, North Lakes, Brisbane, Queensland 4059, Australia.
E-mail: catherine.tran@uqconnect.edu.au

Background – Limited information is available regarding the treatment and outcome of dogs with epitheliotropic lymphoma. The disease typically has a poor prognosis.

Objectives – To characterize the clinical signs, identify prognostic factors and evaluate the treatment outcome of dogs with epitheliotropic lymphoma.

Methods – A retrospective review of medical records from 2003 to 2015. Treatment details, tumour response and survival time were recorded for 148 dogs. Potential prognostic factors were evaluated for their statistical effect on median survival time.

Results – The overall median survival time for dogs was 264 days (cutaneous: 130 days; mucocutaneous/mucosal: 491 days). On multivariate analysis, a shorter median survival time was associated with the cutaneous form ($P < 0.001$) and the presence of multiple lesions ($P < 0.001$). Among 80 dogs with cutaneous lesions, chemotherapy treatment ($P < 0.001$) and having a solitary lesion ($P < 0.001$) were associated with longer median survival. In 72 dogs with multiple cutaneous lesions, chemotherapy intervention ($P < 0.001$), retinoid treatment ($P = 0.001$) and complete remission ($P = 0.001$) were associated with longer median survival. In 68 dogs with mucocutaneous/mucosal lesions, decreasing age ($P = 0.020$) and a solitary lesion ($P = 0.015$) were associated with longer median survival.

Conclusion – Canine epitheliotropic lymphoma may be divided into cutaneous and mucocutaneous/mucosal forms. Solitary lesions have a better prognosis. Dogs with multiple lesions appear to benefit from chemotherapy and retinoid treatment, with those attaining complete remission having longer survival times. Multi-agent chemotherapy could be considered in dogs with cutaneous lesions that fail to respond to single-agent chemotherapy.

Introduction

Epitheliotropic lymphoma (EL) is an uncommon form of lymphoma in dogs, representing 3–8% of canine lymphoma and <1% of canine cutaneous tumours.[1] The aetiology for this malignancy in dogs is unknown.[2] The tumour tends to occur in the epidermis, superficial dermis and periadnexally, although oral mucosal and mucocutaneous forms have been described.[2–9] Canine EL is typically a tumour of T lymphocytes, with the CD3 + and CD4-/CD8+ phenotype most commonly expressed.[3,8,10] The disease tends to occur in older dogs (median age 10–12 years),[2,3,6,8,10] with no obvious gender or breed predilection, although some authors have reported that boxers and cocker spaniels may be over-represented.[2,10]

Canine EL has a poor prognosis; however, in contrast to canine multicentric lymphoma, the prognostic factors that affect survival, either with or without treatment intervention, are not well understood.[2,5,11] The disease is challenging to treat, with variable response rates and a short duration of response typically reported with various systemic therapies including linoleic acid, lomustine (CCNU), masitinib, PEGylated l-asparaginase, PEGylated liposomal doxorubicin, retinoids and VDC-1101.[1,7,11–16] The overall response rate (ORR) reported for all therapies is from 42 to 83% for a median response duration of from 37.5 to 106 days. The reported mean and median survival times

Abbreviations: CI, confidence interval; CR, complete remission; EL, epitheliotropic lymphoma; MST, median survival time; McM, mucocutaneous, mucosal; ORR, overall response rate; PD, progressive disease; PR, partial remission; SD, stable disease; TTP, total time to progression; VCOG-CTCAE, veterinary cooperative oncology group - common terminology criteria for adverse events; VELCAP-EL, is derived from vincristine (v), L-asparaginase (EL), cyclophosphamide (C), Adriamycin (doxorubicin) (A) and prednisone (P), -EL is for epitheliotropic lymphoma.

Accepted 6 January 2017
Preliminary data were presented at the 2008 ACVIM Forum in San Antonio, Texas, USA, and at the 2014 ACVIM Forum in Nashville, Tennessee, USA.
Source of Funding: This study was self funded.
Conflicts of interest: No conflicts of interest have been declared.
[Correction added on 6 November 2017 after first online publication: The article title has been updated for accuracy in this current version.]

with various forms of treatment range from a few months to 2.1 years.[2,5,6,15,16] A standard of care for the treatment of EL has not yet been established; however, systemic chemotherapy (particularly with single-agent CCNU with or without prednisolone) is a common therapeutic approach.[1,6,11–13,17,18] Multi-agent chemotherapy protocols based on standard lymphoma therapy, with increased emphasis on CCNU and other alkylating agents are also used in veterinary oncology referral practices.

The most important prognostic factors for canine lymphoma are the extent of disease (stage), the absence or presence of systemic signs (substages a and b, respectively) and immunophenotype.[19–23] Higher stage (e.g. stage V), substage b and T-cell immunophenotype have been associated with shorter remission and survival times. Using this scheme, cutaneous lymphoma is extra nodal and, therefore, stage V. In humans, epitheliotropic lymphoma progresses through three apparent clinical stages: pre-mycotic, mycotic and tumour stage, with the presence of tumour stage (nodules or masses) conferring a worse prognosis.[24] Clinical staging of EL has not been well-established in dogs.

The primary purpose of this retrospective study was to characterize the clinical course of disease and to identify prognostic factors in a relatively large number of dogs with histopathological features consistent with EL. The secondary aim was to assess the clinical outcomes in dogs that were treated.

Materials and methods

The medical record databases for the Animal Referral Hospital in Sydney and Veterinary Oncology Consultants in Wauchope (both NSW, Australia) from October 2003 to August 2015 were searched to identify records for dogs with EL. Dogs were included in the study if they had histopathological features consistent with EL and a minimum follow-up time of three months (unless confirmed relapse or death occurred during that period). Histology slides were reviewed to determine tumour type and, when available, CD3 and CD79a immunostaining. A histological diagnosis consistent with EL in this study was characterized by neoplastic lymphocyte infiltration exclusively in the epidermis including tropism for hair follicles and sweat glands, with some samples showing Pautrier's microabscesses (collection of neoplastic lymphocytes around cutaneous dendritic cells).[10] Any equivocal cases were excluded.

For each eligible dog, signalment (age, sex, breed), body weight, histopathological findings (including CD3 and/or CD79a immunophenotype when available), lymphoma substage [a (asymptomatic) or b (constitutional signs)], tumour stage (premycotic, mycotic or tumour) when available, tumour location (cutaneous, mucosal or mucocutaneous), number of lesions (solitary or multiple), duration of lesions before a histological diagnosis was made (weeks), extent of lymph node involvement (none, single, locoregional, generalized or distant) and measurable disease (yes or no) were recorded.

All dogs were staged by physical examination, calliper measurement of EL lesions, and palpation of all peripheral lymph nodes, liver and spleen. Thoracic radiography and/or abdominal ultrasonography findings (when performed) were recorded.

Treatment details were recorded including surgery [margins (complete, incomplete or unknown)], radiation therapy, retinoids, safflower oil, prednisolone and chemotherapy {single-agent CCNU, VELCAP-EL combination chemotherapy protocol [VELCAP-EL is derived from vincristine (v), L-asparaginase (EL), cyclophosphamide (C), Adriamycin (doxorubicin) (A) and prednisolone (P); EL is for epitheliotropic lymphoma], other multiple agent chemotherapy or other single-agent chemotherapy}. The dosages and schedule for VELCAP-EL are provided in Table S1. For dogs receiving VELCAP-EL combination chemotherapy protocol and single-agent CCNU, the highest toxicity score [with reference to VCOG-CTCAE (Veterinary cooperative oncology group - common terminology criteria for adverse events) v1.1 criteria[25]] and nature of the toxicity (haematological and gastrointestinal toxicities) were recorded.

For dogs with measurable disease, the best response to therapy was recorded where available according to response evaluation criteria for peripheral nodal lymphoma in dogs.[26] Complete remission (CR) was defined as resolution of all evidence of disease; partial remission (PR) was defined as ≥30% reduction in size of measurable lesions; stable disease (SD) was defined as <30% reduction or <20% increase in size of measurable lesions and no appearance of new lesions; and progressive disease (PD) was defined as ≥20% increase in size of measurable lesions or appearance of new lesions. The overall response rate (ORR) was defined as the number of dogs achieving either a CR or PR, compared to the number of dogs treated.

