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Summary of **'Canine Subcutaneous Mast Cell Tumour: Characterisation and Prognostic Indices - J. J. Thompson, D. L. Pearl, J. A. Yager, S. J. Best, B. L. Coomber, and R. A. Foster**

Abstract

Histologic grading schemes for canine cutaneous mast cell tumours were not developed for mast cell tumours arising within the subcutaneous tissue. Despite this limitation, subcutaneous mast cell tumours are frequently categorized as grade II or higher. The objective of this investigation was to evaluate the pathologic characteristics and clinical outcomes of subcutaneous mast cell tumours in order to provide a more accurate assessment of prognosis. Clinical outcome data for 306 dogs were obtained from referring veterinarians and correlated with histologic features. Mean and median follow-up durations were 842 and 891 days, respectively, with a range from 3 to 2,305 days. Only 27 dogs, representing 9 percent of the cohort, died due to mast cell tumour–related causes. Metastatic disease was identified in 13 dogs, equivalent to 4 percent, and 24 dogs, or 8 percent, developed local tumour recurrence, despite incomplete surgical margins being present in 171 cases, accounting for 56 percent. Median survival time was not reached. Estimated survival probabilities at 6 months, 1 year, 2 years, and 5 years were 95 percent, 93 percent, 92 percent, and 86 percent, respectively. Dogs that died or were euthanized did so as a result of local recurrence, development of additional mast cell tumours at distant sites, or metastatic spread. Reduced survival time was associated with increased mitotic index, infiltrative growth pattern, and the presence of multinucleated neoplastic cells. Both univariable and multivariable analyses demonstrated that mitotic index was a strong predictor of survival, local recurrence, and metastasis. These findings indicate that the majority of subcutaneous mast cell tumours in dogs are associated with a favourable prognosis, prolonged survival, and low rates of recurrence and metastatic disease.

Keywords: mast cell tumour, Cox proportional hazards, mitotic index, canine, survival

Introduction

Most canine mast cell tumours arise within the skin and subcutaneous tissues. While many originate in the dermis and extend into the subcutis, a subset is confined entirely to subcutaneous adipose tissue. Only one prior publication has specifically addressed this tumour subtype. That study reported prolonged survival and low rates of recurrence and metastasis; however, the limited number of cases precluded reliable prognostic conclusions. The foundational grading system described by Patnaik and colleagues did not include subcutaneous mast cell tumours, yet these tumours are frequently grouped with cutaneous mast cell tumours and classified as grade II due solely to their anatomic location.

Intermediate-grade tumours are characterized by substantial prognostic variability and low interobserver agreement among pathologists.

Numerous investigations have sought improved prognostic indicators for cutaneous mast cell tumours, examining factors such as tumour location, surgical margin status, mitotic activity, nuclear morphometry, vascular density, and molecular markers including proliferation indices, KIT expression patterns, vascular endothelial growth factor expression, and mutations in the c-KIT gene. Although mutations within the juxtamembrane domain of c-KIT are associated with higher tumour grade and increased aggressiveness, they are present in fewer than one-third of cases, limiting their utility as a universal prognostic marker.

Some studies have combined subcutaneous and cutaneous mast cell tumours in analyses. If subcutaneous tumours exhibit distinct biological behaviour, such pooling may generate misleading conclusions. The purpose of the present study was therefore to evaluate a large cohort of subcutaneous mast cell tumours independently in order to characterize their histologic features, clinical behaviour, and prognostic indicators.

Materials and Methods

Case Selection

A total of 550 subcutaneous mast cell tumours from 354 veterinary clinics, diagnosed between 2002 and 2008, were retrieved from the pathology archives of Yager-Best Histological and Cytological Services in Guelph, Ontario, Canada. Inclusion criteria required that the tumour represent a primary occurrence, be histologically diagnosed as a subcutaneous mast cell tumour with adequate tissue representation, and have sufficient follow-up data obtained via questionnaire or telephone interview with the submitting veterinary clinic.

