Canine Cutaneous Perivascular Wall Tumors at First Presentation: Clinical Behavior and Prognostic Factors in 55 Cases

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Background: Canine cutaneous perivascular wall tumors (c-PWT) are soft tissue sarcomas recently identified when hemangiopericytomas were reclassified. No previous clinical data are available for c-PWT.

Hypothesis/Objectives: To define the clinical behavior and prognostic role of clinical and pathological variables in a homogeneous population of c-PWT.

Animals: Fifty-five c-PWT in 53 client-owned dogs at first presentation undergoing surgery.

Methods: Retrospective case series. The endpoint was the relapse of tumor (local and/or distant). The prognostic values of clinical (age, sex, weight, site and tumor size, adjuvant therapy) and pathological (status of surgical margins, histological grade, mitosis, percentage of tumor necrosis) variables were investigated by univariate and bivariate analyses ($P < .05$). The pattern of associations between variables was explored by multivariate correspondence analysis (MCA).

Results: Twelve dogs had a relapse. Ten dogs had local recurrence, 1 had metastatic disease, and 1 had both. The estimated probability of local recurrence was 0.02, 0.08, 0.20, and 0.24 at 6 months, 1, 2, and 3 years, respectively. Size of the tumor was a significant prognostic factor while status of margins had only a clinically relevant hazard ratio. In MCA evaluation, young age, tumor size (< 5 cm), grade I, and location in the extremities were associated. Association was also observed for older age, tumor size (> 5 cm), grade II, and other location.

Conclusion and Clinical Importance: C-PWT tend to locally recur a long time after surgery. An early diagnosis of c-PWT associated with small tumor size (< 5 cm) and clean surgical margins ensures a good prognosis independently of histological grade.

Key words: Dog; Neoplasm; Sarcoma; Size.

Soft tissue sarcomas (STS) are a heterogeneous group of mesenchymal tumors accounting for 15% of cutaneous and subcutaneous cancers in dogs.[1] In veterinary oncology, the term STS encompasses tumors with an ample range of differentiations including fibrous, myxoid, muscular, perineural, adipocytic and perivascular tumors, bearing similar histological features and hypothesized to display overlapping behavior.[1–15] This approach has been justified by the difficulty to differentially diagnose STS on the basis of histopathology and routine immunohistochemistry, especially for the sub-group of "spindle cell tumors".[2,16–19] Furthermore, the term STS has been utilized inconsistently since the list of neoplastic entities included in the STS group changes among reports.[2–6]

Abbreviation:

CI	confidence interval
c-PWT	cutaneous perivascular wall tumor
HPC	hemangiopericytoma
HPF	high power field
HR	hazard ratio
MCA	multiple correspondence analysis
STS	soft tissue sarcoma
TTR	time to relapse
WHO	World Health Organization

The role of several clinical and pathological variables has been investigated in canine STS to evaluate their correlation with survival times, recurrence, and metastatic rates; however, prognostic relevance of these variables is still controversial.[6,9–11,13,20–25]

Following the reclassification of canine haemangiopericytoma (HPC), a subset of canine STS arising from the perivascular wall has been described and termed cutaneous perivascular wall tumors (c-PWT).[26] c-PWT are diagnosed on the basis of specific histological growth and immunohistochemical reaction patterns.[26,27] The identification of c-PWT enables the veterinary oncologist to study their behavior as a homogeneous subgroup of neoplasms, in order to possibly assess prognostic variables that might have been missed by studies incorporating c-PWT in the miscellaneous STS group. The aim of this study was to investigate the clinical behavior of canine c-PWT and to evaluate the prognostic role of clinical and pathological variables on the risk of tumor relapse in dogs with c-PWT at 1st presentation treated in a referral institution and diagnosed and graded by the same pathologists. The multivariate pattern of association

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between clinical and pathological variables was also explored.

Materials and Methods

This study was conducted according to the guidelines proposed by Webster et al.[28] Medical records of client-owned dogs with diagnosis of STS collected from January 2001 to December 2009 were retrospectively reviewed. Dogs were included in the study when the following criteria were met: 1st presentation of the tumors, cutaneous location, no previous treatment, surgery performed by the same surgeon, no limb amputation, histological reevaluation and classification of STS into c-PWT,[26] access to tissue specimens to assess histological grade,[6] and status of margins. c-PWT in dogs were diagnosed on the basis of previously reported criteria: growth pattern (perivascular whorling, bundles radiating from tunica media of vessels, placentoid, staghorn vessels) and cell shape (spindle to polygonal and stellate).[26] When fresh tissue was available, specific subclassification was performed by immunocytochemistry or immunohistochemistry as previously described.[26]

Data collected from medical records were breed, age, sex, body weight, tumor location, tumor size (longest diameter measured with a caliper), and medical treatment after excision. The location of the tumor was defined as "extremities" (at or distal to stifle and elbow) and "other site" (head, neck, trunk).