For dogs with solitary lesions, the number of days until development of new lesions or metastasis was recorded. If the dog did not develop a new lesion or metastasis, the number of days the dog was alive with a solitary lesion was utilized. Survival time was evaluated with the end-point being death due to any cause. The day of histological diagnosis was considered to be Day 1. Dogs were censored from survival analysis at the last day of contact if still alive or if they were lost to follow-up. The Kaplan–Meier product limit method was used to estimate the median survival time (MST) and the one, two and three year survival percentage.

Cox regression analysis was used to evaluate the effect on survival time of tumour location (cutaneous versus mucosal and mucocutaneous), solitary versus multiple lesions, age (continuous), sex (male versus female), body weight (continuous), lymphoma substage (a versus b), tumour stage (premycotic versus mycotic versus tumour) and treatment used (surgery; retinoids; safflower oil; prednisolone; and chemotherapy). Chemotherapy protocol types (CCNU versus VELCAP-EL versus other multiple agent chemotherapy) also were evaluated.

All factors were initially evaluated separately for univariate statistical significance. Any factor with $P \leq 0.1$ on univariate analysis was included in multivariate analysis using Cox forward logistic regression. For the final analysis, values of $P < 0.05$ were considered significant. Chi-square methods were used to compare CR rates between dogs treated with VELCAP-EL and dogs treated with CCNU. Pearson correlation was used to assess the relationship between age and survival time in dogs with solitary mucocutaneous and mucosal (McM) EL. A range of analyses evaluating dogs with McM lesions and those with cutaneous lesions was undertaken. Statistical analyses were performed using the software package SPSS 10 (Statistical Analytical Software; Chicago, IL, USA).

Results

One hundred and forty eight dogs met the inclusion criteria. The median age was 11 years (range 2–18 years of age). Sixty were males (46 castrated) and 88 were females (86 spayed). There were 40 breeds included, with cross-bred dogs being most common ($n = 35$). The only breeds with six or more dogs represented were golden retrievers (20), Border collies (9), beagles (8), cocker spaniels (6), Labrador retrievers (6) and Maltese terriers (6). Median body weight was 21.9 kg (range 2.1–55.9 kg).

CD3 (T-cell) and CD79a (B-cell) immunophenotyping was performed on 71 (48.0%) and 62 (41.9%) tumours, respectively. Of these, 69 (97.2%) tumours were CD3 positive and none were CD79a positive. Two (2.8%) were negative for both CD3 and CD79a.

Eighty (54.1%) dogs had cutaneous disease, 24 (16.2%) mucosal disease and 44 (29.7%) had disease at

mucocutaneous junctions (including footpads and nasal planum). Sixty (40.5%) dogs had solitary lesions and 88 (59.5%) multiple lesions.

Toxicity data were available for 44 of 50 dogs treated with the VELCAP-EL combination chemotherapy protocol and for 17 of 19 dogs treated with single-agent CCNU chemotherapy. The highest toxicity score overall and the adverse effects are recorded in Table S2.

On multivariate analysis of the entire group, location (cutaneous versus mucosal versus mucocutaneous locations) ($P < 0.001$) and presence of multiple lesions versus solitary lesions ($P < 0.001$) were the only independent prognostic factors determined.

There was no significant difference in survival time between the mucosal group and the mucocutaneous group (mucocutaneous location versus mucosal location, $P = 0.494$). However, for each of these groups survival time was significantly different for the cutaneous group (cutaneous versus mucocutaneous location $P < 0.001$; and cutaneous versus mucosal location $P = 0.001$). Therefore, further analyses were performed for dogs with tumours with a cutaneous location.

Cutaneous lesions

Eighty dogs had cutaneous disease only. Eight (10%) of these dogs had solitary lesions and 72 (90%) had multiple lesions. The median age was 10.5 years (range 1–16 years of age). Thirty were males (20 castrated) and 50 were females (48 spayed). There were 30 breeds included, with cross-bred dogs being most common ($n = 19$). The only breeds with six or more dogs represented were golden retrievers (8), Labrador retrievers (6), Border collies (5) and beagles (5). Median body weight was 25.1 kg (range 2.1–55.9 kg).

Sixty three of 80 (78.8%) dogs were in lymphoma substage a and 17 (21.2%) dogs were in substage b. Two (2.7%) dogs had premycotic lesions, 34 (46.6%) had mycotic lesions and 37 (50.7%) had tumour lesions. Clinical stage could not be determined for seven dogs.

Lesions were present for a median of eight weeks (range 1–56 weeks) before a diagnosis was confirmed on histological evaluation of a skin biopsy (information available for 63 dogs). Lymph nodes were normal on palpation, cytology, biopsy and/or imaging in 43 of 69 (62.3%) dogs. Nodal involvement was suspected (lymphadenopathy on palpation or imaging) or confirmed (cytological evaluation or biopsy) in 26 of 69 (37.7%) dogs; four involved a single node, six locoregional, 11 generalized, four distant and one not specified. Lymph node evaluation was not recorded for 11 of 69 (13.7%) cases.

Thoracic radiography was performed in 35 of 80 (43.8%) dogs and was considered normal for 27 dogs and abnormal in eight dogs [imaging (pleural effusion, pulmonary infiltrates, pulmonary nodules and/or evidence of lymph node enlargement) and/or via cytological confirmation of lymphoma]. Abdominal ultrasonography was performed in 26 of 80 (67.5%) dogs and was considered normal in 14 dogs, abnormal in 10 dogs [imaging (splenomegaly, hepatomegaly and/or intraabdominal lymphadenopathy) and/or via cytological confirmation of lymphoma], and equivocal, in two dogs.

Of eight dogs with solitary lesions, four (50.0%) developed new lesions (three dogs) or nodal metastasis (one dog) at a median of 167 days (range 73–2063 days) and four dogs (50.0%) did not develop additional lesions for a median follow-up time of 691 days (range 136–2,124 days).

Follow-up

Median survival time was 130 days (range 5–2,198 days, eight dogs censored). Seventy two of 80 (90.0%) dogs were confirmed dead (44 of known EL, 11 of causes believed not to be EL-related and 17 where cause of death was unknown). Of the eight remaining dogs, seven (8.7%) were lost to follow-up (median 281 days, range 85–839 days) and one (1.3%) was still alive at 646 days.

Treatment

Nine of 80 (11.3%) dogs underwent surgery. Of six dogs with solitary lesions, three were completely excised, two incompletely excised and one was excised with margins not described. Of three dogs with multiple lesions, one had all lesions completely excised, one had incomplete excision and one had excision with margins not described. Two of the nine dogs that underwent surgery also received retinoid treatment (22.2%) and three (33.0%) received chemotherapy after surgery.

Two of 80 (2.5%) dogs underwent radiation therapy consisting of one fraction of 8 Gy in one dog and three weekly fractions of 8 Gy in the other dog. Both dogs also received chemotherapy. Nineteen (23.8%) dogs received retinoid treatment [15 dogs received acitretin 1 mg/kg per os (p.o.) once daily to the nearest 10 mg capsule, and four dogs received isotretinoin 1–3 mg/kg p.o. once daily to the nearest 10 mg capsule]. Twenty six (32.5%) dogs received safflower oil (3 mL/kg p.o. once daily). Fifteen (18.8%) dogs received prednisolone alone (20–40 mg/m^2 p.o. every other day to once daily).

Forty nine of 80 (61.3%) dogs received chemotherapy consisting of: CCNU (with or without prednisolone) 50–90 mg/m^2 p.o. every 3–4 weeks delivered to the nearest 5 or 10 mg capsule (11 dogs), VELCAP-EL combination chemotherapy protocol (32 dogs), other multiple agent chemotherapy [consisting of more than three different types of chemotherapeutics (with or without prednisolone), five dogs] or single-agent L-asparaginase 10,000 IU/m^2 subcutaneously once (one dog).

A summary of the descriptive information is provided in Table 1.