Tumours were classified as subcutaneous based on localization within subcutaneous tissue without dermal invasion. At least two histologic sections were examined for each tumour to confirm this designation. In some cases, small numbers of mast cells extended around hair follicles or into underlying panniculus muscle; however, the primary tumour mass was located within subcutaneous tissue. When overlying epithelium was absent, the tumour was entirely surrounded by adipose tissue with no follicular or epidermal involvement. A diagnostic pathology report confirming subcutaneous origin was available for every included case.

Follow-up data included patient signalment, tumour location, dates of subsequent tumour development, evidence of metastasis, date and cause of death or date of last examination, prior history of mast cell tumours, and status at last follow-up. Additional information included whether adjunctive surgery or further diagnostic testing was performed. Cases

were excluded if follow-up was immediately unavailable, if there was a prior history of mast cell tumour, if the specimen represented an incisional or cytoreductive biopsy, or if the dog had a concurrent cutaneous mast cell tumour.

The date of surgical excision was defined as the date of diagnosis. Follow-up time was calculated from diagnosis to death or last contact. Local recurrence was defined as tumour regrowth at the original surgical site. Distant occurrence was defined as development of a new mast cell tumour at a different anatomic location. Metastasis was defined as spread to regional lymph nodes or internal organs, determined by physical examination and at least one diagnostic modality, including cytology, histology, surgery, ultrasonography, magnetic resonance imaging, or buffy coat analysis. Although histologic confirmation was available in only three metastatic cases, all suspected cases were included to avoid bias toward favourable outcomes.

Disease-free interval was defined as the time from diagnosis to the first occurrence of local recurrence, distant tumour development, or metastasis. Dogs lost to follow-up, dogs alive without disease, and dogs that died from unrelated causes were right-censored for survival analyses. Dogs that died from unknown causes were right-censored for risk factor analysis but included as events in sensitivity analyses to model a worst-case scenario. Median survival time was defined as the time at which 50 percent of dogs remained alive, and median disease-free interval as the time at which 50 percent remained free of mast cell tumour–related disease.

Evaluation of Histologic Variables

Histologic assessment was performed without knowledge of clinical outcome and included confirmation of subcutaneous location and evaluation of surgical margins. Margins were considered incomplete if neoplastic cells were present at or within 1 millimeter of the surgical margin. Larger tumours were represented by at least four peripheral margin sections.

All tumours lacked a capsule and consisted of neoplastic mast cells embedded within variably collagenous stroma and preexisting adipose tissue, with variable numbers of eosinophils. Growth pattern was classified into three categories based on low-magnification examination: circumscribed, combined, or infiltrative. Circumscribed tumours were well demarcated, expansile, and densely cellular, often elevating overlying tissues. Combined tumours consisted of nodules demarcated by abundant collagen but showing infiltrative features at the periphery. Infiltrative tumours lacked clear demarcation and exhibited neoplastic cells dispersed singly or in small aggregates within surrounding tissue.

Histologic features were recorded as present or absent. Anisocytosis and anisokaryosis were considered present when greater than a twofold variation was observed in at least 10

percent of 100 evaluated cells. Multinucleation was recorded when at least one cell with more than one nucleus was identified within ten high-power fields. Cytoplasmic granules were considered absent if no granules were discernible throughout the entire section. Quantitative assessment was limited due to regional variability, with the exception of mitotic index. Mitotic index was defined as the number of mitotic figures per ten high-power fields, assessed in the area of highest mitotic activity using a standardized method. In dogs with multiple subcutaneous tumours, the tumour with the highest mitotic index was used for risk factor analysis.

Statistical Analysis

All analyses were conducted using SAS version 9.1. Survival time and disease-free interval were estimated using Kaplan–Meier methods. Risk factors for survival, disease-free interval, local recurrence, distant occurrence, and metastasis were evaluated using Cox proportional hazards models. Variables with a univariable P value less than 0.20 were considered for multivariable modeling. Breed, sex, age at diagnosis, and tumour location were forced into all initial models as potential confounders. Backward elimination was used to derive final models retaining variables with P values less than 0.05. Pairwise interactions and confounding effects were assessed sequentially.