Before admission for surgery, all dogs underwent thoracic radiographs (3 views), abdominal ultrasound, and cytological analysis of enlarged lymph nodes to exclude metastatic disease. Tumors were staged according to the World Health Organization (WHO) clinical staging system.[29,30]

Wide excision was always attempted in relation to the size of the dog and site and size of the tumor until a maximum of 3 cm of normal tissue around the grossly visible mass was obtained. Only 1 dog weighing 3.5 kg underwent marginal excision of a 7-cm c-PWT located in the ventral neck. Tumors located at the extremities were always marginally excised. Adjuvant treatment such as re-excision, radiation therapy, and/or systemic chemotherapy was planned when surgical margins were at risk of recurrence and/or a grade III c-PWT was diagnosed.

Histological grade, mitotic index, percentage of necrosis, and status of surgical margins were recorded. Microscopically, tumor margins were classified as dirty when neoplastic cells were detected at the margins, clean but close if tumor cells were within 1–3 mm from the margins and, clean if > 3 mm of normal tissue separated the neoplastic tissue from the surgical margin. c-PWT with clean but close and dirty margins evidenced by microscopic examination were considered at risk of recurrence as previously reported.[13,31]

All dogs were re-examined at our institution at defined intervals: after surgery, every month for 3 months, every 3 months for the 1st year, and every 6 months for the 2nd year. Thoracic radiographs and abdominal ultrasound were performed at 6, 12, 18, and 24 months postsurgery. After 2 years, follow-up consisted of telephone conversations with referring veterinarians. When relapse was suspected, dogs were re-examined at our institution. Local recurrence, distant metastases or both were confirmed by cytology, histology, or both. Local recurrence was defined as the development of c-PWT at or within 2 cm from the scar of previous surgery. The endpoint (relapse) was the finding of local recurrence and/or distant metastases. Probability of local recurrence and/or distant metastasis, probability of time free of relapse at 6 months, 1, 2, and 3 years from the date of surgery treatment, time to relapse, and time to follow-up were calculated.

Time to relapse was calculated from the date of surgery to the date of the 1st evidence of relapse. For dogs without a relapse, the endpoint time was calculated from the date of surgery to the date of the last clinical control (or lost to follow-up) or to the closing date (censored). Relapse-free survival curves were traced by the Kaplan–Meier method.

The incidence of local recurrence, distant metastasis, or both during follow-up (crude cumulative incidences) was estimated by a method specific for competing risks.[32] The putative prognostic role of the variables was investigated by the Cox regression model. First, each variable was individually considered (univariable analysis models), and then statistically significant variables were adjusted for each of the other variables by bivariate regression models. The multivariable analysis was not performed as the ratio between the number of events and the number of the clinical–pathological variables was below 5. The prognostic role of covariates measured on a continuous scale (eg, tumor size, age) was investigated by regression cubic splines, to allow the identification of possible nonlinear relationships.[33] For categorical variables results are shown in terms of hazard ratios (HR) and their 95% confidence intervals (CI). An HR = 1 indicates no prognostic impact of a variable. An HR shift from 1 indicates prognostic impact of a variable, this impact increases with higher drift of HR from 1. For continuous variables plots of estimated prognostic patterns are also provided, since the regression coefficients were not directly interpretable.

As the statistical significance of the variables does not provide information on the strength of their prognostic role (ie, the possibility to separate subjects with different prognosis) the discriminating prognostic capability was estimated by Harrel's C index.[34] This index is an extension of the area under the receiver operating characteristic curve for survival data. The index values ranged from 0.5 (lack of discriminating capability) to 1.0 (maximal discriminating capability).

The patterns of relationships between clinical and pathological characteristics were explored by multiple correspondence analysis (MCA), a descriptive multivariate technique.[35] Multiple correspondence analysis was applied to tumor size, grade, age and location, which are previously reported relevant variables for canine STS.[6,9,10,13,20,31] Because MCA required the use of categorical variables, tumor size and age were categorized using the median values: age $\leq$ 10 versus > 10 years and tumor size $\leq$ 5 versus > 5 cm. When the amount of variability explained by the first 2 factorial axes (inertia) is high, the structure of the association among categories can be examined considering their projection on a plane. The distance between points, defined according to a χ^2 metric, indicates the dissimilarities between categories. The proximity between categories of variables means that these categories tend to group in each dog. The category proximity of the same variable means that the groups of dogs associated with these 2 categories are similar between each other. Statistical analysis was performed by R software.[a]

Results

Clinical records of 72 dogs with a histological diagnosis of cutaneous STS were retrieved. Seventeen STS did not meet the inclusion criteria: 10 were not c-PWT and 7 were recurrent c-PWT. Fifty-five c-PWT in 53 dogs (2 dogs had 2 tumors each) were enrolled. The majority of dogs were mongrels (16). Breeds more represented were Boxer (8), German Shepherd (5), Labrador Retriever (4), Rottweiler (3), Siberian Husky (3), Doberman (2), and Pinscher (2). Female dogs were 30 (56.6%, 95% CI 43.3–69%), 10 intact and 20 spayed, males were 23, 21 intact and 2 neutered. Median age and weight at presentation were

10 years (range: 3–17) and 28 kg (range: 3.5–52), respectively.