Response to treatment and outcomes

Seventy one of 80 (88.8%) dogs had measurable disease. Of these, 52 were evaluated for a response to therapy. Of 10 dogs with measurable disease treated with CCNU (with or without prednisolone), one (10.0%) dog obtained CR, six (60.0%) obtained PR, one (10.0%) had SD and two (20.0%) had PD. The ORR was 70.0%. MST was 130 days (range 34–281 days, two censored). Of 29 dogs with measurable disease treated with VELCAP-EL protocol, 11 (37.9%) dogs obtained CR, 12 (41.4%) obtained PR, five (17.3%) had SD and one (3.4%) had PD. The ORR was 79.3%. MST was 207 days (range 23–

Table 1. Descriptive information and multivariate analysis on relationship of examined variables on survival time in 80 dogs with cutaneous epitheliotropic lymphoma

Variable	No. of dogs	Median (range)	P-value
Number of lesions			
Solitary	8 (1 censored)	231 days* (95% CI 151–311 days)	<0.001
Multiple	72 (7 censored)	104 days* (95% CI 66–142 days)	
Age (years)	80	10.5 (1–16)	-
Sex			
Female entire	2		-
Female spayed	48		
Male entire	10		
Male neutered	20		
Breed	30 types		N/A
Cross breed	19		
Golden retriever	8		
Labrador retriever	6		
Border collie	5		
Beagle	5		
Weight (kg)	80	25.1 (2.1–55.9)	-
Substage			
a	63		-
b	17		
Tumour stage			-
Premycotic	2		
Mycotic	34		
Tumour	3		
Cannot determine	7		
Duration of lesions before diagnosis confirmed on biopsy (weeks)	63	8 (1–56)	N/A
Nodal involvement	69		-
Normal	43		
Abnormal	26		
Thoracic radiography			
Unknown	45		N/A
Normal	27		
Abnormal	8		
Abdominal ultrasonography			
Unknown	54		N/A
Normal	14		
Abnormal	10		
Equivocal	2		
For solitary lesions, development multiple lesions or metastasis			
Yes	4	167 days (73–2,063 days)	N/A
No	4	691 days (136–2,124 days)	
Treatment			
Surgery			
Yes	9		N/A
No	71		
Radiation therapy			
Yes	2		-
No	7		
Retinoids			
Yes	19		-
No	61		
Safflower oil			
Yes	26		-
No	54		
Chemotherapy			
Yes	49 (8 censored)	207 days* (95% CI 140–274 days)	<0.001
No	31 (0 censored)	64 days* (95% CI 45–83 days)	
Prednisolone alone			
Yes	15		N/A
No	65		

*Median survival time.

2079 days, four censored). Of five dogs with measurable disease treated with other multiple agent chemotherapy, two (40.0%) dogs obtained CR, one (20.0%) obtained PR, one (20.0%) had SD and one (20.0%) had PD. The ORR was 60.0%. MST was 407 days (range 49–856 days, one censored). Of eight dogs with measurable disease treated with prednisolone alone, two (25.0%) dogs obtained CR, four (50.0%) obtained PR, one (12.5%) had SD and one (12.5%) had PD. The ORR was 75.0%. The MST was 58.5 days (range 13–264 days, one censored).

Prognostic factors

For all 80 dogs with cutaneous lesions (eight censored), the MST was 130 days (range 5–2,198 days; 95% CI 69–191 days) and the one, two and three year survival percentages were 25.3%, 16.3% and 14.2%, respectively.

On univariate analysis, use of chemotherapy ($P = 0.006$) and presence of multiple lesions ($P = 0.019$) were found to be potentially associated with survival time. On multivariate analysis, both factors retained statistical significance as independent predictors of survival time ($P < 0.001$ for both).

Thirty one dogs received no chemotherapy; all had died at the end of data collection. Median survival was 64 days (range 5–2,124 days, 95% CI 45–83 days) with 12.9% alive at one year and 9.7% alive at two and three years after diagnosis. Forty nine dogs received chemotherapy, of which eight were censored. Median survival was 207 days (range 23–2,198 days, 95% CI 140–274 days) with 32.6% alive at one year, 20.0% alive at two years and 16.0% alive at three years after diagnosis.

Seventy two dogs had multiple lesions, of which seven were censored. Median survival was 104 days (range 5–2,079 days, 95% CI 66–142 days) with 23.2% alive at one year, and 13.1% alive at two and three years after diagnosis. Eight dogs had solitary lesions, of which one was censored. Median survival was 231 days (range 136–2,198 days, 95% CI 151–311 days) with 42.8% alive at one year, and 28.6% alive at two and three years after diagnosis (Figure 1).

On the basis of these data, further analysis was performed to determine the effect of chemotherapy in 72 dogs that had multiple cutaneous lesions and this was significant on multivariate analysis ($P < 0.001$). There were 25 dogs that received no chemotherapy, of which none were censored. Median survival was 53 days (range 5–2,124 days, 95% CI 45–83 days) with 12.9% alive at one year, 9.7% alive at two years and 4.0% alive at three years after diagnosis. There were 47 dogs that received chemotherapy, of which seven were censored. Median survival was 188 days (range 23–2,198 days, 95% CI 131–245 days) with 31.2% alive at one year, 18.3% alive at two years and 13.7% alive at three years after diagnosis (Figure 2).

In 72 dogs with multiple cutaneous lesions, the effect of retinoid treatment on survival also was found to be significant on multivariate analysis ($P = 0.001$) and therefore independent of whether dogs received chemotherapy. Eighteen dogs received retinoid treatment (12 received retinoids with chemotherapy, five received retinoids alone and one received retinoids with prednisolone) of which three were censored. Median survival was 251 days (range 34–1,290 days, 95% CI 0–570 days) with 48.2% alive at one year, 18.3% alive at two years and 9.2% alive at three years after diagnosis. Fifty four dogs received no retinoid treatment, of which four were censored. Median survival was 98 days (range 5–2,079 days, 95% CI 74–122 days) with 15.3% alive at one year, 10.9% alive at two years and 7.3% alive at three years after diagnosis (Figure 3).

Response to chemotherapy was assessable in 44 of 47 dogs with multiple cutaneous lesions that received chemotherapy. The ORR to treatment with VELCAP-EL combination chemotherapy and single-agent CCNU were 79.3% and 70.0%, respectively. The MST with VELCAP-EL combination chemotherapy and single-agent CCNU

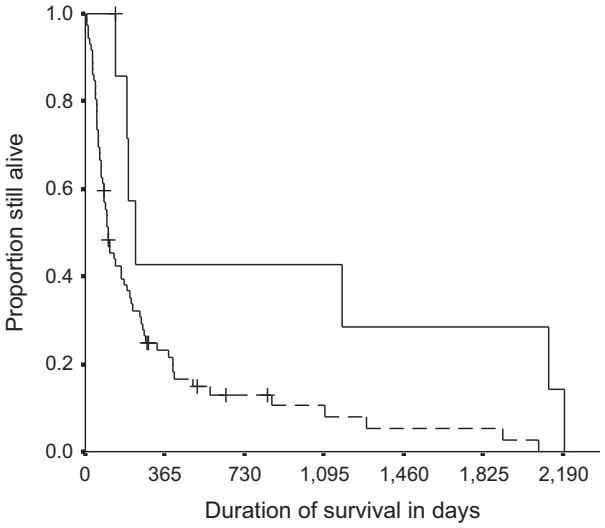

Figure 1. Kaplan–Meier survival curves comparing survival time in 80 dogs with cutaneous epitheliotropic lymphoma that had either solitary lesions (solid line, median survival 231 days, $n = 8$) or multiple lesions (dashed line, median 104 days, $n = 72$). $P < 0.001$.

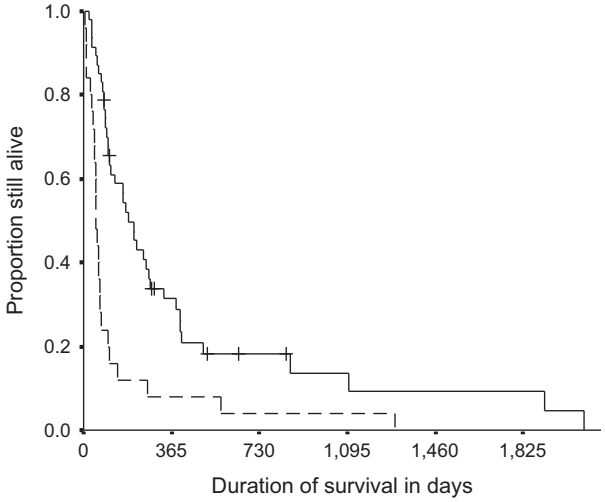

Figure 2. Kaplan–Meier survival curves comparing survival time in 72 dogs with multiple cutaneous epitheliotropic lymphoma that either received chemotherapy (solid line, median survival 188 days, $n = 47$) or did not receive chemotherapy (dashed line, median survival 52 days, $n = 25$). $P < 0.001$.

were 207 days and 130 days, respectively. Achievement of CR was associated with increased survival time on multivariate analysis ($P = 0.001$). Fourteen dogs achieved CR, of which two were censored. Median survival was 401 days (95% CI 363–439 days) with 63.5% alive at one year and 31.7% alive at two years after diagnosis. Nineteen dogs achieved PR, of which four were censored. Median survival was 130 days (95% CI 14–246 days) with 18.7% alive at one year and 9.4% alive at two years after diagnosis. Eleven dogs had no response to therapy (SD and PD), and all had died at study conclusion. Median survival was 110 days (95% CI 55–165 days) with 9.1% alive at one and two years after diagnosis (Figure 4).