Hazard ratios were reported for categorical and continuous variables. Mitotic index was categorized using quantiles to ensure adequate sample sizes. Model assumptions were evaluated using graphical methods and residual analyses, including Schoenfeld and Martingale residuals. Correlations among predictors were assessed using Spearman rank coefficients to ensure that no variables exceeded 60 percent correlation.

Results

Questionnaires were returned by 221 of 354 clinics, providing follow-up data for 367 of 550 dogs. Sixty-one cases were excluded based on predefined criteria, resulting in a final cohort of 306 dogs. Median and mean age at diagnosis were both approximately 8 years. The study population included 54 breeds, with mixed breeds, Labrador Retrievers, and Boxers being most common. Sex distribution was predominantly neutered animals. Tumours were most frequently located on the extremities and trunk.

Sixteen dogs had multiple subcutaneous mast cell tumours. Five dogs received chemotherapy; however, due to small numbers, chemotherapy was not included in multivariable analyses. Exclusion of these cases did not alter model outcomes.

Clinical Outcomes

Follow-up duration ranged from 3 to 2,305 days. Median survival time was not reached. Estimated survival probabilities were high at all evaluated time points. When deaths of unknown cause were treated as mast cell tumour–related events, survival estimates decreased but remained favourable. Half of the dogs died during the study period, but only 9 percent died due to confirmed mast cell tumour–related causes.

Local recurrence occurred in 8 percent of dogs, distant tumour development in 11 percent, and metastasis in 4 percent. Median disease-free interval exceeded 2,000 days.

Survival

Multivariable analysis identified mitotic index, infiltrative growth pattern, multinucleation, and increasing age at diagnosis as significant predictors of reduced survival. Mitotic index exerted the strongest effect. Dogs with mitotic index greater than 4 had markedly higher mortality rates compared to those with lower or zero mitotic activity.

Local Recurrence

Local recurrence occurred most frequently in tumours with mitotic index greater than zero, incomplete surgical margins, and infiltrative growth patterns. Additional surgery following recurrence did not significantly improve survival compared to no further surgery.

Distant Tumour Occurrence

Development of additional mast cell tumours at distant sites was significantly associated with the presence of multiple tumours and multinucleation. Mitotic index was not a significant predictor in multivariable analysis. Additional surgery for distant tumours significantly improved survival.

Metastasis

Metastatic disease was uncommon. Mitotic index greater than 4 was the only significant predictor of metastasis in multivariable analysis. Dogs with metastasis had significantly shorter survival times.

Disease-Free Interval

Mitotic index, infiltrative growth pattern, multinucleation, and presence of multiple tumours significantly reduced disease-free interval. Disease-free interval was considered a particularly robust outcome measure due to reduced confounding by non-disease-related factors.

Discussion

Most dogs with subcutaneous mast cell tumours experienced prolonged survival, long disease-free intervals, and low rates of recurrence and metastasis. Outcomes were substantially more favourable than those reported for grade II cutaneous mast cell tumours. Surgical excision alone was curative in the majority of cases, even when margins were incomplete.

Mitotic index emerged as the most powerful prognostic indicator, consistent with findings in cutaneous mast cell tumours. However, its prognostic value was modified by additional histologic features, including multinucleation and growth pattern, emphasizing the importance of multifactorial assessment.

The infiltrative growth pattern was associated with increased risk of recurrence and reduced disease-free interval, even in cases with complete margins, suggesting a need for closer monitoring. Breed-associated effects were not significant in multivariable analyses, although Boxers tended to have less aggressive tumours.

Potential biological explanations for the favourable behaviour of subcutaneous mast cell tumours include influences of the adipose tissue microenvironment on mast cell differentiation and behaviour. Adipokines and stromal interactions may modulate tumour aggressiveness, although further molecular studies are needed.

Limitations of this retrospective study include reliance on clinical follow-up without routine postmortem confirmation and relatively small numbers of aggressive cases. Nonetheless, inclusion of suspected events avoided bias toward favourable outcomes.

Overall, these findings indicate that subcutaneous mast cell tumours should not be automatically classified as intermediate-grade cutaneous mast cell tumours. While mitotic activity remains a critical prognostic factor, additional histologic features must be considered for accurate prognostication.

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