Thirty c-PWT were located in the extremities and 25 were in other sites (21 trunk, 3 neck, and 1 head). Median tumor size was 5 cm (range: 0.5–15). Tumors were classified as $T_1N_0M_0$ (3), $T_2N_0M_0$ (25), and $T_3N_0M_0$ (24). In 3 c-PWT, the largest diameter was not available. Correlating size of tumors with their anatomical location, the median size of c-PWT at extremities was 5 cm (range 0.5–10) whereas in other sites was 6 cm (range: 1.5–15).

Tumors were graded as I (26; 47.5%), II (25; 45.5%), and III (4; 7%). Mitotic index ranged from 0 to 48 (median, 4 mitoses/HPF). Necrosis was absent in 34 cases and < 50% in 21 tumors. Surgical margins were clean in 7 cases (2 extremities, 5 other site), clean but close in 15 (7 extremities, 8 other site), and dirty in 33 (21 extremities, 12 other site). There was no evidence of association between histological grade and surgical margins ($P = .172$). Median size of c-PWT with clean, clean but close, and dirty margins was 3.25, 5, and 6 cm, respectively. In 36 cases, diagnosis of the c-PWT subtype was myopericytoma (24), angioleiomyosarcoma (5), angioleiomyoma (4), adventitial tumor (2), and angiofibroma (1).

Four dogs received medical treatment after excision. One dog (2 c-PWT) was administered intra incisional 5-fluoruracil,[b] 1 dog received oral piroxicam,[c] and cyclophosphamide[d] at metronomic dosage, 1 dog was administered 4 doses of doxorubicin,[e] followed by oral piroxicam[c] and cyclophosphamide[d] at metronomic dosage.[10,12,36]

Median follow-up time was 665 days; the 25% of cases were followed for < 330 days and 25% of cases were followed for more than 1,140 days.

Relapse was detected in 12 dogs. The 1st relapse was observed at 151 days, the last relapse at 1,395 days for a median time of 408 days.

Relapse-free survival curves are illustrated in Figure 1. The probability of being free of relapse was 0.96 (95% CI: 0.91–1.0), 0.87 (95% CI: 0.78–0.97), 0.76 (95% CI: 0.63–0.91), 0.73 (95% CI: 0.58–0.88) at 6 months, 1, 2, and 3 years after surgery, respectively. Ten dogs had local recurrence. The estimated probability of local recurrence was 0.02 (95% CI: 0.0–0.06) at 6 months, 0.08 (95% CI: 0.04–0.162) at 1 year, 0.20 (95% CI: 0.07–0.33) at 2 years and 0.24 (95% CI: 0.09 –0.39) at 3 years.

One dog developed pulmonary metastases at 365 days. The estimated probability of distant metastases was 0.025 (95% CI: 0.0–0.074) at 1 year.

One dog had local recurrence and pulmonary metastases at 180 days. The estimated probability of combined event was 0.020 (95% CI: 0.0–0.058).

Prognostic Impact

In univariate analysis, only tumor size had a significant prognostic impact. Because of the low number of c-PWT smaller than 2 cm (3 tumors) the WHO categories T1 and T2 were combined (Table 1; Fig 2). Dogs with tumors larger than 5 cm had an estimated hazard of relapse approximately 7 times greater than dogs with smaller tumors. The prognostic impact was better evidenced when the variable was considered in its original measurement scale: the increased risk correlated with 1 cm raises in tumor size was 1.3 (Fig 3) and this impact was maintained when the effect of tumor size was adjusted for each other variable (Table 2). Moreover, tumor size was the only variable with a significant discriminating prognostic ability (CI of Harrell C does not include the "null" discriminant 0.5 value) and its predictive ability increased from 0.70 to 0.72 when the dicotomic categorization was replaced by continuous variable. Status of margins and adjuvant therapies were not statistically significant prognostic factors, however, a clinically relevant estimated HR of relapse suggested a possible prognostic role (Table 1).