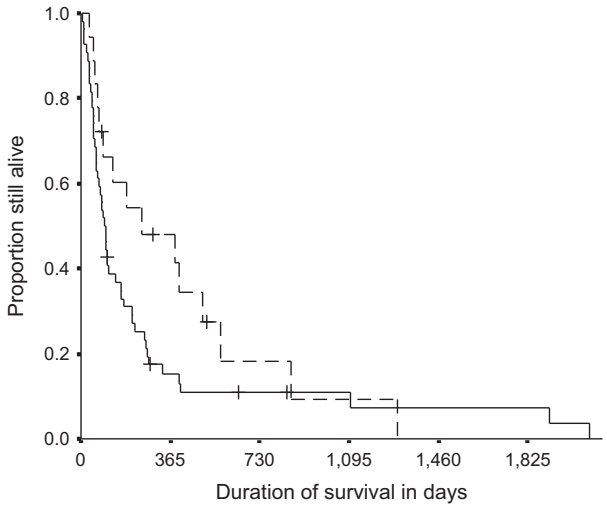

Figure 3. Kaplan–Meier survival curves comparing survival time in 72 dogs with multiple cutaneous epitheliotropic lymphoma that either received retinoids (dashed line, median survival 251 days, $n = 18$) or did not receive retinoids (solid line, median survival 98 days, $n = 54$). $P = 0.001$.

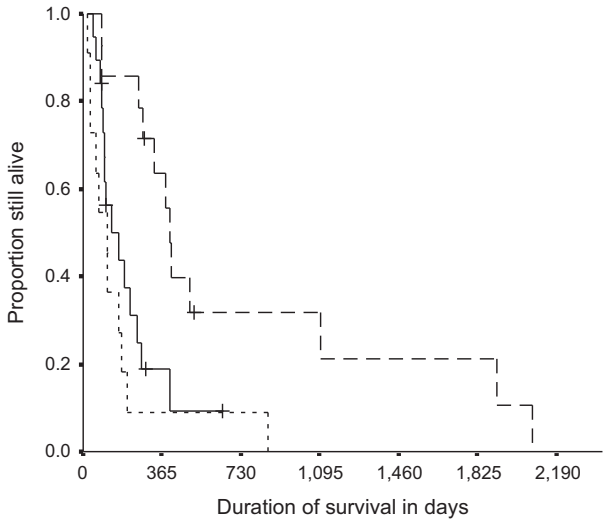

Figure 4. Kaplan–Meier survival curves comparing survival times in 44 dogs with multiple cutaneous epitheliotropic lymphoma lesions that obtained either complete remission to therapy (dashed line, median survival 401 days, $n = 14$) or partial remission to therapy (solid line, median survival 130 days, $n = 19$) or no response to therapy (stable disease and progressive disease) (dotted line, median survival 110 days, $n = 11$). $P = 0.001$.

The effect of type of chemotherapy treatment (VELCAP-EL versus CCNU versus other multiple agent chemotherapy) was not associated with survival time ($P = 0.634$). Dogs receiving VELCAP-EL showed a trend toward being more likely to achieve CR than dogs receiving CCNU. One of 10 (10%) dogs treated with CCNU achieved CR with an overall survival of 281 days and 11 of 29 (37.9%) dogs treated with VELCAP-EL achieved CR with a MST of 401 days, although the CR rates were not significantly different ($P = 0.102$).

Mucocutaneous and mucosal (Mcm) location

Twenty four dogs (35.3%) had mucosal disease and 44 (64.7%) had disease at mucocutaneous junctions (including footpads and nasal planum) for a total of 68 dogs. Fifty two (76.5%) dogs had solitary lesions and 16 (23.5%) had multiple lesions.

The median age was 11 years (range 2.5–18 years of age). Thirty were males (26 castrated) and 38 were females (all spayed). There were 24 breeds included, with cross-bred dogs being most common ($n = 16$). The only breeds with four or more dogs represented were golden retrievers (12), cocker spaniels (5), Border collies (4) and Maltese terriers (4). Median body weight was 18.2 kg (range 2.9–51.3 kg).

Sixty (88.2%) dogs were in lymphoma substage a and eight (11.8%) dogs were in substage b. Eight (13.8%) dogs had premycotic lesions, 26 (44.8%) had mycotic lesions and 24 (41.4%) had tumour lesions. Clinical stage could not be determined for 10 dogs from the records.

Lesions were present for a median of four weeks (range 0-52 weeks) before a diagnosis was confirmed on histological examination of a tissue biopsy (information available for 55 dogs). Lymph nodes were normal on palpation, cytological evaluation, biopsy and/or imaging in 38 of 60 (63.3%) dogs. Nodal involvement was suspected (lymphadenopathy on palpation or imaging) or confirmed (cytology or biopsy) in 22 of 60 (36.7%) dogs; 11 single node, eight locoregional, two generalized and one distant. Lymph node assessment was not recorded for eight (11.7%) cases.

Thoracic radiography was performed in 40 of 68 (58.8%) dogs and was considered normal in 35 dogs, abnormal (pleural effusion, pulmonary nodules and/or evidence of lymph node enlargement) in three dogs, and equivocal in two dogs. Abdominal ultrasonography was performed in 29 of 68 (42.7%) dogs, and was considered normal in 26 dogs and abnormal [imaging (splenomegaly and/or intraabdominal lymphadenopathy) and/or via cytological confirmation of lymphoma] in three dogs.

Of the 52 dogs with solitary lesions, 15 (28.8%) developed new lesions (10 dogs), nodal metastasis (four dogs) or systemic metastasis (one dog) at a median of 275 days (range 9–1,190 days); and 37 (71.2%) dogs did not develop additional lesions for a median follow-up time of 501 days (range 32–2,207 days).

Follow-up

The median survival time was 491 days (range 30–2,992 days, 24 censored). Forty four (64.7%) dogs were known to be dead (20 of known EL, seven of causes not

EL-related and 17 where cause of death was unknown). Of the 24 remaining dogs, 11 (16.2%) were lost to follow-up (median 329 days, range 131-1,305 days) and 13 (19.1%) were still alive (median 656 days, range 274–2,207 days).

Treatment

Thirty nine of 68 (57.4%) dogs underwent surgery. Of 34 dogs with solitary lesions, 12 had excision with complete margins, 12 with incomplete margins and 10 with margins not described. Of five dogs with multiple lesions, three dogs had all their lesions completely excised and two had excision with margins not described. After surgery, seven of 39 (17.9%) dogs received retinoid treatment and 20 of 39 (51.3%) received chemotherapy.

Ten of 68 (14.7%) dogs underwent radiation therapy consisting of 54 Gy in 18 daily fractions (one dog), or one to five weekly or bi-weekly fractions of 6–8 Gy fractions (nine dogs). Eight of these dogs also received chemotherapy.

Sixteen of 68 (23.5%) dogs received retinoid treatment (eight dogs received acitretin 1 mg/kg p.o. once daily to the nearest 10 mg capsule, and eight dogs received isotretinoin 1–3 mg/kg p.o. once daily to the nearest 10 mg capsule). Sixteen (23.5%) dogs received safflower oil (3 mL/kg p.o. once daily). Twelve (17.7%) dogs received prednisolone alone (20–40 mg/m^2 p.o. every other day to once daily).

Thirty two of 68 (47.1%) dogs received chemotherapy consisting of: CCNU (with or without prednisolone) 50–90 mg/m^2 p.o. every three to four weeks administered to the nearest 5 or 10 mg capsule (n = 8), VELCAP-EL combination chemotherapy protocol (n = 18), other multiple agent chemotherapy [consisting of more than three different types of chemotherapeutics (with or without prednisolone), n = 4], or single-agent chlorambucil at 20 mg/m^2 p.o. every 2 weeks (n = 1) or melphalan at 20 mg/m^2 p.o. every 2 weeks (n = 1). A summary of the descriptive information is provided in Table 2.

