I. Title: Evaluation of tumor factors on outcome in dogs following re-excision of the surgical scar in previously incompletely resected soft tissue sarcomas.

II. VSSO Member

Brandan Wustefeld-Janssens, BVSc, DECVS
Flint Animal Cancer Center, Colorado State University
300 W Drake
Fort Collins, CO 80525
Tel: 970-800-1214

III. Aims and objectives:

The **purpose** of the study is to determine the effect tumor factors have on local recurrence and disease-free interval in dogs that have surgical scar revision following inadequately excised soft tissue sarcoma.

Aims:

1. Determine if local recurrence following revision surgery is associated with tumor histologic grade[1] determined at the index surgery
2. Evaluate if other factors have an impact of local recurrence risk and disease free interval such as original tumor size, revision surgical dose, clinical stage, pattern of tumor invasion on original histology, histologic margin using the residual tumor classification (R0, R1, R2) and evidence of disease found on pathology examination at revision surgery.

IV. Background and significance

The current dogma is that local control is vital for overall treatment success in soft tissue sarcoma in dogs.[2] In most scenarios, the first consideration given to tumors that have been incompletely resected is to re-excise the surgical scar with a wide margin. A study by Bacon *et al.* (2007) examined 41 dogs that had surgical scar revision following inadequate resection and found that regardless of the extent of excision of the scar, the local recurrence risk was 15%.[3] Local recurrence risk was not found to be associated with tumor grade but the analysis was likely insufficiently powered to definitively conclude this. In contrast, local recurrence risk for tumors marginally resected were reported as 7%, 34% and 75% for grade I, II and III tumors respectively.[4] Similarly local recurrence following adjuvant cobalt radiation therapy (21 fractions, 3Gy/fraction, three times a week to target dose of 63Gy) of incompletely resected soft tissue sarcomas irrespective of grade was 17%.[5]

The scenario of a dog presenting with an incompletely resected soft tissue sarcoma is common in clinical practice and it is not clear if decision making should be made on the original histologic specimen in terms of adjuvant treatment, if the tumor bed can truly be deemed free of neoplastic cells or what impact tumor grade should have on decision making either before or after revising the surgical scar. An interesting finding of the Bacon (2007) study is that extent of surgery or surgical dose did not have a

bearing on outcome independent of tumor grade. We contest that although the cited study has some useful information, the body evidence available to guide treatment decisions is severely lacking.

We propose to expand on the Bacon (2007) study with a larger cohort of dogs from multiple institutions and specially examine tumor factors and its impact on local control and disease free interval.

V. Pilot data:

None

VI. Experimental design

(a) This will be a multi-institutional retrospective study where VSSO members will be invited to contribute cases that were treated between January 2005 and September 2017.

(b) Dogs will be eligible for inclusion if they are treated by the contributing institution for an incompletely excised soft tissue sarcoma by scar revision surgery, have a detailed pathology report (or histology slides) available for review, follow up of least two years and complete medical records.

(c) Dogs will be **ineligible** if:

i. Gross disease present at revision surgery
ii. The surgical site has been previously treated with radiation therapy or is treated with radiation therapy following the revision surgery
iii. Medical records are incomplete including pre-operative staging information. Minimum clinical staging size of original tumor and thoracic radiographs.
iv. Histopathology reports of the index surgery and subsequent revision are unavailable for review
v. Sarcomas with distinct biology such as hemangiosarcoma, lymphangiosarcoma, rhabdomyosarcoma and myxoid fibrosarcoma will be excluded from analysis. Tumor subtypes that will be included will be fibrosarcoma, perivascular wall tumor, peripheral nerve sheath tumor, liposarcoma or if subtypes are not indicated then descriptors such as spindle cell sarcoma, soft tissue sarcoma or poorly differentiated will be accepted.
vi. Dogs with stage IV disease at presentation for scar revision
vii. Lost to follow up before two years

(d) Patient accrual will occur over 3 months from announcement to close of recruitment period. We expect that at least 100 cases will be recruited. Any expenses that may be incurred during the course of the study, including publishing

costs will be covered by the PI. Co-authorship criteria will be set at 10% or more of the final case load and will be agreed upon before inclusion in the study. All co-authors will be required to review and contribute toward the final manuscript. Any co-author not responding within three weeks of acknowledged receipt of the manuscript will be acknowledged as a contributor. Contributors with less than 10% of the final case number will be acknowledged as a contributor.

(e) Not applicable

(f) Analysis end points:

i. Confirmed recurrence (locally and/or distant) and date of recurrence. Confirmation of local recurrence will be done by cytology or histology. Distant recurrence will be a radiographic pattern that is consistent with soft tissue sarcoma metastatic disease
ii. Date of death and cause of death
iii. Censoring indicators – death for a reason unrelated to soft tissue sarcoma or local recurrence that is suspected but not confirmed.

Histologic margins at the index and revision surgery will be defined by the International Union against Cancer (UICC) residual tumor classification scheme and the R-classification.[6]

(g) Anticipated toxicities – not applicable

(h) Criteria for stopping treatment – not applicable

(i) Patient follow up schedule – not applicable

(j) Duration of data accrual estimated at 3 months with a further 6 months to analyze data, write manuscript and receive feedback from co-authors.

(k) Statistical design

Data will be collected by a MS Excel Spreadsheet (see attached), which will be imported into statistical software programs SPSS and/or Prism 8 Graft pad. Continuous data will be analyzed for normality with the Kolmogorov-Smirnov test. If normal data will be expressed as mean $\pm$ sdev and median (95% CI) if not normally distributed. Comparisons will be made with either parametric or non-parametric tests based on distribution. Categorical data will be expressed as frequency and percentage. Chi-squared tests will be test for associations between categorical data. Kaplan-Meier survival curves will be used to determine median disease-free interval and median survival times. Differences between curves will be done by log rank tests. A *P*-value of 0.05 will be considered statistically significant.

References

1. Dennis MM, McSporran KD, Bacon NJ, et al: Prognostic factors for cutaneous and subcutaneous soft tissue sarcomas in dogs. Vet Pathol 48:73-84, 2011.
2. 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 211:1147-1151, 1997.
3. Bacon NJ, Dernell WS, Ehrhart 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 230:548-554, 2007.
4. McSporran KD: Histologic grade predicts recurrence for marginally excised canine subcutaneous soft tissue sarcomas. Vet Pathol 46:928-933, 2009.
5. McKnight JA, Mauldin GN, McEntee MC, et al: Radiation treatment for incompletely resected soft-tissue sarcomas in dogs. J Am Vet Med Assoc 217:205-210, 2000.
6. Kainhofer V, Smolle MA, Szkandera J, et al: The width of resection margins influences local recurrence in soft tissue sarcoma patients. Eur J Surg Oncol 42:899-906, 2016.