The prognostic effect of tumor size maintained its significance also when the other variables were taken into account by bivariate analysis (Table 2). Bivariate analysis showed that the prognostic effect of the other variables did not change compared with the results of univariate analysis. The only exception was for age,

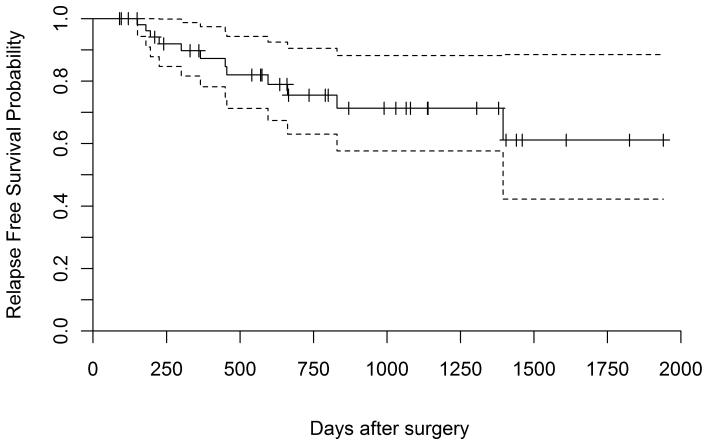

Fig 1. Relapse-free survival probabilities (solid line) estimated by Kaplan–Meier method and 95% CI (dashed lines). Small vertical bars on the curve represent censored times.

Table 1. Univariate analysis of clinical and pathological variables of c-PWT in dogs.

Variables	Hazard Ratio (95% CI)	Wald Test (*P* value)	Harrell C (95% CI)
Sex			
F/M ratio	1.5 (0.45–4.99)	0.433 (.51)	0.54 (0.39–0.68)
Site			
Extremities/other site ratio	1.44 (0.46–4.46)	0.39 (.53)	0.53 (0.38–0.69)
Tumor size (cm)			
"≤ 5 versus > 5"	7.29 (1.57–3.88)	6.42 (.01)	0.70 (0.57–0.84)
1 cm increase	1.29 (1.1–1.52)	9.729 (< .001)	0.72 (0.54–0.89)
Surgical margins status			
Dirty versus clean/close	1.99 (0.53–7.44)	1.045 (.31)	0.55 (0.40–0.70)
Mitoses (x/HPF)			
"≥ 10 versus 1–9"	1.1 (0.33–3.67)	0.024 (.88)	0.53 (0.38–0.67)
1 mitosis increase	1.001 (0.95–1.06)	0.017 (.9)	0.54 (0.37–0.71)
% Tumor necrosis			
"< 50% versus absent"	1.34 (0.42–4.26)	0.249 (.62)	0.58 (0.42–0.74)
Adjuvant therapy			
"yes versus no"	2.33 (0.49–11.09)	1.135 (.29)	0.59 (0.43–0.74)
Tumor grading			
"GII+GIII versus GI"	0.76 (0.22–2.58)	0.194 (.66)	0.56 (0.41–0.70)
Age			
1 year decrease	0.79 (0.6–1.03)	2.956 (.09)	0.61 (0.44–0.77)
Weight			
1 kg decrease	0.97 (0.92–1.03)	0.918 (.34)	0.59 (0.36–0.81)

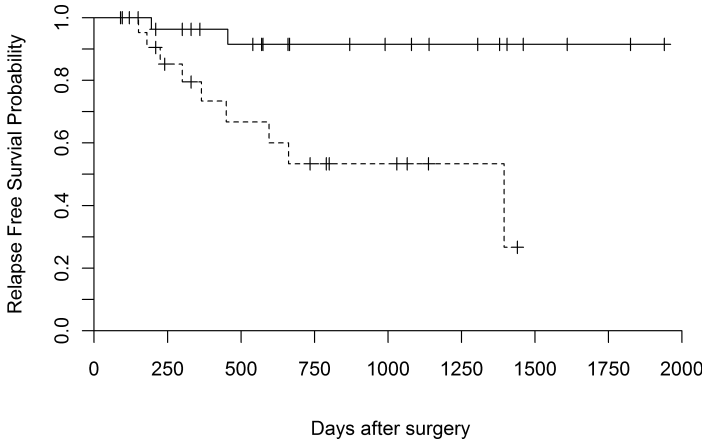

Fig 2. Relapse-free survival probabilities estimated by Kaplan–Meier method for tumors ≤ 5 cm (solid line) and tumors > 5 cm (dashed line). Small vertical bars on the curves represent censored times.

when the prognostic effect of age was adjusted for tumor size, the HR changed from 0.79 to 0.71, the decrease of the hazard becoming statistically significant (95% CI: 0.54–0.94, Wald test 5.65, $P = .02$).

Association among Variables

The pattern of associations was explored by MCA (Fig 4). For this analysis, 3 c-PWT (1 locally recurred) were excluded due to lack of tumor size. The plane accounted for the 83.6% of the total variability (*inertia*) so the profiles, identified by position of the modalities in the plane, were well represented.

Younger dogs tended to have lower dimension and grade I tumors while older dogs tended to have larger size and grade II tumors. Tumor location in the extremities was more associated with younger age. Older age, on the contrary, seemed associated with the development of tumors in other site.