Response to treatment and outcomes

Thirty five of 68 (51.5%) dogs had measurable disease at the time systemic therapy was instituted; of these, 27 were evaluated for a response to therapy.

Of three dogs with measurable disease treated with CCNU (with or without prednisolone), all three (100.0%) dogs obtained PR. No dogs obtained CR, SD or PD. The survival times for the dogs that obtained PR were 100 and 707 days (one censored at 140 days). Of 11 dogs with measurable disease treated with VELCAP-EL protocol, seven (63.6%) dogs obtained CR, three (27.3%) obtained PR, one (9.1%) had SD and none had PD. The ORR was 90.9%. MST was 281 days (range 32–1,440 days, two censored). Of two dogs with measurable disease treated with other multiple agent chemotherapy, one (50.0%) dog obtained CR and one (50.0%) dog had PD. No dogs obtained PR or SD. Survival time for the dog that obtained CR was 376 days (censored at last known follow-up) and survival time for the dog that had PD was 281 days. Of 11 dogs with measurable disease treated with prednisolone alone, two (18.1%) dogs obtained CR, three (27.3%) obtained PR, three (27.3%) had SD and six (54.6%) had PD. The ORR was 45.4%. The MST was 309 days (range 30–641 days, four censored).

Prognostic factors

For all 68 dogs with McM lesion location (24 censored) the MST was 491 days (range 30–2,992 days; 95% CI 158–824 days) and the one, two and three year survival proportions were 59.5%, 44.3% and 25.6%, respectively.

On univariate analysis, the presence of multiple lesions ($P < 0.001$) and increasing age at diagnosis ($P = 0.001$), were found to be potentially associated with survival time and were offered to multivariate analysis. On multivariate analysis, both factors retained statistical significance as independent predictors of poor survival at $P = 0.015$ and $P = 0.020$, respectively.

Sixteen dogs had multiple lesions, of which one was censored. Median survival was 241 days (range 30–1,873 days, 95% CI 156–326 days) with 6.8% alive at one year, two years and three years after diagnosis. Fifty two dogs had solitary lesions, of which 23 were censored. Median survival was 849 days (range 32–2,992 days, 95% CI 651–1,047 days) with 76.1% alive at one year, 56.0% alive at two years and 30.5% alive at three years after diagnosis (Figure 5). Using Pearson correlation, there was a moderate negative correlation [r (50) = –0.374, $P = 0.006$] between increasing age of dogs with solitary McM EL and their survival time.

In addition, when subsets of 52 dogs with solitary lesions and 16 dogs with multiple lesions were evaluated; increasing age retained statistical significance as an independent predictor of poor survival in dogs with solitary lesions ($P = 0.021$, multivariate analysis) but not in dogs with multiple lesions ($P = 0.717$, univariate analysis).

Discussion

To the best of the authors' knowledge, this is the largest study published of dogs with clinical and histological lesions consistent with EL. The median age of affected dogs in the present study was 11 years, which is comparable to other studies.[2,3,6,8,10] However, in contrast to other studies,[2,10] which demonstrated no gender or breed predilection, our study demonstrated a slight female predilection (female:male ratio of 1.5:1) and a breed predilection for the golden retriever.

Previous studies have shown that canine EL is typically a tumour of T lymphocytes.[3,8,10] Our study supports these findings with 97.2% of tumours evaluated expressing CD3, none expressing CD79a and 2.8% expressing a null cell immunophenotype (negative for both CD3 and CD79a).

Three studies to date have evaluated prognostic factors for dogs affected with EL.[2,5,11] A significant survival advantage was observed in 14 dogs with oral mucocutaneous lymphoma (of which 12 had EL) that had no lymph node metastasis and had achieved CR with radiotherapy.[5] In contrast, two studies were not able to demonstrate any effect of lymph node involvement or any other parameter on response to therapy, response duration or survival.[2,11]

Table 2. Descriptive information and multivariate analysis of relationship of examined variables on survival time in 68 dogs with mucocutaneous/mucosal epitheliotropic lymphoma

Variable	No. of dogs	Median (range)	*P*-value
Tumour location			
Mucocutaneous	44		-
Mucosal	24		
Number of lesions			
Solitary	52 (23 censored)	849 days* (95% CI 651–1,047 days)	<0.015
Multiple	16 (1 censored)	241 days* (95% CI 156–326 days)	
Age (years)	68	11 (2.5–18)	0.020
Sex			
Female entire	0		-
Female spayed	38		
Male entire	4		
Male neutered	26		
Breed	24 types		N/A
Cross breed	16		
Golden retriever	12		
Cocker spaniel	5		
Border collie	4		
Maltese	4		
Weight (kg)	68	18.2 (2.9–51.3)	-
Substage			
a	60		-
b	8		
Tumour stage			
Premycotic	8		-
Mycotic	26		
Tumour	24		
Cannot determine	10		
Duration of lesions before diagnosis confirmed on biopsy (weeks)	55	4 (0–52)	N/A
Nodal involvement	61		-
Normal	38		
Abnormal	22		
Equivocal	1		
Thoracic radiography			N/A
Unknown	28		
Normal	35		
Abnormal	3		
Equivocal	2		
Abdominal ultrasonography			N/A
Unknown	39		
Normal	26		
Abnormal	3		
For solitary lesions, development multiple lesions or metastasis			N/A
Yes	15	275 days (9–1,190 days)	
No	37	501 days (32–2,207 days)	
Treatment			
Surgery			N/A
Yes	39		
No	29		
Radiation therapy			-
Yes	10		
No	58		
Retinoids			-
Yes	16		
No	52		
Safflower oil			-
Yes	16		
No	52		
Chemotherapy			-
Yes	32		
No	36		
Prednisolone alone			N/A
Yes	12		
No	56		

*Median survival time.

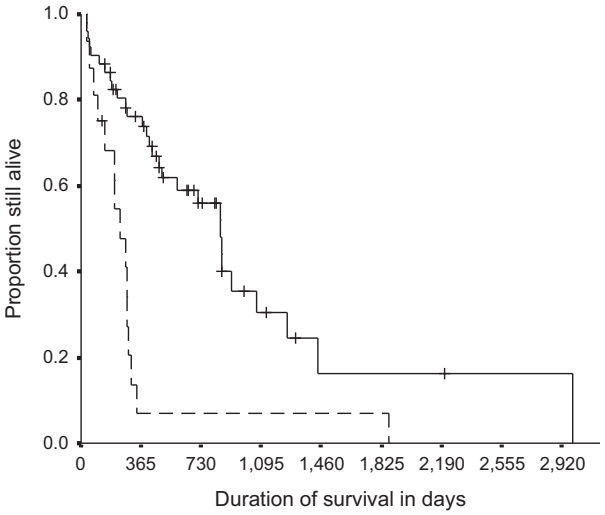

Figure 5. Kaplan–Meier survival curves comparing survival times in 68 dogs with mucocutaneous and mucosal epitheliotropic lymphoma that had either solitary lesions (solid line, median survival 849 days, $n = 52$) or multiple lesions (dashed line, median 241 days, $n = 16$). $P = 0.015$.

In this study, independent predictors of poor survival were having the cutaneous form of the disease ($P < 0.001$) and multiple lesions ($P < 0.001$). Different prognostic factors were identified for dogs with cutaneous versus McM disease, supporting the clinical impression that these respond differently to treatment intervention. For dogs with McM lesions, younger dogs and dogs with solitary lesions had a statistically significant survival advantage not reported previously.

Lymph node involvement as a prognostic indicator for canine EL is controversial.[5,11] In this study, lymph node involvement was not associated with survival times for either cutaneous or McM forms of EL.

In contrast to most other forms of canine lymphoma, the absence or presence of systemic signs (substage a and b, respectively) was not associated with survival time. In humans, the presence of advanced tumour stage (nodules or masses) confers a worse prognosis.[24] This was not found to be the case in this series of dogs.