Discussion

The novel classification of canine PWT has detailed this subgroup of STS allowing their specific diagnosis.[26] Consequently, in this report a uniform caseload of c-PWT in dogs was collected to evaluate possible distinctive biological characteristics compared to canine STS and the old HPC. According to this approach, c-PWT in dogs displayed a favorable prognosis. Relapses were detected in 12 dogs, and only 2 dogs developed metastases, one of which in conjunction with local recurrence. The relapse incidence was

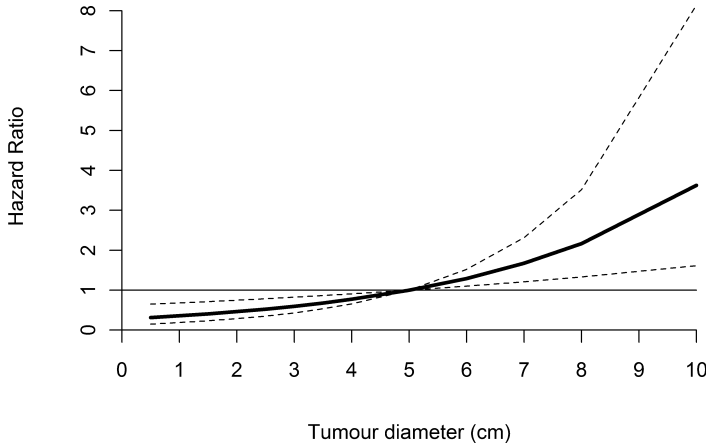

Fig 3. Ratio between the hazard of relapse for a given tumor size and the hazard of relapse for a 5-cm tumor. The shape of the prognostic pattern (solid line) with 95% CI (dashed lines) is estimated by Cox regression model. Hazard of relapse is significantly lower in < 5 cm tumors than in tumors > 5 cm. HR decreases with decreasing tumor size. Tumors larger than 5 cm shows a hazard of relapse significantly greater, HR increases with increased tumor size.

Table 2. Bivariate analysis. Prognostic effect of tumor size adjusted for other variables.

Tumor Size Adjusted For:	HR (95% CI)	Wald Test
Sex	1.29 (1.09–1.53)	8.685 (< 0.01)
Site	1.29 (1.08–1.53)	8.041 (< 0.01)
Surgical margins status	1.31 (1.1–1.56)	8.906 (< 0.01)
Mitoses	1.31 (1.1–1.55)	9.325 (< 0.01)
% Tumor necrosis	1.29 (1.1–1.52)	9.41 (< 0.01)
Grading	1.3 (1.1–1.53)	9.329 (< 0.01)
Age	1.37 (1.15–1.63)	12.234 (< 0.01)

unexpectedly low taking into account the elevated number of cases with surgical margins at risk (33 dirty and 15 clean but close) and the absence of adjuvant therapy after surgery. A statistical method based on competing risks was needed to estimate the incidence of the 3 possible relapses as the 1st occurrence of one of them prevented the observation of the others. The most frequent relapse was local recurrence alone with a higher incidence observed between 1 and 2 years after 1st excision (12.0%). These findings suggest that c-PWT at 1st presentation have a higher tendency to locally recur than to metastasize and they do so after a long latency pointing out that c-PWT in dogs have a generally low to nonaggressive biological behavior similarly to what has been described in human.[37,38] Additionally, these results parallel previously reported data on cutaneous STS in dogs,[6,9,31] although the number of c-PWT in these studies cannot be adequately estimated. Compared with this c-PWT caseload and with other STS in dogs, previous reports evidenced a more frequent recurrence rate and a reduced interval of time among recurrences for HPC in dogs, even when adjuvant therapies were administered.[21–23,39,40] This discrepancy could derive from an incomplete overlap between the old HPC and c-PWT since in this case series additional diagnostic

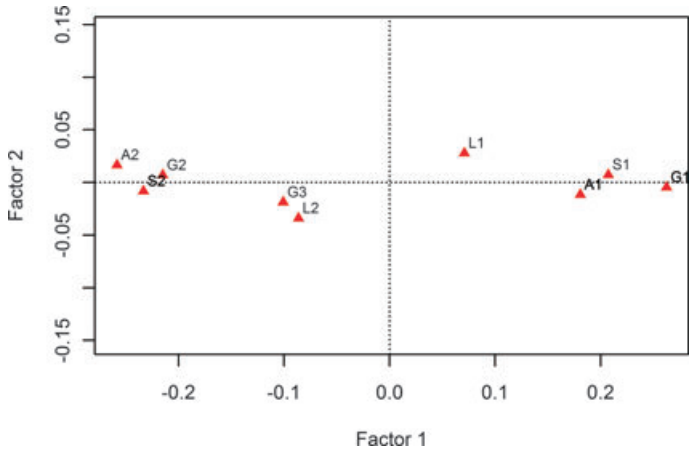

Fig 4. Plot of the first 2 factorial axes of the MCA (83% of the total variability). Modalities of the variables are projected in the plot. Age in 2 categories: A1 ($\leq$ 10 years), A2 (> 10 years). Grading in 3 categories: G1 (grade I), G2 (grade II),G3 (grade III). Tumor size in 2 categories: S1 ($\leq$ 5 cm), S2 (> 5 cm). Tumor location in 2 categories: L1 (extremities), L2 (other sites).

histological patterns previously not described for HPC have been considered (placentoid, staghorn vessels, bundles radiating from vascular wall).