Alkylating agents may play a role for the treatment of multicentric T-cell lymphoma.[27–31] Chemotherapy is not widely reported for EL in dogs, with most of the information available for CCNU. The reported ORR using CCNU for 82 dogs in two studies was 80% for approximately 100 days median duration.[7,11] Other chemotherapy agents include: PEGylated L-asparaginase with a short PR in seven treated dogs;[12] masitinib with an ORR of 70% in 10 dogs for a median of 85 days;[1] and nine dogs treated with PEGylated liposomal doxorubicin with an ORR of 44% with three of dogs achieving CR for a median of 90 days.[15] Dacarbazine treatment was associated with CR for more than one year in one dog with localized EL.[17] VDC-1101 (a nucleotide prodrug) and prednisolone resulted in a 45% ORR in 11 dogs with cutaneous lymphoma (nine had EL) for a median of 37.5 days.[14]

In general, combination chemotherapy is preferred over single-agent chemotherapy for treatment of lymphoma in people, dogs and cats. The VELCAP-EL combination protocol, described in this study, uses more alkylating agents than typical lymphoma protocols and emphasizes CCNU. In this study, the ORR in dogs with cutaneous and McM forms of EL were 79.3% and 90.1%, respectively, which compares favourably with previous reports.[1,7,11–16]. However, although ORR were high, CR rates differed and those dogs achieving PR to therapy did not have the same survival advantage as those dogs achieving a CR. Only 10% of dogs that received CCNU achieved CR, compared to 38% of dogs treated with the combination protocol. A further 60% of dogs treated with CCNU and 41% of dogs treated with a multi-agent protocol achieved a PR, but the duration of that response was shorter at 4.3 months.

In this study, there was no demonstrated benefit of using chemotherapy for dogs with McM lesions or solitary cutaneous lesions. However, for dogs with multiple cutaneous lesions, and thus a poorer prognosis, the administration of any form of chemotherapy ($P < 0.001$) or retinoid treatment ($P = 0.001$) had a significant positive impact on survival. This contrasts with previous reports,[2,11] and suggests that tumour location and number are relevant when comparing survival outcomes for dogs with EL. In addition, dogs with multiple cutaneous lesions that experienced CR to therapy lived significantly longer compared to those that experienced PR or no response (SD or PD) to therapy. Clinically, this suggests that if there is an incomplete response to chosen chemotherapy (for example CCNU alone), it is worth continuing with other chemotherapy agents to try to achieve a CR, as that would be associated with longer survival.

In addition to responses to chemotherapy, a 42% ORR was reported for 14 dogs with cutaneous lymphoma (five with EL) treated with isotretinoin or etretinate for a median of 11 months.[15] Linoleic acid (in the form of safflower oil) resulted in clinical improvement in six of eight dogs with cutaneous EL for up to two years duration;[16] however, it was not clear whether these were CR or PR. The response rates and response duration for dogs receiving retinoids and/or linoleic acid were unable to be determined in this study; however, it was determined that dogs with multiple cutaneous EL treated with retinoids had a significantly longer MST ($P = 0.001$, Figure 3) that was independent of whether dogs received chemotherapy.

Radiotherapy can be used for local treatment or palliation for canine EL.[5] In a retrospective case series of 14 dogs with mucocutaneous oral lymphomas (of which 12 had EL) treated with coarse fractionation radiotherapy, the ORR was 67% with a MST of 770 days.[5] Radiation was part of treatment for 12 dogs in our study, but did not appear to influence survival times. Two dogs treated with radiation as a monotherapy for solitary mucosal lesions had long control of their disease (>700 days). Controlled studies using radiotherapy as primary therapy for the treatment of EL are indicated.

Surgery is an alternate option for solitary lesions with some dogs disease-free for longer than two years.[6] Fifty percent of dogs with solitary cutaneous lesions and 71.2% of dogs with solitary McM lesions did not develop new lesions for a median follow-up time of 691 days and 501 days, respectively. This suggests that local surgical excision may be useful. Dogs with solitary lesions should be carefully monitored for recurrence. In this study, one dog with a solitary cutaneous lesion and one dog with a

solitary McM lesion developed new EL lesions more than five years (2,063 and 2,207 days, respectively) after the initial diagnosis.

The limitations of the present study were those typical for retrospective studies and included the lack of standardized treatment, monitoring and staging. Dogs were not randomized to receive various treatments, but rather such treatments depended on the choices of individual owners and attending veterinarians. Data collection may have been hindered by incomplete medical records. Thus, there is potential for flaws in the accuracy of information obtained. In addition, due to the retrospective nature of the study that spans over a period of 12 years, review of histological slides by a single person, and CD3 and CD79a immunohistochemistry could not be performed on all tumours to confirm EL.

Total time to progression (TTP) would have been an additional end-point to evaluate in this study, however was not able to be reliably determined, as the frequency of scheduled rechecks was not standardized in this study and there were many dogs where TTP could not be obtained. Therefore, we did not assess and perform statistical evaluations with TTP as an end-point. Survival was a more robust end-point, especially with the long follow-up data available and majority of dogs confirmed dead at the time the study concluded.

Lastly, we did not gather extensive chemotherapy toxicity data, as this was not a primary aim of our study. However, based on the data that were available, there appeared to be more VCOG-CTCAE grade 4 toxicity in dogs treated with VELCAP-EL combination chemotherapy compared to single-agent CCNU (Table S2). The toxicity is likely higher for dogs treated with VELCAP-EL combination chemotherapy because there were seven drugs used, and thus mathematically a greater risk for toxicity. However, combination chemotherapy should still be considered in dogs with EL that has not responded to CCNU, as CR to therapy was shown to be an independent predictor of longer survival in dogs with multiple cutaneous EL; in addition the use of multi-agent chemotherapy may increase the chances of obtaining CR.

In conclusion, based on survival times of dogs in this study, we suggest that EL in dogs may be clinically separated into a cutaneous form and an McM form of the disease. The occurrence of solitary lesions also confers an improved prognosis and was more commonly seen in the McM form of EL. Dogs with multiple cutaneous lesions appear to benefit from receiving chemotherapy, and/or retinoid treatment, with those attaining a CR to therapy having better survival times. This study suggests that the diagnosis of EL does not uniformly confer a poor prognosis and that the above prognostic factors should be evaluated in individual cases to assess their chances for longer survival and potential for benefit with different treatment options.

Acknowledgements

We express our gratitude to our referring veterinarians for their contribution to animal care and provision of follow-up data.

References

1. Holtermann N, Kiupel M, Kessler M et al. Masitinib monotherapy in canine epitheliotropic lymphoma. *Vet Comp Oncol* 2016; 14(Suppl 1): 127–135.
2. Fontaine J, Heimann M, Day MJ. Canine cutaneous epitheliotropic T-cell lymphoma: a review of 30 cases. *Vet Dermatol* 2010; 21: 267–275.
3. Moore PF, Affolter VK, Graham PS et al. Canine epitheliotropic cutaneous T-cell lymphoma: an investigation of T-cell receptor immunophenotype, lesion topography and molecular clonality. *Vet Dermatol* 2009; 20: 569–576.
4. Day MJ. Immunophenotypic characterization of cutaneous lymphoid neoplasia in the dog and cat. *J Comp Pathol* 1995; 112: 79–96.
5. Berlato D, Schrempp D, Van Den Steen N et al. Radiotherapy in the management of localized mucocutaneous oral lymphoma in dogs: 14 cases. *Vet Comp Oncol* 2012; 10: 16–23.
6. Wilcock BP, Yager JA. The behavior of epidermotropic lymphoma in twenty-five dogs. *Can Vet J* 1989; 30: 754–756.
7. Williams LE, Rassnick KM, Power HT et al. CCNU in the treatment of canine epitheliotropic lymphoma. *J Vet Intern Med* 2006; 20: 136–143.
8. Magnol JP, Ghernati I, Marchal T et al. Clinical, morphologic and immunophenotypic data based on 10 cases of canine mucocutaneous epidermotropic T-lymphoma (analogous to Mycosis Funcgoide). Important of an animal model of spontaneous pathology (In French). *Bull Acad Natl Med* 1996; 180: 449–462.
9. Nemec A, Zavodovskaya R, Affolter VK et al. Erythema multiforme and epitheliotropic T-cell lymphoma in the oral cavity of dogs: 1989 to 2009. *J Small Anim Pract* 2012; 53: 445–452.
10. Moore PF, Olivry T, Naydan D. Canine cutaneous epitheliotropic lymphoma (mycosis fungoides) is a proliferative disorder of CD8+ T cells. *Am J Pathol* 1994; 144: 421–429.
11. Risbon RE, de Lorimier LP, Skorupski K et al. Response of canine cutaneous epitheliotropic lymphoma to lomustine (CCNU): a retrospective study of 46 cases (1999-2004). *J Vet Intern Med* 2006; 20: 1,389–1,397.
12. Moriello K, MacEwen E, Schultz K. PEG-L-asparaginase in the treatment of canine epitheliotropic lymphoma and histiocytic proliferation dermatitis. In *Advances in Veterinary Dermatology, volume 3*. PJ Ihrke, IS Mason and SD White, eds. Oxford, United Kingdom: Pergamon Press, 1993; 293–299.
13. Vail DM, Kravis LD, Cooley AJ et al. Preclinical trial of doxorubicin entrapped in sterically stabilized liposomes in dogs with spontaneously arising malignant tumors. *Cancer Chemother Pharmacol* 1997; 39: 410–416.
14. Morges MA, Burton JH, Saba CF et al. Phase II evaluation of VDC-1101 in canine cutaneous T-cell lymphoma. *J Vet Intern Med* 2014; 28: 1,569–1,574.
15. White SD, Rosychuk RA, Scott KV et al. Use of isotretinoin and etretinate for the treatment of benign cutaneous neoplasia and cutaneous lymphoma in dogs. *J Am Vet Med Assoc* 1993; 202: 387–391.
16. Iwamoto KS, Bennett LR, Norman A et al. Linoleate produces remission in canine mycosis fungoides. *Cancer Lett* 1992; 64: 17–22.
17. Lemarié SL, Eddlestone SM. Treatment of cutaneous T-cell lymphoma with dacarbazine in a dog. *Vet Dermatol* 1997; 8: 41–46.
18. London CA, Hannah AL, Zadovoskaya R et al. Phase I dose-escalating study of SU11654, a small molecule receptor tyrosine kinase inhibitor, in dogs with spontaneous malignancies. *Clin Cancer Res* 2003; 9: 2,755–2,768.
19. Greenlee PG, Filippa DA, Quimby FW et al. Lymphomas in dogs. A morphologic, immunologic, and clinical study. *Cancer* 1990; 66: 480–490.
20. Teske E, van Heerde P, Rutteman GR et al. Prognostic factors for treatment of malignant lymphoma in dogs. *J Am Vet Med Assoc* 1994; 205: 1,722–1,728.

21. Ruslander DA, Gebhard DH, Tompkins MB et al. Immunophenotypic characterization of canine lymphoproliferative disorders. *In Vivo* 1997; 11: 169–172.
22. Baskin CR, Couto CG, Wittum TE. Factors influencing first remission and survival in 145 dogs with lymphoma: a retrospective study. *J Am Anim Hosp Assoc* 2000; 36: 404–409.
23. Ponce F, Magnol JP, Ledieu D et al. Prognostic significance of morphological subtypes in canine malignant lymphomas during chemotherapy. *Vet J* 2004; 167: 158–166.
24. Abel EA, Wood GS, Hoppe RT. Mycosis fungoides: clinical and histologic features, staging, evaluation, and approach to treatment. *CA Cancer J Clin* 1993; 43: 93–115.
25. Veterinary cooperative oncology group - common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.1. *Vet Comp Oncol* 2016; 14: 417–446.
26. Vail DM, Michels GM, Khanna C et al. Response evaluation criteria for peripheral nodal lymphoma in dogs (v1.0)–a Veterinary Cooperative Oncology Group (VCOG) consensus document. *Vet Comp Oncol* 2010; 8: 28–37.
27. Goodman IH, Moore AS, Frimberger AE. Treatment of canine non-indolent T cell lymphoma using the VELCAP-TSC protocol: A retrospective evaluation of 70 dogs (2003-2013). *Vet J* 2016; 211: 39–44.
28. Sorenmo K, Overley B, Krick E et al. Outcome and toxicity associated with a dose-intensified, maintenance-free CHOP-based chemotherapy protocol in canine lymphoma: 130 cases. *Vet Comp Oncol* 2010; 8: 196–208.
29. Morrison-Collister KE, Rassnick KM, Northrup NC et al. A combination chemotherapy protocol with MOPP and CCNU consolidation (Tufts VELCAP-SC) for the treatment of canine lymphoma. *Vet Comp Oncol* 2003; 1: 180–190.
30. Brodsky EM, Maudlin GN, Lachowicz JL et al. Asparaginase and MOPP treatment of dogs with lymphoma. *J Vet Intern Med* 2009; 23: 578–584.
31. Rassnick KM, Moore AS, Collister KE et al. Efficacy of combination chemotherapy for treatment of gastrointestinal lymphoma in dogs. *J Vet Intern Med* 2009; 23: 317–322.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1. Schematic for administration of chemotherapy drugs in VELCAP-EL 20-week combination chemotherapy protocol for canine epitheliotropic lymphoma.

Table S2. Highest VCOG-CTCAE v1.1 criteria toxicity score and nature of toxicity recorded in dogs treated with VELCAP-EL combination chemotherapy protocol and single-agent CCNU chemotherapy.

Résumé

Contexte – Peu d'information est disponible sur le traitement et l'évolution des chiens atteints de lymphome épithéliotrope. La maladie est typiquement de mauvais pronostic.

Objectifs – Caractériser les signes cliniques, identifier les facteurs pronostiques et évaluer l'efficacité du traitement des chiens atteints de lymphome épithéliotrope.

Méthodes – Une revue rétrospective des données médicales de 2003 à 2015. Les détails de traitement, la réponse tumorale et le temps de survie ont été enregistrés pour 148 chiens. Les facteurs pronostics potentiels ont été évalués pour leur effet statistique sur le temps de survie moyen.

Résultats – Le temps de survie moyen global pour tous les chiens était de 264 jours (cutané : 130 jours, muqueux/cutanéo-muqueux : 491 jours). Sur les analyses multivariables, un temps de survie médian plus court a été associé avec la forme cutanée ($P < 0.001$) et la présence de lésions multiples ($P < 0.001$). Parmi 80 chiens avec des lésions cutanées, recevoir une chimiothérapie ($P < 0.001$) et avoir une lésion unique ($P < 0.001$) étaient associés à un temps de survie plus long. Pour 72 chiens avec des lésions cutanées multiples, la chimiothérapie ($P < 0.001$), les rétinoïdes ($P = 0.001$) et une rémission complète ($P = 0.001$) étaient associés avec une médiane de survie plus longue. Pour 68 chiens avec des lésions muqueuses/cutanéo-muqueuses, un âge bas ($P = 0.020$) et une lésion unique ($P = 0.015$) étaient associés à une médiane de survie plus longue.

Conclusion – Le lymphome épithéliotrope canin peut être divisé en deux formes cutanée et muqueuse/cutanéo-muqueuse. Les lésions uniques ont un meilleur pronostic. Les chiens avec des lésions multiples semblent bénéficier de la chimiothérapie et des rétinoïdes, ceux atteignant une rémission complète ayant des temps de survie plus longs. La chimiothérapie à agents multiples pourrait être envisagée chez les chiens atteints de lésions cutanées qui ne répondent pas à une chimiothérapie en monothérapie.

Resumen

Introducción – Se dispone de información limitada sobre el tratamiento y los resultados de perros con linfoma epiteliotrópico. La enfermedad típicamente tiene un mal pronóstico.

Objetivos – Caracterizar los signos clínicos, identificar los factores pronósticos y evaluar el resultado del tratamiento de los perros con linfoma epiteliotrópico.

Métodos – Una revisión retrospectiva de los historiales clínicos de 2003 a 2015. Detalles del tratamiento, la respuesta del tumor y el tiempo de supervivencia estaban disponibles para 148 perros. Se evaluaron los posibles factores pronósticos para determinar su efecto estadístico sobre el tiempo medio de supervivencia.

Resultados – El tiempo medio de supervivencia global para perros fue de 264 días (cutáneo: 130 días, mucocutáneo / mucoso: 491 días). En análisis multivariado, se asoció la mediana del tiempo de supervivencia más corta con la forma cutánea ($P < 0,001$) y la presencia de múltiples lesiones ($P < 0,001$). Entre 80 perros con lesiones cutáneas, el tener tratamiento de quimioterapia ($P < 0,001$) y una lesión solitaria ($P < 0,001$) se asociaron con una mayor mediana de supervivencia. En 72 perros con lesiones cutáneas múltiples, la intervención quimioterapéutica ($P < 0,001$), el tratamiento con retinoides ($P = 0,001$) y la

remisión completa (P = 0,001) se asociaron con una mayor mediana de supervivencia. En 68 perros con lesiones mucocutáneas / de mucosas, una menor edad (P = 0,020) y lesión solitaria (P = 0,015) se asociaron con una mediana de supervivencia más prolongada.
Conclusión – El linfoma epiteliotrópico canino puede dividirse en formas cutánea y mucocutánea / de mucosas. Las lesiones solitarias tienen un mejor pronóstico. Los perros con lesiones múltiples parecen beneficiarse de la quimioterapia y el tratamiento con retinoides, y aquellos que alcanzan la remisión completa presentan mayor tiempos de supervivencia. La quimioterapia con agentes múltiples podría considerarse en perros con lesiones cutáneas que no responden a la quimioterapia con un solo agente.