In this caseload, the homogeneous selection of cases minimized heterogeneity and provided a suitable cohort for statistical analysis of potential significant prognostic variables.[28] Tumor size demonstrated statistically significant prognostic influence both when evaluated by categorization or, more so, by a continuous scale. The greater prognostic impact of size in a continuous scale analysis could be explained by the absence of fragmentation of canine c-PWT with different probability of relapse. In fact, the use of a cut-off value implies the estimate of a prognostic effect which is common for all subjects falling in the same category (below or above the cut-off value), which is a poor approximation when the probability of death increases (or decreases) to the increasing of the values of the prognostic factor.[33] The finding of a prognostic value for c-PWT tumor size bears resemblance with previous data for STS in dogs.[6] However, the tumor caseload was highly heterogeneous, including tumors of muscular, perineural, pericytic, lymphatic, fibrous and lipocytic differentiation.[6] On the contrary, when evaluating the role of tumor size for the previously called canine HPC as a single tumoral entity this variable lacked prognostic significance.[21]

Despite the fact that tumor size was the only prognostic factor identified in this report, lack of statistical evidence of other variables having significant prognostic impact should be considered with caution. Lack of significance may derive from the low power of the statistical test as a consequence of the low number of relapses in this c-PWT series. In fact, considering as clinically relevant a HR value of about 2, with 12 relapses the power of the test is approximately 20%. In order to obtain a power of 80%, a case series with 71 relapses is needed.[32] Moreover, the correct evaluation of the prognostic role should be performed by multivariable analysis. To support and better explain the need for multivariable analysis, the correlation of age with prognosis is one of the best examples in this caseload. Bivariate analysis demonstrated that age increased its prognostic impact becoming statistically significant when tumor size was taken into account. This result could be explained in view of the association between age and tumor size: older dogs tended to present with larger tumors than juvenile dogs. Concurrently, a better prognosis was evidenced for aged dogs. However, if size of the tumor is not taken into account, the "protective" effect of age is decreased because of the inverse prognostic relationship of age raise and tumor size increase. This is a well-known statistical effect termed confounding effect.[41] Unfortunately, multivariable analysis was not feasible because of the low number of relapses. A minimum ratio of 1 : 5 between the number of variables and the number of relapses is necessary to obtain reliable results.[33] Thus, in order to evaluate the joint effect of the 10 variables (Table 1), a case series including at least 50 relapses is necessary. This caseload with just 12 relapses allowed the application of bivariate analysis only.

The large size of the tumors and their location in the extremities hampered a complete resection and accounted for the elevated number of high risk surgical margins observed. Remarkably, quality of surgical margins seemed not to have statistical significance either in univariate or in bivariate analysis, contrasting with the documented prognostic role of surgical margins for canine STS but no data on surgical margin status are available for HPC in dogs.[6,13,14] This result should not be interpreted as margins not bearing any clinical relevance. In fact, c-PWT with clean surgical margins did not relapse at all and c-PWT with dirty margins had approximately twice the likelihood to relapse when adjuvant treatments were not administered. At the same time, this data could be influenced by the absence of grade III tumors into the clean surgical margin group; however, no evidence of a confounding effect due to grading was detected.[41]

The anatomical location of the tumor was also analyzed for canine c-PWT but seemed not to influence the rate of tumor relapse. Noteworthy, this result contrasts with the current literature where cutaneous canine STS in the extremities are reported to bear a more benign behavior.[6,9,14,31]

Pathological variables were also evaluated statistically. In this caseload, histological grade did not bear significance probably as a consequence of the rarity of grade III tumors and in consideration that only 1 out of 4 grade III tumors with surgical margins at risk relapsed. These results differ strikingly from most reports where grade is regarded as one of the most significant prognostic variables of canine cutaneous STS.[6,10,13,20] This unexpected finding encouraged a further evaluation of single grading components. However, neither mitotic index, nor percentage of necrosis, nor tumor differentiation demonstrated prognostic correlation with relapse. This again differed from previous studies where mitotic index and necrosis were associated with canine STS outcome.[6,13,24,25] Similar to our findings, a lack of association between mitotic index and relapse has been reported for the previously called canine HPC whereas the role of grade has never been assessed for this tumor type.[21] These results further support our approach, demonstrating a distinctive behavior of canine c-PWT compared to the whole group of cutaneous STS and the old classified HPC.