Zusammenfassung
Hintergrund – Es gibt nur limitierte Informationen über die Behandlung und das Ergebnis von Hunden mit Epitheliotropem Lymphom. Diese Erkrankung zeigt typischerweise eine schlechte Prognose.
Ziele – Die Charakterisierung der klinischen Zeichen, die Identifizierung prognostischer Faktoren und eine Evaluierung der Behandlungsergebnisse bei Hunden mit Epitheliotropem Lymphom.
Methoden – Eine retrospektive Durchsicht der medizinischen Krankengeschichten von 2003 bis 2015. Behandlungsdetails, Tumorantwort und Überlebensdauer wurden von 148 Hunden festgehalten. Mögliche prognostische Faktoren wurden in Bezug auf ihren statistischen Einfluss auf die mediane Überlebenszeit evaluiert.
Ergebnisse – Die insgesamte mediane Überlebenszeit der Hunde betrug 264 Tage (kutanes EL: 130 Tage; mucokutanes/muköses EL: 491 Tage). In der multivariaten Analyse zeigte sich eine kürzere mediane Überlebensdauer bei der kutanen Form (P < 0,001) und beim Auftreten von multiplen Läsionen (P < 0,001). Unter 80 Hunden mit kutanen Läsionen wurde eine chemotherapeutische Behandlung (P < 0,001) und das Auftreten einer solitären Läsion (P < 0,001) mit einer längeren medianen Überlebenszeit gesehen. Bei 72 Hunden mit multiplen kutanen Veränderungen wurde eine längere mediane Überlebenszeit nach chemotherapeutischer Behandlung (P < 0,001), Behandlung mit Retinoiden (P = 0,001) und nach kompletter Remission (P = 0,001) gesehen. Bei 68 Hunden mit mucokutanen/mukösen Veränderungen, abnehmendem Alter (P = 0,020) und solitären Läsionen (P = 0,015) wurde eine längere mediane Überlebenszeit festgestellt.
Schlussfolgerungen – Das Epitheliotrope Lymphom des Hundes kann in kutane und mucocutane/muköse Formen eingeteilt werden. Solitäre Veränderungen haben eine bessere Prognose. Hunde mit multiplen Veränderungen scheinen von einer chemotherapeutischen Behandlung und von einer Behandlung mit Retinoiden zu profitieren, wobei jene, die eine komplette Remission erzielen längere Überlebenszeiten haben. Eine multimodale Chemotherapie sollte bei Hunden mit kutanen Läsionen erwogen werden, die nicht auf eine Chemotherapie mit einem einzelnen Agens ansprechen.

要約
背景 – 上皮向性リンパ腫を有する犬に関する治療および予後に関した情報は限られている。この疾患は、一般的に予後不良である。
目的 – 上皮向性リンパ腫を有する犬の臨床症状を特徴付け、予後因子を同定し、治療効果を評価すること。
方法 – 2003年から2015年までの診療記録の回顧的評価。148頭の犬について、治療の詳細、腫瘍の治療反応性および生存時間が記録された。潜在的な予後因子については、生存期間中央値に対する統計学的効果として評価した。
結果 – 全体的な生存期間中央値は264日(皮膚:130日、皮膚粘膜/粘膜:491日)であった。 多変量解析では、皮膚型(P < 0.001)および多発性病変の存在(P < 0.001)がより短い生存期間中央値と関連していた。皮膚病変を有する80頭の犬のうち、化学療法(P < 0.001)および孤立性病変(P < 0.001)は、より長い生存期間中央値と関連していた。多発性皮膚病変を有する72頭の犬において、化学療法(P < 0.001)、レチノイド治療(P = 0.001)および完全寛解(P = 0.001)は、より長い生存期間中央値と関連していた。皮膚粘膜病変を有する68匹の犬において、年齢の減少(P = 0.020)および孤立性病変(P = 0.015)は、より長い生存期間中央値と関連していた。
結論 – 犬の上皮向性リンパ腫は、皮膚型および粘膜皮膚/粘膜型に分類され得る。孤立性病変はより良好な予後を有する。複数の病変を有する犬は化学療法およびレチノイド治療の恩恵を受ける傾向にあり、完全寛解に達する犬はより長い生存時間を有する。多剤化学療法は、単一薬剤化学療法に反応しない皮膚病変を有する犬において考慮され得る。

摘要
背景 — 关于犬趋上皮性淋巴瘤的治疗和转归的资料比较少。该病普遍预后不良。
目标 — 确定犬趋上皮性淋巴瘤的临床特点、预后因素并评估治疗效果。
方法 — 回顾2003年至2015年病历记录。记录中找到148只犬的治疗细节、肿瘤反应和生存时间。评估可能的预后因素对中位生存时间的统计学影响。
结果 — 犬的总体中位生存时间为264天(皮肤:130天;粘膜皮肤/粘膜:491天)。在多变量分析中,较短的中位生存时间与皮肤形态(P < 0.001)和多发性病变相关(P < 0.001)。在80例皮肤病变犬中,化疗(P < 0.001)和单个

病变($P < 0.001$)与较长中位生存期相关。在72例多发皮肤病变的犬中,化疗干预($P < 0.001$)、类维生素A治疗($P = 0.001$)和完全缓解($P = 0.001$)与较长的中位生存期相关。 68例粘膜皮肤/粘膜病变、年龄($P = 0.020$)和单个病变($P = 0.015$)与较长中度生存期相关。
结论 — 犬趋上皮性淋巴瘤可分为皮肤和粘膜皮肤/粘膜形式。单个病变有较好的预后。化疗和类维生素A治疗对多发病变的犬似乎有效,其中症状完全缓解的存活时间更长。皮肤病变的犬如果单一药物化疗无效,可以考虑用药物组合化疗。

Resumo
Contexto – As informações a respeito do tratamento e da evolução de cães com linfoma epiteliotrópico são limitadas. A doença tipicamente apresenta um prognóstico pobre.
Objetivos – Caracterizar os sinais clínicos, identificar fatores de prognóstico e avaliar os resultados do tratamento de cães com linfoma epiteliotrópico.
Métodos – Uma revisão retrospectiva dos prontuários entre 2003 e 2015. Os detalhes de tratamento, resposta tumoral e tempo de sobrevivência de 148 cães foram extraídos dos históricos clínicos. Os potenciais fatores prognósticos foram avaliados para o seu efeito estatístico no tempo médio de sobrevivência.
Resultados – O tempo médio de sobrevivência geral foi de 264 dias (cutâneo: 130 dias; mucocutâneo/mucosas: 491 dias). Em uma análise multivariada, um menor tempo de sobrevivência médio foi associado à forma cutânea ($P < 0.001$) e à presença de lesões múltiplas ($P < 0.001$). Entre os 80 cães com lesões cutâneas, o tratamento quimioterápico ($P < 0.001$) e a presença de lesões solitárias ($P < 0.001$) foram associados a um tempo de sobrevivência médio mais longo. Nos 72 cães com lesões múltiplas, a quimioterapia ($P < 0.001$), o tratamento com retinóides ($P = 0.001$) e a remissão completa ($P = 0.001$) foram associados a um tempo de sobrevivência mais longo. Em 68 cães com lesões cutâneas/mucocutâneas, idade decrescente ($P = 0.020$) e lesões solitárias ($P = 0.015$) foram associadas a um tempo de sobrevivência mais longo.
Conclusão – O linfoma epiteliotrópico canino deve ser dividido nas formas cutânea e mucocutânea/mucosa. Lesões solitárias possuem um prognóstico melhor. Cães com lesões múltiplas parecem se beneficiar da quimioterapia e do tratamento com retinóides, e aqueles apresentando remissão completa possuem um tempo de sobrevivência mais longo. A quimioterapia com múltiplos agentes pode ser considerada em cães com lesões cutâneas que não respondem bem à quimioterapia com apenas um agente.