Last, MCA statistical analysis was applied to explore the significant association among putative prognostic factors. Some variables tended to associate into clinically distinct groups. Young dogs tended to present with small c-PWT on the extremities and mainly of grade I. On the contrary, older dogs had larger tumors, developing in other sites and more frequently of grade II. The correlation between tumor size and site can be explained by the straightforward detection of neoplasia on the extremities ensuring an early submission for clinical evaluation. We are not able to substantiate the observed association between histological grade, site, tumor size, and age. However,

given the results, this association should be taken into account clinically.

The association among clinical presentation, relapse, and histological variables could not be fully explored because of the low number of grade III tumors. For a better insight on the recognized associations, dog profiles with c-PWT at 1st presentation could be defined by clustering dogs on the basis of their clinical–pathological characteristics; however, the number of cases was too low for this approach.

Additional limitations of this study, other than the number of cases included, were the retrospective design, the low number of local recurrences and distant metastases that hampered a multivariate analysis and decreased the power of the statistical analysis. Unfortunately, at least in relation to the number of adverse events in c-PWT clinical course, this is a fact the authors had no power to control.

This study confirms that canine c-PWT are a unique subgroup of STS characterized by low to nonaggressive behavior with recurrence developing after a long latency with very low tendency to metastasize and lack of correlation of recurrence with grade. Tumor size was identified as the most relevant prognostic parameter for c-PWT in dogs. The high prognostic impact of tumor size evidenced by continuous scale analysis stresses the need for an early diagnosis to allow a prompt and complete excision.

In conclusion, c-PWT in dogs represent a more "benign" form of STS. Moreover, the diagnosis of specific subtypes of c-PWT may bear prognostic relevance that should be investigated provided that adequate numbers of each tumor type will be assembled.

Footnotes

[a] http://www.r-project.org/. Packages: survival, Design, Hmisc, CA

[b] Fluorouracile; Teva Pharma Italia, Milan, Italy

[c] Feldene; Pfizer Italia S.r.l., Latina, Italy

[d] Endoxan, Baxter S.p.A., Rome, Italy

[e] Adriblastina; Pfizer Italia S.r.l.

References

1. Theilen GH, Madewell BR. Tumors of the skin and subcutaneous tissues. In: Theilen GH, Madewell BR, ed. Veterinary Cancer Medicine. Philadelphia, PA: Lea & Febiger; 1979:123–191.

2. Liptak JM, Forrest LJ. Soft tissue sarcoma. In: Withrow SJ, Vail DM, ed. Withrow and MacEwen's Small Animal Clinical Oncology, 4th ed. St. Louis, MO: Saunders–Elsevier; 2007:425–454.

3. Mauldin GN. Soft tissue sarcomas. Vet Clin North Am Small Anim Pract 1997;27:139–148.

4. Ettinger SN. Principles of treatment for soft-tissue sarcomas in the dog. Clin Tech Small Anim Pract 2003;18:118–122.

5. Ehrhart N. Soft-tissue sarcoma in dogs: A review. J Am Anim Hosp Assoc 2005;41:241–246.

6. Kuntz CA, Dernell WS, Powers BE, et al. Prognostic factors for surgical treatment of soft-tissue sarcomas in dogs: 75 cases (1986-1996). J Am Vet Med Assoc 1997;211:1147–1151.

7. Dernell WS, Withrow SJ, Kuntz CA, et al. Principles of treatment for soft tissue sarcoma. Clin Tech Small Anim Pract 1998;13:59–64.

8. Forrest LJ, Chun R, Adams WM, et al. Postoperative radiotherapy for canine soft tissue sarcoma. J Vet Intern Med 2000;14:578–582.

9. McKnight JA, Mauldin N, McEntee MC, et al. Radiation treatment for incompletely resected soft-tissue sarcomas in dog. J Am Vet Med Assoc 2000;217:205–210.

10. Selting KA, Powers BE, Thompson LJ, et al. Outcome of dogs with high-grade soft tissue sarcoma treated with or without adjuvant chemotherapy: 39 cases (1996-2004). J Am Vet Med Assoc 2005;227:1442–1448.

11. Bacon NJ, Dernell WS, Enrhart N, et al. Evaluation of primary re-excision after recent inadequate resection of soft tissue sarcomas in dogs: 41 cases (1999-2004). J Am Vet Med Assoc 2007;230:548–554.

12. Elmslie RE, Glawe P, Dow SW. Metronomic therapy with cyclophosphamide and piroxicam effectively delays tumor recurrence in dogs with incompletely resected soft tissue sarcomas. J Vet Intern Med 2008;22:1373–1379.

13. McSporran KD. Histologic grade predicts recurrence for marginally excised canine subcutaneous soft tissue sarcomas. Vet Pathol 2009;46:928–933.

14. Chase D, Bray J, Ide A, et al. Outcome following removal of canine spindle cell tumours in first opinion practice: 104 cases. J Small Anim Pract 2009;50:568–574.

15. Luong RH, Bear KE, Craft DM, et al. Prognostic significance of intratumoral microvessel density in canine soft-tissue sarcomas. Vet Pathol 2006;43:622–631.

16. McColl Williamson M, Middleton DJ. Cutaneous soft tissue tumors in dogs: Classification, differentation, and histogenesis. Vet Dermatol 1998;9:43–48.

17. Pérez J, Bautista MJ, Rollòn E, et al. Immunohistochemical characterization of haemangiopericytomas and other spindle cell tumors in the dog. Vet Pathol 1996;33:391–397.

18. Chijwa K, Uchida K, Tateyama S. Immunohistochemical evaluation of canine peripheral nerve sheath tumors and other soft tissue sarcomas. Vet Pathol 2004;41:307–318.

19. Hanharyani E, Ochiai K, Kadosawa T, et al. Canine hemangiopericytoma: An evaluation of metastatic potential. J Vet Diagn Invest 1999;11:474–478.

20. Banks T, Straw R, Thomson M, et al. Soft tissue sarcomas in dogs: A study assessing surgical margin, tumour grade and clinical out come. Aust Vet Pract 2004;34:142–147.

21. Postorino NC, Berg J, Powers BE, et al. Prognostic variables for canine hemangiopericytoma: 50 cases (1979-1984). J Am Anim Hosp Assoc 1988;24:501–509.

22. Graves GM, Bjorling DE, Mahaffey E. Canine hemangiopericytoma: 23 cases (1967-1984). J Am Vet Med Assoc 1988; 192:99–102.

23. Bostock DE, Dye MT. Prognosis after surgical excision of canine fibrous connective tissue sarcomas. Vet Pathol 1980;17:581–588.

24. Ettinger SN, Scase TJ, Oberthaler KT, et al. Association of argyropgilic nucleolar organizing regions, Ki-67, and proliferating cell nuclear antigen scores with histologic grade and survival in dogs with soft tissue sarcoma: 60 cases (1996-2002). J Am Vet Med Assoc 2006;228:1053–1062.

25. Simon D, Ruslander DM, Rassnick KM, et al. Orthovoltage radiation and weekly low dose of doxorubicin for the treatment of incompletely excised soft-tissue sarcomas in 39 dogs. Vet Rec 2007;160:321–326.

26. Avallone G, Helmbold P, Caniatti M, et al. Spectrum of canine perivascular wall tumors: Morphologic, phenotypic and clinical characterization. Vet Pathol 2007;44:607–620.

27. Weiss SW, Golblum JR. Perivascular tumor. In: Weiss SW, Goldblum JR, ed. Soft Tissue Tumors, 4th ed. St Louis, MO: Mosby; 2001:985–1035.

28. Webster JD, Dennis MM, Dervisis N, et al. Recommended guidelines for the conduct and evaluation of prognostic studies in veterinary oncology. Vet Pathol 2011;48:7–18.

29. Graham JC, O'Keefe DA. Diagnosis and treatment of soft tissue sarcoma. The Compendium 1993;15:1627–1635.

30. Owen LN. TNM Classification of Tumors in Domestic Animal, 1st ed. Geneva: World Health Organization; 1980.

31. Stefanello D, Morello E, Roccabianca P, et al. Marginal excision of low-grade spindle cell sarcoma of canine extremities: 35 dogs (1996-2006). Vet Surg 2008;37:461–465.

32. Marubini E, Valsecchi MG. Analysing Survival Data from Clinical Trials and Observational Studies. Chichester: Wiley & Sons; 1994:331–344.

33. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 2007;165:710–718.

34. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–387.

35. Lebart L, Morineau A, Piron M. Statistique Explorative Multidimensionnelle. Paris: Dunod; 1995:108–135.

36. Marconato L, Comastri S, Lorenzo MR, et al. Postsurgical intra-incisional 5-fluorouracil in dogs with incompletely resected, extremity malignant spindle cell tumours: A pilot study. Vet Comp Oncol 2007;5:239–249.

37. Metzel T, Dei Tos AP, Sapi Z, et al. Myopericytoma of the skin and soft tissues clinicopathologic and immunohistochemical study of 54 cases. Am J Surg Pathol 2006;30:104–113.

38. Dray MS, McCarthy SW, Palmer AA, et al. Myopericytoma: A unifying term for a spectrum of tumours that show overlapping features with myofibroma. A review of 14 cases. J Clin Pathol 2006;59:67–73.

39. Evans SM. Canine hemangioperycitoma – A retrospective analysis of response to surgery and orthovoltage radiation. Vet Radiol 1987;28:13–16.

40. Richardson RC, Anderson VL, Voorhees WD III, et al. Irradiation-hyperthermia in canine hemangiopericytoma: Large-animal model for therapeutic response. J Natl Cancer Inst 1984;73:1187–1194.

41. Thrusfield M. Veterinary Epidemiology, 3rd ed. Oxford: Blackwell Science LTD Publishing; 2005.